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Chronic Haemolysis is the Underlying Cause of Progressive Morbidities and Mortality in PNH

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- PE/DVT
- Cerebral
- Dermal
- Hepatic/Portal
- Abdominal Ischaemia

Arterial
- Stroke/TIA
- MI

PULMONARY HYPERTENSION
- Dyspnoea
- Cardiac Dysfunction

CHRONIC KIDNEY DISEASE
- Renal insufficiency
- Dialysis
- Anaemia

END ORGAN DAMAGE
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- Liver
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4. RELPAX Product Information, 11 March 2010

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In recent years it has become accepted that anyone submitting an article to a medical journal or making a scientific presentation should for ethical reasons disclose any financial interests that might have influenced their contents. The reasons for this are clear: there is abundant evidence that the results of studies with commercial support are significantly more likely than those without support to favour products under investigation,¹,² and presentations have been shown to influence audience behaviour in favour of products associated with the sponsor.³ This is of concern because it suggests that commercial interests have the capacity to influence, and maybe distort, the scientific record and to direct the behaviour of clinicians, thereby undermining the primary ethical commitment to patient welfare and the interests of society. A shift from ethical to commercial values as the basis of medicine and science would undermine the trust of the community in these important social institutions and thereby put them fundamentally at risk.⁴

The response of medical journals to these concerns has been to develop increasingly rigorous requirements for authors to disclose their interests and influences. To make the system more uniform many journals, including the Internal Medicine Journal, have adopted the disclosure form developed by The International Committee of Medical Journal Editors. This form requires that every author at the time of submission should declare:⁵

- Financial relationships that could be perceived to influence the submitted work
- All sources of revenue obtained by the author over the 36 months prior to submission
- All financial relationships outside the submitted work, including grants, consulting fees, honoraria, support for travel, payment for writing or reviewing manuscripts, medicines, equipment and administrative support
- Other financial relationships, such as board memberships, consultancies, employment, expert testimony, etc.
- Patents, royalties and other benefits unrelated to the reported study
- Any other relationships or activities that may have influenced the work

These disclosure requirements are clearly very demanding and potentially impose a significant administrative burden on journal staff, and hence the current administrative processing procedure is being monitored. However, few would argue against the admirable commitment to openness and transparency they implicitly proclaim. Less obvious, however, is the impact of the new disclosure regime on actual practices of authors and readers and whether it is likely to succeed in maintaining a separation between industry on the one hand, and science and medicine on the other. In fact, there are reasons for doubting that disclosure requirements in themselves, however Draconian, are likely to provide the kind of protection the community evidently seeks. These reasons fall into four main areas:

First, it is not obvious that the requirement to disclose alters the practices of authors with respect to veracity of data or the reliability of interpretations. Indeed, it has never been claimed that commercial sponsorship is associated with lack of accuracy of data. Rather, the biases associated with funding support arise at an earlier stage, and may affect the choice of the study question, study design (including the choice of sample population, the intervention under investigation and the response variables) and the selection of data for presentation.⁶ It is unlikely that the requirement to disclose would affect any of these steps and there is at present no evidence that it actually does so.

Second, it is even less likely that compulsory disclosure affects the practices of readers. Journal readers assume the integrity of data appearing in medical journals regardless of author affiliations, and if they possess adequate skills they impose their own interpretations on data rather than accepting the conclusions proposed by authors. There is no evidence to support the view that data will be viewed with more suspicion if they were to arise from commercially supported studies, and it is not obvious that this would in any case be desirable.

Third, it is possible that, far from increasing the critical scrutiny of readers, mandatory disclosure of interests may actually undermine it, by inducing a false sense of security that issues relating to potential conflicts of interest have been effectively dealt with through the disclosure process alone. Furthermore, the overemphasis on pecuniary interests versus non-pecuniary ones diverts attention from the fact that for most clinicians and scientists the main drivers are not commercial benefits but...
rather the non-financial incentives of career advancement, status, fame and power, none of which is detected or modified by mandatory disclosure.  

Fourth, it is possible that the focus on commercial funding obscures more fundamental biases in the institutions, practices and methods of clinical science itself. Scientific facts are not ‘objective’ in a pure, unqualified sense but are dependent on the theoretical contexts that engender them. It may be argued that medical journals and clinical scientists would do better to foster critical reflections on the limitations of the randomized, placebo-controlled trial, on the narrow choice of end-points which they usually incorporate or on the narrow, medicalized representations of many ordinary life experiences they commonly assume.

How should a reader utilize the information provided in a disclosure statement? Unfortunately, there is no satisfactory answer to this question. It is unlikely that even the most rigorous disclosures will enhance or refine our knowledge of scientific truth. As disappointing as this may seem, it does not imply that the elaborate bureaucracy erected around the need for journal disclosures has been completely without effect. Rather, its main importance lies not in the filling in of the forms or what they contain but in the reflection and dialogue that have given rise to them. Like all ethics, it is not the consequences that count so much as the processes that generated them: it is not the act of following a law or a rule but the deeper understanding of values and goals that they provoke.  

If it is ethics we want there is no short cut: disclosure forms are not an end in themselves but only a step along the way or, more precisely, a sign that the issues to which they refer are under active consideration.

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References

3 Komesaroff PA, Kerridge IH. Ethical issues concerning the relationships between medical practitioners and the pharmaceutical industry. *Med J Aust* 2002; 176: 118–21.
8 Komesaroff P, Kerridge I. It is time to move beyond a culture of unexamined assumptions, recrimination, and blame to one of systematic analysis and ethical dialogue. *Am J Bioeth* 2011; 11: 31–3.
Incretin-based therapies – review of the physiology, pharmacology and emerging clinical experience

J. H. Martin, C. F. Deacon, M. D. Gorrell and J. B. Prins

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Key words
incretin, type 2 diabetes, GLP-1, GIP, DPP4.

Abstract
Diabetes therapies based on manipulation of the incretin system are now widely available, with millions of people receiving treatment. The incretin hormones, glucose-dependent insulinotropic peptide and glucagon-like peptide-1 are released from endocrine cells in the small intestinal mucosa primarily in response to oral nutrient ingestion. They have various effects, but those most relevant to metabolic dysfunction include stimulation of insulin and suppression of glucagon secretion, with resultant reduction in fasting and postprandial glucose. Incretin secretion and/or action is impaired in type 2 diabetes, leading to development of strategies aimed at redressing this abnormality. These strategies include pharmacological inhibition of dipeptidyl peptidase-4, the enzyme responsible for the short half-life of endogenous incretins, and administration of long-acting dipeptidyl peptidase-4-resistant peptides that bind to and activate the glucagon-like peptide-1 receptor. In this review, we address aspects of incretin biology and pharmacotherapy with a view to highlighting potentially clinically relevant issues and areas of basic research that may impinge on these.

History of incretin discovery
In 1902, the physiologists Bayliss and Starling first proposed that food intake induces release of a chemical from the duodenal and jejunal mucosa that stimulates pancreatic secretion. Soon after was discussion around treating diabetes with the ‘acid extract of duodenal mucous membrane’ (reviewed in1), and subsequently the term ‘incretin’ was used in reference to these glucose-lowering, intestinal-derived factors.2 However, it was not until the 1960s, when plasma insulin concentrations were able to be measured that the effects of oral glucose on insulin concentrations were compared with the relatively smaller increase seen with intravenous glucose administration; the differences in concentrations were related to incretins.3

In the 1970s, the ‘entero-insular axis’ was defined4 with the incretin gastric inhibitory peptide (GIP) isolated, sequenced and shown to stimulate insulin secretion.3 The discovery of a second incretin hormone, glucagon-like peptide (GLP)-1 in 1983 followed the cloning and sequencing of mammalian proglucagon gene.6 Both appear to contribute relatively equally to the incretin effect (the potentiation of glucose-stimulated insulin secretion) in an additive manner in healthy subjects.7

Biology of the endogenous incretins
The proglucagon gene is expressed in the human brain, pancreas and intestine, where tissue-specific processing gives rise to a number of different products (Fig. 1). In the intestinal L-cells, this includes the insulinotropic peptide GLP-1 (7-37) (which in humans is efficiently amidated to GLP-1 (7-36) amide), and GLP-2.8 Both GLP-1 (7-36) amide and (7-37) are biologically active, but once secreted, they are rapidly degraded by dipeptidyl...
peptidase-4 (DPP4) to form the metabolites (GLP-1 (9-36) amide/(9-37)), which account for up to 80% of immunoreactive GLP-1 in the plasma.9 These metabolites are inactive, at least with respect to their insulinotropic activity, although there is some evidence that they may possess other actions (see later).

GIP is derived by proteolytic processing of the 153-residue precursor, preproGIP, expressed in the intestinal K-cells.8 Once released, GIP is also degraded by DPP4,10 albeit more slowly (half-life of 7 min) to GIP (3-42), which accounts for up to 60% of the total GIP in plasma.10

The K- and L-cells are open-type endocrine cells that have direct contact with luminal nutrients through their apical surfaces and with neural and vascular tissues through their basolateral surfaces. A diversity of nutrient, neural and endocrine factors, such as fat, protein and carbohydrate intake, muscarinic-receptor agonists stimulate GLP-1 secretion, whilst inhibitors of GLP-1 secretion include muscarinic-receptor antagonists, insulin, somatostatin and the neuropeptide galanin.11

Whereas the product of DPP4-mediated cleavage of GIP is believed to be biologically inactive, there is increasing evidence that the GLP-1 cleavage product may possess biological activity. For example, GLP-1 (9-36) amide can lower blood glucose by a mechanism independent of insulin secretion.12 However, this pharmacological effect is small and its physiological relevance is undefined.13 Interestingly, GLP-1 (9-36) amide, like intact GLP-1, may have cardioprotective effects.14–16

Both intact GLP-1 and its active metabolite GLP-1(9-36) amide are cleared renally, with elevated plasma concentrations of the metabolite occurring in patients with renal failure.17 Clinically, dose adjustment with the GLP-1 analogues exenatide and liraglutide is not required in subjects with mild renal impairment, or with moderate renal impairment with exenatide but GLP-1 analogues are currently not recommended for subjects with severe renal impairment (due to some evidence that gut side effects are increased here).18 DPP4 inhibitors on the market or in late-stage clinical development (except linagliptin) are renally cleared, but can be used without dose adjustment in subjects with mild renal impairment.

**Receptors**

GIP and GLP-1 have distinct yet overlapping actions and act through specific G-protein receptor complexes, gastric inhibitory peptide receptor (GIPR) and GLP-1 receptor (GLP-1R) respectively. The actions of GIP are assumed to be fully mediated by GIPR. In contrast, not all of the documented GLP-1 actions, specifically those of the GLP-1 (9-36) amide metabolite, can be accounted for by binding and activation of the classic pancreatic GLP-1R. These observations have raised the concept of a putative ‘second GLP-1 receptor’ although molecular evidence for its existence is still lacking. Contributory observations to this concept come from studies using the GLP-1R antagonist exendin (9-39) and studies in GLP-1R knockout animals.15,19

Incretins induce physiological effects by binding to these G-protein receptor complexes receptors, resulting in activation of a number of second messenger systems known to be important in the diabetic pathophysiological
process such as cAMP, ERK1, caveolin-1 and upregulation of control genes such as the homeobox gene PDX-1 in beta cells.\textsuperscript{20–22}

**Site of action (Fig. 2)**

Both the GIPR and GLP-1R are highly expressed in the pancreatic beta cell, but are also expressed in areas such as the hypothalamic centres controlling energy intake.\textsuperscript{23,24} GLP-1R is also found in kidney, liver cholangiocytes, heart, adipocytes, intestine and in the C-cells of the thyroid in rodents.\textsuperscript{25,26} GLP-1 binding has been detected in several neuroendocrine and lung tumours\textsuperscript{27} and in osteoblastic cells, although the classical pancreatic GLP-1 receptor was not detected.\textsuperscript{28} Other groups have similarly failed to find any GLP-1R in osteoblasts or osteoclasts or any direct effects of GLP-1 on these cells in culture.\textsuperscript{26} In humans no changes in markers of bone turnover following acute administration of either GLP-1 or GIP have been reported.

**Effects**

There are now numerous studies showing that the incretin hormones play an important role in the normal regulation of glucose homeostasis. In the pancreas, both GLP-1 and GIP improve beta cell function, not only stimulating insulin secretion, but also replenishing insulin stores by increasing insulin biosynthesis. They also upregulate expression of a number of genes whose products (e.g. glucose transporters and glucokinases) are essential for coupling insulin secretion to glucose levels, whereby the ability of the beta cells to sense and respond to glucose is improved.\textsuperscript{8} Additionally, preclinical studies have indicated that both incretins promote beta cell proliferation and reduce beta cell apoptosis, leading to increased beta cell mass, although whether this also occurs in humans has yet to be demonstrated. In the alpha cell, GLP-1 suppresses glucagon secretion (mediated indirectly via a paracrine pathway involving somatostatin\textsuperscript{29}), thereby reducing hepatic glucose output. GLP-1 also has central effects, reducing appetite.

![Figure 2. Glucoregulatory effects of glucagon-like peptide (GLP) and GLP-1. GIP, gastric inhibitory peptide.](image_url)
and increasing the sensation of satiety. This, together with actions of GLP-1 to decrease gastric emptying, leads to a reduction in food intake and, in the longer term, to body weight loss. In contrast, GIP has a direct stimulatory effect on glucagon secretion. Further, GIP has no effect on gastric emptying or satiety at physiological concentrations, and has no effect on body weight in humans.

**Approaches to increase incretin action in type 2 diabetes (T2D)**

It is now generally accepted that the incretin effect (i.e. the ability of orally ingested nutrients to further augment glucose-induced insulin secretion) is impaired in people with T2D. This has been attributed to the combination of both a GLP-1 secretory defect and GIP resistance. However, while it appears that GLP-1 levels may be reduced, particularly in patients with long-standing or poorly controlled diabetes, this is not a generalized defect, and some subjects, especially those with newly diagnosed or well-controlled diabetes have relatively normal post-prandial GLP-1 responses. The actions of GLP-1 are largely preserved in T2D (although its insulinotropic potency is reduced compared to healthy individuals and infusion of GLP-1 significantly reverses the postprandial glucose abnormality in T2D animal models and in humans. In contrast, while levels of GIP are unaltered in T2D, its insulinotropic effects are severely impaired, even if concentrations are raised well into the pharmacological range.

Thus, the rationale to elevate the GLP-1 concentration in T2D is clear. However, the pharmacokinetic properties of the endogenous incretin with its short half-life make it less than ideal for therapeutic use. Two strategies have thus emerged to increase incretin action in T2D – inhibition of DPP4 and administration of GLP-1 receptor agonists that are DPP4 resistant and thereby longer-acting.

**DPP4 inhibitors**

DPP4 (CD26) is a serine protease (dipeptidyl peptidase) that specifically cleaves dipeptides from the amino terminus of proteins, thus modifying or ablating their activity. Four DPP4 inhibitors have been approved for treatment of T2D (sitagliptin, vildagliptin, saxagliptin and recently, alogliptin (Japan only)) and a number of others, including linagliptin, are in late-stage clinical development. These are all small molecules that are rapidly absorbed following oral dosing, resulting in over 80% inhibition of DPP4 activity for the full 24-h period. Typically, they raise peripheral plasma concentrations of the intact forms of both incretins by twofold to threefold. Although as a class they differ widely in their chemistry, they are all selective for DPP4.

DPP4 is widely expressed by epithelial cells, endothelial cells, adipocytes and lymphocytes and is thus found in most organs as well as plasma. There are dozens of in vitro substrates for DPP4 but the physiological relevance of most of these, apart from the incretins, is not evident. For example, both growth hormone releasing hormone (GHRH) and insulin-like growth factor-1 (IGF-1) can be degraded by DPP-4 in vitro, but there is no change in IGF-1 or growth hormone levels in people treated with DPP4 inhibitors. Substance P, bradykinin and stromal-derived factor 1 alpha may be endogenous physiological substrates, perhaps explaining an increased incidence of headache and nasopharyngitis compared to placebo noted in some clinical trials, although larger pooled safety analyses have not confirmed this trend. Two potential benefits of incretin therapy have been identified in mouse studies but not yet tested in humans: DPP4 inhibitor treated mice have an stromal-derived factor 1 alpha mediated cardiac benefit, and high fat-fed mice treated with either exenatide or DPP4 inhibitor exhibit less steatosis.

Advantages of DPP4 inhibitors over existing diabetes treatments include a low risk of hypoglycaemia, a neutral effect on body weight and the potential for preservation or enhancement of beta-cell function.

**Development of longer-acting incretin analogues**

There are several analogues in development, but most human data relate to exenatide and liraglutide, which have both been approved for treatment of T2D.

Exenatide (exendin-4) is a 39-amino-acid peptide originally isolated from the salivary secretions of the lizard *Heloderma suspectum*. It shares 53% amino acid sequence identity with human GLP-1 and has been shown to mediate its insulinotropic effects through binding to the GLP-1 receptor on pancreatic beta cells. Exenatide is more potent and has a longer duration of action than GLP-1 due to resistance to DPP4, and its slower renal clearance. Exenatide has effects for up to 8 h after subcutaneous administration and is therefore usually administered twice daily. It has also been encapsulated in biodegradable microspheres that gradually dissolve, releasing the peptide over a prolonged period. This ‘once-weekly’ formulation, which is currently undergoing regulatory review, gives more sustained elevations in plasma concentrations with a flatter...
profile (i.e. without the large peaks and troughs) compared to twice-daily exenatide.\\(^{50}\)

Liraglutide \((\text{Arg}34\text{Lys}26-(N-(\text{Glu(N-hexadecanoyl)}))-(7-37) \text{GLP-1})\) is made by derivatizing human GLP-1 with a fatty acid side chain, promoting albumin binding and reducing degradation by DPP4. This results in a plasma half-life of 10–12 h when injected subcutaneously in man, making it suitable for once-daily injection.\\(^{51}\)

### Efficacy of incretin-based therapies

Comparative studies – either for efficacy or safety – between the incretin analogues are sparse, as are solid comparative data between the DPP4 inhibitors and the exogenous incretins or incretins and insulin. In the only study so far published to compare the DPP-4 inhibitors, HbA1c lowering efficacy of sitagliptin and saxagliptin was equivalent.\\(^{35}\) In head-to-head studies, the longer-acting GLP-1 analogues appear to give better efficacy than shorter-acting analogues and to be generally associated with fewer gastrointestinal side effects. Thus, there are data directly comparing weekly versus daily exenatide with efficacy data favouring the former,\\(^{36}\) and once-daily liraglutide versus twice-daily exenatide favouring liraglutide.\\(^{31}\) In direct comparisons between the longer-acting GLP-1 analogues and the DPP4 inhibitors, exenatide once weekly showed greater reductions in HbA1c \((-1.7\%); \text{baseline HbA1c 8.5\%}) than either sitagliptin \((-1.0\%)) or pioglitazone \((-1.4\%)).\\(^{34}\) Exenatide once weekly was also associated with body weight loss and reduction in blood pressure, whereas gastrointestinal side effects were less frequent with sitagliptin. Similar observations were made in a 26-week study comparing sitagliptin with liraglutide.\\(^{39}\) On the other hand, in a pilot study comparing the addition of either sitagliptin or the shorting-acting twice-daily exenatide as add-on therapy to insulin + metformin, efficacy was similar with both agents.\\(^{36}\) At present, however, there are still insufficient data to enable a robust direct comparison of long-term efficacy and safety between the analogues and inhibitors, controlling for not only HbA1c, weight and other outcomes and side effects, but also issues such as compliance and discontinuations, data that would be truly useful in the clinical setting. Moreover, it is also relevant to see how these newer incretin-based therapies compare with existing antihyperglycaemic therapies. Several head-to-head studies with the various DPP4 inhibitors have indicated that, broadly speaking, they have similar or only slightly less efficacy to metformin when used in monotherapy, and are non-inferior to the glitazones and sulphonylureas when used as add-on therapy to metformin, typically giving reductions in HbA1c of 0.6–1.0\% from baseline HbA1c levels of around 8.0\%, with greater reductions from higher baseline HbA1c. Notably, glycaemic efficacy with the inhibitors was achieved without the weight gain seen with the sulphonylureas or glitazones or the increased incidence of hypoglycaemia associated with the sulphonylureas.\\(^{37}\) When used as initial combination therapy with either metformin or pioglitzone, the combination therapy yielded greater HbA1c reduction than either component agent in monotherapy, but was not associated with any increased incidence of adverse events; in subgroups with baseline HbA1c >8.6\%, reductions of >1.5–2.0\% have been noted.\\(^{37}\) A few studies comparing the GLP-1 analogues with other therapies have also been published. Liraglutide was demonstrated to improve glycaemic control when added to existing oral antidiabetic agents (typical reductions in HbA1c 1.0–1.2\% from baseline levels of around 8.3\%), and to have superior HbA1c lowering efficacy than glimepiride when used in monotherapy.\\(^{37,58}\) Similarly, in patients with suboptimal glucose control using existing therapies, the addition of either liraglutide or exenatide once weekly resulted in greater improvements in glycaemic control than the addition of insulin glargine (reductions of 1.3–1.5\% with the analogues vs. 1.1–1.3\% with insulin glargine, from baseline HbA1c levels of 8.2–8.3\%).\\(^{37,59,60}\) These improvements seen with the analogues were not associated with increased incidence of hypoglycaemia, and were accompanied by weight loss.

### Comparability of endogenous and exogenous incretin effects

The effective GLP-1 concentrations achieved with the GLP-1 analogues versus meal-related incretin levels following DPP4 inhibition are major points of distinction between the two classes of incretin-based therapies. Continuous activation of GLP-1R with high agonist concentrations may have advantageous or disadvantageous effects. Theoretical deleterious effects could include pancreatic beta-cell overgrowth (although this has not been seen in the clinical trials to date), or receptor downregulation. Potential beneficial effects might include a more marked cardioprotective and/or anorexic effect. It is noteworthy that high-dose treatment and transgenic animal studies in which prolonged suprapharmacological levels of GLP1-R activation are achieved display a phenotype of leanness, insulin sensitivity, absence of hypoglycaemia, long survival and mild lymphatic overgrowth.\\(^{61}\) With respect to potential receptor downregulation, so far this appears not to occur clinically as evidenced by the absence of tachyphylaxis in prolonged exenatide therapy.
Additional non-glycaemic effects of incretin-based mechanisms

Pancreatitis

The safety profile of the incretin-based therapies in the clinical trials had not given much cause for concern until the Food and Drug Administration issued a warning in 2007 following reports of pancreatitis in some patients taking exenatide (http://www.fda.gov/safety/medwatch/safetyinformation/safetyalertsforhumanmedicalproducts/ucm079781.htm). Since then, additional cases have been reported in patients using exenatide, including a few cases of haemorrhagic or necrotizing pancreatitis, and six deaths have occurred in patients who had experienced pancreatitis. Post-marketing surveillance has also identified isolated cases of pancreatitis in patients taking sitagliptin. However, analysis of a US healthcare database showed that rates of pancreatitis with exenatide or sitagliptin were no different from metformin or glyburide, supported also by the safety analyses with sitagliptin and vildagliptin so while a definitive causal relationship between GLP-1R signalling and pancreatitis has not been established, a possible association cannot yet be fully excluded.

Malignancy

Until recently, the incretins had not appeared to have had an effect on tumourigenesis with knockout, transgenic and animal toxicology studies not convincingly demonstrating any change in malignancy rates. However, it has been reported that liraglutide and exenatide have been associated with benign and malignant thyroid C-cell tumours in rats and mice and malignant fibrosarcomas in male mice. The presence of GLP-1 receptors has been reported in normal rat thyroid and in rat medullary thyroid carcinoma cell lines and in these tissues, GLP-1 has been shown to stimulate both expression and secretion of calcitonin. In rodents, in vivo administration of liraglutide increased plasma calcitonin levels and was associated with C-cell hyperplasia and tumour formation. However, in a human C-cell line, expression of the GLP-1 receptor is reported to be low, and liraglutide is not reported to cause calcitonin release or C-cell proliferation in non-human primates. Moreover, in the clinical trials with liraglutide where calcitonin concentrations were measured, levels were low at baseline and remained well within the normal range even after exposure to liraglutide for up to 2 years.

While the preclinical studies in rodents do appear to reveal a link between GLP-1, C-cell hyperplasia and the development of thyroid tumours, the relevance of these findings for humans is unclear. This should be seen in the light that not only are there marked differences in the way that rodent and human C-cells respond to GLP-1, but also that spontaneous C-cell tumours occur in rats at relatively high frequency, whereas medullary thyroid cancer in humans is rare. Nevertheless, patients will be exposed to GLP-1 agonists over many years, and the effect of sustained GLP-1R signalling over the long term on the human thyroid remains unknown.

Skin

Animal studies with some, but not all, DPP4 inhibitors have noted necrotic skin lesions affecting the extremities. However, this has not been reported in patients in controlled clinical studies with sitagliptin, vildagliptin, alogliptin or saxagliptin. Isolated incidences of serious hypersensitivity reactions including Stevens-Johnson syndrome have been reported in the post-marketing environment, but no causal relationship has been established.

