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PROGRESS REPORT

Project / Program Title		The effect of regularly dosed paracetamol on renal function in Plasmodium knowlesi malaria
Name		Dr Bridget Barber
Award Received		2018 AstraZenica Research Establishment Fellowship in Medical Research
Report Date		23 June 2018
Chief Investigator / Supervisor		Supervisor: Nicholas Anstey
Administering Institution		Menzies School of Health Research
Funding Period	Start Date:	1 March 2018
	Finish Date:	28 Feb 2019

PROJECT SUMMARY

Acute kidney injury (AKI) is a common complication of malaria from any species. AKI independently predicts death, and in survivors can have long-term consequences including increased risk of chronic kidney disease and cardiovascular disease. In falciparum malaria (responsible for most malaria deaths worldwide), breakdown of red blood cells contributes to AKI via oxidative damage. Preliminary data has shown that this may be inhibited by the widely available drug paracetamol. In knowlesi malaria, the most common type of malaria in Malaysia, AKI is at least as common as in falciparum malaria, and hemolysis (breakdown of red blood cells) is more severe. We therefore conducted a randomised trial to assess whether paracetamol can reduce AKI in knowlesi malaria. Malaysian adults and children (>5y) hospitalised with knowlesi malaria were randomly assigned to receive either regularly-dosed paracetamol, or no paracetamol, together with standard anti-malarial treatment. The primary endpoint was the relative change in creatinine at 72 hours, in those with, and without, significant haemolysis. A total of 396 patients were enrolled, and data analysis is currently underway. Paracetamol is cheap and widely available. If this study demonstrates that regular dosing prevents or reduces kidney damage in knowlesi malaria, then this intervention could be readily implemented and will have substantial short and long-term benefits.

PROJECT AIMS / OBJECTIVES

Aims

1. To determine pathophysiological correlates of AKI in adults and children with severe and non-severe knowlesi malaria. We will relate longitudinal measurements of AKI (serum

creatinine, urinary neutrophil gelatinase-associated lipocalcin [NGAL], urine albumin:creatinine ratio) to parasite biomass and markers of haemolysis, oxidative damage and endothelial activation.

2. To determine if regularly-dosed paracetamol, compared to no paracetamol, will reduce AKI in adults and children (>5 years) with severe and non-severe knowlesi malaria, and if this hypothesised renoprotective effect is dependent on the degree of intravascular haemolysis. We have conducted an open-label RCT to assess the ability of paracetamol to reduce renal dysfunction caused by CFHb-induced oxidative damage. Patients were randomised into two groups to receive either regularly-dosed oral paracetamol or no paracetamol. Both groups received standard artemisinin-based antimalarial treatment.

SIGNIFICANCE AND OUTCOMES

Data analysis for this study is currently underway. If this study demonstrates that paracetamol protects against acute kidney injury in knowlesi malaria, this will provide evidence for policy change to recommend regular paracetamol for all patients with knowlesi malaria and, by confirming the effect and mechanism seen in the pilot study in adult falciparum malaria (K. Plewes et al, Clin Infect Dis 2018), for adults hospitalised with severe and moderately severe falciparum malaria. If paracetamol is efficacious in these settings, it would not only lead to reduced mortality associated with acute kidney injury, but decreased long-term risk of chronic kidney disease (CKD) and cardiovascular disease

PUBLICATIONS / PRESENTATIONS

Data analysis for this study is currently underway. The protocol for the study has been recently published:

Cooper DJ, Plewes K, Grigg MJ, Rajahram GS, Piera KA, Williams T, Chatfield MD, Yeo TW, Dondorp AM, Anstey NM & Barber BE. A study protocol for a randomised controlled trial assessing the effect of regularly dosed paracetamol versus no paracetamol on renal function in Plasmodium knowlesi malaria (PACKNOW). Trials 2018; 19:250