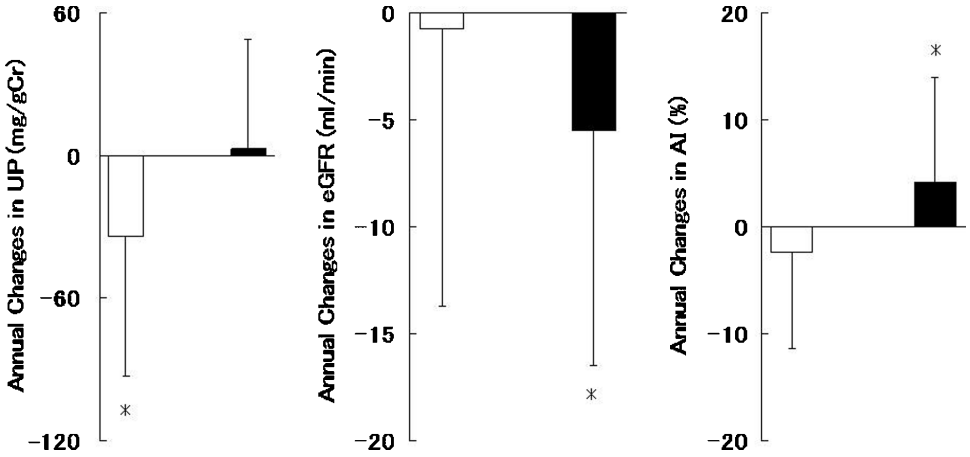

Fig. 1. Annual changes in urinary protein (UP, left panel), estimated glomerular filtration rate (eGFR, middle panel) and augmentation index (AI, right panel). *$P < 0.05$ from zero. Significant decreases in UP (116 ± 93 to 82 ± 67 mg/g creatinine, $n = 27$, $P < 0.005$) and eGFR (53 ± 53 to 47 ± 49 ml/min, $n = 26$, $P < 0.01$) were observed in the benidipine (open bar) and amlodipine groups (closed bar), respectively. AI (79 ± 14 to 84 ± 14, $n = 26$, $P < 0.05$) and serum creatinine (3.8 ± 3.5 to 4.1 ± 3.6 mg/dl, $n = 26$, $P < 0.01$) were considerably increased in the amlodipine group.

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Potentially serious medication errors with a new once-daily preparation of tacrolimus (Advagraf™)

Sir,

Tacrolimus is a widely used immunosuppressant drug in solid-organ transplantation. A new once-daily formulation (Advagraf™, Astellas, Tokyo) has been licensed in Europe in 2007 and shown to be safe and efficacious [1,2]. It is conceivable that the new formulation offers an advantage regarding compliance when compared to twice-daily Tacrolimus (Prograf™, Astellas) although this remains unproven.

A 31-year-old renal transplant recipient with stable transplant function [glomerular filtration rate (GFR) 27 ml/min] was maintained on Prograf™ 2.5 mg BD and prednisolone. While participating in a teaching event in November 2008, she produced a box of once-daily Tacrolimus (Advagraf™) and stated that she had taken this 'new' drug twice daily for 2 months. A mild rise in Tacrolimus blood levels was noted although her GFR had remained stable. We prescribed Prograf™ and investigated the incident. It transpired that she ordered repeat prescriptions through a web-based system (EMISaccess™, Egton Ltd, Leeds, UK). When updating her medication, the GP had erroneously chosen Advagraf™ M/R (modified release) from the two options for Tacrolimus that the software provided but maintained treatment twice daily. Advagraf™ had then been dispensed. However, the patient had not read the package insert and taken Advagraf™ twice daily, as suggested by her medication plan, thus maintaining her previous total Tacrolimus dose. In December 2008, we double-checked her medication again. It turned out that she now took Prograf 2 mg BD and Advagraf 0.5 mg BD. Again, we rectified the error while GFR and Tacrolimus levels remained stable.

We [3] and others [4] have previously voiced concern regarding two different formulations of Tacrolimus being available concurrently. This incident underpins our concern. No untoward consequences have occurred, chiefly because the patient took Advagraf™ twice daily. Had she taken the drug according to the package insert, and halved her daily Tacrolimus dose, she may have sustained rejection and graft loss. Conversely, if transplant patients erroneously take Advagraf™ twice daily, this may cause over-immunosuppression and infection with a potentially fatal outcome.

Various healthcare providers are involved in prescribing the immunosuppression in transplant recipients. All of them should be very aware of this potentially life-threatening issue. We appreciate that Astellas takes this matter very seriously and we understand that the company plans additional warning labels on the package. Prescribing software should feature similar warnings and should not allow treatment with Advagraf™ twice daily. Others, such as the health authorities in Wales, have decided against Advagraf™ to avoid errors and because they feel that the drug does not convey any particular advantage over Prograf™ [5]. We have alerted general practitioners and begun to scrutinize patients on Tacrolimus. We consider approaching all our transplant patients. Finally, we now provide an

information leaflet to all patients whom we intentionally convert to Advagraf™.

Conflict of interest statement. A.W. has given talks for Amgen, Pfizer and Sankyo and received honoraria. He has given one talk for the cardiovascular division of Novartis (a competitor of Astellas in transplantation) in 2007 and received honorarium. He has also participated in clinical studies in transplant patients with Novartis and Wyeth (another competitor of Astellas in transplantation). The other authors declare no conflict of interest.

Renal Unit, Lancashire Teaching Hospitals NHS Foundation Trust
Preston, UK
E-mail: Alex.Woywodt@LTHTR.NHS.UK

Imran Saif
Margaret Delargy
Zoe Thain
Alexander Woywodt

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