PROJECT TITLE: Pharmacokinetic investigations of tafenoquine

FIELD OF RESEARCH CODE: 1115; 1103

PROJECT SYNOPSIS:

Background: Malaria remains a significant global disease burden, with an estimated 228 million cases of malaria worldwide in 2018. Each year over 4 million Australians travel to malaria endemic areas, hence, malaria chemoprophylaxis plays an important role in population health. Most of the currently available antimalarial drugs require daily dosing or have significant side effects, both of which raise issues with patient compliance. The approval of tafenoquine by the Therapeutic Goods Administration in Australia in September 2018 was timely, with a recommended dosing regimen of 3 daily doses prior to travel, and weekly dosing whilst in the malarious region. However, despite excellent prophylactic efficacy being reported from >1000 participants over a number of clinical trials, the majority of the participants were healthy adults of normal body mass index. Of those who were overweight, participant pharmacokinetics suggested that dose modification would be required to ensure prophylactic efficacy. Based on these data, it is imperative to ascertain if obesity, or co-administered
antimalarials, significantly influences tafenoquine pharmacokinetics, requiring higher drug doses to provide effective antimalarial prophylaxis for travellers.

Rationale: This research project aims to:

1. Develop, optimise and validate a high-performance liquid chromatography (HPLC) assay for the measurement of tafenoquine, and its active metabolites, in human plasma.
2. Develop, optimise and validate a HPLC assay for the measurement of a novel antimalarial partner drug ("AS1", not for publication), in human plasma.
3. Investigate the chemical compatibility of tafenoquine, naphthoquinone and AS1.

1. Strategic Project Summary

2. Conduct pharmacokinetic studies of tafenoquine and AS1 in healthy rats.
3. Evaluate the pharmacokinetics of tafenoquine in healthy adults across a range of body mass indexes (BMI)
4. Develop a population pharmacokinetic model to predict required dose modifications for tafenoquine prophylaxis based on patient weight.

Study design: This research program will incorporate both laboratory and clinical components.

a) Tafenoquine and AS1 HPLC assays: Robust assay methods for the determination of tafenoquine, AS1 and their active metabolites using HPLC will be developed, optimised and validated by the student, based on literature and validated methods for the chemically similar compounds already assayed in our research laboratories. Thermal and storage stability testing will also be conducted prior to evaluation of research samples.

b) Compatibility studies: To investigate the chemical compatibility of potential co-formulations, each experiment will comprise of two components: (i) tafenoquine suspension alone and combined with either ‘test drug’ solution/suspension (naphthoquinone or AS1), and (ii) tafenoquine powder (alone, and combined with either ‘test drug’) formulated in standard compressed tablets. Compatibility samples will be stored at 4oC, 22oC and 35oC and assayed periodically over a 12 month period using our validated HPLC method to determine stability and compatibility.

c) Pharmacokinetic study of tafenoquine in healthy adults: Healthy adults (n=45) will be recruited from the community and undergo an initial clinical assessment to confirm their eligibility, health status and BMI for group allocation (Group 1 (BMI 18.5 to 25), Group 2 (BMI 25 to <30) or Group 3 (BMI >30); n=15 per group). Participants will undergo pre-dose (baseline) testing including collection of blood for pathology and pharmacokinetic analysis. A single oral treatment dose will be administered to each participant as directly observed treatment with food. Venous blood samples (2mL) will collected for drug analysis at 4, 8, 24 and 72 hours, and Days 7, 14, 28 and 56, post drug administration. Concentrations of tafenoquine will be assayed from each clinical sample using previously validated HPLC methods. *Note: All clinical aspects of this study will be conducted by our study nurse, or physician.

d) Pharmacokinetic modelling: Supported by our research group pharmacometrician, the student will develop a population pharmacokinetic model for tafenoquine using non-
linear mixed effects modelling. As with our previous studies, NONMEM (v 7.2.0, ICON Development Solutions, Ellicott City, MD, US) with an Intel Visual FORTRAN 10.0 compiler will be used for all modelling procedures. The influence of covariates will be assessed in the model and a bootstrap procedure will be used to evaluate model parameter precision. Once developed, the model will be used to simulate predicted optimal dosing regimens for patients of varying body weight.

Research team: Participation in this research program will see you join an established, productive research team with extensive experience and an international standing in antimalarial pharmacology research. The team comprises a core group of successful researchers (both clinical and laboratory focus) who have worked together (nationally and internationally) for >10 years on malaria treatment trials and anti-infective pharmacology (ERA 4). The team maintains a high standard of publication (97% Q1 journals) and grant success (group currently holds three NHMRC funded project grants and two NHMRC Fellows).

FEASIBILITY AND RESOURCING – DESCRIPTION OF THE SUPPORT THIS PROJECT WILL RECEIVE:

All laboratory components will be undertaken in our pharmacology laboratories within the School of Pharmacy and Biomedical Sciences, which has adequate facilities, equipment, technical support and resources for all proposed assays. Clinical aspects of the study will be conducted at the Harry Perkins Medical Research Institute, South where our research group clinical team is based and Dr Moore holds an adjunct appointment with the Medical School, UWA. Our research group pharmacometrician will provide supervision and mentorship for all population pharmacokinetic modelling related activities. The proposed research aligns with Tier 1 funding applications submitted by Dr Moore and colleagues in 2020.

THE SIGNIFICANCE OF THE PROJECT/ PROGRAM FOR THE ENROLLING SCHOOL OR INSTITUTION:

Current tafenoquine dosing recommendations, a standardised 200mg dose for all adults, is likely resulting in reduced antimalarial prophylactic efficacy in adults who are overweight or obese. It is therefore imperative to ascertain whether higher doses of tafenoquine are required to ensure sufficient protection from malaria whilst travelling. Undertaking this project will not only contribute novel and essential pharmacokinetic data for tafenoquine and the novel therapeutic AS1, but also strengthen relationships with Industry and collaborative partners. The subject aligns with the Research Group’s strategic focus, and will contribute significant data to strengthen future NHMRC funding applications.

Students must express interest in this scholarship opportunity by emailing the Project Lead listed below. Please provide a copy of your current curriculum vitae and detail your suitability to be involved in this strategic project.

PROJECT LEAD CONTACT:

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