Cardiac effects

Both DPP4 inhibitors and GLP-1 analogues have beneficial effects on classical cardiac risk factors by reducing blood pressure, weight, triglycerides and low-density lipoprotein cholesterol and increasing high-density lipoprotein cholesterol in addition to direct effects on the myocardium and vasculature. Whether or not these surrogate outcomes will translate into clinical benefit is unknown, although human GLP-1 infusion has benefit in the settings of acute myocardial ischaemia, chronic heart failure and post-infarction and early clinical trial data have so far shown no adverse cardiovascular effect of GLP-1 analogues or DPP4 inhibition. Several large cardiovascular outcome trials are currently underway which will specifically address the impact of the incretin-based therapies on macrovascular risk.

Conclusions

Much is still to be learned about the biology and pharmacology of the incretin system although our understanding of the system has increased greatly since the introduction of the current drugs. Incretin-based therapy does have an effect on HbA1c, plasma glucose, body weight and beta-cell secretory function in T2D. However, much of the clinical relevance depends on the relationship between these surrogate variables and...
clinical outcomes, which need to be further evaluated in longer-term studies involving larger and more heterogeneous patient populations with differing residual beta-cell function, on different background therapies and using comparative arms that include both DPP4 inhibitors, the longer-acting incretin mimetics and insulins.

Since the introduction of the first GLP-1 analogue in 2005, and the first DPP4 inhibitor in 2006, millions of prescriptions have been issued. Nevertheless, the incretin therapies are considered relatively new agents, and clinical experience with them is still limited, particularly with regard to any side effects or adverse events which may occur at a low incidence. Despite their apparently benign side effect profiles, it cannot yet be fully excluded that undesirable effects could occur with long-term stimulation of the GLP-1R, or that unexpected off-target effects could arise. Pharmacovigilance for anti-incretin antibodies, cancer risk, pancreatitis and other adverse events is therefore warranted.

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References

The influence of GLP-1 on postprandial metabolism in humans.


Ligueros-Saylan M, Foley J, Schweizer A, Couturier A, Kothny W. An assessment of adverse effects of vildagliptin versus comparators on the liver, the pancreas, the immune system, the skin and in patients with impaired renal function from a large pooled database of Phase II and III clinical trials. Diabetes Obes Metab 2010; 12: 495–509.

Incretin based therapies – an update


Hospital doctors’ attitudes towards older people
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Key words
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Abstract

Background: Ageism among health professionals is increasingly recognized, but few studies investigated hospital doctors’ attitudes towards older people. The aims of this study were to investigate hospital doctors’ attitudes towards older people and to determine whether factors, which were identified in studies on other health professionals, influence hospital doctors’ attitudes.

Methods: Hospital doctors who worked in General Medicine or Aged Care units in two tertiary public hospitals in metropolitan Victoria, Australia, in 2008 were surveyed with Fraboni’s Scale of Ageism (FSA), a validated instrument used to investigate attitudes towards older people. Demographic data from participants were collected.

Results: Of the 235 questionnaires distributed, 122 were returned (overall response rate 51.9%). Response rate was highest among consultants (80.4%), followed by registrars (64.1%) and lowest among interns and residents (35.2%). The mean FSA score attained by the respondents was 61.5 (SD 11.0), representing a point between a neutral and a positive disposition. Doctors’ characteristics that were associated with more positive attitudes towards older people included age of 30 years or older ($P<0.001$), female gender ($P=0.003$), more senior in position ($P<0.001$), postgraduate years of 10 or more ($P<0.001$), previous working experience in Aged Care ($P<0.001$), interest in Aged Care ($P<0.001$) and more frequent social contacts with healthy older people ($P<0.001$).

Conclusion: Hospital doctors of different demographic features and background characteristics display different attitudes towards older people. These findings can be used to inform future development of undergraduate and postgraduate medical curricula and form a basis for future studies on the effectiveness of these interventions in improving doctors’ attitudes.

Introduction

The proportion of the Australian population aged over 65 years is projected to increase from 13% in 2004 to 20% by 2024. Older people are more frequent users of hospitals and, on average, have longer hospital stays compared with their younger counterparts. The ageing of the Australian population is expected to impact significantly on both the demand for and the provision of hospital services.

Ageism was defined by Butler and Lewis in 1973 as a process of systemic stereotyping of, and discrimination against, people because they are old. Ageist attitudes among healthcare professionals negatively impact on the quality of care older patients receive. Ageism among doctors is an increasingly recognized phenomenon. Many doctors have negative perceptions about older patients, especially those over the age of 85 years and nursing home residents. Doctors tend to be less engaged when talking to older patients and they patronize older patients by providing oversimplified information and presenting information to the family instead of the patient. Doctors tend to put in less effort in saving the lives of older patients and prevention therapy is often ignored. A survey found that 16% of general practitioners decided in some cases not to refer older patients for secondary treatment because they suspected that the patients would not be treated due to their age.

In an attempt to combat ageism among doctors, several studies evaluated the effect of geriatrics education within medical curriculums in promoting positive attitudes towards older people. Studies showed that geriatrics
clerkship programmes, which offer students interaction with healthy older people, help students acquire positive attitudes towards older people.8–11 One study found that a month-long geriatric rotation, including conducting comprehensive assessments with ‘well’ older people, significantly improved interns’ attitudes towards older adults as patients.12 These findings suggest that increased contacts with well older people may promote positive attitudes towards older people.

Despite these findings, few studies have investigated the factors that may have contributed to ageism in doctors. On the contrary, studies investigating the attitudes of nurses have identified several significant factors. Nurses working in aged care wards were found to have more positive attitudes towards older patients compared with nurses working in acute medical wards.13 Nurses who were more knowledgeable or had more years of experience were also found to have more positive attitudes towards older people.4 The age, gender and ethnicity of nurses may influence their attitudes. One study showed that male and black and Asian nurses had less favourable attitudes towards older people.14 While some studies showed that younger people, including nursing students aged less than 25 years, had less favourable attitudes towards older people, the same correlation was not seen in studies evaluating nurses’ attitudes.13,13 Whether these findings occur with other health professionals, for example, hospital doctors, is unknown.

The aims of this study were: (i) to investigate hospital doctors’ attitudes towards older people and (ii) to determine whether factors that were identified in studies on other health professionals (age, gender, cultural background, work experience and social contact) influence hospital doctors’ attitudes.

Methods

Data collection

General information collected from participants includes age, gender, country of birth, language other than English, preferred or current career specialty, years’ experience and social contact with well people aged 65 years or older.

Instruments

Multiple instruments have been developed to identify attitudes towards older people.16 There is no gold standard instrument as many of the existing tools have limitations.17–20 Fraboni’s Scale of Ageism (FSA, 1990) was used to assess the attitudes of hospital doctors towards older people in this study. It is a questionnaire that consists of 29 statements. Responses are recorded according to a 5-point score scale. For all the negatively worded statements, the scoring system is as follows: 1, strongly disagree; 2, disagree; 3, neither agree nor disagree; 4, agree; 5, strongly agree.

A reverse in the scoring system applies for all the positively worded statements. The total score ranges from 29 to 145, with a lower score indicating a more positive attitude.

FSA was chosen for this study on the basis of several perceived advantages: (i) FSA is compatible with the theoretical framework of ageism, comprising of both cognitive and affective components, proposed by Butler and Lewis.21 (ii) FSA appears to be the first measure of ageism to show a connection between affect and behaviour and stereotypes and behaviour.22 (iii) FSA is more recently developed. (iv) Although FSA has not been validated in Australia, it has been adopted in studies involving different groups (students, healthcare professionals, council employees, etc.), in different settings (university, age awareness workshops, workplace, etc.) and in different countries (Canada, USA, UK, etc.).16,20–22 It has been shown to be a reliable, valid and multidimensional measure of ageism.21

Study participants

A list of all the doctors who worked in General Medical or Aged Care units of two tertiary public hospitals in metropolitan Victoria in 2008 was obtained from their corresponding medical workforce units. The doctors were categorized into three groups according to their position: (i) interns and residents, (ii) registrars and (iii) consultant physicians. Written information of the study, the general information collection forms and the survey questionnaires were distributed between March 2008 and June 2008 to potential participants for completion in their own time and return through reply-paid envelopes. Voluntary and anonymous participation was solicited through letters from the Director of Medicine of the two hospitals. Return of survey questionnaires was regarded as implied consent from participants in taking part in the project.

This study was approved by the Human Research Ethics Committee of Melbourne Health and the Office of Research of Western Health.

Statistical analysis

Data were entered in full into Stata8 statistical package (StataCorp LP, College Station, TX, USA) and statistical analyses were undertaken. The t-tests or analyses of
variance (ANOVA) were used to identify the differences in total score between doctors of different work experience, age group, gender, cultural background and social contact. A multivariate analysis was carried out using factors significantly associated with a response difference on a univariate level. A stepwise regression analysis was carried out on these factors in order to determine a best model fit.

Results

Respondent characteristics

Of the 235 questionnaires distributed, 122 were returned (51.9% response rate). Response rate varied across position groups: (i) 35.2% for interns and residents (44/125), (ii) 64.1% for registrars (41/64) and (iii) 80.4% among consultant physicians (37/46). Respondent characteristics are summarized in Table 1.

FSA score

Of the 122 responses, the FSA score ranged from 39 to 98, with a mean score of 61.5 (SD 11.0) and a median score of 62.

Doctors aged 30 years or more reported more positive attitudes towards older people than doctors aged less than 30 years (mean score 56.55 vs 65.13, \( P < 0.001 \)).

Female doctors reported more positive attitudes than male doctors (mean score 58.29 vs 64.21, \( P = 0.003 \)).

Doctors who were more senior reported more positive attitudes towards older people: (i) consultant physicians reported more positive attitudes than registrars who in turn reported more positive attitudes than interns and residents (mean score 56.22 vs 61.34 vs 66.2, \( P < 0.001 \)).

(ii) Doctors who were 10 or more years post graduate reported more positive attitudes than doctors who were less than 10 years post graduate (mean score 56.31 vs 64, \( P < 0.001 \)).

Doctors who had working experience in Aged Care reported more positive attitudes than doctors who did not (mean score 57.75 vs 65.86, \( P < 0.001 \)). Doctors who were interested in Aged Care reported more positive attitudes than those who were not (mean score 53.26 vs 64.87, \( P < 0.001 \)).

Doctors who had more than weekly social contacts with well older people reported more positive attitudes towards older people than those who had less than weekly, but more than monthly contacts, who in turn reported more positive attitudes than those who had less than monthly contacts (mean score 57.16 vs 60.97 vs 68.08, \( P < 0.001 \)).

There was no significant difference in the attitudes reported by doctors with different country of birth or by doctors who spoke different languages.

<table>
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<tr>
<th>Table 1</th>
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<tr>
<td></td>
<td>Asia</td>
</tr>
<tr>
<td></td>
<td>Europe</td>
</tr>
<tr>
<td></td>
<td>Others</td>
</tr>
<tr>
<td>Language other than English</td>
<td>English only</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
</tr>
<tr>
<td></td>
<td>European</td>
</tr>
<tr>
<td>Postgraduate year</td>
<td>Less than 10</td>
</tr>
<tr>
<td></td>
<td>10 or more</td>
</tr>
<tr>
<td>Position</td>
<td>Interns/Medical residents</td>
</tr>
<tr>
<td></td>
<td>Medical registrars</td>
</tr>
<tr>
<td></td>
<td>Consultant physicians</td>
</tr>
<tr>
<td>Worked in Aged Care</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td>No</td>
</tr>
<tr>
<td>Interest in Aged Care</td>
<td>Consider or currently specializing in Aged Care</td>
</tr>
<tr>
<td></td>
<td>Undecided or not considering specializing in Aged Care, or currently specializing in other specialities</td>
</tr>
<tr>
<td>Contact with well older people</td>
<td>More than weekly</td>
</tr>
<tr>
<td></td>
<td>More than monthly</td>
</tr>
<tr>
<td></td>
<td>Less than monthly</td>
</tr>
</tbody>
</table>
These results are displayed in Table 2.

A multivariate analysis was carried out for all the factors that were significantly associated with a response difference. Of these factors, gender, position, interest in Aged Care and social contacts with well older people were found to predict significantly doctors’ attitudes towards older people. These results are displayed in Table 3.

A correlation analysis was carried out for all the factors that were significantly associated with a response difference. A close correlation was found between gender and position. This was due to a higher proportion of male doctors among consultants and registrars compared with residents and interns ($P = 0.03$). The use of gender, instead of position, in predicting attitudes resulted in a better model fit. A close correlation was also found between working experience in Aged Care and interest in Aged Care. Doctors who had working experience in Aged Care were more likely to consider specializing or specialize in Aged Care ($P = 0.00$).

**Discussion**

Are hospital doctors’ attitudes towards older people positive?

For the full cohort of hospital doctors, the mean score of 61.5 indicated that each statement averaged 2.12. This represents a point between a neutral and a positive

---

**Table 2 Fraboni’s Scale of Ageism Score**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Descriptions</th>
<th>Mean</th>
<th>SD</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Less than 30</td>
<td>65.13</td>
<td>10.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>30 or above</td>
<td>56.55</td>
<td>8.98</td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td>Male</td>
<td>64.21</td>
<td>10.5</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>58.29</td>
<td>10.77</td>
<td></td>
</tr>
<tr>
<td>Country of birth</td>
<td>Australia</td>
<td>61.21</td>
<td>10.92</td>
<td>0.255</td>
</tr>
<tr>
<td></td>
<td>Asia</td>
<td>64</td>
<td>10.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Europe</td>
<td>58.6</td>
<td>11.37</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Others</td>
<td>49</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Language other than English</td>
<td>English only</td>
<td>61.12</td>
<td>11.01</td>
<td>0.095</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>64.18</td>
<td>10.64</td>
<td></td>
</tr>
<tr>
<td></td>
<td>European</td>
<td>55.9</td>
<td>10.68</td>
<td></td>
</tr>
<tr>
<td>Postgraduate year</td>
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<td>64</td>
<td>11.1</td>
<td>&lt;0.001</td>
</tr>
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<td></td>
<td>10 or more</td>
<td>56.31</td>
<td>8.87</td>
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</tr>
<tr>
<td>Position</td>
<td>Interns/Medical residents</td>
<td>66.2</td>
<td>11.92</td>
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<td></td>
<td>Medical registrars</td>
<td>61.34</td>
<td>9.44</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Consultant physicians</td>
<td>56.22</td>
<td>9.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yes</td>
<td>57.75</td>
<td>9.84</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>65.86</td>
<td>10.76</td>
<td></td>
</tr>
<tr>
<td>Done Aged Care</td>
<td>Yes</td>
<td>57.16</td>
<td>10.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>60.97</td>
<td>9.04</td>
<td></td>
</tr>
<tr>
<td>Interest in Aged Care</td>
<td>Yes</td>
<td>58.08</td>
<td>10.43</td>
<td></td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>65.86</td>
<td>10.76</td>
<td></td>
</tr>
<tr>
<td>Contact with well older people</td>
<td>More than weekly</td>
<td>57.16</td>
<td>10.63</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>More than monthly</td>
<td>60.97</td>
<td>9.04</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Less than monthly</td>
<td>68.08</td>
<td>10.43</td>
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</tr>
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</table>

**Table 3 Multivariate analysis**

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>95% confidence interval</th>
<th>$P$</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-2.481</td>
<td>-5.907 to 0.946</td>
<td>0.156</td>
</tr>
<tr>
<td>Gender</td>
<td>5.642</td>
<td>2.331–8.954</td>
<td>0.001</td>
</tr>
<tr>
<td>Postgraduate year</td>
<td>2.898</td>
<td>-1.551 to 7.348</td>
<td>0.202</td>
</tr>
<tr>
<td>Position</td>
<td>-3.620</td>
<td>-6.540 to -0.701</td>
<td>0.015</td>
</tr>
<tr>
<td>Done Aged Care</td>
<td>2.476</td>
<td>-1.015 to 5.996</td>
<td>0.168</td>
</tr>
<tr>
<td>Interest in Aged Care</td>
<td>6.082</td>
<td>2.036–10.129</td>
<td>0.003</td>
</tr>
<tr>
<td>Contact with well older people</td>
<td>3.558</td>
<td>1.561–5.554</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant; S, significant.
disposition (i.e. agreeing with a positive statement and disagreeing with a negative statement). Analysis of the median score indicated a very similar score. It may be possible to conclude that the attitudes of hospital doctors towards older people were overall positive. There is, however, an issue relating to the merits of interpreting the FSA score in this fashion. The FSA score represents a spectrum, with a lower score indicating a more positive attitude. It was not designed with a cut-off score so that a score above which indicated a negative attitude or a score below which indicated a positive attitude. A more meaningful interpretation of the score requires comparison among different groups or comparison of the same group at different times. The average score attained by the hospital doctors in this study was similar to that of various population groups as reported in previous studies.17,21 This suggests that the attitudes of hospital doctors towards older people may be similar to that of the general population. Caution with this interpretation must be exercised as it is based on comparison with historic data. Nonetheless, this observation should raise concerns about the current medical curriculum as it does not appear to have a positive effect on raising the average attitudinal levels of doctors above that of the general population.

Factors associated with difference in attitudes

Hospital doctors of different demographic features and background characteristics have different attitudes towards older people. Doctors’ characteristics that were found to be associated with more positive attitudes towards older people included age of 30 years or above, female gender, postgraduate years of 10 or more, being more senior in position, previous working experience in Aged Care, interest in specializing in Aged Care and more frequent social contacts with well older people. The findings regarding age, gender, working experience in Aged Care, interest in Aged Care and social contacts were consistent with previous findings in other health professionals and students. There was no significant difference in the attitudes reported by doctors with different cultural background, which was a contrast to the findings in some previous studies. This may be explained by the complex nature of cultural diversity and the heterogeneity within cultural groups. The study was not powered to assess this relationship.

Among the above factors, two were potentially modifiable: (i) work experience and (ii) social contacts. There are two possible explanations for the finding that doctors with working experience in Aged Care reported more positive attitudes towards older people. On the one hand, it may be that doctors with more positive attitudes tend to seek work in Aged Care. On the other hand, their experience in Aged Care may have promoted positive attitudes towards older people. It is worth noting that hospital rotations are allocated to interns, residents and registrars only partly according to their preferences. A fair proportion of junior doctors who have been allocated an Aged Care rotation may not have a preference in Aged Care initially. The latter explanation may therefore hold true in these cases. Providing junior doctors with more job opportunities in Aged Care, such as making Aged Care rotations compulsory for interns, may therefore promote more positive attitudes in hospital doctors. An interesting topic to look into further is to find out which component of the Aged Care rotation helps promote positive attitudes, whether it is the environment of the Aged Care work setting or the improvement in knowledge in the care of older people. Similar explanations may account for the finding that doctors with more frequent social contacts with well older people reported more positive attitudes. On the one hand, doctors with more positive attitudes may be more likely to seek social company with older people. On the other hand, social contacts with healthy older people may have promoted positive attitudes. As professional attitudes are often formed early in training, providing medical students with more exposure to healthy older people from early in their course may help students acquire positive attitudes. Unfortunately, the current model of medical education bases primarily on tertiary centres where medical students come in contact with very sick and frail older patients. Such biased exposure contributes to the development and reinforcement of negative attitudes towards older people.6 To combat this problem, undergraduate medical education should be designed to offer students, early in their course, regular interactions with healthy, active older people, particularly with focus on exploring older people’s experiences with the biological, psychological and social aspects of ageing. This should be complemented by teaching students on how to do a comprehensive geriatric assessment at the beginning of their clinical exposure. Subsequent consolidation of positive attitudes could be achieved by providing junior doctors with Aged Care educational sessions, which involve interaction with healthy older people.

Limitations

This study investigated the attitudes of hospital doctors who were working in General Medicine or Aged Care units. The sample size was small and the sample was confined to two specialty areas in two metropolitan hospitals. The generalizability of the conclusions on this non-randomized sample is limited. Further research into the attitudes of hospital doctors working in other specialties
and from a wider range of metropolitan and rural hospitals would be warranted.

The overall response rate was low (51.9%), particularly among interns and residents (35.2%), but there was a disproportionally high response rate among consultants (80.4%). Potential barriers to engaging the non-respondents include lack of interest in the topic, lack of awareness of ageism and lack of time in responding to the survey. The respondents may therefore have self-selected for their interest in Aged Care and their more positive attitudes towards older people. It could be arguable that the level of ageism in doctors was underestimated. The issue with self-selection could be partially addressed if all medical staffs were sampled. If the study timeline and costs permitted, a follow-up protocol, including sending a reminder letter a week after sending out the questionnaire and sending a second cover letter and questionnaire a few weeks later, might have improved the response rate and thus the generalizability of the conclusions. It is important to recognize that ‘older people’ are a heterogeneous group with different characteristics based on age, gender, cultural background, health status, etc. Evaluating attitudes towards older people as one single category may potentially be overgeneralizing.

Conclusion

This study has indicated that hospital doctors of different demographic features and background characteristics occupy different positions on a dimension related to their attitudinal disposition towards older people. These findings can be used to inform future development of undergraduate and postgraduate medical curricula and form a basis for future studies on the effectiveness of these interventions in improving doctors’ attitudes.

Furthermore, difference in attitudes does not predict specific behaviours. Further research will then be needed to show that improvement in attitudes results in improvement in behaviours and the ultimate goal of providing better quality of care for our ageing population.

Acknowledgements

The study was undertaken with the assistance of the Medical Workforce Units of the participating hospitals. The authors would like to thank Alexandra Gorelik (Clinical Epidemiology and Health Service Evaluation Unit, Melbourne Health) who assisted with statistical analysis and all medical staff who participated in this study.

References

Eliciting views of Australian pharmaceutical industry employees on collaboration and the concept of Quality Use of Medicines

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Abstract

Background: Pharmaceutical industry involvement in biomedicine has produced major benefits but has also caused concern. At present, there is no consensus as to how medical and government organizations should relate to the pharmaceutical industry and this is partly due to the absence of systematic study of the various alternatives. In Australia industry cooperation has been elicited through the ‘Quality Use of Medicines’ (QUM) framework within the ‘National Medicines Policy’. Little is known about the way employees of pharmaceutical companies respond to the QUM policy and strategies.

Aims: To examine the engagement of the Australian pharmaceutical industry with QUM with a view to assisting medical, government and consumer organizations who may wish to collaborate with industry.

Methods: We carried out a qualitative study using in-depth, semistructured interviews with industry employees, primarily from medical and regulatory affairs departments.

Results: Employees of pharmaceutical companies claim that collaboration is important, and that they are altruistic and committed to QUM. At the same time, there is little evidence from this study to support the notion that QUM has brought about structural changes to industry or is positioned as the central goal or framework in designing a company’s operational strategies. Moreover, there is a significant degree of ambivalence towards governments and medical organizations.

Conclusions: Employees within the pharmaceutical industry claim a commitment to collaboration and QUM. While these claims cannot be taken entirely at face value, there is potential for meaningful collaboration with industry.

Introduction

Medicines have made, and continue to make, major contributions to improving individual and public health. But medicines can also cause significant harm, and it is crucial that any new or established therapy is truly an advance over existing therapy: is safe and effective; is marketed, priced, prescribed and used appropriately; and is monitored to establish long-term benefits and harms, cost-effectiveness and impact upon quality of life. This way of thinking about medicines has recently been elucidated in...
the ‘Quality Use of Medicines’ (QUM) framework within the Australian government’s National Medicines Policy, which emphasizes the degree to which all of the above activities are both necessary and interdependent.\textsuperscript{1,2}

The pharmaceutical industry is responsible for many of the above activities, and the perceived importance of the pharmaceutical industry is evident in the increasing number and variety of alliances between researchers, clinicians, government bodies and the pharmaceutical industry. The National Medicines Policy, for example, has among its central objectives the need to maintain a responsible and viable medicines industry.\textsuperscript{3} Medical organizations, such as the Royal Australasian College of Physicians (RACP), also acknowledge that health professionals work with industry in a variety of situations and that industry has a valuable and legitimate role in the healthcare sector.\textsuperscript{5}

While effective collaboration with the pharmaceutical industry is highly desirable, the interests of pharmaceutical companies are fundamentally different from those of clinicians, academic researchers, patients and policymakers. In recent years, several concerns have been raised about activities of pharmaceutical industry, including the tendency to fund studies that are likely to enhance profits rather than be innovative, and which tend to be relevant and accessible to only the wealthiest people in the wealthiest countries (the ‘90–10 divide’);\textsuperscript{4} the exploitation of vulnerable research populations, particularly in the developing world;\textsuperscript{5} the influence that industry has over academic researchers and clinicians and government organizations;\textsuperscript{6} and the techniques used to market medicines to consumers.\textsuperscript{5,8}

In response to such concerns, organizations, such as the RACP and the World Health Organization, have developed guidelines for interactions with the pharmaceutical industry.\textsuperscript{1,3} Medicines Australia (the peak body representing the interests of prescription pharmaceutical manufacturers in Australia) has also developed a Code of Conduct in response to professional and community consultation that has undergone many revisions and continues to be developed (Edition 16 has recently been approved by the Australian Competition and Consumer Commission).\textsuperscript{10}

**Rationale for this study**

In order for such policies to be effective, and in order to maximize the potential benefits of engagement with the pharmaceutical industry, it is vitally important that we have a sophisticated understanding of the issues at stake. At present, however, debates about pharmaceutical involvement in biomedicine have a polarizing quality, with people tending to take strong pro- or anti-industry positions. Because debates about the influence of the pharmaceutical industry tend to be characterized more by passion and polemic than by reasoned study, there has been limited consideration given to the range of policy, regulatory and clinical responses to issues raised by the participation of the pharmaceutical industry in medicine.

