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LETTER TO THE EDITOR

A pilot study on sublingual administration of tacrolimus

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The immunosuppressant tacrolimus has a narrow therapeutic index and a high variability of its pharmacokinetics, e.g. oral bioavailability of tacrolimus is very variable [mean 25% (4–93%)]. Reams *et al.* showed that sublingual administration of tacrolimus results in therapeutic blood levels in patients after lung transplantation [1,2]. We questioned whether the results of this study were not biased by absorption of dissolved tacrolimus in swallowed saliva in the gut. Therefore we conducted a pilot study to confirm their findings in renal transplant candidates with rigid measures to avoid enteral resorption.

Three renal transplant candidates, a patient with cystic fibrosis and a healthy volunteer had been treated sublingually with 0.04 mg/kg tacrolimus. The day thereafter, the renal transplant candidates received tacrolimus 0.1 mg/kg orally. Following the protocol of Reams *et al.*, commercially available tacrolimus capsules were opened and the content was dispersed under the tongue. In contrast to the study of Reams *et al.*, the person was explicitly instructed not to swallow during 15 min and afterwards to spit out saliva and rinse the mouth with water.

The study was approved by the Medical Ethical Board. Blood levels were taken at t = 0, ¼, ½, 1, 2, 4, 8, 12 and 24 h postdose and were analyzed by high-performance liquid chromatography and tandem mass spectrometry (LOQ = 1 μg/l; LD = 0.05 μg/l).

In contrast to the study of Reams *et al.*, [1,2] very low tacrolimus blood levels were measured after sublingual administration of tacrolimus. We have discussed these findings with Reams and suggested that in their study, enteral absorption could not be excluded after sublingual administration, because patients were not instructed not to swallow and also to rinse their mouth. Also, the patient with cystic fibrosis and the healthy volunteer in our study did not show sublingual absorption.

A recent case report [3] of a kidney transplant patient treated sublingually with tacrolimus, showed similar blood levels after sublingual administration as after oral administration. However, the observed concentration-time profile was compatible with absorption in the digestive tract instead of the sublingual mucosa. Goorhuis *et al.* [4] compared tacrolimus trough levels after buccal administration to pediatric liver transplant patients in the first week after transplantation to trough levels after administration by a nasogastric tube. Again, trough levels after both routes of administration were comparable but enteral absorption could not be excluded (Fig. 1).

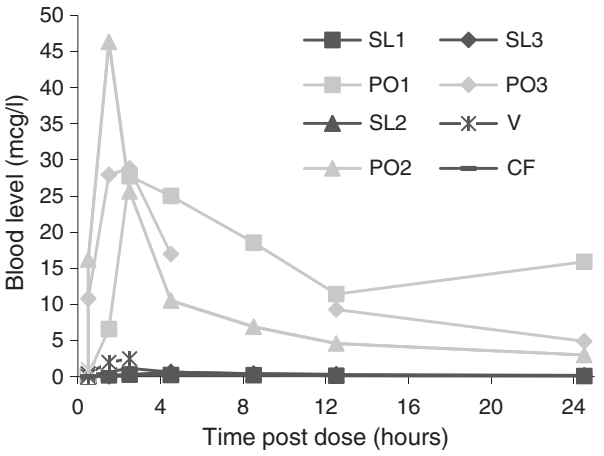

Figure 1 Tacrolimus whole blood levels (μg/l) against time postdose (h). SL1, SL2, SL3; sublingual administration in kidney transplant patient 1, 2 and 3, PO1, PO2, PO3; oral administration in kidney transplant patient 1, 2 and 3, V; sublingual administration in volunteer, CF; sublingual administration in a lung transplant patient with cystic fibrosis.

We conclude that sublingual administration in this way does not seem to be a suitable alternative for oral administration. In contrast to earlier studies, very low blood levels were measured after sublingual administration. In our opinion, enteral absorption after sublingual administration of tacrolimus in the earlier studies could explain the good absorption after sublingual administration.

Afke van de Plas,[1] John Dackus,[2]
Maarten H. L. Christiaans,[2] Leo M. L. Stolk,[1]
Johannes P. van Hooff[2] and Cees Neef[1]
1 Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, The Netherlands
2 Subdivision of Nephrology, Department of Internal Medicine, Maastricht University Medical Centre, Maastricht, The Netherlands

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