LETTER TO THE EDITORS

Tacrolimus pharmacokinetics after kidney transplantation – Influence of changes in haematocrit and steroid dose

Christine E. Staatz,[1] Elisabet Størset,[2] Troels K. Bergmann,[3] Stefanie Hennig,[1] Nick Holford[4]

1. School of Pharmacy, University of Queensland, Brisbane, Australia; 2. Department of Transplant Medicine, Oslo University Hospital Rikshospitalet, Oslo, Norway; 3. Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark; 4. Department of Pharmacology and Clinical Pharmacology, University of Auckland, Auckland, New Zealand.

Correspondence

Dr Christine Staatz, PhD

School of Pharmacy, University of Queensland, Brisbane, Australia 4072.

Tel: +61 3365 1974. Fax: +61 3346 1999. E-mail: c.staatz@uq.edu.au

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We read with interest the accepted paper by de Jonge and colleagues [1] examining possible mechanisms behind the commonly observed phenomenon of a gradual decrease in tacrolimus dose-requirements and increase in dose-corrected whole blood exposure following kidney transplantation. We were pleased to see that they have added confirmation of our explanation of how haematocrit and steroid dose can account for observed changes in tacrolimus whole blood clearance [2] but were surprised they had not mentioned this in their publication.

Results reported by de Jonge et al. of 65 patients are generally in agreement with our findings from building a theory-based population pharmacokinetic model of tacrolimus in 242 adult kidney transplant recipients [2]. In our study we found that a model that accounted for differences in tacrolimus whole blood concentrations due to haematocrit variation, via estimation of tacrolimus plasma concentration, was superior to empirical use of haematocrit as a covariate for whole blood clearance. De Jonge et al. have not clearly described how they used haematocrit but it seems they may have used an empirical approach. The empirical approach leads to misspecification of the pharmacokinetic model because the influence of haematocrit is only on clearance and not both volume and clearance as expected in theory.

During modelling we tested different approaches to describe the possible induction effect of prednisolone, on CYP3A isoenzymes and/or P-glycoprotein in the small intestine and/or liver, on tacrolimus pharmacokinetics. Such an effect could theoretically lead to altered tacrolimus bioavailability and/or plasma clearance. A model based on decreasing tacrolimus bioavailability rather than increasing unbound tacrolimus clearance with increasing prednisolone dose was found to be slightly superior. In our study the maximum reduction in tacrolimus bioavailability caused by use of prednisolone was estimated to be -67% (95% CI -41%, -89%) and the prednisolone daily dose exerting half maximum effect was estimated to

be 35mg (95% CI 7mg, 50mg). Additionally, tacrolimus plasma clearance was estimated to be 30% higher and bioavailability 18% lower in CYP3A5*1 carriers (CYP3A5 expressers) compared to CYP3A5*3/*3 homozygous patients (CYP3A5 non-expressers).

The population model that we developed allowed for a corticosteroid inductive effect in all individuals (not just CYP3A5 non-expressers). This could be an important consideration if the inductive effect corticosteroids have is on P-glycoprotein as well as CYP3A isoenzymes. As alluded to by de Jonge et al, increased P-glycoprotein expression/activity at the apical membrane due to corticosteroid usage could increase tacrolimus efflux to the gut lumen, which might decrease tacrolimus oral bioavailability either directly or indirectly by increasing the access of tacrolimus to intestinal CYP3A isoenzymes [3, 4]. The net effects of these intestinal process could be a progressive decrease in tacrolimus oral bioavailability, without changes in *in vivo* CYP3A activity.

Further research, particularly *in vivo* studies are required to fully elucidate the mechanisms by which corticosteroids and tacrolimus interact. A tacrolimus-corticosteroid interaction is likely to have clinically significant consequences for interpretation of concentrations and use for dose adjustment, especially during steroid tapering or high dose therapy for acute rejection after transplantation.

COMPETING INTERESTS

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: NH had salary support from University of Auckland, ES had salary support from South-Eastern Norway Regional Health Authority, SH, TKB and CS have nothing to disclose. There are no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years, no other relationships or activities that could appear to have influenced the submitted work.

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