In Australia, the Commonwealth Government takes the view that pharmaceutical industry activities are best mediated through both voluntary collaboration and regulation. In particular, the pharmaceutical industry is seen to have a key role to play in achieving QUM and is expected to participate in implementing the ‘National Strategy for Quality Use of Medicines’.\textsuperscript{2}

QUM comprises three principles that address the effective, safe and cost-efficient use of medicines: (i) selecting management options wisely, (ii) choosing suitable medicines if a medicine is considered necessary and (iii) using medicines safely and effectively. This means that the pharmaceutical industry is expected to contribute not only to the development and testing of medicines, but also to their safe and effective use. A recent development in this regard is that demonstration of compliance with QUM is now a prerequisite for listing medicines on the national Pharmaceutical Benefits Scheme, reflecting the government’s growing emphasis on ‘purchasing’ QUM outcomes.\textsuperscript{11}

These efforts to engage the pharmaceutical industry in QUM are based on the assumption that individual companies are committed to QUM, even when it threatens their commercial ‘bottom line’. While this is an appealing notion, the question of whether or not industry is willing and able to engage in truly collaborative activity is ultimately an empirical one. While studies have been conducted into the effects of QUM on prescribing\textsuperscript{12-14} we do not know how industry has responded to QUM. We set out therefore to examine the engagement of the Australian pharmaceutical industry with the QUM policy and strategy.

**Methods**

We carried out a qualitative study using in-depth, semi-structured interviews with a range of pharmaceutical industry employees. The goal of sampling was to obtain a wide range of responses and opinions, so we used ‘snow-ball sampling’ to recruit professional staff from various departments and across different seniority levels in different types of pharmaceutical companies. While we interviewed people from all departments (sales, marketing, medical, regulatory affairs and executive), the majority of volunteers came from medical and regulatory/public affairs and we chose to focus on these departments because they have primary responsibility for ensuring
adherence to promotional standards as well as to aspects
of QUM. Eleven companies were represented: six were
innovative multinational companies, four were generic
producers (both Australian and multinational) and one
company produced non-prescription (complementary)
medicines.
Participants were asked about their understanding of
and attitudes towards QUM, with questions being open-
ended in order to elicit a depth of response that might
reveal detailed and possibly unanticipated viewpoints.
Emergent themes were grouped together into analytic
categories and developed into more abstract ‘concepts’.
Although thematic saturation was reached after approxi-
mately 15 interviews (i.e. no novel issues emerged), a
total of 24 interviews was completed to cover the range of
respondents from whom we wanted to hear. Interviews
were analysed independently by two researchers.
Ethics approval was obtained from the research ethics
committee at St Vincent’s Hospital, Sydney and UNSW
Human Subjects Protection Committee.

Results
Twenty-four interviews were carried out with Australian
employees of 11 largely multinational pharmaceutical
companies. Demographic characteristics of the partici-
pants are shown (Table 1). Our results suggest that phar-
maceutical company employees show signs of both
acceptance of, and resistance to, QUM.

Signs of acceptance of QUM
Awareness, understanding and integration of QUM
Without exception, study participants described them-
selves as being personally aware and having a good
understanding of QUM. When asked to elaborate on their
understanding, participants demonstrated both a general
understanding of the goal of QUM (‘the right drug, for
the right patient, at the right time’) and a sense of how
QUM is expressed and enacted in their particular depart-
ment. All participants agreed that QUM is important.
QUM was described as a ‘framework’ or ‘context’ within
which all company decisions are made and as a set of
principles that are ‘embedded’ and ‘integrated’ into

Box 1 Illustrations of acceptance
1.1 I think we are getting to a stage that, QUM is not this ‘add on’ bit you might think it is. It is actually a way of
working so that the QUM is embedded in the operational strategies of the company that everything I do, or in
medical and marketing, that we do understanding QUM principles. It’s just the way of how we work and it is not
something separated. [#22 External relations]
1.2 I can’t think of anyone in the company that you would be able to go to them and say, ‘what you are advocating
is not QUM.’ So I think it’s very broadly and implicitly there but possibly not explicitly. [#23 Public affairs and policy]
1.3 Interviewer: how important is [QUM] overall to you?
Participant: to me personally, it is very important. I think to me that’s because I have never put my physician hat
off. Having worked for 10 years as clinician, I haven’t forgotten what that means to patients so that every decision
that I make, every interaction that I have whether I consciously think about QUM or not, it’s always there. [#15
Medical advisor]
1.4 I keep coming back to the theme that the reason we are here is to improve the health outcome and that’s for
everybody, the doctors, the pharmacists, nurses and everybody here. That’s the bottom line. [#21 Cooperative
affairs]
1.5 I think it is important if you want to get long-term appropriate use. Say, we have sales spike for 3 months
followed by a big dip. It’s not our interest. We want long-term sales. To do that you have to be credible you have
to be appropriate, which means QUM. [#9 Medical director]
everyday pharmaceutical practice (see Box 1.1). Interestingly, these principles were seen by some to be learned implicitly, understood tacitly and applied unconsciously, such that integration did not require knowledge of the particular ‘QUM’ phrase or policy (and may even have preceded the formal implementation of the policy) (Box 1.2).

**Willingness to collaborate with government in implementing QUM**

Participants had several ideas as to how pharmaceutical compliance with QUM might be improved. They argued both for more industry self-regulation (with a view to harnessing the power of commercial competition as a regulatory mechanism) as well as more collaboration and coordination among stakeholders. Governments were seen to have an important role in educating both the pharmaceutical industry and prescribers and in coordinating shared industry–government post-marketing surveillance.

**Reasons for acceptance of QUM**

The acceptance of QUM appeared, in turn, to be underpinned by personal and corporate identification with QUM, and by association of QUM with both altruism and commercial self-interest.

**Identification with QUM**

At the corporate level, QUM was described as ‘what we do’; as ‘the reason we are here’; and as what a company ‘represents’ in terms of its ‘mission’, ‘principles’, ‘values’ and ‘philosophy.’ Indeed, for some companies, commitment to QUM was seen as a kind of rite of passage and a measure of whether somebody is an appropriate company employee. Identification with QUM was described also at the personal level, with participants seeing QUM as intrinsic not only to their current roles and responsibilities, but also to their ‘pre-corporate’ identities as doctors, pharmacists and researchers (Box 1.3).

**Altruism**

The desire to be altruistic appeared to be another key driver of acceptance of QUM, and it was argued repeatedly that people who work for pharmaceutical companies, and even the companies themselves, are concerned not only about money, but also about contributing to individual and population health (Box 1.4). Many participants noted that QUM activities, and the need to focus on ‘total healthcare’ take time, require commercial sac-

cifice, and demand effort, moderation, leadership and a willingness to tolerate criticism.

**Commercial self-interest**

At the same time, uptake of QUM was explained on the basis of company self-interest, with almost all participants observing that the application of QUM can lead to both improved clinical and economic outcomes and increased industry credibility, which ultimately impacts positively on the commercial ‘bottom line’ (Box 1.5).

**Signs of resistance to QUM**

On the other hand, there was evidence of resistance to QUM, in the form of both divisions within companies, and deeper ambivalence pervading the whole company.

**Divisions within the company**

While most participants described themselves as being deeply committed to QUM, most acknowledged that the same could not be said of their colleagues in sales and marketing. This led many participants to admit that they lacked power within their companies and that they could not assume collaboration among all of their colleagues. They also reflected on the need for significant cultural change and/or strict internal regulatory controls as well as incentives and ‘checks and balances’ to ensure that sales priorities did not entirely override QUM concerns.

**Pervasive ambivalence**

There is nothing surprising about the finding that people in sales and marketing departments may lack commitment to QUM, but close questioning and analysis revealed a significant degree of ambivalence even among our participants. In contrast to claims of identification and altruism, participants also described QUM as something ‘forced’ upon them through external regulation or by competition from other companies. Ambivalence was evident also in some participants’ focus on the need to be rewarded for compliance and punished for non-compliance. While not incompatible with altruism and a genuine acceptance of QUM, this focus on compliance and incentives does suggest that some individuals and companies may be motivated more by external rewards and/or punishments than by intrinsic commitment to QUM.

**Reasons for resistance to QUM**

Resistance to QUM among those in sales and marketing was not difficult to explain, and was attributed to several
factors ranging from a simple lack of awareness or understanding (perhaps because of non-medical backgrounds) (Box 2.1) to deeply conflicting commercial priorities. The more pervasive ambivalence expressed by our participants appeared to have a more subtle basis, arising from both mistrust of other stakeholders and a sense of disempowerment.

Mistrust of other stakeholders

Mistrust of government was pervasive, and the government was seen to be, at best, well-intended but under-resourced or faced with conflicting priorities and, at worst, closed-minded, biased and short-sighted in its commitment to cost-cutting. This was frequently attributed to cost-shifting caused by the split in Australia between Federal and State health systems. There was a sense that the government is a competitor rather than a collaborator, and is not truly committed to QUM, and this was noted to be a powerful barrier to collaboration (Box 2.2). This mistrust of government was, in turn, embedded in a more general mistrust of other pharmaceutical companies (which were seen to be less committed to QUM) and of non-industry stakeholders. Even doctors and pharmacists were seen by participants to lack an understanding of, and genuine commitment to QUM.

Taking a particularly pessimistic view, some participants argued that QUM is merely rhetoric and that nobody in the current health system can be trusted to advocate for patients (Box 2.3).

Disempowerment

This mistrust of other stakeholders was accompanied by a pervasive sense of disempowerment, and it was frequently noted that the ultimate power to implement QUM lay with governments and clinicians rather than with industry. Several participants expressed frustration that their companies’ efforts to implement QUM were frequently thwarted by poor clinical practice (Box 2.4), while only one participant argued that the industry might have some responsibility for ensuring QUM (Box 2.5). Disempowerment also manifested itself in frequent complaints about being misunderstood and mistreated, and medical organizations and governments were seen to be overtly ‘hostile’ or ‘antagonistic’ towards the pharmaceutical industry, failing to acknowledge that industry can contribute to health outcomes (Box 2.6).

Taken together, this sense of mistrust and disempowerment provides an explanation for ambivalence towards QUM even among those who claimed to be convinced of its importance.
Discussion

Key findings

Our findings suggest that employees of pharmaceutical companies see collaboration with other stakeholders as important, and see themselves as being altruistic and deeply committed to QUM. At the same time, there is little evidence from this study to support the notion that QUM has brought about structural changes to industry or is positioned as the central goal or framework in designing a company’s operational strategies. Moreover, there is a significant degree of ambivalence towards QUM. Taken together, these findings suggest that uptake of QUM is far from perfect and that the ‘collaboration’ is infused with issues of power and vulnerability; trust and mistrust; altruism, self-interest and coercion.

Strengths and weaknesses

This study is, to our knowledge, the first systematic empirical exploration of the attitudes of pharmaceutical company employees towards industry–government collaboration around a QUM strategy within a national medicines policy. This study has three limitations. First, this is a small qualitative study that aimed for depth and variety of responses rather than for generalizability. Our numbers were also not sufficiently large to draw conclusions about differences in uptake of QUM between innovative companies, companies producing generic medicines and companies producing non-prescription or complementary medicines (it could be hypothesized that it would be easier for producers of generic medicines to comply with QUM because they do not face the same pressures as innovative companies do to recoup investment). Second, our participants were primarily from medical and regulatory affairs departments and, as our results suggest, cannot necessarily be generalized to other pharmaceutical company employees. Third, this is a study of attitudes rather than outcomes and therefore does not tell us how pharmaceutical company practice has been affected by the QUM strategy, and whether this has had real effects on resource allocation and health outcomes.

Practical implications

While this study focused on a particular collaboration between industry and government, the results have implications for any organization (medical, government, consumer) wishing to form partnerships with the pharmaceutical industry. On the one hand, these findings show that while employees of industry may profess altruism and allegiance to collaborative efforts, they are also subject to commercial pressures and other, more subtle forms of ambivalence, which cannot be ignored. This suggests that industry claims of commitment to a collaborative effort cannot be taken at face value – a conclusion that would come as no surprise to those with a sceptical view of the pharmaceutical industry and its motives. However, these findings also point to at least some potential for meaningful collaboration. In particular, this study shows that pharmaceutical company employees in medical and regulatory affairs departments continue to identify with their original professions (medicine, pharmacy, research etc.) and this suggests that their altruism is likely to be both genuine and a potential anchor for collaboration.

On a more practical note, these results suggest that collaboration with industry would be best achieved through several simultaneous approaches that tap into all industry motives for cooperation. Altruism could be harnessed by giving more respect and responsibility to those within industry who are likely to respond to such measures. At the same time, it seems important to acknowledge the reality of self-interest and the potential for abuse of power, by retaining at least some restrictive regulation and making use of financial incentives and disincentives to motivate cooperation. This is, of course, aspirational at this point in time. For such measures to be effective, pharmaceutical companies would need to be provided with clear guidance as to how to make a strong case for their compliance with QUM; clear measures of compliance would need to be developed (e.g. performance indicators, milestones) and sources of funding for financial incentives (perhaps by redistributing funds accrued from penalties) would need to be found.

Finally, these results point to several ways in which relationships between industry and other stakeholders might be improved, as the causes of the translation failures identified in this study are not necessarily irreparable. It seems reasonable to assume, for example, that collaborative efforts could be improved by greater clarity regarding roles and responsibilities; by all stakeholders, including governments and medical organizations, demonstrating their genuine commitment to the policy; and by all stakeholders showing more genuine inclusion of, and respect for, their industry partners.

Conclusion

The results of this study provide a solid framework for larger-scale investigations of collaborative relationships between the pharmaceutical industry and other organizations (government, professional or consumer). These findings also suggest novel ways of conceptualizing and studying the collaborative relationship between industry and healthcare practitioners.
References

Metropolitan–rural divide for stroke outcomes: do stroke units make a difference?

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Key words
stroke, outcome assessment (healthcare), rural hospital, metropolitan hospital, New South Wales.

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Abstract

Background: Stroke care across Australian hospitals is variable. The impact on health outcomes, in particular levels of disability for patients in rural areas, is unclear. The aim of this study was to determine whether geographic location and access to stroke units are associated with differences in health outcomes in patients with acute stroke.

Methods: Retrospective cohort study of consecutive eligible admissions from 32 hospitals (12 rural) in New South Wales between 2003 and 2007. Health status measured at discharge included level of independence (modified Rankin score: mRS) and frequency of severe complications during hospitalization. Multivariable analyses included adjustment for patient casemix and clustering.

Results: Among 2254 eligible patients, 55% were treated in metropolitan hospitals. Stroke unit treatment varied significantly (rural 3%; metropolitan 77%). Age, gender and stroke type did not differ by location (mean age 74, 50% female). After adjusting for age, gender, ethnicity, important risk factors and validated stroke prognostic variables, patients treated in rural hospitals had a greater odds of dying during hospitalization compared with those treated in metropolitan hospitals (adjusted odds ratio (aOR) 1.46, 95% confidence interval (CI) 1.03–2.05). There were no differences in mortality or frequency of severe complications between patients treated in rural and metropolitan hospitals when we adjusted for access to stroke units (aOR 1.00, 95% CI 0.62–1.61). Nevertheless, patients treated in rural hospitals were more dependent (mRS 3–5) at discharge (aOR 1.82, 95% CI 1.23–2.70) despite adjusting for stroke unit status.

Conclusion: Patients with stroke treated in rural hospitals have poorer health outcomes, especially if not managed in stroke units.

Introduction

Stroke is Australia’s second largest cause of death1 and greatest cause of adult disability.2 The most generalizable, effective intervention for acute stroke is management in a stroke care unit (SCU). Evidence from systematic reviews indicates about a 20% improvement in survival and independence if treated in an SCUs as compared with general ward management.3 Access to SCU remains an ongoing issue worldwide, in particular in rural locations.

There is some suggestive evidence that the geographic location of admission to hospital for stroke may influence

the likelihood of survival or disability with patients treated in rural hospitals more likely to have poorer outcomes.4 The Australian Institute of Health and Welfare report more cases of stroke mortality for persons aged less than 65 years living in rural or remote regions.5 In Western Australia use of linked hospitalization and death records of 7784 patients showed that place of residence ‘rural or remote’ was important in terms of survival after stroke.6 In the Hunter Region of New South Wales (NSW), hospitalized stroke attack rates were reported to be greater in the lower and upper Hunter rural areas as compared with metropolitan Newcastle, a finding thought to be related to sociocultural factors.7

A retrospective medical audit of 150 stroke patients in Queensland provided evidence of differences in stroke care practices and use of evidence-based care pathways
between regional/smaller hospitals with metropolitan or larger hospitals. Importantly, however, more detailed analyses of the outcomes (excluding mortality) of stroke patients treated in rural Australian hospitals have not been reported.

In 2001, the NSW government funded a clinician-led health system redesign that included inpatient stroke services. The Greater Metropolitan Clinical Taskforce (GMCT) stroke programme was created and resulted in the establishment of 23 new SCU. An external evaluation to determine the effects on improvements in access to stroke care, quality of care and health outcomes has been ongoing. Pre- and post-programme analysis showed that the metropolitan focussed stroke programme had provided improvements in patient survival and level of independence (proportional odds ratio 0.73, 95% confidence interval (CI) 0.57–0.94) when adjusted for patient clustering and casemix. In 2005, NSWHealth sought a review of the options for models of stroke units in rural NSW in preparation for rural SCU establishment. With awareness of the value of data to drive clinical practice and policy change, rural hospitals volunteered to use the NSW Stroke Audit tool developed by the National Stroke Research Institute.

Using the audit information obtained from both the metropolitan and rural health services, we aimed to assess whether the quality of stroke care and health outcomes were different among patients treated in metropolitan hospitals compared with hospitals in rural areas.

Materials and methods

NSW Stroke Audit programme data collected between 2003 and 2007 were used. This period reflected data collected after the GMCT stroke service enhancements had been undertaken in metropolitan, but not rural areas. Purposeful sampling ensured that audit data from rural sites was obtained before investment in the NSW Rural Stroke Project. In November 2007, the NSW government provided funding to establish specialized stroke services in rural NSW. This was achieved following a Phase I evaluation report where evidence to support stroke service enhancements proposed by Area Health Services was presented. Phase II of the Rural Stroke Project encompasses the establishment of stroke services in seven sites within five designated services in rural NSW. The models of stroke service enhancements proposed in each successful submission implemented vary and include establishment of acute SCU and rural stroke care coordinators.

It was important that the data presented in this paper reflect the period of time before the government-driven service enhancements to rural stroke care were initiated. Only one of the 12 rural hospitals in this study had implemented an SCU before the Phase II government initiative to enhance rural stroke care. Data from this hospital were included because this situation reflects the reality elsewhere in Australia where hospitals have established SCUs within their own resource. The findings presented in this paper include data from both the successful and unsuccessful rural sites who applied for Phase II funding. Therefore, these data provide an unbiased contrast between rural and metropolitan settings.

Methods for the NSW Stroke Audit programme have been previously published. In brief, consecutive medical records audits were conducted by trained data abstractors using a validated audit tool. Patient eligibility criteria were confirmed diagnosis of a first-ever or recurrent stroke, admission to hospital for acute management and availability of the medical record for audit. For this analysis, consecutive audits of up to 50 medical records from metropolitan sites and 100 from rural hospitals with a discharge International Classification of Diseases (ICD-10) code for stroke for each time period were used. The larger sample size for rural hospitals was to ensure sufficient patient numbers to enable reliable comparisons, as there were fewer rural hospitals eligible to participate. Patients transferred from other hospitals to participating sites were not included. This was to avoid a potential source of sampling bias for assessments of quality of care, as adherence to clinical indicators in these patients may have varied and we wanted to compare fairly homogenous groups (e.g. direct admissions).

Data included demographic characteristics (including age, gender, country of birth), and stroke outcomes included: (i) health status at discharge; (ii) dependence according to modified Rankin score (mRS); and (iii) severe complications during hospitalization. Severe complications were defined as events determined to be life-threatening and/or required interventions or prolonged the hospitalization, for example falls, aspiration pneumonia, urinary tract infection and decubitus ulcers.

Hospitals were classified as either ‘metropolitan’ or ‘rural’ based on NSW Area Health service categorization and location and was verified by the State Manager for Stroke Services NSW (ML). Regional centres in Newcastle, Gosford and Wollongong were classified as ‘metropolitan’.

Statistical analysis

Data were analysed using STATA software (version 10.1, Stata Corporation PL, College Station, TX, USA). Chi-squared tests were used for categorical variables. Fisher exact test for dichotomous variables and the Wilcoxon Mann–Whitney rank sum test for continuous variables.
Univariate and multivariate logistic regression models were used to predict the probability of stroke outcomes. Demographic variables found to differ between the rural and metropolitan cohort were included in multivariable models. In addition, adjustment for patient casemix was based on a validated prognostic model when comparing patient outcomes. These variables included: arm deficit, speech impairment, incontinence within 72 hours and ability to walk unaided on admission. Adjustments were also made for whether the patient was treated in a stroke unit at any time during their hospitalization and also for patient clustering within hospitals. As certain types of patients may cluster within particular settings or geographical locations and are often more likely to respond in a similar manner, hence these samples cannot be assumed to act independently. Therefore, statistical adjustment for patient clustering within hospitals, in addition to individual patient factors, provides a further measure against overstating differences in outcomes where location of treatment may be important. We present odds ratios, adjusted odds ratios and 95% confidence intervals.

Results

Thirty-two hospitals (12 rural) participated in the audit, which included 2254 admissions, 1240 (55%) from 1 January 2003 until 21 December 2007 for metropolitan hospitals and 1014 from 4 January 2003 and 19 August 2007 for rural hospitals. The median number of audits per site in metropolitan hospitals was 50 and 92 in rural hospitals.

Table 1 shows baseline demographic characteristics and level of stroke severity between patients treated at metropolitan and rural hospitals. The samples were similar for age, gender, stroke type and history of previous stroke. The mean age of the patients was 74 (standard deviation (SD) 14) and about half were men. Patients with stroke treated in metropolitan hospitals were more likely to have documented a history of high cholesterol, hypertension or diabetes as compared with patients treated in rural hospitals. However, rural patients were more likely to be born in Australia, be unable to walk on admission, and a larger number was incontinent in the first 72 hours (borderline statistical significance) as compared with patients treated in metropolitan hospitals.

Length of stay (LOS) was longer in metropolitan hospitals compared with rural hospitals, and the median LOSs were the same for all patients or just those who were discharged (metropolitan median LOS 10 days, interquartile range (IQR) 6–19 and rural LOS 7, IQR 4–13; \( P < 0.001 \)). This finding could in part be explained by the fact that metropolitan patients have greater discharge delays reported (metropolitan 18% compared with rural 12%, \( P < 0.001 \)).

Health outcomes

Overall, in-hospital mortality was 10% \( (n = 227; \) rural 13% and metropolitan 8%). Patients dependent (mRS grade 3–5) at time of discharge was 66% in rural and 58% for metropolitan patients. A severe complication during admission was experienced by 190 (8%) patients (rural 10%; metropolitan 7%). Figure 1 illustrates the significant difference in mRS grades at discharge or 7–10 days after stroke according to location of treating
hospital \( (\chi^2 = 55.72, P = 0.0001) \). After adjusting for age, gender, country of birth, hypertension, high cholesterol, ability to walk on admission and incontinence within 72 hours, patients treated in rural hospitals had a greater odds of death (adjusted odds ratio (aOR), 1.46; 95% CI, 1.03–2.05) compared with patients treated in metropolitan hospitals. Stroke treatment in rural hospitals was also associated with greater odds of being dependent (aOR, 1.75; 95% CI, 1.35–2.28) or having a severe complication (aOR, 1.66; 95% CI, 1.16–2.38) when adjusted for the same variables.

### Stroke patients treated in an SCU

Overall, the proportion of patients treated in an SCU was 56% (rural 3% and metropolitan 77%).

Table 2 shows the results of the multivariate analyses adjusting for whether the patient was treated in an SCU and also adjusted for location category of hospital. After adjustment, there was no difference in mortality or having a severe complication between patients treated in rural and metropolitan hospital. However, those patients treated in rural hospitals continued to have a greater odds of being dependent when compared with metropolitan hospitals.

### Discussion

Our data support previous findings of higher in-hospital mortality outcome for stroke sufferers in rural communities and, for the first time, provide evidence that rates of dependency are also greater at discharge in rural stroke patients. Our data provide direct evidence that in the context of overall stroke outcome, location of treating hospital and presence of an SCU are important. This suggests that ongoing investment in organized SCU care in rural NSW is needed and would be expected to reduce the occurrence of unfavourable stroke outcomes for rural residents.

The lower stroke mortality seen in metropolitan stroke care compared with care in rural settings was significantly influenced by access to SCU. Interestingly, national stroke audit data indicate a similar proportion of in-hospital stroke deaths (13% of all cases), but a

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**Table 2**: Stroke outcomes of patients treated in rural as compared with metropolitan hospitals with adjustment for admission to stroke unit at any time or patient clustering in different hospitals

<table>
<thead>
<tr>
<th>Stroke outcomes</th>
<th>Unadjusted odds ratio (95% CI)</th>
<th>Adjusted odd ratio† (95% CI)</th>
<th>Adjusted odd ratio‡ (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Independent (mRS 0–2)</td>
<td>0.61 (0.49–0.75)</td>
<td>0.55 (0.37–0.81)</td>
<td>0.55 (0.32–0.96)</td>
</tr>
<tr>
<td>Dependent (mRS 3–5)</td>
<td>1.64 (1.32–2.03)</td>
<td>1.82 (1.23–2.70)</td>
<td>1.82 (1.03–3.19)</td>
</tr>
<tr>
<td>Died (mRS 6)</td>
<td>1.60 (1.21–2.11)</td>
<td>1.00 (0.62–1.61)</td>
<td>1.00 (0.53–1.87)</td>
</tr>
<tr>
<td>Any severe complication§</td>
<td>1.49 (1.11–2.02)</td>
<td>1.23 (0.74–2.05)</td>
<td>1.23 (0.61–2.49)</td>
</tr>
</tbody>
</table>

†Adjusted for stroke unit status, age, gender, Australian born, living alone, history of hypertension, diabetes or cholesterol, walk on admission and incontinent within 72 hours. ‡Adjusted for clustering of patients within hospitals, stroke unit status, age, gender, Australian born, living alone, history of hypertension, diabetes or cholesterol, walk on admission and incontinent within 72 hours. §Included falls, aspiration pneumonia, urinary tract infection and decubitus ulcers. 95% CI, 95% confidence interval; mRS, modified Rankin score.
breakdown by geographic location or by access to SCU is unavailable. The lower levels of dependency seen at discharge from metropolitan hospitals, even when adjusted for access to SCU, were interesting. This requires further investigation, but may be related to the fact that the rural SCU included in this sample (contributing only 32 SCU treated patients) was recently established and, although gains were in made for improved mortality, an impact on dependency could not be shown. Other aspects of care received in rural hospitals may also be responsible for some of these disparities in health outcomes. Overall, there was a low rate of severe complications, which probably reduced the statistical power of multivariable models resulting in wide confidence intervals.

Few investigators have assessed differences in stroke outcomes for rural and metropolitan patients. The strength of our study is the large sample size allowing sufficient power to detect differences in most health outcomes examined. Stroke patients who were treated in rural hospitals had fewer comorbidities, were more likely to be born in Australia and a larger proportion were able to walk on admission than those patients treated at metropolitan hospitals. These features in rural stroke patients would generally bias towards a better outcome. It appears therefore that the poorer outcomes for rural stroke patients were not due to confounding from stroke severity or measured comorbidities. Therefore, organized stroke care is a likely factor influencing the difference in outcomes between metropolitan and rural NSW hospitals.

We have previously shown that greater adherence to important clinical processes of care is more often undertaken in metropolitan hospitals with SCU and this has an impact on survival. Other potential influences are access to specialist clinical assessment and diagnostic testing, or access to prompt higher dependency care in the situation of clinical deterioration or serious complications of stroke, such as infection. Access to stroke thrombolysis is unlikely to have had a significant influence on our findings as implementation of the licensed thrombolytic agent, tissue plasminogen activator (tPA), remains at very low rates (3% in urban sites and 1% in rural sites), and randomized evidence suggests tPA does not reduce stroke mortality.

The findings from this present study are likely to be generalizable to other parts of Australia and continuing efforts need to be made to improve stroke treatment in rural areas to narrow the ‘inequity of outcomes’ gap between rural communities and their metropolitan counterparts. The National Stroke Foundation 2009 organizational report on stroke services in rural Australia confirmed that there are clear disparities between metropolitan and rural hospitals in adherence to important processes of care and in access to SCU (4% rural versus 96% urban).

Several means for narrowing the gap in health outcomes between rural and metropolitan settings include having strategic government policies and funding, as well as clinician driven initiatives, such as adopting evidence-based clinical guidelines and protocols for management; and ensuring ongoing education of rural clinicians. These data from the NSW Stroke Audit have also been used to contribute to ongoing service enhancements. Since November 2007, the NSW government has provided funding to establish specialized stroke services in rural NSW as part of its Rural Health Plan commitments to provide services closer to home. This funding has been used to implement or enhance SCU in rural NSW and increase access to specialist staff through the appointment of stroke care coordinators. We hope that initiatives in other parts of Australia will also be influenced by our findings.

**Conclusion**

The disparity in death and dependency between rural and metropolitan patients with stroke is greatly influenced by whether a patient has access to SCU. Initiatives to increase the equitable access to evidence-based stroke services in Australia are important if we are to reduce the burden of this disease.

**Acknowledgements**

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References

How reliable is eGFR when calculating drug dosage in acute medical admissions?

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Key words
acute renal failure, glomerular filtration rate estimates, acute disease, drug dosage calculations, low molecular weight heparin.

Abstract

Background: The Modification of Diet in Renal Disease-derived estimation of glomerular filtration rate (eGFR) is used widely. Although validated in stable chronic kidney disease (CKD) outpatients, it is not known how it performs in those presenting with acute medical illness.

Aim: We aimed to compare eGFR with Cockroft Gault (CG) – the renal function assessment tool available prior to eGFR – to assess the difference in clinical outcome that would occur when one over another estimation is used in practice. In particular, we wished to assess whether use of eGFR would have resulted in a change of dose of commonly used acutely administered medications.

Methods: Acute medical admissions presenting to a tertiary hospital between August and December 2008 were included. Serum creatinine concentration, age, sex, height and weight were collected. Renal function was estimated by both estimates. Movement from CKD class 3 to 4 or 5 was measured – a clinically used cut-off point for changes in management.

Results: A total of 54 patients was included. eGFR values were higher than those estimated by CG. Almost half of patients categorized as CKD stage 4–5 using CG were only categorized as CKD stage 3 using eGFR.

Conclusion: Although we did not use a gold standard estimation of GFR, this study shows that estimates of renal function vary in a clinically significant manner. As estimates of GFR are used to adjust drug dosages and to stratify for many other treatments, it is imperative that we find a method of estimating kidney function that is readily available, consistent and accurate.

Introduction

Acute kidney injury is a common occurrence in acute medical admissions and carries a significant mortality and morbidity. During the initial period of assessment, the acute medical patient may be exposed to further morbidity from incorrectly dosed renally excreted medications, such as aminoglycosides and intravenous contrast agents. It is therefore important that an accurate initial estimation of glomerular filtration rate (eGFR) is made. In addition, it is critical that GFR monitoring continues throughout the acute admission as the medical state changes. Acute renal recovery or deterioration may lead to under or overdosing of renally excreted therapies.

In 2002, the National Kidney Foundation published a new classification system for staging chronic kidney disease (CKD) based on a creatinine-based eGFR¹ derived from the Modification of Diet in Renal Disease (MDRD) Study. eGFR is now in widespread use internationally as an estimate of CKD. Even though initial guidelines highlighted MDRD’s lack of validity in non-steady state situations, it is currently calculated automatically on every serum chemistry sample by many biochemistry laboratories. Inherently, this has led to an eGFR being calculated in acute medical admissions whether or not it is requested by the admitting physician.

Although eGFR was shown to correlate with actual GFR in a population of people with stable CKD, it is not known how this performs in hospitalized people with acute medical illness.³ In particular, the eGFR equation assumes a body surface area (BSA) of 1.73 m² adjusted for population-standardized age and sex, but not actual
body size (a surrogate for drug clearance). As many acute medical subjects have a period of physiological and acute nutritional instability prior to admission in addition to comparatively reduced muscle mass and acute kidney injury, it is likely that this assumption does not hold for this population. Specifically in Queensland, which has a large indigenous population, the performance of this formula in either detecting renal disease or adjusting dosage of renal cleared drugs has never been examined.

The currently accepted clinical gold standard methods for estimating GFR include measurement of clearance of various radionuclide markers, such as ⁹⁹mTc-labelled diethylenetriaminepentaacetic acid and ¹²⁵I-labelled iothalamate although gentamicin clearance and 24-h urinary creatinine clearance calculation have also been used in the hospital setting. However, these techniques can be costly and impractical in the acute medical setting. Prior to eGFR, the Cockcroft Gault (CG) equation was the method used to estimate renal function in the acute medical population and to assist drug dosing. The practicality of this method is limited because of its incorporation of weight, which is not always performed by admitting nursing staff and which does not take into account whether weight is lean or fat. Recently, a more accurate estimation of GFR using a patient’s ‘fat-free mass’ or ‘ideal body weight’ (IBW) has been discussed. The disadvantage of this equation when compared with eGFR even though intuitively more appropriate for today’s obesity epidemic is that it requires the patient’s height to calculate it accurately. However, it is likely to be a more scientific method of assessing body size than total body weight in a general medical population with its extremes of fat mass.

In this study we aim to compare eGFR with CG using IBW. In particular, we wish to assess whether use of eGFR to estimate admission GFR would have resulted in a change of dose of commonly used acutely administered medications (such as low molecular weight heparin (LMWH) or gentamicin) and ability to access radiology tests using contrast. Secondly, we wish to assess whether there is a change in eGFR following the acute admission. We wish to gain an insight into how often a dose adjustment of renally excreted medication would be required following the initial acute admission period.

Methods

Acute medical admissions were identified on a weekly basis in the Royal Brisbane and Women’s Hospital Medical Assessment and Planning Unit (MAPU) between August and December 2008. Admissions were identified through the hospital electronic patient log. Patients admitted to the MAPU between 14.00 and 17.00 were included. Elective or semi-elective patients were excluded from the study. De-identified serum creatinine, age, sex, documented admission height and weight were collected. All creatinines were measured by the Royal Brisbane Hospital, Department of Clinical Chemistry by means of the Jaffe reaction using auto analysers (Beckman Coulter, CA, USA). As data collection was undertaken prior to the implementation of an isotope dilution mass spectrometry traceable assay, eGFR was calculated using the formula as originally described, rather than the newer ‘175’ equation. Patients who did not have a serum creatinine, height or weight recorded were excluded from the study. We recorded serum creatinine concentrations at the initial point of acute admission, eGFR (eGFR in mL/min/1.73 m² = 186 × (serum creatinine/88.4) − 0.203 × age0.174 × height0.725 × weight0.425 if female × 1.21 if African American), Cockroft Gault adjusted for IBW (creatinine clearance in (mL/min) = [(140 – age (years)] × IBW (kg) × constant)/plasma creatinine (µmol/L) where constant is 1.23 for men and 1.04 for women, where IBW is calculated as: IBW (men) = 50 kg + 0.9 kg for each cm over 152, IBW (women) = 45.5 kg + 0.9 kg for each cm over 152) and CKD stage was calculated (Table 3). eGFR was similarly recalculated with an adjustment for BSA using the Du Bois formula (BSA (m²) = 0.20247 × height (m)⁰⁷²⁵ × weight (kg)⁰⁴²⁵). Dose of LMWH for each estimation of GFR was calculated. A re-measured serum creatinine between 3 and 10 days following acute admission was also recorded. It was then estimated whether dose of LMWH should be adjusted. Results were initially collated and equations calculated using Microsoft Excel software. Subsequent statistical analysis was performed using Stata 9.1 (StataCorp LP, College Station, TX, USA). CKD stages for both groups were defined. Pearson correlation between eGFR and CG groups was calculated.

Results

Demographics

A total of 64 patients was identified over a 4-month period, but 10 were excluded because of incomplete height or weight measurements. Thus, data from 54 patients were studied. Some 54% of the study population were male and 46% were female. Ten patients (19%) had a body mass index (BMI) of greater than 30. Nine patients (17%) had a BMI of less than 18.5. Seven patients had creatinine levels of less than 60. Demographic data are summarized in Table 1.
Differences between estimations of glomerular filtration rate

MDRD eGFR values were generally higher than IBW CG (Tables 2, 3, Fig. 1). The Pearson correlation between eGFR and IBW CG was 0.910 (P < 0.01). Ten of 20 (50%) of patients categorized as CKD stage 3 (GFR 30–60 mL/min) using IBW CG were re-categorized as stage 2 by eGFR. Five of 13 (38%) patients categorized as CKD stage 4–5 (GFR less than 30 mL/min) using IBW CG were up-categorized as CKD stage 3 using the eGFR equation. Overall, the mean difference between eGFR and IBW CG was 11 mL/min (95% CI 6–15 mL/min). Results for MDRD eGFR were similar to unadjusted values (Tables 2, 4).

Variation in estimation of glomerular filtration rate over hospital admission

In total, 52 of 54 (96%) of patients had a further serum creatinine concentration measured between 3 and 10 days following their acute admission at ‘steady state’, that is, when creatinine concentrations were stable (defined as change only within error of the creatinine assay). The mean difference in eGFR was a rise of 3 mL/min from time of admission.

When analysing by CKD stage, there were no patients who were in CKD stage 3 or less at admission who moved into CKD stage 4 following the subsequent serum creatinine measurement. Two of eight (25%) patients, who had CKD stage 4–5 on admission, had an eGFR compatible with CKD stage 3 on subsequent re-measurement.

Discussion

Our study demonstrates that significant renal impairment is prevalent within the acute medical admission population. Whether GFR is measured using eGFR or IBW CG, stage 3 was the most prevalent identified CKD stage within our study population. The high prevalence of renal impairment in these subjects suggests it is clearly important for medical admission units to have processes in place to identify these patients, so investigations and therapy can be adjusted accordingly.

We have also demonstrated that it is possible to collate and record height and weight measurements from patients admitted to a busy medical admission unit. The Royal Brisbane and Women’s Hospital MAPU uses a structured nursing admission document where measurement of height and weight forms part of the standard nursing admission process. The recognition of the importance of early assessment of BMI for both under-nutrition and over-nutrition has acted as a catalyst for the collection of these measurements.

Lastly, there is a clear difference in GFR calculation when using the eGFR and IBW CG equations. Although we did not have gold standard measure by which to ascertain which of the estimations were better, this uncertainty and variation between the methods is of concern as both estimates of renal function are used

<table>
<thead>
<tr>
<th>Table 1 Demographic data</th>
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<tr>
<td>Variable</td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Weight (kg)</td>
</tr>
<tr>
<td>Lean Body weight (kg)</td>
</tr>
<tr>
<td>Height (cm)</td>
</tr>
<tr>
<td>BSA (m²)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>Serum creatinine (μmol/L)</td>
</tr>
</tbody>
</table>

BSA, body surface area; BMI, body mass index.

<table>
<thead>
<tr>
<th>Table 2 GFR estimation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measurement</td>
</tr>
<tr>
<td>MDRD eGFR (mL/min/1.73 m²)</td>
</tr>
<tr>
<td>MDRD eGFR adjusted for actual BSA (mL/min)</td>
</tr>
<tr>
<td>IBW CG (mL/min)</td>
</tr>
</tbody>
</table>

CG, Cockroft Gault; eGFR, estimation of glomerular filtration rate; IBW, ideal body weight; MDRD, Modification of Diet in Renal Disease.
(correctly or incorrectly) to alter dosages of renally cleared drugs.6 LMWH is increasingly prescribed in medical admission units as medical teams strive to reduce the incidence of hospital-associated venous thromboembolic disease. However, in patients with an estimated GFR of less than 30 mL/min, a dose reduction is recommended in order to prevent drug accumulation and subsequent haemorrhagic complications.9 Therefore, accurate estimation of GFR in the acute medical population is essential if drug errors and their associated mortality and morbidity are to be avoided. We have demonstrated in this clinically based study that 43% of patients classified as CKD stage 4 or 5 using IBW CG would have only been classified as CKD stage 3 using eGFR. This difference is crucial as although there is potentially greater current evidence for using IBW CG for drug dosing, it is eGFR that is clinically more readily available to the attending physician in the medical admission unit. Furthermore in our hospital, radiologists will not perform contrast scans if the eGFR is <30 mL/min, regardless of the actual GFR.

Based on this study, if eGFR was the sole calculation of GFR used in our acute medical study population, 43% of patients who had severe kidney impairment by another measure would have received an unadjusted dose of LMWH, potentially exposing them to toxicity and may not been identified as requiring modified administration of radiological contrast agent.

We demonstrated that 25% of patients, who had calculated severe kidney disease (CKD 4–5) on admission, underwent some renal recovery; that is, calculated GFR rose to greater than 30 mL/min during their admission. This has clear clinical significance if renally cleared antibiotics, such as gentamicin, are being considered as increased clearance can predispose to ineffectiveness and resistance if the dose is not increased.10 There is a similar concern with the use of LMWH. Our institution does not have robust systems in place to track changes in calculated GFR and a flag to consider drug dose adjustment.

**Limitations**

This study has obvious limitations. The number of patients recruited to this study is small and the data are collected from a single institution serving one particular urban population. In particular, the study is clearly not powerful enough to examine the significance of MDRD adjusted for correct BSA. It could be argued that this study’s true use should be: (i) as a reminder that eGFR should not be assumed to be ‘safe’ as a method of adjusting doses of renally cleared drugs in acute medical patients and (ii) as a pilot project for a multicentre study.

**Table 4** GFR estimation 3–10 days following acute admission

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Median</th>
<th>Mean</th>
<th>Inter-quartile range</th>
<th>Standard deviation</th>
<th>Standard error mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDRD eGFR (mL/min/1.73 m²)</td>
<td>76</td>
<td>73</td>
<td>49–93</td>
<td>32</td>
<td>4.4</td>
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<tr>
<td>MDRD eGFR adjusted for actual BSA (mL/min)</td>
<td>74</td>
<td>77</td>
<td>47–105</td>
<td>47</td>
<td>5.3</td>
</tr>
<tr>
<td>IBW CG (mL/min)</td>
<td>52</td>
<td>62</td>
<td>37–84</td>
<td>36</td>
<td>5.0</td>
</tr>
</tbody>
</table>

BSA, body surface area; CG, Cockroft Gault; eGFR, estimation of glomerular filtration rate; IBW, ideal body weight; MDRD, Modification of Diet in Renal Disease.
recruiting a greater number of patients across a greater range of population areas. Our study has no clear comparative gold standard GFR measurement, so it is uncertain in which direction any bias and imprecision are operating. However, it is clear that both are operating. It is also beyond the scope of this study to prove the validity of one method of estimating GFR against another – it is likely that neither eGFR nor CG is an accurate measure of GFR, let alone drug clearance in the acute medical population. Our concern is that there is a clinically relevant difference in medical management instituted depending on which estimation is used. The uncertainty around this issue lends support for a more easily accessible measure of GFR to be available to clinicians in this setting, and for doctors to use clinical skills and therapeutic drug monitoring, rather than estimations of GFR to adjust drug dosages in this setting.

**Conclusion**

Our study suggests that eGFR may be an imprecise predictor of GFR in the acute medical population. Accurate drug dosing is vital in the acute medical population, so accurate assessment of renal function can be made when considering drugs that are renally cleared. It is also important that we use a method of estimating kidney function that is both readily available and accurate.

We have also shown how an acute medical patient’s renal function can change during an acute admission. Systems must also be in place that enable continued renal monitoring and appropriate adjustment of drug dosage throughout the patient’s clinical course. Further study needs to be undertaken to assess whether clinically relevant outcomes, such as bleeding or death, are altered depending on which estimate of function is used.

**References**

Improved anticoagulant control in patients using home international normalized ratio testing and decision support provided through the internet

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Key words
anticoagulant monitoring, warfarin, decision support, internet, telemedicine.

Abstract
Aim: To compare anticoagulant control using self-testing and decision support provided via the internet with standard laboratory testing.

Methods: A prospective comparative study of 41 patients on long-term warfarin. All patients were monitored using a laboratory-based service for at least 12 months prior to changing to self-testing using a portable testing device and online decision support. The level of anticoagulant control was assessed using the time the international normalized ratio (INR) was within the therapeutic range (TTR), the proportion of INR results in range and the interval between tests. This was a non-inferiority study.

Results: There was no statistically significant difference between the two methods of anticoagulant control with a trend in favour of self-testing; the mean TTR was 72% vs 81%. However, a small cohort of patients with poor control (TTR 38%) during laboratory testing achieved a significant improvement (TTR 71%) using self-testing. The INR was above the therapeutic range for a similar time in both groups but below the range for a significantly shorter period during self-testing suggesting a lower risk of complication in this group.

Conclusion: Self-testing with online computer decision support achieved anticoagulant control at least as good as laboratory management. Additional benefits of a home-based service make this an attractive option for selected patients.

Introduction
It is well established that oral anticoagulants significantly reduce the risk of systemic emboli in patients with atrial fibrillation1 and mechanical heart valves, and prevents further thromboses in patients with venous thromboembolic disease. It has been estimated that approximately 1% of the population could benefit from anticoagulant therapy based on the incidence of atrial fibrillation2-3. A significant number of patients is deemed unsuitable for anticoagulation for sound clinical reasons, but some patients are denied treatment because of difficulties with access to appropriate monitoring4. In New Zealand, patients in remote areas may have to travel considerable distances for blood tests and could benefit from the convenience of home monitoring.

There is no consistent method for monitoring anticoagulants in New Zealand. It is largely managed by general practitioners, but in some cities there are laboratory or hospital-based services with dosing provided by hospital doctors. The level of control is difficult to assess as audit of these services is complex and carried out infrequently. An audit in Auckland5 showed that control by general practitioners achieved a mean time in the therapeutic range (TTR) of only 58%, which is considered suboptimal as international guidelines recommend that the TTR should be greater than 60%.

The availability of home testing devices has removed some of the problems associated with anticoagulant management and has led to an increased interest in patient self-testing and patient self-management. Patient self-testing is where a patient measures his or her own international normalized ratio (INR) with dose adjustment by a physician; patients’ self-management is where the patient is responsible for both the INR measurement and dose adjustment. Several studies have shown that the quality of anticoagulant control achieved by patients is as
good as or better than control attained using conventional management. Although patient self-management is an attractive option for some patients it is likely that only a relatively small number will feel comfortable taking on full control of their treatment; in one clinical trial using self-management only 13% of eligible patients agreed to participate. Patient self-testing may be easier for more patients, but has the disadvantage that a supervising doctor has to be contacted for advice, which can be time-consuming and cumbersome. In order to overcome these problems we have developed an internet-based warfarin management system that allows patients to carry out self-testing at home and enter their INR results into a secure website and receive immediate dosing advice. If the result is outside a specified range the result is automatically sent for review by a doctor. The website is designed with several safeguards to minimize the risk of complications.

We carried out a prospective study in which the quality of warfarin control achieved using patient self-testing and the internet-based management system was compared with control achieved using conventional laboratory-based management.

**Patients and methods**

Patients on long-term warfarin attending the laboratory at Palmerston North Hospital, New Zealand were invited to participate. The patients were self-selected and could be included if they had been on anticoagulant therapy for more than 12 months, were willing to perform their own INR blood test using the CoaguChek XS (Roche Diagnostics NZ, Auckland, NZ) and had access to the internet. The study was approved by the central ethics committee in New Zealand and all patients provided written informed consent.

**Methods**

This was a comparative study comparing retrospective data from patients using laboratory-based anticoagulant management with prospective data from the same patients using self-testing and internet-based decision support. During the 12 months before the study, all patients had INR tests performed at their local laboratory and anticoagulant control managed by medical staff in the laboratory or by their own general practitioner. Dosing information and INR results were collected for all patients during the 12 months before the study.

Each patient was provided with a CoaguChek XS monitor (Roche Diagnostics NZ Ltd). The testing devices and test-strips were provided free by Roche Diagnostic for the trial period. The patients were taught how to perform an INR test using a finger prick blood sample. The patients used an online decision support package (INR Online Ltd, Palmerston North, NZ) to assist with dose recommendations. Each patient had access to a secure website protected by username and password. Access was free for the trial period.

There were three steps to the self-testing procedure. First, the INR was performed on the CoaguChek XS. Second, the patient logged-on to a secure website and answered questions about compliance, bleeding complications and changes to concomitant medication since their previous test. This information was recorded and was accessible to the reviewing doctor. Finally, the patient entered the INR result and received an immediate dose recommendation and date for the next test. The patient also received an email with the same information and a dosing schedule that could be printed to assist with compliance. If the INR was outside the recommended therapeutic range, the result was automatically flagged for review by a doctor. Following review the patient received a second email with details of any further dose adjustment.

**Sample size**

This is a non-inferiority study. The hypothesis is that anticoagulant control using self-management is at least as good as standard laboratory monitoring.

In the audit of general practitioner warfarin management in the community performed by the principal investigator, 58% of INR measurements were within the therapeutic range (sample size 9000 INR measurements). It is assumed that anticoagulant control using near-patient testing is as good as standard if the percentage of INR measurements within the therapeutic range differs by less than 5% of our previous study. We conclude that computerized monitoring is non-inferior if the calculated one-sided P-value is less than 0.05. With a test power of 0.8, a sample size of 750 INR measurements is sufficient to reject the null hypothesis. Each patient will perform an INR every 1 to 2 weeks for 12 months using self-testing. Therefore, each patient will perform approximately 40 tests during the self-testing period of the study. A total of approximately 50 patients would provide sufficient results.

**Data analysis**

The time within the therapeutic range was calculated by assuming a linear change in INR between tests using the method described by Rosendaal et al. The following data were recorded for each patient: (i) The percentage of time the INR results were above, below...
and within the therapeutic range; (ii) the percentage of INR results above, below and within the therapeutic range; (iii) the percentage of INR results above 4.0 and above 5.0; and (iv) the mean interval between test.

Patients were defined as having ‘good control’ if their INR results were within the therapeutic range for >60% of the time (based on BCSH Guidelines9).

**Statistical method**

The Wilcoxon signed-rank test was used to test for difference between paired data as the results showed a non-normal distribution. A $P$-value of <0.05 was considered statistically significant.

**Results**

A total of 46 patients was entered into the study, five patients withdrew early and were not included in the assessment; three had difficulties performing self-testing (two before entering any results and one after three INR tests); one died in a road traffic accident; and one stopped warfarin after the diagnosis of pancreatic cancer. The results of 41 patients were included in the analysis.

**The time in range**

The TTR was calculated from the sum of all patient results. During the 12 months of laboratory testing before the study, the TTR was 72.4% (based on 14 847 patient days), which improved during the self-testing period to 79.6% (based on 10 786 patient days). In several patients control was unstable during the first month of self-testing. If data during this period were excluded, control improved even further to 81.3% of the time in range (Table 1).

Patients had results below the therapeutic range for a significantly longer time during the laboratory testing period than during self-testing (mean 20.3% vs 10.8%; $P < 0.005$). There was no significant difference in the time above the therapeutic range between the two groups; 6.3% with laboratory testing and 9% with self-testing ($P = 0.095$). The highest INR recorded during laboratory testing was 7.0 with four INR results above 5.0. In the self-testing group the highest INR was 5.6 with three results above 5.0. When the unstable results during the first month of self-testing were excluded there were no INR measurements above 5.0 in the self-testing group.

**INR results in range**

The INR results in range were calculated using a composite of all INR results. During the laboratory testing there were 876 INR results recorded; 63% of INR results were in range, 25% were below range and 11% over range. During self-testing, control improved with 70% of INR results in range, 15% below and 14% above based on 1120 INR results (Table 1).

**Individual results**

The composite results give an overall assessment of control, but do not truly reflect the changes for individual patients. During the 12 months of laboratory testing we calculated the time in range for each patient. This gave a wide scatter of results from 19.9% of time in range to 100% with a median of 78.5%. This allowed us to divide the patients into two groups based on anticoagulant control. We categorized patients as having ‘good’ control if the TTR was greater than or equal to 60% and ‘poor’ control if the TTR was less than 60%.

During the period of laboratory testing, 32 patients had good control and nine patients had poor control. The
patients with ‘good’ control had a mean TTR of 83%, which was virtually unchanged during self-testing with a mean TTR of 82.5%; however, the patients with ‘poor’ control using laboratory testing showed a significant improvement in mean TTR from 38.8% to 71.1%, with seven patients achieving a TTR of >60% (Fig. 1).

Discussion

This study uses an internet-based automated decision support system giving patients the advantage of full anticoagulant management from home. The patients performed self-testing using the CoaguChek XS testing device, entered their INR results through a webpage and received immediate treatment advice. Remote medical review of results was provided for INR results outside the therapeutic range and any further dose changes were conveyed to the patient by email.

Our results show that this method of anticoagulant control was at least as good as conventional laboratory testing maintaining the INR within the therapeutic range for 80% of the time. The study was designed as a non-inferiority study and was not intended to show a significant difference between methods; however, there is a trend in favour of the self-testing model. Interestingly, the level of anticoagulant control in our patients during the period of laboratory testing was higher than we expected with a mean time in range of 72%, which is considerably better than the level of control reported in our earlier audit where patients maintained a time in range of only 58%. The reason for the good control in this group may be related to the patient selection. Those choosing to participate in the study are likely to be well motivated with some understanding of warfarin control and more likely to be compliant.

Although the mean values show no statistically significant benefit, the self-testing model does show a significant improvement in control for a selected group of patients, namely those with poor control using the conventional laboratory-based service. In our series nine patients had poor control during the 12 months before self-testing with a mean time in range of only 38%. The reason for poor control is uncertain, but in some cases testing was infrequent. During self-testing, control improved in this group of patients with the mean time in range increasing significantly to 71% with seven cases achieving a time in range of greater than 60% (Fig. 1). Although this is only a small number of patients, improving control in this group has a major clinical benefit as patients with TTR <45% have a high risk of complications.

The close control of warfarin is important to minimize both haemorrhagic and thrombotic complications. Our study was not powered to detect a significant difference in the incidence of complications, but an assessment of risk is possible using the TTR and the level of INR control as surrogate markers. The TTR is directly related to the risk of both bleeding and embolic complications. A retrospective study showed that an improvement in TTR by 7% reduced major haemorrhage by 1 event per 100 patient years, and a 12% increase in TTR reduced thromboembolic complications by a similar amount. Our results suggest that self-testing may reduce the risk of thrombotic complications as the INR was below the therapeutic range for a significantly shorter time (10.9% of the time) than during laboratory testing (20.3% of the time). The reason for the difference between the computerized dosing and clinician dosing is uncertain, but may be explained by doctors tending to be cautious when increasing the warfarin dose. A similar difference has been reported in a study comparing clinician and computer dosing, which showed comparable results at a low therapeutic range but at a higher range the computer achieved better control as doctors tended to under dose.

The risk of bleeding can also be assessed using a surrogate as there is a strong association between an
elevated INR and bleeding with the incidence rising rapidly when the INR exceeds 5.0. In our series there was no significant difference in the number of INR measurements above 5.0 between the two groups with no episodes of serious bleeding requiring admission or transfusion. There were only three INR measurements above 5.0 in the self-testing group.

Our results are in line with two other studies showing improved control for patients performing self-testing with clinical support provided through the internet. These both showed a similar level of improvement with the TTR increasing from 63% to 74.3%13 in one study and from 58.6% to 74.14 in the other. Several other studies of self-testing or self-management of warfarin have also shown improved control. A meta-analysis of 13 publications showed that patient self-testing had a lower risk of bleeding and thrombosis, and in several series achieved a better time in the therapeutic range than conventional testing.6 There are several suggested reasons for the improved control, including better compliance, consistent dosing using an automated algorithm and an automated recall system; however, more frequent testing is probably the major factor.6,15 One study showed that it is possible to achieve a TTR of 90% with self-testing every 4 days and 76% with weekly testing however, control fell to only 48% when tested every 24 days.16 In our series the mean interval between tests was significantly shorter while patients were self-testing (10 days) than during the period of laboratory control (19.6 days)

In addition to the measured improved control, an automated internet-based service provides a number of advantages for both clinicians and patients. A general practice-based service can be inefficient and time-consuming. There is often no established system for dosing, record keeping, patient recall or audit, where as these problems are easily managed by a computer system. An online service also has the advantage that the doctor does not need to purchase expensive software for the management of a small number of cases and can access the service from anywhere.

There are also considerable benefits for the patient. The process is more convenient as there is no need to attend a blood collecting room or laboratory for a blood test, which may require time-off work, lengthy travel and difficulties with parking. The home-based system allows patients to test anywhere at any time, which is particularly beneficial for patients who travel overseas. The system also offers consistent dosing, a printable dosing calendar and automated email reminders to assist with safety and compliance. Cost benefit analysis of this type of service has been assessed. In a Canadian study the set-up costs for self-testing including training were higher than laboratory testing at approximately C$1500; however, the ongoing costs for monitoring were similar, with self-testing patients performing weekly tests and usual care patients testing every month. In New Zealand the set-up costs are approximately NZ$1000 with ongoing costs around $15/month including internet supervision. In the Canadian model the benefits achieved by improved control off-set the increased cost. The cost-effectiveness of self-managed long-term anticoagulation therapy over physician-managed care was C$14,129 per quality-adjusted life year gained over 5 years,17 implying this is a cost-effective intervention. In New Zealand there is no public funding or insurance cover for this type of service.

Conclusion

A consumer survey was sent to all participants who completed the study. All respondents expressed a preference for home-based testing over the conventional laboratory management. We have shown that patient self-testing using an internet-based service achieves good anticoagulant control for the majority of patients. The added convenience makes this method of management an attractive option for selected motivated individuals.

References

6 Heneghan C, Alonso-Coello P, Garcia-Alamino JM, Perez R, Meats E, Glasziou P. Self-monitoring of oral anticoagulation: a systematic review and
Prothrombin complex concentrates used alone in urgent reversal of warfarin anticoagulation

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Abstract

Background: Prothrombinex-VF (a three-factor prothrombin complex concentrate) contains little factor VII. Therefore, the Warfarin Reversal Consensus Guidelines from 2004 published by The Australasian Society of Haemostasis and Thrombosis recommend that it be administered with fresh frozen plasma to reverse warfarin anticoagulation.

Aim: To evaluate the efficacy and safety of Prothrombinex-VF used alone in warfarin reversal.

Methods: Adult patients requiring urgent reversal of warfarin anticoagulation were defined as having achieved complete (target international normalized ratio (INR) <1.4) or partial reversal (target INR 1.4–2.0) of their anticoagulation. Prothrombinex-VF was given at doses of between 25 and 50 IU/kg based on the intent of reversal and an INR was obtained 30 min post infusion.

Results: A total of 50 patients (mean age 72 years, range 32–85 years) was included. The median initial INR in the complete reversal arm (n = 35) was 3.5 (range 1.7–20) with 91% achieving the target INR (mean 1.1, range 0.9–1.4). In the partial reversal arm (n = 15) the mean initial INR was 5.6 (range 2.5–12) with 93% achieving the target INR (mean 1.6, range 1.4–2.2). There were no adverse effects attributed to Prothrombinex-VF.

Conclusions: Prothrombinex-VF is very effective and safe when used alone to reverse warfarin anticoagulation. The supplementary use of fresh frozen plasma in these patients is not required. A review of the current Warfarin Reversal Consensus Guidelines is needed.

Key words

prothrombin complex concentrate, warfarin reversal, anticoagulation, bleeding.
Introduction

As anticoagulation with warfarin is effective in the treatment and prevention of thromboembolic events, it is the most widely used oral anticoagulant worldwide. There are almost one-quarter of a million patients prescribed warfarin therapy in Australia, with this number expected to grow by approximately 9% per year.

Warfarin has a narrow therapeutic index, hence regular monitoring is required, with the typical therapeutic international normalized ratio (INR) range defined as between 2.0 and 3.0 (extending up to 3.5 for some indications, e.g., mechanical mitral valve). Bleeding is the major side-effect and increases dramatically once the INR is greater than 4.0. Furthermore, up to one-third of patients on chronic warfarin therapy will return an INR of greater than 6.0 over a 5-year period. Life-threatening haemorrhage occurs in up to 3% of patients per year with cerebral haemorrhage mortality rates as high as 79%. Indications for urgent reversal of warfarin anticoagulation include active bleeding, patients with a high INR who are deemed to be at high risk of bleeding and those who are on stable anticoagulation and require urgent procedures. In the past fresh frozen plasma (FFP) replacement was the only therapy available with doses of 10–15 mL/kg used. While this is an effective way to reverse the effects of warfarin, several units may be required. There are unavoidable delays associated with the use of this product, including the need to obtain the blood group, thawing of the plasma and the time taken to infuse the several units of plasma. Inherent risks of the use of plasma include volume overload, allergic reactions, anaphylaxis, infection and transfusion-related acute lung injury (TRALI).

Prothrombinex complex concentrates (PCC) contain high levels of the vitamin K-dependent coagulation factors. They are formulated with three factors (FII, FIX and FX) or four factors (FII, FVII, FIX and FX). These products have many advantages over FFP. Reconstitution times are rapid with only a small volume required (40–200 mL) for infusion over 20–30 min. There is minimal risk of viral transmission and TRALI because of dual pathogen inactivation and lack of circulating anti-human leukocyte antigen/granulocyte antibodies respectively. INR reversal occurs within 15 min of the infusion.

Prothrombinex-VF (CSL), three-factor PCC is the most common product used in Australia for warfarin reversal. Because of its negligible content of FVII, the Warfarin Reversal Consensus Guidelines published in 2004 recommended that it be supplemented with FFP. Since that time there have been at least four separate reports of the successful use of a three-factor concentrate without FFP. However, in one study the product was not efficacious in fully reversing the effects of warfarin in patients presenting with a supra-therapeutic INR >5.0.

There are scant data on optimal dosing of PCCs. One review article calculates PCC doses needed to reverse warfarin by assigning approximate levels of coagulation factors for ranges of INR. In addition, little is known about the duration of effect of Prothrombinex-VF. In this study we examined the efficacy of Prothrombinex-VF used alone in adult patients receiving warfarin therapy who required urgent reversal. We measured the INR up to 24 h post infusion in a subgroup of these patients. From this we derived a simple dosing algorithm based on initial INR and patient weight to enable clinicians to reverse effectively the effects of warfarin using Prothrombinex-VF alone.

Materials and methods

Study population

The study was approved by the Research and Ethics Unit at The Alfred Hospital, Melbourne. Adult patients on warfarin who required urgent reversal of anticoagulation were invited to participate. Exclusion criteria were concomitant use of FFP, known allergy to substances contained in Prothrombinex-VF, past history of heparin-induced thrombocytopenia and disseminated intravascular dissemination.

Sampling and laboratory assessment

INR measurements were obtained 30 min post infusion of Prothrombinex-VF. For patients who were subsequently admitted to hospital and did not receive vitamin K, written informed consent was obtained for serial INR measurements 6, 12 and 24 h post Prothrombinex-VF infusion.

PCC characteristics

Each vial of Prothrombinex-VF contains 500 IU of factor IX, approximately 500 IU of factor II, 500 IU of factor X, 25 IU of antithrombin III, 192 IU of heparin sodium and ≤500 mg of plasma proteins (which includes low levels of factors V and VII). The manufacturer recommends each vial be reconstituted with 20 mL water.

Treatment

According to the treating team’s intent, each patient received an amount of Prothrombinex-VF to achieve
complete (defined as 30 min post-INR <1.4) or partial reversal (defined as 30 min post-INR 1.4–2.0) of anticoagulation. Individualized dosing of Prothrombinex-VF was given only to those patients where the treating team sought haematology advice. Each patient received only one dose of Prothrombinex-VF and FFP was not administered to any patients.

Study outcomes

The primary efficacy end-point of this prospective cohort study was the proportion of patients obtaining INR values of <1.4 and 1.4–2.0 in the complete and partial reversal arms respectively. The safety clinical end-points were monitored during the hospital stay and included any adverse event attributed to the Prothrombinex-VF (infusion reactions, death, continued bleeding, delay to surgery, prolonged bleeding during or after surgery and thromboembolism). The data derived from this study were pooled with a cohort of 25 patients studied prospectively by one of the investigators (HHS). This group was recruited from Box Hill Hospital, Melbourne between March and September 2008 and underwent a similar reversal programme using identical inclusion and exclusion criteria. The preliminary results were presented as an oral abstract at the Annual Scientific Haematology Meeting in Perth in October 2008.10

Results

From March to November 2009, 25 patients on warfarin from The Alfred Hospital required urgent reversal of anticoagulation. As previously stated, data derived from this cohort were combined with the result of reversal of another 25 patients performed by one of the investigators. Baseline characteristics and reason for reversal are summarized in Table 1 for the 50 patients. Of these 35 patients were fully reversed. The indication for warfarin therapy is shown in Table 2, as expected atrial fibrillation was the main indication for anticoagulation.

The mean initial INR was 3.5 in the complete reversal arm (see Fig. 1). After Prothrombinex-VF infusion, the mean post-INR was 1.1. Complete reversal was achieved in 91% (32/35) of patients with only three patients failing to achieve a post-reversal INR <1.4 (see Table 3). Two of these patients were given relatively small doses of Prothrombinex-VF in relation to their initial INR (3.1 and 7.0); the other patient had an initial INR 20. The mean Prothrombinex-VF dose given was 34.7 IU/kg (25–50 IU/kg).

Table 1 Baseline characteristics of patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean age, years (range)</th>
<th>Mean INR in combined group (range)</th>
<th>Mean INR in complete reversal arm (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (range)</td>
<td>71.7 (32–85)</td>
<td>4.1 (1.7–20)</td>
<td>3.5 (1.7–20)</td>
</tr>
<tr>
<td>Mean INR in complete reversal arm (range)</td>
<td>1.5–1.9</td>
<td>6</td>
<td>22</td>
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<tr>
<td>Reason for complete reversal</td>
<td>Serious active bleeding</td>
<td>11</td>
<td>22</td>
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<tr>
<td>Reason for partial reversal</td>
<td>Minor active bleeding</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Mean INR in partial reversal arm (range)</td>
<td>1.5–1.9</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>Mean INR in complete reversal arm (range)</td>
<td>5.6 (2.5–12)</td>
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<tr>
<td>Reason for partial reversal</td>
<td>Minor active bleeding</td>
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<tr>
<td>Reason for partial reversal</td>
<td>Mechanical heart valves</td>
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<tr>
<td>Reason for partial reversal</td>
<td>Venous thromboembolism</td>
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<td>Reason for partial reversal</td>
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<tr>
<td>Reason for partial reversal</td>
<td>Mechanical heart valves</td>
<td>13</td>
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</table>

Table 2 Indications for warfarin use

<table>
<thead>
<tr>
<th>Indication</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atrial fibrillation</td>
<td>30 (60%)</td>
</tr>
<tr>
<td>Mechanical heart valves</td>
<td>13 (26%)</td>
</tr>
<tr>
<td>Venous thromboembolism</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>Severe cardiomyopathy</td>
<td>1 (2%)</td>
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</tbody>
</table>
In the partial reversal arm, Prothrombinex-VF was successful in achieving the desired target INR in 93% (14/15) of patients. Their mean INR was 5.6 before infusion and the mean post-reversal INR was 1.6 (see Fig. 2). Only one patient did not achieve an INR 1.4–2.0, his initial INR was 3.9 and he received 25 IU/kg of Prothrombinex-VF for a post-INR value of 2.2. Patients in this group received a mean dose of 29.7 IU/kg (25–45 IU/kg).

The duration of warfarin reversal was examined in eight patients. An effect lasting at least 24 h when no vitamin K was administered was noted in seven patients (see Fig. 3). Only one patient (patient 2) had a minor rebound of his INR to 3.1 at the 24 h post infusion time point. This patient originally presented with an INR 10.7 and received 45 IU/kg Prothrombinex-VF.

All patients with active bleeding achieved haemostasis and those undergoing procedures or surgery had no bleeding complications (see Tables 4,5). There were no delays in patients planned for intervention. The infusions were well tolerated with no reported adverse reactions.

<table>
<thead>
<tr>
<th>Initial INR</th>
<th>Post-reversal INR (target INR)</th>
<th>Prothrombinex-VF dose (IU/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
<td>1.4 (&lt;1.4)</td>
<td>30†</td>
</tr>
<tr>
<td>3.9</td>
<td>2.2 (1.4–2.0)</td>
<td>25†</td>
</tr>
<tr>
<td>7.0</td>
<td>1.6 (&lt;1.4)</td>
<td>25†</td>
</tr>
<tr>
<td>20</td>
<td>1.4 (&lt;1.4)</td>
<td>50</td>
</tr>
</tbody>
</table>

†Indicates suboptimal dosing. INR, international normalized ratio.

Five patients died and in four this occurred during hospitalization (two acute renal failure, one ruptured aortic aneurysm and one diffuse alveolar lung damage). The 50th patient a 72-year-old woman died of an acute myocardial infarct (AMI) 71 days after admission. None of these deaths was found to be directly related to Prothrombinex-VF.

**Discussion**

With increasing numbers of patients (particularly elderly) prescribed long-term warfarin therapy, many of these

![Figure 2](image2.png)

**Figure 2** Efficacy of Prothrombinex-VF in the partial reversal arm. INR, international normalized ratio.

![Figure 3](image3.png)

**Figure 3** INR values after Prothrombinex-VF in patients not given vitamin K. Initial INR, [----] 0.5 h, [---] 6 h, [----] 12 h, [----] 24 h. INR, international normalized ratio.
patients will at some stage require urgent reversal. FFP is effective in achieving complete reversal of anticoagulation; however, large volumes may be required depending on the initial INR. This increases the chance of an adverse event. In Australia the only PCC registered and funded by the National Blood Authority is Prothrombinex-VF. (It was originally marketed in 1993 as Prothrombinex-HT, and was superseded in 2006 by Prothrombinex-VF.) Its use has reduced the volume of FFP required. As it is a three-factor concentrate, many centres use Prothrombinex-VF in combination with FFP as recommended by the Warfarin Reversal Consensus Guidelines published in 2004.

Our study demonstrates the efficacy, safety and versatility of Prothrombinex-VF when used to reverse anticoagulation in warfarinized patients. The target INR was attained in over 90% of patients in both complete and partial reversal arms. Of the four patients who did not achieve the desired INR, three received suboptimal dosing (see Table 3); therefore, the efficacy would have approached 100% in both arms had they received the correct dose. These observations are consistent with previous published results using a three-factor PCC. Imberti et al. showed the effectiveness and safety of Protroplex (Baxter, Rome, Italy) prospectively in 92 patients suffering from acute intracranial haemorrhage (ICH). Their median initial and post-INR were 3.3 and 1.4 respectively. Chiu et al. also analysed the use of Prothrombinex-VF retrospectively in 50 patients undergoing vascular surgery or angiography. All had baseline therapeutic INR (2.0–3.9) and were successfully reversed to INR <1.4 following infusion of the PCC. In both studies the post-reversal INR was measured 30–60 min after completion of the PCC infusion. More importantly and similar to our findings, there were no bleeding issues or adverse events in any of the patients.

In the published literature we found one study that demonstrated poor efficacy of a three-factor PCC used in warfarinized patients. Holland et al. studied 40 patients who presented with INR >5. The patients received either 25 IU/kg (low dose) or 50 IU/kg (high dose) of Profilnine-SD (Grifols, Los Angeles, CA, USA). The mean initial INR were 9.0 and 8.6 in the two groups respectively, reducing to an INR of 4.6 and 4.7 respectively, after the PCC infusion. This study differs from the other cited studies in several respects. First, the PCC used is different to the one available in Australia and the post-INR was measured anywhere from 2.5 to 40 h after PCC administration. Vitamin K was given at varying doses of 2–10 mg through varying routes in up to 52% of patients. Patients with ICH were excluded. Of concern is that there were at least two patients who had identical INR before and after PCC infusion. We are also unable to explain why no patient achieved a normal INR even with the addition of FFP. Clinical outcomes were not reported in this study.

The duration of effect of PCC has been studied by Yasaka et al. and Imberti et al. using a four-factor and three-factor PCC respectively. Both studies used vitamin K and showed the duration of effect was between at least 24 and 96 h. In our study eight patients not given vitamin K had serial INR for 24 h. There was only one patient with a mild rebound (INR 3.1 at 24 h, initial INR 10.7). These results suggest that one dose of PCC is adequate and effective in maintaining a safe INR. There is no doubt that the combination of PCC and vitamin K is required to maintain the INR in the normal range, a necessary target in patients with bleeding.

Although the INR is used primarily to monitor warfarin anticoagulation and may not reflect in vivo haemostasis after PCC infusion, it is gratifying to note the good correlation between the correction of the INR with the

### Table 4 Site of bleeding, reversal intent and outcome in 14 patients

<table>
<thead>
<tr>
<th>Site</th>
<th>Reversal intent</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>GIT (4)</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Skin/joint (3)</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>GUT</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Vascular</td>
<td>Complete</td>
<td>Death‡</td>
</tr>
<tr>
<td>GIT (2)</td>
<td>Partial</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Skin/joint</td>
<td>Partial</td>
<td>Haemostasis achieved</td>
</tr>
</tbody>
</table>

†Haemostasis achievement defined as the cessation of bleeding without the need for surgical exploration (or re-exploration) and no further blood product administration. ‡Patient died from ruptured aortic aneurysm. GIT, gastrointestinal; GUT, genito-urinary; ICH, intracranial haemorrhage.

### Table 5 Procedure/surgery type, reversal intent and outcome in 27 patients

<table>
<thead>
<tr>
<th>Procedure/surgery</th>
<th>Reversal intent</th>
<th>Outcome†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular (12)</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Orthopaedic (3)</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Device insertion</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Genito-urinary (2)</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Angiography</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Gastric biopsy</td>
<td>Complete</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Endoscopy (2)</td>
<td>Partial</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Fluid drainage</td>
<td>Partial</td>
<td>Haemostasis achieved</td>
</tr>
<tr>
<td>Angiography</td>
<td>Partial</td>
<td>Death§</td>
</tr>
</tbody>
</table>

†Haemostasis achievement defined as the cessation of bleeding without the need for surgical exploration (or re-exploration) and no further blood product administration. ‡Patient died from primary illness (diffuse alveolar damage reported from biopsy). §Patient died from progressive renal failure.
achievement of haemostasis post PCC infusion in our patients. Bleeding was rapidly controlled in patients presenting with this complication, whereas patients reversed in preparation for surgery underwent their procedure without any bleeding complication. Crawford and Auguston observed cessation of bleeding in patients post Prothrombinex-HT despite INR >1.3. They postulated that haemostasis may have resulted from increased thrombin rather than factor VII replacement.

The results of our study suggest that factor VII content is not critical in achieving warfarin reversal (correction of the INR) and haemostosis. To date there are no head-to-head trials comparing three-versus four-factor PCC. One may postulate that the reduced factor VII content in the three-factor concentrate has the added benefit of minimizing the risk of thrombosis when compared with a four-factor concentrate. Several reports have appeared describing thromboembolic complications in patients receiving a four-factor concentrate. Schulman et al. reported one stroke in 100 patients in pooled data from six cases series. Lankiewicz et al. could not definitely attribute any thrombotic complications to PCC use in 58 patients. There was one pulmonary embolism occurring in 43 patients reported by Pabinger et al. This patient received a total of 70 IU/kg of a four-factor PCC (50 IU/kg on day 1 and 20 IU/kg on day 4). We found only one study where thrombotic complications were monitored using a three-factor PCC. There were five late thrombotic complications reported, none of which was related to the PCC. In our study there were no thrombotic complications observed in the 50 patients during their hospital stay. A late death (71 days after PCC administration) due to AMI was noted.

With optimal dosing the target INR can be achieved in almost all cases. Published studies on PCC dosing use a range of 25–50 IU/kg. However, all these trials were performed using four-factor PCC. Vitamin K was also given to nearly all patients and the first INR measured post PCC administration ranged from 10 min to 5 h. All of our patients were given Prothrombinex-VF at doses of 25–50 IU/kg, with post-INR measured 30 min after. As our post-INR were taken at an identical time point for all patients, we were able to analyse the data retrospectively and derive an optimal dosing algorithm (see Table 6). We plan to use this prospectively to validate our algorithm.

In our study we stratified the need for warfarin reversal into two groups: partial or complete. We find this approach simple and practical. For example, there will be instances where patients with supra-therapeutic INR who while at risk of bleeding are also at risk of thrombosis. Examples include patients with recent venous thromboembolism or those with prosthetic valves. In these patients we recommend partial reversal of warfarin and the recommencement or continuation of warfarin therapy at an adjusted dose. Full reversal on the other hand would be recommended in patients with active bleeding and those undergoing a major surgical procedure. In the latter group warfarin therapy can be recommenced as soon as practical and low molecular weight heparin may be used for temporary thromboprophylaxis until the INR is therapeutic. In patients in whom full reversal is required because of active bleeding we recommend the concomitant use of vitamin K to PCC infusion to ensure sustained reversal of the effects of warfarin.

We see two limitations of our study. First, there is a lack of a comparator arm where FFP was used in addition to Prothrombinex-VF. As the vast majority of our patients achieved the target INR with Prothrombinex-VF alone, there would be no benefit in the supplemental use of FFP. Our cohort size, demographics, indication for warfarin use and reversal are similar to other published studies. Hence our results can be generalized to patient groups from other hospitals. The other potential limitation is the small number of patients with INR requiring complete reversal. It is this group that would cause concern for many clinicians as these patients would be at a higher risk of bleeding and the efficacy of Prothrombinex-VF when used alone is paramount. The two studies previously mentioned that used a three-factor PCC alone also had small numbers of patients with supra-therapeutic INR (Imberti et al. and Chiu et al. included only 21% and 0% of patients with INR > 3.9 respectively). In future studies with individualized dosing using our proposed algorithm, we intend to recruit larger numbers and hope to capture more patients with supra-therapeutic INR.

**Conclusion**

Prothrombinex-VF, a three-factor PCC, is effective and safe in reversing warfarin anticoagulation when used alone. It has many benefits over FFP and its duration
oleffect is between 12 and 24 h. In light of our study, we do not see any benefit from using FFP in addition to Prothrombinex-VF in warfarin reversal. The Warfarin Reversal Consensus Guidelines from 2004 were written at the time when there were limited data on the use of Prothrombinex-VF. With our experience and that of other centres we recommend a review of the guidelines to best reflect current evidence-based clinical practice.

References

1 Bereznicki L. Unit for Medication Outcomes Research and Education (UMORE): Tasmanian School of Pharmacy, University of Tasmania. Media Release 10 November 2008.
8 PROTHROMBINEX-VF Approved Product Information. Date of most recent amendment: 11 February 2009.
10 Hatem JS, Poultton L. Warfarin anticoagulation can be effectively reversed with Prothrombinex®-VF without the need for fresh frozen plasma. Abstract 053 HAA 2008 Perth.
POSITION PAPER

Guidelines for patient selection and performance of carotid artery stenting

The Carotid Stenting Guidelines Committee: An Inter-collegiate Committee of the RACP (ANZAN, CSANZ), RACS (ANZSVS) and RANZCR

Key words
carotid stroke, endarterectomy, carotid stenosis, guidelines, stents.

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Received 15 November 2009; accepted 23 September 2010.

Abstract
The endovascular treatment of carotid atherosclerosis with carotid artery stenting (CAS) is controversial. The inter-collegiate Carotid Stenting Guidelines Committee (CSGC) recommends that CAS should not be performed in the majority of patients requiring carotid revascularization. CAS may be considered for specific high risk patients with symptomatic severe carotid stenosis who have contraindications for carotid endarterectomy, or in those under 70 years of age where carotid re-vascularization is considered appropriate. Advances in endovascular technologies and the long-term results of randomized controlled trials will guide future revisions of these guidelines.

Introduction
The Australasian Carotid Stenting Guidelines Committee (CSGC) was formed from expert representatives of the Royal Australasian College of Physicians (including the Australian and New Zealand Association of Neurologists, Stroke Society of Australasia, and Cardiac Society of Australia and New Zealand), The Royal Australasian College of Surgeons (Australian and New Zealand Society of Vascular Surgeons) and the Royal Australian and New Zealand College of Radiologists. Since initial publication, the Australasian guidelines on carotid artery stenting (CAS) presented here have now been updated following recent publication of a large North American randomized controlled trial and a meta-analysis of European randomized controlled trials.3,4

Methodology
Consensus for guideline parameters was reached using the modified Delphi consensus method of iterative consultation.5

Recommendations for carotid artery stenting

Rationale
Evidence level: NHMRC grade C (Table 1)
The overall results of randomized controlled trials indicate that CAS is not as safe as carotid endarterectomy (CEA) for treatment of symptomatic carotid stenosis for prevention of ipsilateral stroke.6-10 The results of three major European studies (Endarterectomy Versus Angioplasty in Patients With Symptomatic Severe Carotid Stenosis trial (EVA-3S), Stent-Supported Percutaneous Angioplasty of the Carotid Artery versus Endarterectomy (SPACE), International Carotid Stenting Study (ICSS)) for the treatment of symptomatic stenosis demonstrated that CAS was more hazardous than CEA for the
The definitions used for MI and greater number of but this was offset by an increased risk of MI, related to significantly reduced rate of stroke and death in the CEA group, Internal Medicine Journal © 2011 Royal Australasian College of Physicians.

In CREST there was a significant rates of stroke, myocardial infarction (MI) and death in both CAS and CEA groups in the peri-procedural period, and at 4 years. In CREST there was a significantly reduced rate of stroke and death in the CEA group, but this was offset by an increased risk of MI, related to the definitions used for MI and greater number of outcomes of stroke and death during the peri-procedural period (30 days) and on longer-term follow up, a finding further supported by pooled analysis of these studies. The North American Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) demonstrated equivalent rates of stroke, myocardial infarction (MI) and death in both CAS and CEA groups in the peri-procedural period, and at 4 years. In CREST there was a significantly reduced rate of stroke and death in the CEA group, but this was offset by an increased risk of MI, related to the definitions used for MI and greater number of patients with ischaemic heart disease. Use of cerebral protection devices (CPD) during CAS were mandated in CREST but not in European studies. The value of CPD is unclear with evidence indicating that CPD were no more effective in reducing the clinical risk of stroke than unprotected stenting. Moreover, data from an MRI sub-study undertaken as part of ICSS indicated that compared with CEA there was a threefold increase silent brain infarctions in CAS with use of CPD (adjusted OR: 3.28 CI: 1.5–7.2). Since the initial publication of the Australasian guidelines, recent data from CREST and a meta-analysis of three European trials indicate that CAS is at least as safe as CEA in patients under 70 years of age, while there is a greater risk of stroke with CAS in those older than 70 years.

CAS may be considered a treatment option for patients with symptomatic severe carotid stenosis who are at high risk of stroke, but are surgically unsuitable for CEA. There is currently no evidence to support CAS as a treatment for asymptomatic carotid stenosis.

### Rationale

#### Cognitive requirements for CAS (Table 2)

Knowledge of randomized controlled trials and of the pathophysiology, diagnosis, investigation, assessment and management of carotid artery disease are essential before considering endovascular treatment. The assessment of medical and/or surgical risk can be complex and is often best carried out as a team approach to ensure that all relevant medical, surgical and radiological issues are addressed by discipline experts. It is important that all patients being considered for carotid intervention have pre-procedural neuro-imaging and an independent neurological assessment before and after the procedure. Accurate, standardized neurological audit data allow direct comparison with the results of randomized control trials where neurological evaluation of all patients is routine and serves as a benchmark for best clinical practice. The monitoring, assessment and certification (including case numbers) of CAS are determined by the joint College committees of the RACP, RACS and RANZCR – the RACP/RANZCR/RACS Conjoint Committee for the Recognition of Training in Peripheral Endovascular Therapy (CCoPET).

#### Technical requirements for CAS (Table 3)

The risk of neurological deficit as a result of diagnostic cerebral angiography is not inconsiderable.
Silent strokes only detected on neuroimaging are more common than clinically evident neurological complications. MRI studies using diffusion weighted imaging (DWI) demonstrate evidence of cerebral infarction in

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<table>
<thead>
<tr>
<th>Table 2</th>
<th>Cognitive recommendations for the performance of carotid stenting (adapted from SCAI/SVMB/SVS guidelines13)</th>
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</thead>
<tbody>
<tr>
<td>1. Pathophysiology of carotid artery disease and stroke</td>
<td></td>
</tr>
<tr>
<td>a. Causes of stroke</td>
<td></td>
</tr>
<tr>
<td>i. Embolization (cardiac, carotid, aortic, other)</td>
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<tr>
<td>ii. Vasculitis</td>
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<tr>
<td>iii. Lacunes/small vessel disease</td>
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<tr>
<td>iv. Arteriovenous malformation</td>
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<tr>
<td>v. Intracranial haemorrhage (including sub-arachnoid haemorrhage, subdural)</td>
<td></td>
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<tr>
<td>b. Causes of carotid artery narrowing</td>
<td></td>
</tr>
<tr>
<td>i. Atherosclerosis</td>
<td></td>
</tr>
<tr>
<td>ii. Fibromuscular dysplasia</td>
<td></td>
</tr>
<tr>
<td>iii. Spontaneous dissection</td>
<td></td>
</tr>
<tr>
<td>c. Atherogenesis (pathogenesis and risk factors)</td>
<td></td>
</tr>
<tr>
<td>2. Clinical manifestations of stroke</td>
<td></td>
</tr>
<tr>
<td>a. Knowledge of stroke syndromes</td>
<td></td>
</tr>
<tr>
<td>b. Distinction between anterior and posterior circulation events</td>
<td></td>
</tr>
<tr>
<td>3. Natural History of carotid artery disease</td>
<td></td>
</tr>
<tr>
<td>4. Associated pathology (e.g. coronary and peripheral artery disease)</td>
<td></td>
</tr>
<tr>
<td>5. Diagnosis of stroke and carotid artery disease</td>
<td></td>
</tr>
<tr>
<td>a. History and physical examination</td>
<td></td>
</tr>
<tr>
<td>i. Neurologic examination including NIHSS</td>
<td></td>
</tr>
<tr>
<td>ii. Non-neurologic (cardiac, other) examination</td>
<td></td>
</tr>
<tr>
<td>b. Non-invasive imaging</td>
<td></td>
</tr>
<tr>
<td>i. Duplex ultrasound</td>
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<tr>
<td>ii. MRA</td>
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<tr>
<td>iii. CTA</td>
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<tr>
<td>6. Angiographic anatomy (arch, extracranial, intracranial, basic collateral circulation, common anatomic variants and non-atherosclerotic pathogenic processes)</td>
<td></td>
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<tr>
<td>7. Knowledge of evidence-based treatment options for carotid stenosis</td>
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<tr>
<td>a. Pharmacology (e.g. anti-platelet agents, anticoagulation, lipid-lowering agents)</td>
<td></td>
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<tr>
<td>b. Carotid endarterectomy</td>
<td></td>
</tr>
<tr>
<td>i. Results from major trials (NASCET, ACAS, ECST, ACST)</td>
<td></td>
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<tr>
<td>ii. Results in patients with increased surgical risk</td>
<td></td>
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<tr>
<td>c. Stent revascularization</td>
<td></td>
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<tr>
<td>i. Results of carotid angioplasty and stenting with and without distal embolic protection</td>
<td></td>
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<tr>
<td>8. Appropriate case selection</td>
<td></td>
</tr>
<tr>
<td>a. Indications and contraindications for revascularization to prevent stroke</td>
<td></td>
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<tr>
<td>b. High risk criteria for carotid endarterectomy</td>
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<tr>
<td>c. High risk criteria for endovascular intervention</td>
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<tr>
<td>9. Role of post-procedure follow up and surveillance</td>
<td></td>
</tr>
<tr>
<td>a. Surgical/endovascular audit including independent neurological assessment</td>
<td></td>
</tr>
<tr>
<td>b. Knowledge of post-procedural anti-platelet therapies</td>
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</table>

ACAS, Asymptomatic Carotid Atherosclerosis Study; ACST, European Asymptomatic Carotid Surgery Trial; CTA, computed tomography angiography; ECST, European Carotid Surgery Trial; MRA, magnetic resonance angiography; NASCET, North American Symptomatic Carotid Endarterectomy Trial; NIHSS, National Institutes of Health Stroke Score; SCAI, Society for Cardiovascular Angiography and Interventions; SVMB, Society for Vascular Medicine and Biology; SVS, Society for Vascular Surgery.

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<tr>
<th>Table 3</th>
<th>Technical recommendations for performance of carotid stenting</th>
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<tbody>
<tr>
<td>1. High level of expertise in use of anti-platelet therapy and procedural anticoagulation</td>
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<tr>
<td>2. Digital subtraction angiographic skills:</td>
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<tr>
<td>a. Vascular access skills</td>
<td></td>
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<tr>
<td>b. Selection of guidewires and angiographic catheters</td>
<td></td>
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<tr>
<td>c. Appropriate manipulation of guidewires and catheters</td>
<td></td>
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<tr>
<td>d. Use of ‘closed system’ manifold</td>
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<tr>
<td>e. Knowledge of angiographic vascular anatomy and common variants</td>
<td></td>
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<tr>
<td>f. Knowledge of Circle of Willis and typical/atypical collateral pathways</td>
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<tr>
<td>g. Proper assessment of aortic arch configuration, as it affects carotid intervention</td>
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<tr>
<td>h. Familiarity with angulated views and appropriate movement of the X-ray gantry</td>
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<tr>
<td>3. Interventional skills</td>
<td></td>
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<tr>
<td>a. Guide catheter/sheath placement</td>
<td></td>
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<tr>
<td>b. Appropriate selection of various types of balloons, stents and embolic protection devices</td>
<td></td>
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<tr>
<td>c. Deployment and retrieval of embolic protection devices</td>
<td></td>
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<tr>
<td>d. Pre- and post-dilatation</td>
<td></td>
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<tr>
<td>e. Familiarity with angulated views and appropriate movement of the X-ray gantry</td>
<td></td>
</tr>
<tr>
<td>4. Recognition and management of intra-procedural complications</td>
<td></td>
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<tr>
<td>a. Cerebral events</td>
<td></td>
</tr>
<tr>
<td>i. Stroke or TIA</td>
<td></td>
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<tr>
<td>ii. Embolization</td>
<td></td>
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<tr>
<td>iii. Haemorrhage</td>
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<tr>
<td>iv. Thrombosis</td>
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<tr>
<td>v. Dissection</td>
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<td>vi. Seizure and loss of consciousness</td>
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<tr>
<td>vii. Arterial spasm</td>
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<tr>
<td>viii. Hyperperfusion syndrome</td>
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<tr>
<td>b. Cardiovascular events</td>
<td></td>
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<tr>
<td>i. Arrhythmias</td>
<td></td>
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<tr>
<td>ii. Hypotension</td>
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<tr>
<td>iii. Hypertension</td>
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<tr>
<td>iv. Myocardial ischaemia/infarction</td>
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<tr>
<td>c. Vascular access events</td>
<td></td>
</tr>
<tr>
<td>i. Bleeding</td>
<td></td>
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<tr>
<td>ii. Ischaemia</td>
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<td>iii. Thrombosis</td>
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<tr>
<td>iv. Retroperitoneal bleed</td>
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<tr>
<td>5. Management of vascular access site</td>
<td></td>
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<tr>
<td>i. Proper sheath removal and attainment of haemostasis</td>
<td></td>
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<tr>
<td>ii. Closure device utilization</td>
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Technical elements for competence in both diagnostic angiography and interventional techniques (adapted from SCAI/SVMB/SVS guidelines14).

about 25% of patients after diagnostic cerebral angiography with correlation to longer procedural times, and use of multiple catheters.16,17 Patients with symptomatic atherosclerotic cerebrovascular disease have a two- to threefold higher risk of stroke from diagnostic cerebral angiography (0.5–5.7% risk), compared with asymptomatic lesions (0.1–1.2% risk).14,15,18 Non-invasive methods (e.g. Duplex ultrasound, CT or MR angiography) of investigation are therefore preferred, with cerebral angiography performed as infrequently as possible.

### Conclusion

For patients with severe symptomatic carotid stenosis CAS may be considered in specific patients who are unsuitable for CEA, or in those under 70 years of age if, after careful consideration, carotid re-vascularization is considered appropriate. There is no evidence to support CAS as a treatment for asymptomatic carotid stenosis. Advances in endovascular technologies and the further publication of long-term results from recent randomized controlled trials will guide future revisions of these guidelines.

### References

BRIEF COMMUNICATION

Multiple myeloma presenting with a fever of unknown origin and development of thrombotic thrombocytopenic purpura post-bortezomib

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Key words
plasma cell dyscrasia, fever, p53 deletion, microangiopathic haemolytic syndrome.

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Abstract
Multiple myeloma rarely presents with a fever of unknown origin and diagnosis may be delayed. We describe a case of myeloma presenting in this way with raised serum-free light chains and TP53 deletion on cytogenetics. The patient developed thrombotic thrombocytopenia purpura (TTP) following bortezomib therapy but recovered spontaneously and was successfully re-challenged. We believe this is only the second case to describe this phenomenon post-bortezomib and the first to rechallenge the patient successfully without further recurrence of TTP. Possible mechanisms for this successful rechallenge are discussed.

An otherwise well 57-year-old woman presented in August 2008 with a 6-month history of fatigue, weight loss and feeling unwell with fevers and drenching night sweats. A full blood count revealed Hb 86 g/L, MCV 81.9 fL, Plt 418 $\times$ 10^9, WBC 17.79 $\times$ 10^9, ANC 14.45 $\times$ 10^9. Inflammatory markers were elevated (C-reactive protein (CRP) 116 mg/L). Investigations including all imaging, looking for causes of her fever including autoimmune, infectious and underlying lymphoproliferative disorders were negative. She continued to have well-documented fevers and night sweats and blood cultures taken during these times were consistently negative while her CRP remained high (>200 mg/L).

After a prolonged admission, she underwent a bone marrow examination which showed heavy plasma cell infiltration and the diagnosis of multiple myeloma (MM) was made. Serum electrophoresis demonstrated a band of lambda light chains and a positive urinary Bence Jones protein was detected. Serum-free light chains (SFLC) showed lambda light chains 1220 mg/L, kappa light chain 1.28 mg/L with a markedly reduced ratio of 0.001. Cytogenetic analysis revealed a normal karyotype but fluorescence in situ hybridization (FISH) demonstrated deletion TP53. The patient was commenced on our standard induction regime of cyclophosphamide and dexamethasone.

The patient was reviewed in the outpatient clinic following several cycles of chemotherapy. It was noted that SFLC and CRP were increasing following an initial reduction when treatment was started (CRP 140 mg/L and lambda light chains 421.0 mg/L). Treatment was then changed to thalidomide 100 mg daily, prednisone 40 mg daily and bortezomib 2 mg/m^2 as per standard dosing schedule.

The patient was admitted to hospital 2 days after the initial dose of bortezomib, following a collapse (presumed vasovagal) at home. On questioning, her urine had been darker than usual and she was feeling more tired but denied other symptoms. Clinical examination demonstrated pallor only. Blood results revealed Hb 55 g/L, Plt 10 $\times$ 10^9, WBC 9.54 $\times$ 10^9, with biochemical evidence of haemolysis (raised LD, low haptoglobin and elevated serum bilirubin). Serum creatinine was also increased. Examination of the blood film revealed a picture consistent with a microangiopathic haemolytic anaemia (MAHA). Only a few days prior all blood parameters had been within normal limits. A diagnosis of Thrombotic thrombocytopenic purpura (TTP) was made, most likely secondary to bortezomib given the timing of events.
was transfused 2 units of platelets and 4 units of red cells. Plasmapheresis was not performed as the patient’s blood parameters recovered spontaneously with Hb 103 g/L, plt 60 x 10^9, creatinine normal on discharge 3 days later. The patient remained clinically well and did not develop any physical manifestations of TTP.

ADAMTS13 testing was unfortunately not performed until 2 weeks after the initial event but this was 12% (ref > 50%) supporting the diagnosis of TTP. A decision was made to rechallenge the patient with bortezomib as this would offer the best chance of disease control if it could be successfully administered. After fully informed consent, a further dose of bortezomib was administered in hospital 3 weeks later. All blood parameters at the time of the admission were within normal limits. ADAMTS13 was repeated on admission and was still low at 8%. This was an uneventful admission with no biochemical or haematological evidence of TTP recurrence and the patient remained clinically well. Lambda light chains and CRP were also evaluated and both showed a reduction at 119 mg/L and 88 mg/L, respectively. A repeat ADAMTS13 2 weeks after the rechallenge was within the normal range. The patient went on to receive further cycles of bortezomib without complication and has subsequently undergone an autologous stem cell transplant (ASCT). Most recent SFLC show lambda light chains 54.4 mg/L, kappa light chains 4.19 mg/L and ratio 0.077 with CRP <3 mg/L. The patient is not taking any regular medications currently.

Discussion

Several days after the initial dose of bortezomib, the patient developed haematological, biochemical and morphological evidence of microangiopathic haemolytic anaemia, consistent with a diagnosis of TTP. There has been only one other case reported in the literature of thrombotic microangiopathy (TMA) following bortezomib and dexamethasone in a 54-year-old man with refractory MM. This patient had already undergone both autologous and allogeneic bone marrow transplantation, had chronic Graft versus Host Disease (GvHD) and received bortezomib and dexamethasone for disease progression. His previous treatments with TBI, tacrolimus and GvHD are all risk factors for TMA but in this case allogeneic transplant had occurred 1-year prior and the onset of TMA occurred just after treatment with bortezomib.

Traditionally TTP was described as a pentad of clinical and laboratory features (fever, MAHA, thrombocytopenia, acute renal failure and neurological abnormalities) but now only thrombocytopenia and MAHA without any other clinically apparent aetiology are required to suspect the diagnosis. The evidence to support the efficacy of plasma exchange (the usual treatment for TTP) for syndromes that appear similar to TTP/HUS following chemotherapy or HSCT is, however, sporadic and anecdotal. Our patient was not treated with plasma exchange and the condition resolved spontaneously.

An underlying cause of, and the mechanism for, platelet consumption in many patients with TTP is deficiency of ADAMTS13 and ADAMTS13 activity is typically absent or severely deficient in many patients with classical TTP and is highly specific for TTP. However, similarly low levels without manifestations of TTP can be found in some cases of severe sepsis with associated DIC or ischaemic organ failure and absent ADAMTS13 activity without manifestations of TTP can be found in several families with congenital TTP. The role of ADAMTS13 in the pathogenesis of TTP has yet to be fully determined. In our patient ADAMTS13 levels were found to be low at 12% 2 weeks after her presentation with TTP. It was also low at the time of rechallenge when TTP did not recur and has subsequently been recorded at normal levels. In the other case report, ADAMTS13 activity was also reduced below normal levels.

C-reactive protein is a member of the class of acute phase proteins as its levels rise dramatically during inflammatory processes occurring in the body. This increment is due to a rise in the plasma concentration of IL-6, which is produced predominantly by macrophages as well as adipocytes. Research has shown that the growth of myeloma cells is regulated by cytokines. Both in vitro and in vivo observations have shown that interleukin-6 (IL-6) plays a key role in the pathogenesis of MM. Especially in patients with active and/or terminal disease, serum IL-6 levels have been found to be elevated.

Bortezomib is the first of a new class of medications called proteasome inhibitors. It is a modified dipeptidyl boronic acid that reduces the NF-κB translocation/ transactivation activity and blocks drug-related signalling pathways critical to vital functions of myeloma cells. This drug has also been shown to inhibit the adherence between bone marrow stroma and myeloma cells, to block apoptosis resistance, and to inhibit IL-6-induced proliferation and angiogenesis. Bortezomib administration may enhance the release of pro-inflammatory cytokines (including IL-6 and TNF-α) and the generation of a cell-mediated immune response, which has been reported as having a possible role in bortezomib-induced cutaneous reactions.
for autoantibody production. In this case, this autoantibody was directed at the Von Willebrand multimembrane protease enzyme, ADAMTS13, leading to the clinical manifestation of TTP. Once disease control was obtained (as documented by falling CRP and serum-free light-chain levels), this pro-inflammatory milieu no longer existed which may explain why the TTP did not recur on repeated administration of bortezomib.

MM rarely presents with pure fever alone. In the single largest case report, only nine patients out of 5523 (0.2%), with a final diagnosis of MM seen at the Mayo Clinic 2001, met the criteria for fever of unknown origin as originally defined by Petersdorf and Beeson. In these cases and ours, the patients were similar in that all of them underwent exhaustive evaluations to identify the cause of the fever prior to the diagnosis of MM being made.

This patient was identified with the cytogenic abnormality p53 deletion. TP53 deletion detected by FISH has been reported to occur in 9–34% of patients with MM and is associated with a poor prognosis. Chang et al demonstrated that patients with TP53 deletions had significantly shorter progression-free (median 7.9 vs 25.7 months) and overall survival (median 14.7 vs 48.1 months) than patients without TP53 deletion following high dose chemotherapy and ASCT, which has been confirmed by other groups. Recent evidence suggests that novel agents other than thalidomide produce the highest overall response rate in relapsed and refractory MM with TP53 deletion.

In summary, this is only the second documented case of presumed bortezomib associated TTP and, the first to rechallenge successfully a patient with the implicated drug without recurrence of symptoms. The potential mechanisms for the cause of the TTP and successful rechallenge have been described. The low level of ADAMTS13 at the time of drug rechallenge also suggests that the role of ADAMTS13 in the pathogenesis of TTP continues to be not fully understood.

References

2 Amorosi EL, Ultmann JE. TTP report of 15 only nine patients out of 5523 (0.2%), with a final diagnosis of MM seen at the Mayo Clinic 2001, met the criteria for fever of unknown origin as originally defined by Petersdorf and Beeson. In these cases and ours, the patients were similar in that all of them underwent exhaustive evaluations to identify the cause of the fever prior to the diagnosis of MM being made.
Prevalence and molecular study of G6PD deficiency in Malaysian Orang Asli

F. Amini,1 E. Ismail1,2 and B-A. Zilfalil3

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Key words
G6PD, mutation, Negrito, Orang Asli, prevalence.

Abstract
This study aims to define the prevalence and the molecular basis of G6PD deficiency in the Negrito tribe of the Malaysian Orang Asli. Four hundred and eighty seven consenting Negrito volunteers were screened for G6PD deficiency through the use of a fluorescent spot test. DNA from deficient individuals underwent PCR-RFLP analysis using thirteen recognized G6PD mutations. In the instances when the mutation could not be identified by PCR-RFLP, the entire coding region of the G6PD gene was subjected to DNA sequencing. In total, 9% (44/486) of the sample were found to be G6PD-deficient. However, only 25 samples were subjected to PCR-RFLP and DNA sequencing. Of these, three were found to carry Viangchan, one Coimbra and 16, a combination of C1311T in exon 11 and IVS11 T93C. Mutation(s) for the five remaining samples are unknown. The mean G6PD enzyme activity ranged 5.7 IU/gHb in deficient individuals. Our results demonstrate that the frequency of G6PD deficiency is higher among the Negrito Orang Asli than other Malaysian races. The dual presence of C1311T and IVS11 T93C in 64% of the deficient individuals (16/44) could well be a result of genetic drift within this isolated group.

The Orang Asli (OA), otherwise referred to as aboriginal people, have been living in different regions of the Malay Peninsula for an extensive period of time. The OA are divided into three main tribal groups: Negrito, Senoi and Proto-Malay. The Negrito is the smallest group of the OA with a population of just 4851. The Negrito group itself is comprised of six sub-ethnic groups: Kensiu, Kintak, Lanoh, Jahai, Bateq and Mendriq. An important point to note is that the OA suffer from several specific health problems besides malnutrition and hygiene issues, which include: malaria, tuberculosis, leprosy, filariasis, upper respiratory infections and skin problems. However, very little information is available on the genetic markers or background of the Malaysian OA and their origins due to the fact that little research has been undertaken on genetic associations.

G6PD deficiency is one of the most common human hereditary diseases. Over 400 million people worldwide are affected by some 140 different G6PD variants. G6PD deficiency is also highly prevalent in Asian countries, including Malaysia. While Malaysia is a multi-racial country, the only aboriginal people residing in the Malaysian Peninsula are the OA. Furthermore, although comprehensive studies on the G6PD deficiency have been undertaken, they have predominantly focused on the Malay and Chinese.4

The incidence rate of malaria in the OA area has been argued to be 20 times greater than in urban areas. Interestingly, complications associated with the drug treatment for malaria would largely be avoidable if the G6PD status was known by the local health provider. Consequently, the introduction of simple G6PD screening to this population is considered vital as a means to prevent future G6PD-associated death through increasing their awareness level.

As the majority of OA babies are delivered at home, there is very little information available on the OA neonatal jaundice status. It has been shown, however, that from a total of 65 OA admissions into the neonatal unit in one hospital, more than half (33/65) were jaundiced whereby 22 of them had G6PD deficiency. In addition, the OA community is recorded as having the highest mortality-rate for children under the age of five-years-old in Malaysia.8

Consequently, given the lack of information on the G6PD deficiency among the OA, the aim of this study was...
to determine the prevalence and the molecular basis of G6PD deficiency, in order to help improve the healthcare delivery among the Negrito tribe of the OA.

This study was approved by the University Kebangsaan Malaysia (UKM) hospital’s ethics committee, whereby all subjects provided their written informed consent. A population screening was performed on 487 Negritos using a fluorescent spot test. This method is the most rapid and appropriate method for collecting samples in geographically isolated areas. The majority of the OA villages were visited using four-wheel-drive vehicles due to isolated locations within the remote jungle of the Malay Peninsula. Sample collection took place between November 2004 and February 2008. A G6PD quantification test was undertaken using the G6PD Kit from RANDOX Laboratory LTD (Antrim, UK) according to the manufacturer’s instructions and DNA was extracted using the Salting Out method. However, for the further molecular study, blood samples could only be collected from 25 individuals. PCR-RFLP was undertaken for 13 mutations, namely: Viangchan, Mediterranean, Mahidol, Canton, Gaohe, Coimbra, Andalus, Orissa, Union, Chatham, Kaiping, Vanua Lava and A- as described. These mutations were selected based on their high frequency among Asian populations. Assuming the African origin of the OA, the African A- mutation was selected for molecular mutational screening.

Table 1 shows the frequency of G6PD deficiency for each sub-tribe separately. The highest incidence was found among Lanoh (28%), while the lowest among Kensiu (0%). The mean G6PD enzyme activity ranged 5.7 IU/gHb in deficient individuals. Through the use of the PCR-RFLP method for detecting the 13 known G6PD mutations, the mutation types of four males were identified. Three of the males from Lanoh, two of who were siblings, carried the Viangchan mutation and one male from Jahai was found to carry the Coimbra mutation (Table 2).

By using DNA sequencing for all coding exons (12 exons) and flanking introns, 16 cases with the combined mutations of C1311T in exon 11 and IVS11 T93C were found. Three of the females were double heterozygotes for C1311T and IVS11 T93C; two others were heterozygotes for C1311T and homozygotes for IVS11 T93C; and lastly two females were homozygotes for both mutations. No mutation was found in the DNA of five deficient individuals.

Malaysia has implemented nationwide neonatal screening for G6PD deficiency since 1980; however, to date, no data relating to its incidence among Malaysian Orang Asli (OA) have come into existence. The reason for this is because OA children are predominantly delivered at home. However, the incident rates of G6PD deficiency among Malaysia males is cited as 5.3%. The current study has shown that the incidence rate of G6PD deficiency among Negrito is 11% for male and 7% for female. Nevertheless, due to the weakness of the fluorescent spot test to detect all the heterozygotes females, a higher frequency of G6PD deficiency is expected in female Negrito. While the frequency of G6PD deficiency in OA Negritos was higher than among other Malaysian races, this finding was expected as it was considered a likely result of the high epidemic of Malaria in the OA settlement area. Individuals with an inherited G6PD deficiency are at risk of developing anaemia if they are exposed to certain substances, such as anti-malaria drugs. The results from this study strongly suggest there is need to implement an appropriate screening method which would effectively detect G6PD-deficient OAs. This would be a pre-requisite to any successful health programme. Ainoon et al. have reported that 11 mutations are responsible for the G6PD deficiency in Malays and that 79% of Malay carry Viangchan, Mediterranean and Mahidol. However, an absence of these mutations in 87% of the study samples

<table>
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<tr>
<th>Tribe</th>
<th>% G6PD (deficient/total)</th>
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<tr>
<td>Jahai</td>
<td>3% (5/170)</td>
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<tr>
<td>Kintak</td>
<td>18% (11/63)</td>
</tr>
<tr>
<td>Lanoh</td>
<td>28% (18/68)</td>
</tr>
<tr>
<td>Kensiu</td>
<td>0% (0/118)</td>
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<tr>
<td>Bateq</td>
<td>15% (10/67)</td>
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<tr>
<td>Total</td>
<td>9% (44/487)</td>
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proves that the Negrito has been an isolated group for a period of time. On the other hand, the presence of Viangchan and Coimbra variants in a few of the OA samples could well be the result of interbreeding with other groups in the distant past. Unlike C1311T and IVS11 T93C, the majority of the known G6PD variants are single missense mutations. Individuals who carry this combination are deficient even though the G6PD protein was unchanged. A significant reduction in enzyme activity (and consequently its clinical implications) has been reported for this combined mutation. It has been assumed that there are further yet-to-be identified mutation(s) or SNP(s) causing this low enzyme activity. The presence of the combined mutation of C1311T and T93C in a large portion of the study samples is considered to be most likely the result of the genetic drift in this small isolated population over time. This result concurs with Hill et al. who analysed mitochondrial DNA control-region and coding-region markers in the OA and concluded that all OA groups have undergone high levels of genetic drift.

No A- variant has been observed in the OA which is in line with other reports which suggested that the A-mutation is 3840 to 11 760 years old and Negrito were the earliest inhabitants of the Malay Peninsula, having migrated from Africa over 50 000 years ago.

In summary, we conclude that the prevalence of G6PD is high in the Negrito and postulate that the molecular homogeneity of the G6PD mutation in this group may be a result of genetic drift. Further studies are required, however, to uncover specific mechanism(s) which correlate with the role of C1311T and IVS11 T93C in combination in the G6PD deficiency.

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References

Medically refractory neurosarcoidosis treated with infliximab

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Key words
sarcoidosis, infliximab, monoclonal antibody, tumour necrosis factor-alpha, anti-inflammatory agent.

Abstract
Neurosarcoidosis can worsen despite standard immunosuppressive therapy, a situation for which there is no established medical management. We present three cases of medically refractory neurosarcoidosis treated with infliximab. All three patients showed a clinical response to this treatment and side effects were limited. A summary of reported cases of neurosarcoidosis treated with infliximab is included. This case series supports a role for infliximab in the treatment of patients with medically refractory neurosarcoidosis.

Sarcoidosis is a multisystem disease characterized histologically by noncaseating granulomata. The aetiology of sarcoidosis is unknown but evidence suggests individuals with this disease have an underlying genetic susceptibility to an enhanced T helper cell-1 response.1 The central nervous system (CNS) is involved in less than 10% of patients with multisystem disease.2 CNS lesions due to neurosarcoidosis can occur both within the brain parenchyma and the meninges resulting in a variable clinical presentation.3 Sarcoidosis requires treatment when the disease is progressive or involves vital organs such as the heart or brain. Corticosteroids are first-line therapy and may be combined with immunosuppressants such as methotrexate, hydroxychloroquine, azathioprine or cyclophosphamide.3 The development of novel therapies for patients with neurosarcoidosis is needed as progression often occurs despite standard treatment.4 Infliximab is a chimeric monoclonal antibody that inactivates the pro-inflammatory cytokine, tumour necrosis factor alpha (TNF-α). It has a potential role in the treatment of medically refractory neurosarcoidosis based on animal data and a number of case reports. We report our experience of infliximab in three patients with neurosarcoidosis not responsive to standard immunosuppressant therapy.

Patients
Patient 1, a 36-year-old man, first presented at the age of 29 with sequential bilateral recurrent optic neuritis. He was treated with corticosteroids, azathioprine, cyclophosphamide, intravenous immunoglobulin, cyclosporin, methotrexate and plasma exchange, but despite this, over 4 years his vision deteriorated to no light perception.
Six months prior to starting infliximab he developed progressive right upper and bilateral lower limb upper motor neurone weakness. Magnetic resonance imaging (MRI) showed nodular, enhancing intraparenchymal cerebral lesions and extensive intramedullary spinal cord disease. A cerebrospinal fluid examination showed 12 × 10⁶/L white cells, protein 0.62 g/L, glucose 2.2 mmol/L and negative oligoclonal bands. A quantiferon-TB gold test was negative and full blood count, urea and electrolytes, liver and thyroid function tests, B12, folate, protein electrophoresis, antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA) were normal. A high-resolution CT of the chest was negative. A biopsy was not performed as the patient declined this procedure. No disease outside the CNS was identified. The clinical impression was that of isolated neurosarcoidosis. His condition deteriorated despite further treatment with corticosteroids and cyclophosphamide, such that he was paraplegic and in urinary retention. Infliximab treatment was initiated at an intravenous dose of 5 mg/kg at weeks zero, two and four. Infliximab was then continued monthly for 5 months and then the dose was reduced to 3 mg/kg administered every 6 weeks.

Patient 2 is a 29-year-old man with biopsy-proven neurosarcoidosis. He originally presented 6 years earlier with inflammatory brain disease thought to be acute disseminated encephalomyelitis. Over the next 2 years he had two intracerebral haemorrhages. Despite extensive investigation no cause was found for the haemorrhages and there was no evidence of disease outside the CNS. At the age of 27, he developed progressive, upper motor neurone, moderate to severe lower limb paralysis and urinary retention. MRI showed old zones of haemorrhage in the right temporal and left frontal lobes and spinal leptomeningeal disease. A sacral nerve root biopsy showed granulomatous inflammation with aggregates of epithelioid histiocytes and multinucleated giant cells. There was no evidence of tuberculosis or malignancy. This confirmed the diagnosis of neurosarcoidosis. His condition deteriorated, with progressive weakness of the lower limbs, despite steroid treatment. He was commenced on infliximab at a dose of 5 mg/kg at week zero, two and six. Subsequent doses were given every 8 weeks.

Patient 3, a 33-year-old woman, also has biopsy-proven neurosarcoidosis isolated to the CNS. She presented with a subacute onset of headache and vomiting. MRI showed intracerebral and extensive leptomeningeal disease of the brain and spine. A leptomeningeal biopsy showed non-necrotizing granulomata, composed of multinucleated and mononuclear histiocytes. Investigations for tuberculosis and malignancy were negative. This confirmed the diagnosis of neurosarcoidosis and she was treated with prednisone and methotrexate. Four years after her initial presentation, despite immunosuppression, she developed worsening headaches and imbalance and a neurological examination showed bilateral papilloedema and gait ataxia. An MRI brain scan showed persistent soft tissue deposits around the brainstem, in the cerebello-pontine angles, the cavernous sinuses and left occipital lobe. There was ventricular dilatation for which the patient underwent a ventriculoperitoneal shunt. Intravenous infliximab was started at a dose of 5 mg/kg at weeks zero, four and eight. Subsequent doses were given every 8 weeks.

Discussion

All three patients have responded well to treatment and continue receiving infliximab. Patient 1, 20 months after the initiation of infliximab, remains blind but is ambulant with a walking stick with only mild right leg weakness and has returned to full time employment. Repeat MRI 14 months after starting infliximab shows resolution of the previous areas of nodular enhancement with only a trace of residual T2 and FLAIR signal change in the brainstem. Patient 2 regained normal urinary function and the ability to walk short distances with a frame after the first two doses of infliximab; he has remained neurologically stable since then after 12 months of treatment. Patient 3 was asymptomatic with stable, minimal residual meningeal disease on MRI (Fig. 1) until at sixteen months she developed mild ataxia and diplopia. MRI showed a cystic lesion in the right middle cerebellar peduncle due to entrapment of the right lateral recess of the fourth ventricle. There was no increase in the size of the meningeal lesions and there were no new lesions when the MRI was compared with the imaging performed 6 months earlier.

Infliximab was tolerated well without infusion reactions, infection or hepatitis. Patient 1 had an episode of transient leukopenia which spontaneously resolved and the patient was able to continue infliximab therapy. Infliximab was safe and effective therapy for three patients who presented with neurosarcoidosis that progressed despite standard immunosuppressive therapy. The clinical and radiological outcomes add to a growing number of similar cases reported in the literature (Table 1). The responsiveness of neurosarcoidosis to infliximab strengthens the hypothesis that sarcoidosis is a Type 1 helper T cell mediated disease with increased TNF-α production.1

The three patients described in this case series developed severe progressive neurological dysfunction due to neurosarcoidosis refractory to standard medical
Table 1 Patients with neurosarcoidosis treated with infliximab.

<table>
<thead>
<tr>
<th>Case series</th>
<th>Patients</th>
<th>Neuroanatomic location</th>
<th>Biopsy proven</th>
<th>Previous therapies</th>
<th>Infliximab dose</th>
<th>Response</th>
<th>Adverse events</th>
<th>Follow-up (months)</th>
</tr>
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<tbody>
<tr>
<td>Pereira 2009</td>
<td>1</td>
<td>Optic nerve, intramedullary spinal cord</td>
<td>No</td>
<td>CS, MTX, CP, AZA, IVIg, PLEX, CYs</td>
<td>3 mg/kg</td>
<td>Yes</td>
<td>Transient leukopenia</td>
<td>20</td>
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<tr>
<td>Moravan and Segal 2009</td>
<td>2</td>
<td>Meningeal, intracerebral</td>
<td>Yes</td>
<td>CS</td>
<td>5 mg/kg</td>
<td>Yes</td>
<td>No</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Meningeal, intracerebral</td>
<td>Yes</td>
<td>CS, AZA, MTX</td>
<td>5 mg/kg MTX, P 5 mg</td>
<td>Yes</td>
<td>No</td>
<td>26</td>
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<tr>
<td></td>
<td>4</td>
<td>Meningeal, extra-CNS</td>
<td>Yes</td>
<td>CS, MMF</td>
<td>5 mg/kg MMF</td>
<td>Yes</td>
<td>No</td>
<td>24-39</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>Intramedullary spinal cord, pulmonary</td>
<td>Yes</td>
<td>CS</td>
<td>5 mg/kg MMF</td>
<td>Yes</td>
<td>No</td>
<td>24-39</td>
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<td></td>
<td>6</td>
<td>Intramedullary spinal cord, pulmonary</td>
<td>Yes</td>
<td>CS, Cy, EC, HC, MMF</td>
<td>5 mg/kg, MMF</td>
<td>Yes</td>
<td>No</td>
<td>24-39</td>
</tr>
<tr>
<td>Moravan and Segal 2009</td>
<td>7</td>
<td>Meningeal, intramedullary spinal cord</td>
<td>Yes</td>
<td>CS, MMF, VP shunt</td>
<td>5 mg/kg, MMF</td>
<td>Yes</td>
<td>Shingles</td>
<td>24-39</td>
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<td>8</td>
<td>Intramedullary spinal cord</td>
<td>Yes</td>
<td>CS, CP</td>
<td>5 mg/kg MTX</td>
<td>Yes</td>
<td>NR</td>
<td>13 inf</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>Meningeal</td>
<td>Yes</td>
<td>CS, CP</td>
<td>5 mg/kg MTX, P 5 mg</td>
<td>Yes</td>
<td>No</td>
<td>13 inf</td>
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<tr>
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<td>10</td>
<td>Optic nerve, pulmonary</td>
<td>Yes</td>
<td>CS, MTX, CP</td>
<td>NR, MTX P 10 mg</td>
<td>Yes</td>
<td>NR</td>
<td>16 inf</td>
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<tr>
<td>Moravan and Segal 2009</td>
<td>11</td>
<td>Intracerebral, optic nerve</td>
<td>Yes</td>
<td>CS, MTX, CP</td>
<td>3 mg/kg MMF</td>
<td>Yes</td>
<td>NR</td>
<td>8 inf</td>
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<td>12</td>
<td>Optic nerve, meningeal, pulmonary</td>
<td>Yes</td>
<td>CS, AZA, MMF</td>
<td>3–5 mg/kg P 20 mg</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
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<td>13</td>
<td>Intracerebral, meningeal, extra CNS</td>
<td>Yes</td>
<td>CS, AZA, CP, MTX</td>
<td>3–5 mg/kg</td>
<td>Yes</td>
<td>No</td>
<td>NR</td>
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<tr>
<td></td>
<td>14</td>
<td>Meningeal, pulmonary</td>
<td>Yes</td>
<td>CS, AZA, MTX</td>
<td>3–5 mg/kg P 10 mg</td>
<td>Yes</td>
<td>NR</td>
<td>NR</td>
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<td>Dolhun and Sirmak 2008</td>
<td>15</td>
<td>Meningeal, intramedullary spinal cord, pulmonary</td>
<td>Yes</td>
<td>CS, PLEX</td>
<td>5 mg/kg</td>
<td>Yes</td>
<td>NR</td>
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<td>Toth et al. 2007</td>
<td>16</td>
<td>Leptomeningeal</td>
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<td>CS</td>
<td>3 mg/kg</td>
<td>Yes</td>
<td>Yes†</td>
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<td>Kumar et al. 2007</td>
<td>17</td>
<td>Intracerebral</td>
<td>Yes</td>
<td>CS</td>
<td>NR</td>
<td>Yes</td>
<td>NR</td>
<td>5</td>
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<td>Salama et al. 2006</td>
<td>18</td>
<td>Optic nerve, meningeal, pulmonary</td>
<td>Yes</td>
<td>CS, AZA, MTX</td>
<td>5 mg/kg</td>
<td>Yes</td>
<td>NR</td>
<td>6</td>
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<td>Sollberger et al. 2004</td>
<td>19</td>
<td>Intracerebral, meningeal and pulmonary</td>
<td>Yes</td>
<td>CS, AZA</td>
<td>5 mg/kg</td>
<td>Yes</td>
<td>No</td>
<td>7</td>
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<tr>
<td>Carter 2004</td>
<td>20</td>
<td>Intracerebral, optic nerve</td>
<td>Yes</td>
<td>CS, MTX, CP</td>
<td>5 mg/kg MTX, P 5 mg</td>
<td>Yes</td>
<td>No</td>
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<td>Katz et al. 2003</td>
<td>21</td>
<td>Meningeal</td>
<td>Yes</td>
<td>CS, CP</td>
<td>3 mg/kg</td>
<td>Yes</td>
<td>Shingles</td>
<td>13</td>
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<td>Pettersen et al. 2002</td>
<td>22</td>
<td>Intracerebral, extra-CNS</td>
<td>Yes</td>
<td>CS, Rtx, CP MTX, CQ, HC</td>
<td>5 mg/kg</td>
<td>Yes</td>
<td>No</td>
<td>7.5</td>
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</table>

†Infusion reaction at 1-year deranged LFTs, low titre ANA (1:100). AZA, azathioprine; CNS, central nervous system; CQ, chloroquine; CP, cyclophosphamide; CS, corticosteroids; CYs, cyclosporine; EC, etanercept; HC, hydroxychloroquine; inf, infusions; IVIg, intravenous immunoglobulin; MMF, mycophenolate mofetil; MTX, methotrexate; NR, not reported; P, prednisone; PLEX, plasma exchange; Rtx, radiotherapy; SR, surgical resection; VP, ventriculoperitoneal.
therapy and infliximab was initiated. The natural history of neurosarcoidosis is uncertain. Although spontaneous remission is not uncommon in systemic sarcoidosis, involvement of the CNS has a less favourable prognosis and clinical experience suggests spontaneous remission is rare in patients with neurosarcoidosis. Therefore the improvement in the symptoms, signs and imaging in our three patients was more likely to be due to infliximab than a spontaneous improvement. Ultimately, however, a multicentre randomized study will be required for a more rigorous assessment of the efficacy of infliximab in these patients.

References
Blood transfusion: old blood, new blood or no blood
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Key words
anaemia, blood transfusion, immunomodulation, intensive care, morbidity.

Abstract
Vigorous blood transfusion has long been regarded as having an essential role in the management of acute gastrointestinal haemorrhage. Two new studies, one a nationwide audit of acute gastrointestinal haemorrhage in the UK and another, a complex physiological study of stored blood from the USA, offer new insights.

By doubting we come to enquiring and by enquiring we perceive the truth. (Abelard. C 1120)

Vigorous blood transfusion has long been regarded as having an essential role in the management of acute gastrointestinal haemorrhage (GIH), as well as similar bleeding episodes but there have been dissenting voices. Morton Grossman, one time President of the American Gastroenterological Association, in an extensive review of peptic ulcer more than 60 years ago pointed out ‘there are no crucial data proving that blood transfusion decreases the mortality of haemorrhage(sic) from peptic ulcer’.2

A Cochrane Report reviewed the effects of blood transfusion in 10 adequately controlled trials.3 Only one of these evaluated the effect of blood transfusion in GIH and it found no evidence of benefit.4 A recent Cochrane review concluded that the available studies ‘do not provide useful data regarding outcomes following red blood cell transfusion [in GIH]’ but ‘appear to exclude large survival benefit’.5

While this counter-intuitive view has gained little credence, there is a growing recognition of significant ill-effects of blood transfusion with the risk of transmission of infections such as HIV and hepatitis viruses, now largely controlled, and more recently of transfusion suggesting induced immunosuppression, increases the risk of infection.

Two new studies, one a nationwide audit of acute GIH in the UK and another, a complex physiological study of stored blood from the USA, offer new insights.

The UK study, the UK Comparative Audit of Upper Gastrointestinal Bleeding and the Use of Blood, the AUGIB Study6 involved the prospective collection of data from 217 hospitals supplying 6750 cases in May and June 2007. The mass of data collected led to a host of conclusions and recommendations. The overall mortality rate was 7.8%, a fall from the 14% of the previous 1993–1994 study and it was only 5.4% for new admissions. One blood transfusion was given to 44% of patients within 12 h of presentation. The Audit found that for all Rockall Scores the rate of re-bleeding was higher in the transfused group. Mortality was greater in those receiving earlier red blood cells (RBC) transfusion at all levels of the complete Rockall score (a measure of severity) with the increases being relatively greater in the less serious episodes.

It has been known for decades that the progressive loss of 2–3 DPG from stored red blood cells impairs O2 release on transfusion as part of the ‘storage lesion’ but this explanation is inadequate. However, considerable clarity has been given by more recent analyses of changes in stored red blood cells related to oxygen uptake and release.7,8

It now seems that in the systemic micro-circulation, blood flow is regulated by vasoconstriction and vasodilation to ensure that blood flow matches oxygen demand. The red blood cells can synthesize nitric oxide (NO) which is then stored on haemoglobin or released by red cells in response to the ambient partial pressure of oxygen.9
hypothesis vasodilatation associated with NO content \( (P < 0.0005) \), replacement of NO to bank blood restored its vasodilatatory activity and such blood increased coronary blood flow in dogs over that with NO depleted blood, a difference accentuated by hypoxaemia.7 However, these changes have been challenged.10

Overall the evidence suggests that stored blood impairs O2 supply by four mechanisms: impaired oxygen release due to reduced 2-3 DPG levels, NO reduction impairing red cell capillary passage and finally, NO deficient red blood cells scavenging oxygen from the patient’s normal red blood cells.

These changes do not explain the considerable evidence for blood transfusion as an independent predictor of mortality in Intensive Care Unit (ICU) admissions and length of stay (LOS). In a study of 15534 patients admitted to a level 3 trauma unit after controlling for age, gender, race, Glasgow Coma Score and Injury Severity Score logistic regression analysis showed that blood transfusion was highly significantly associated with mortality (odds ratio (OR) = 2.83) admission to ICU (OR = 3.27) ICU and hospital LOS.11

A recent meta-analysis of the 45 adequate studies involving 272 596 patients has supported these conclusions.12 In 42 of the 45 studies the risks outweighed the benefits; in only one study, of elderly anaemic patients with myocardial infarction did the benefits outweigh the risks. Overall, red cell transfusion was associated with death (pooled OR 1.7; 95% CI 1.4–1.9) and nosocomial infection (OR 1.8; 95% CI 1.5–2.2).

There is evidence that an immunomodulatory effect of allogeneic blood transfusion may have an important role here although the evidence is conflicting.13,14 The clinician faced with a bleeding or anaemic patient is now presented with a dilemma: to transfuse blood with its problems or to withhold it and risk, particularly in the elderly, cardiovascular and other complications. One conclusion is clear: to transfuse blood requires a serious consideration of the risks and benefits. For example, in 2001 over one third of blood transfusions in New South Wales were inappropriate.15 Now even this figure appears to be an underestimation.

With the above outline of the physiological and immunological consequences of blood transfusion, one can only echo the call of the UK Audit Report16 that a large trial of restrictive and liberal transfusion policies is no longer required.

References

A 42-year-old healthy man complained of bilateral reduced visual acuity for a week. Because of chronic back pain, the patient received a corticosteroid injection in the epidural space 5 days before the ocular symptoms appeared. Visual acuity was 20/30 bilaterally. Fundus examination showed serous detachment at the posterior pole in the right (Fig. 1a) and in the left (Fig. 1b) eye. Ocular coherence tomography (OCT) examination of the right eye showed a large detachment of the neurosensory retina and a pigment epithelial detachment (Fig. 1c). Gradually, over 2 months, the serous detachment resolved (Fig. 1d), and visual acuity returned to 20/20.

Central serous chorioretinopathy (CSCR) is a disorder characterized by the accumulation of subretinal fluid at the posterior pole of the fundus resulting in diminished visual acuity and distortion of visual perception. Although most reported cases are idiopathic, CSCR is a rare adverse effect of corticosteroids.1–3 Any patient with hypercortisolaemia or on steroid therapy, who reports decreased visual acuity or distorted visual perception, should have a prompt ophthalmologic examination to exclude CSCR because continued steroid therapy may cause irreversible visual damage.

References

Acneiform eruption following molecular targeted chemotherapy

A 63-year-old man with stage IV metastatic colon adenocarcinoma presented with a papulopustular eruption that had persisted for 1 month. The tumour was diagnosed 2 years before: he had undergone a left hemicolectomy with lymph node dissection and partial hepatectomy, and then had been treated with 5-fluorouracil in combination with oxaliplatin and irinotecan. Due to a refractory course, combination therapy was started with irinotecan and cetuximab, a monoclonal antibody against the epidermal growth factor receptor (EGFR).

On physical examination there were multiple erythematous follicular papules, pustules and haemorrhagic crusts on the seborrhic areas of the face, chest and back, with no comedones. Intense pruritus and burning were also present. Histological examination of a biopsy specimen revealed folliculitis with perifollicular dense inflammatory infiltrate and partial follicle destruction (Fig. 1).

Acneiform eruption in the course of therapy with anti-EGFR monoclonal antibodies is a well-known phenomenon in oncologic patients, EGFR being constitutively expressed in many normal epithelial tissues, including the skin and the hair follicle. Rash generally first appears, within the first 1 to 3 weeks of treatment, on the face, particularly around the nose or on the cheeks, and trunk, but may extend to the upper and lower extremities. Cetuximab is relatively well tolerated, with skin toxicity representing the major side-effect. About 85% of treated patients develop an acneiform eruption of variable extent, the severity of which appears to be dose-dependent, being increasingly considered an indirect marker of relevant in vivo EGFR targeting and a predictor of therapeutic response.

The treatment of this rash has not yet been well standardized. Our patient was started on 1% clindamycin and 4% benzoyl peroxide gel applied nightly and 4% colloidal sulphur galenic cream in the morning. After 3 weeks, he had a significant improvement in lesion count, with flattening of many of those remaining. His rash continued to improve over the next several months.

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LETTERS TO THE EDITOR

Clinical-scientific notes

Spontaneous adrenal haemorrhage in pregnancy

A 24-year-old primigravida presented at 24-week gestation with acute right upper quadrant abdominal pain radiating to the right flank, worsening on inspiration. She was haemodynamically stable, afebrile, and not dyspnoeic. Examination revealed diffuse right upper quadrant tenderness without peritonism. She had a normal haemoglobin level (134 g/L) and platelet count, but leukocytosis (16.2 × 10⁹/L) with predominant neutrophilia. Her liver function, serum lipase and urine culture were normal. Abdominal ultrasound demonstrated a viable foetus and no obvious cause for her symptoms. Computerized tomographic (CT) pulmonary angiogram excluded pulmonary embolism but showed a 55 × 35 mm low density right adrenal mass. Magnetic resonance imaging (MRI) (Fig. 1) demonstrated an isointense T1-weighted and hypointense T2-weighted right adrenal lesion consistent with acute adrenal haemorrhage (AH). There was no central enhancement on gadolinium sequence to suggest an underlying adrenal neoplasm. Furthermore, there was a right adrenal vein thrombus extending into the inferior vena cava. There was no clinical and biochemical evidence of adrenal insufficiency (morning serum cortisol: 670 nmol/L), phaeochromocytoma, thrombophilia or coagulopathy. We postulated that the right adrenal vein thrombosis (AVT) was the underlying cause of spontaneous adrenal haemorrhage (SAH) in pregnancy. The patient was managed conservatively with therapeutic anticoagulation, bed rest, and supportive care. At 39-week gestation, she delivered a healthy male baby and she has remained well. Post-partum MRI showed complete resolution of the adrenal haemorrhage and venous thrombosis.

This case highlights an unusual cause of abdominal pain in pregnancy. Although uncommon, AH is potentially catastrophic with adrenal crisis ensuing if both glands are affected. Even though the diagnosis could be easily missed due to its variable clinical presentations, advances in imaging coupled with raised clinical awareness have significantly enhanced the detection of AH in recent times. Important risk factors for AH include the presence of antiphospholipid antibodies, heparin-induced thrombocytopenia, postoperative period, anticoagulation and trauma. Underlying adrenal tumours such as adenoma, phaeochromocytoma or carcinoma need to be excluded. The adrenal gland is inherently susceptible to haemorrhage due to its predisposition to adrenal medullary venous congestion and thrombosis during stress or sepsis. Pregnancy is associated with adrenal cortex hyperplasia and hypertrophy, which may predispose to venous congestion and haemorrhage. SAH in pregnancy is rare and previous reported cases have been associated with pre-eclampsia, adrenal pseudocyst and congenital aneurysm of supra-renal arteries. Adrenal vein thrombosis can initiate SAH but to our knowledge there is no previous report of this in pregnancy.

Current practice favours a conservative approach in both traumatic and non-traumatic AH which includes

References
supportive care, serial haemoglobin measurements and blood transfusion as needed.1 Such approach has been reported in a recent case of SAH in pregnancy with success.4 However, haemodynamically unstable patients with massive haemorrhage might warrant emergency adrenalectomy and preterm delivery.4 On the contrary, when AH is due to AVT, anticoagulation is warranted. Assessment of adrenal function and appropriate glucocorticoid and mineralocorticoid replacement is crucial, especially in bilateral AH if ≥90% of adrenal cortex is destroyed.3 Full recovery of adrenal function with discontinuation of steroid replacement might be expected in most cases.6 Post-partum imaging and evaluation of adrenal function are essential to ensure resolution of haematoma and exclude underlying tumour.3

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References

Voriconazole toxicity related to polymorphisms in CYP2C19

A 43-year-old Indian woman was admitted for investigation of visual blurring in her right eye. She had a 17-year history of relapsing Wegener’s granulomatosis, which had resulted in complete loss of vision of her left eye and bilateral hearing deficits. Six months prior to her presentation, she had been recommenced on intravenous cyclophosphamide for relapsed pulmonary disease.

The patient suffered multiple iatrogenic complications, including avascular necrosis of the femoral head, infection of her prosthetic hip joint with *Staphylococcus aureus* and secondary hypogammaglobulinaemia, for which she received immunoglobulin replacement. She was treated for hypertension, glaucoma and reflux disease. Her medications included prednisone (35 mg/day), metoprolol, cotrimoxazole, moxifloxacin, esomeprazole, oxycodone, morphine and lantanoprost.

Fundoscopy revealed a right juxta-foveal lesion suspicious for fungal retinitis; the differential diagnosis included toxoplasmosis and cytomegalovirus (CMV). Several vitreal biopsies, followed by a vitrectomy, were performed.

In view of her single functioning eye and immunocompromised state she was treated empirically for all differentials while microbiological tests were pending. Intraocular injections of ganciclovir, foscarnet and amphotericin were undertaken. She was commenced on intravenous ganciclovir, oral sulphadiazine, pyremethamine and voriconazole at the standard oral dose of 400 mg bd on Day 1 followed by 200 mg bd thereafter.

Seven days after the commencement of voriconazole, the patient reported frequent visual hallucinations. Two days later, her liver function tests became abnormal (peak ALP 283 U/L, GGT 886 U/L, ALT 409 U/L, AST 347 U/L). Her CD4 T cell count was 239 cells/μL. Voriconazole toxicity was suspected and a serum trough concentration measured 7.8 mg/L (therapeutic range 1–5 mg/L, target 1.5 mg/L). Genotyping of cytochrome P450 P450 (CYP) 2C19 confirmed the patient was heterozygous for the 681G>A polymorphism (CYP2C19*2 allele) (Fig. 1), which would be expected to confer an intermediate-metaboliser phenotype. DNA testing of the vitreal samples for CMV, toxoplasmosis, mycobacterium, fungi, varicella zoster and herpes simplex were all negative.

Voriconazole doses were withheld, resulting in resolution of the hallucinations and normalization of the liver function tests. Reintroduction of voriconazole at a lower dose (100 mg daily) with monitoring of drug levels was uncomplicated.

There is increasing recognition of the clinical importance of genetic polymorphisms that alter either the efficacy or toxicity of therapeutic agents. This is particularly so in patients with severe illnesses where optimal efficacy is essential, and in those with comorbidities that increase the detrimental effects of unpredicted toxicity, as highlighted in this report.

Voriconazole was chosen in a circumstance of threat to a single eye, and subsequent outcome established it as the likely effective agent in saving the patient’s sight. It acts principally by the inhibition of fungal cytochrome P450 14-α-demethylase, required for ergosterol synthesis. Voriconazole is a substrate for, and an inhibitor of, CYP2C9, CYP2C19 and CYP3A4, although CYP2C19 is the predominant enzyme responsible for its metabolism.

Modelling suggests that CYP2C19 polymorphisms alone account for almost half of the variance seen in the clearance of an oral dose of voriconazole.2 Furthermore, voriconazole exhibits non-linear pharmacokinetics, likely due to the saturation of the hepatic metabolism of the drug.3 CYP2C19 expression is polymorphic, and loss-of-function polymorphisms are very common in the South Indian population. One study of 58 individuals in this ethnic group detected the heterozygous 681G>A polymorphism in 32 (57%), with 6 (10%) being homozygotes.4 Studies in other racial groups suggest the prevalence of CYP2C19 polymorphisms are lower, but still common.4 The high allele frequency of the loss-of-function polymorphism suggests an unexplained function of CYP2C19 for which such a variant may confer a selective advantage. Polymorphisms that result in an ultra-rapid metaboliser phenotype, such as 2C19 991A>G (CYP2C19*17), are much less common.

Of her other medications, esomeprazole, the S-isomer of omeprazole, inhibits CYP2C19. However, one study has shown that omeprazole has no clinically relevant effect on voriconazole exposure,3 although there is no
esomeprazole-specific data. It is therefore unlikely that interference from other drugs contributed significantly to the slow metabolism of voriconazole.

While the problems reported here could be expected, this is to our knowledge, the first reported clinical occurrence. It demonstrates the need for caution when commencing voriconazole in patients from populations with a high prevalence of CPY2C19 polymorphisms and the importance of therapeutic drug monitoring. It also indicates the availability of genetic testing (albeit in a research environment) at an acceptable cost and the need for funding agencies to adapt to important advances in pharmacogenetic testing.

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References

General correspondence

Approach to those placing others at risk of HIV infection in NSW

With regard to the article by Tong et al.,1 we would like to clarify the public health approach to the management of people with HIV who risk infecting others in NSW. In line with nationally agreed principles, a graduated approach to achieving behaviour change is employed commencing with counselling, and being escalated if necessary, to a Public Health Order as a last resort.

In the article, reference was made to the NSW Panel for the Management of People with HIV who Risk Infecting Others recommending against a Public Health Order. This was not the case. As with most situations in which guidance is sought, the case was managed through advice provided by the Chair of the Panel to the treating clinicians. The Chair did discuss with the treating clinicians the context in which public health orders are appropriate. This is consistent with NSW policy and national guidelines. The advice provided to the clinicians was subsequently noted by the Panel. At no stage did the Panel consider or discuss a Public Health Order in relation to this case.

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Reference
Lung transplantation-associated leukoencephalopathy, not necessarily the posterior reversible encephalopathy syndrome?

Tsang and colleagues described four cases of posterior reversible encephalopathy syndrome (PRES) after lung transplantation. I agree that PRES should be considered, since leukoencephalopathy, hypertension and reversible clinical manifestations were found in these cases. However, other differential diagnoses were not completely excluded in this case series.

PRES (also termed reversible posterior leukoencephalopathy syndrome) is a clinico-radiological diagnosis. The pathogenesis of PRES is related to autoregulation failure of cerebral blood circulation and endothelial dysfunction. Reversible vasogenic oedema, evidenced by increased signal intensity in apparent diffusion coefficient (ADC) maps elaborated from diffusion-weighted imaging, preferably involving posterior white matter, and reversible clinical manifestations like headache and seizures contribute to the diagnosis of typical PRES.

ADC maps can distinguish vasogenic from cytotoxic oedema in patients with PRES. In this case series, however, the authors failed to show evidence from ADC maps to support vasogenic oedema. Moreover, the levels of tacrolimus were supratherapeutic in case 2 and case 4 when clinical symptoms occurred. In this context, the clinical and radiological findings reported by the authors may result from neurotoxicity caused by calcineurin inhibitor therapy, at least in some cases, even if not in all. Additionally, postepileptic vasospasm and cytotoxic oedema may also appear as hyperintensity in the fluid-attenuated inversion recovery sequences.

References

Reply

We appreciate the letter by Zhang highlighting the differential diagnosis of reversible posterior leukoencephalopathy syndrome (RPLS, also known as posterior reversible encephalopathy syndrome (PRES)) and the role of apparent diffusion coefficient (ADC) maps in narrowing the differential radiologically.

Important differentials of RPLS include generalized epilepsy, progressive multifocal leukoencephalopathy, cerebral infections, cerebral venous thrombosis, demyelinating disorders, hyperammonaemia syndrome, and stroke. We are confident that these differentials were excluded given the time course of symptom resolution with blood pressure control and switch of immunosuppression, without the use of antiepileptic medications or...
antimicrobial agents. In addition, the magnetic resonance imaging (MRI) findings were not consistent with the aforementioned possibilities.

Zhang commented that our findings could be a result of calcineurin inhibitor (CNI) neurotoxicity alone. The distinction in the medical literature between RPLS and neurotoxicity, a traditionally all-encompassing term, is rather subtle and has been used interchangeably. Calcineurin inhibitor neurotoxicity is thought to occur in approximately 10–28% of patients and commonly manifests as tremors, peripheral neuropathy, and acute confusional state, but less commonly as leukoencephalopathy, status epilepticus and major speech or language abnormalities.2,3 Given the clinical and radiologic features of our case series, we believe our patients fit Hinchey’s original definition of RPLS4 better than neurotoxicity per se. As mentioned in our discussion, CNI-induced RPLS can occur even when drug levels are not supratherapeutic.

Zhang raises the exciting prospects of using ADC maps to distinguish vasogenic from cytotoxic oedema in the radiologic diagnosis of RPLS. It has been hypothesized that a breakdown in cerebral autoregulation results in leakage of fluid into the interstitium, which is detected as vasogenic oedema on MRI4. High ADC values in areas of
abnormal T2 signal and matching areas of normal or slight decreased signal intensity with diffusion-weighted imaging (DWI) have been shown to correspond to areas of vasogenic oedema. Occasionally patients with RPLS have areas of high DWI signal intensity with normal or slightly elevated ADC values, a phenomenon known as pseudonormalization. This finding has been associated with a worse prognosis. Only the two most recent cases in our series (cases 3 and 4) had ADC maps. Case 4 was consistent with vasogenic oedema with high ADC values corresponding to areas of high T2 abnormalities (see Figs 1–3), and case 3 was consistent with pseudonormalization. Although we agree with Zhang that ADC mapping is a useful adjunct in the diagnosis of RPLS, we believe it should not be used as a primary diagnostic tool in the detection of RPLS and that pseudonormalization in RPLS cases should also be considered. Of greater interest is the growing evidence of decreased cerebral blood flow (CBF) and cerebral blood volume (CBV) in MRI studies of RPLS patients. We are currently exploring the utility of DWI, ADC maps, CBF and CBV values in all our suspected RPLS cases.

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References

Letters to the Editor

Difficult physician–patient encounters: when doctors make things worse. A case series

The skills of a practising physician are many and varied. Increasingly non-technical, professional skills are being indentified and education aimed at such skills has become part of the core training in our college and others. The Professional Qualities Curriculum includes such skills. They include being a patient advocate, being a sympathetic and honest communicator and working in teams with respect for other providers of care and support of colleagues. The paper in the Internal Medicine Journal by Breen and Greenberg1 aiming to raise awareness of difficult physician-patient encounters contributes to such an educational effort. It does not, however, address the role of physicians in exacerbating such difficulties when commenting on the care given by others.

Systems have been developed that enable patients and their representatives to complain about the care they have received from health providers. In New Zealand the Health and Disability Commission (HDC) is the independent statutory body charged with assessing such complaints.

I wish to draw the attention of physicians to the need to be cautious about how they communicate with their patients, especially about care provided by others. I will use three illustrative case reports where comments by doctors have been instrumental in provoking complaints to the HDC. Certain details are obscured to © 2011 The Authors
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ensure privacy. Neither the patients nor the doctors concerned have consented to their inclusion in this case series.

**Case 1**

A homeless woman in her 40s is admitted to with cryptococcal meningitis on a background of heavy alcohol intake. She was reviewed by psychiatry when the acute illness was over and diagnosed with an ‘alcoholic amnestic disorder’. After three and a half months, she is discharged to a residential care facility. Fifteen months later she is admitted to a different psychiatric unit. The written discharge summary following that admission includes the comment that she ‘had been inappropriately placed in a rest home due to the belief that she suffered from dementia . . .’. A complaint to the HDC is made 5 weeks later.

**Case 2**

A 70-year-old man has a radical nephrectomy and splenectomy for a renal cancer. The surgery goes well, he is discharged but readmitted after 2 days with fever, hallucinations and confusion. He is septic, shocked and hypoxic. A subphrenic abscess is diagnosed and drained. He responds to antibiotics and is discharged after 13 days. Three years later he has a computed tomography head scan performed ‘for another reason’ in another part of the country. This shows a cerebral infarct in the right parietal area. The neurologist has ‘no hesitation’ in stating that this stroke had ‘almost certainly occurred . . . around the time of his complications following nephrectomy’. A complaint to the HDC is made asking ‘Why wasn’t [the] stroke picked up at Auckland Hospital?’.

**Case 3**

A 74-year-old man is admitted with chest pain. He is assessed and undergoes an exercise test which is normal and he is discharged. His general practitioner refers him to a private cardiologist who repeats the exercise test with the same result. The cardiologist then proceeds to angiography and places two stents in the coronary arteries. The patient, on asking why the tests at Auckland Hospital were normal, is told by the cardiologist that it was because ‘my machine is much better’. A complaint is made to the Minister of Health who forwards it to the HDC.

These three cases illustrate the importance of careful communication with patients and families by doctors when commenting on care give by other health care providers. While it is essential that we are honest with our patients, it is very important that we do not directly contradict other professionals (case 1), ascribe current diagnoses to events in the past without good grounds (case 2) or disparage the diagnostic tests in other settings especially when one’s own give the same results (case 3). Such behaviours are unprofessional and lead to increased anxiety and a diminished level of care. They also contribute to complaints and make subsequent management and communication with patients and families difficult.

I acknowledge a conflict of interest in case 2 as I was the physician responsible for the care of the patient when admitted with septic shock.

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**Reference**

vitamin D regulates immune function. Indeed, all cells of the immune system that have been evaluated express the vitamin D receptor (VDR). In particular, poor vitamin D status has been linked to the development of a number of different type-one (Th1) mediated autoimmune diseases, and mounting evidence suggests that genetically predisposed individuals that either do not maintain adequate vitamin D levels or perhaps have polymorphisms in genes important for vitamin D metabolism, catabolism or function have an increased likelihood of developing IBD.

Vitamin D deficiency and VDR deficiency have been shown to exacerbate chronic IBD in interleukin-10 knockout mice. Furthermore, treatment of interleukin-10 knockout mice with 1,25(OH)2 vitamin D3, the active form of vitamin D, resulted in the suppression of IBD symptoms. Recently, it has been found that VDR agonists possess the capacity to inhibit production of tumour necrosis factor-α and interferon-γ by lamina propria T cells from IBD patients, thus confirming an important role of the vitamin D endocrine system in the pathogenesis of IBD.

Therefore, we suggest that all patients with IBD should reach an adequate vitamin D status, before considering other biological therapies, which carry a definite safety risk.

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References
