

Case Report

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Renal ischaemic injuries during the use of zolmitriptan for treatment of migraines in a transplanted patient under tacrolimus therapy

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Case report

A 26-year-old female patient underwent kidney transplantation from a 38-year-old deceased donor in 2001. Her renal disease was a focal segmental hyalinosis secondary to congenital vesico-ureteral reflux. She was started on triple immunosuppressive therapy [tacrolimus, mycophenolate mofetil (MPM) and prednisone]. Renal transplantation was complicated by delayed graft function and a renal biopsy was performed on the day 8, showing histological signs of tubular necrosis without acute rejection. Thereafter, evolution was excellent and corticosteroids were stopped after 1 year. Creatinine at 1 year was 100 µmol/l. She had arterial hypertension which was treated with four antihypertensive drugs just after renal transplantation; the treatment was progressively decreased and 18 months after transplantation, she required no further antihypertensive therapy. A routine renal biopsy was performed after steroid withdrawal in 2002, showing no evidence of rejection but a moderate interstitial fibrosis (10–20%). Tacrolimus and MPM were continued and trough levels of tacrolimus were aimed for 6–8 µg/l. All follow-up visits between 2002 and 2005 were unremarkable, except one respiratory infection which was treated with antibiotics for 7 days. Renal function was extremely stable with values averaging 100 µmol/l (83–114 µmol/l) of creatinine during these 3 years (Figure 1). She had no proteinuria (170 mg/day). Tacrolimus trough level was kept between 6 and 8 µg/l with 1.5 mg b.i.d. During this period, she was also taking an oral contraception

(estradiol and progesterone), magnesium and paracetamol for common migraines. She did not smoke or drink alcohol.

During the summer of 2005 her common migraines became exacerbated, no longer relieved by paracetamol. In September 2005, her general practitioner prescribed zolmitriptan 2.5 mg to good effect. She used this medication 3–4 times a month. In October 2005 she had a slight increase of creatinine at 120 µmol/l, but no other changes which might have raised any concerns for her renal function; a control in January was stable at 115 µmol/l. Due to an increase in her headaches, she took zolmitriptan more frequently during the following 2 months, reporting an average consumption of 10 pills per week (Figure 1). She did not complain of abdominal pains. In March 2006, a control showed a creatinine value at 161 µmol/l associated with an increase in proteinuria (500 mg/day) (Figure 1). There was no clinical explanation for this rise, but tacrolimus trough levels were at the upper limit of the target (8 µg/l) during the last 4 months under the same drug regimen (1.5 mg b.i.d). A renal biopsy was performed. Several cortical ischaemic scars were observed with globally sclerotic glomeruli and arteriosclerosis (Figure 2A). The cortical region without scars included eight glomeruli, four of them globally sclerosed. Two glomeruli showed severe ischaemic injury with corrugation of the basement membranes (Figure 2B). In the two other glomeruli, lesions of focal and segmental sclerosis were observed. Some intratubular calcifications were detected. Arterioles appeared unremarkable. A 99m-Tc-DMSA renal scintigraphy was done, which did not reveal renal defects compatible with large scars. Zolmitriptan and tacrolimus were suspected to be involved in this acute decline in renal function. Zolmitriptan was stopped and tacrolimus dosage was slightly decreased, to 1 mg in the morning and 0.5 mg in the evening. Creatinine slowly decreased to 141 µmol/l and a renal biopsy was performed again in June 2006. The histology showed the same cortical scars, and moderate arteriolar lesions

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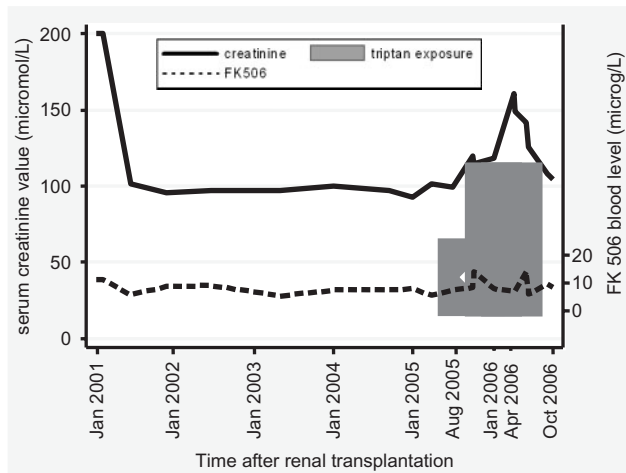


Fig. 1. Creatinine and tacrolimus (FK 506) values since the beginning of the renal transplantation. Increase of creatinine parallels the exposure to zolmitriptan (cubes). The patient started zolmitriptan in September 2005 with a moderate use of 3–4 pills per month (small cube). In January 2006, she did increase zolmitriptan doses to an average of 10 pills per week (large cube). When zolmitriptan was stopped, creatinine came back slowly to previous values.

that were compatible with calcineurin inhibitors toxicity. The cortical region without scars included 12 glomeruli, six of which were globally sclerosed. Six glomeruli showed open capillary loops and thin basement membranes. Renal function continued to improve and since October 2006, she has returned to her usual creatinine values of 100 $\mu\text{mol/l}$.

Discussion

This young patient had a transient decline in the function of her renal graft, associated with severely ischaemic glomeruli and cortical scars on the renal biopsy, which were attributed to ischaemic injuries secondary to the introduction of zolmitriptan. Zolmitriptan is a 5HT₁ receptor agonist which is very efficient in reversing the abnormal cerebral vasodilatation associated with common migraine. As with the other triptans, it acts through agonism at the HT_{1D/B} receptor subtype, a G-protein-coupled receptor [1]. Its vasoconstrictor activity is mediated with the vascular smooth muscle 5HT_{1b} receptor subtype. This receptor is described in human coronary, cerebral and peripheral artery [2]. In young healthy and in elderly subjects, administration of zolmitriptan increased mean peak diastolic pressure from 6 to 10 mmHg. In addition, in the elderly, mean peak systolic blood pressure values were 9–16 mmHg higher after zolmitriptan than after placebo [3]. The vasoconstrictive properties of the ‘triptans’ have been incriminated in rare complications such as cerebro-vascular accident, myocardial infarction, ischaemic colitis, spinal cord infarction and renal infarction [4–7]. Renal arterial vasospasm was shown to be 5-HT mediated in a rat [8] and produces contractions and increased tone in the renal artery in the rabbit [9]. 5HT_{1B} receptor has not

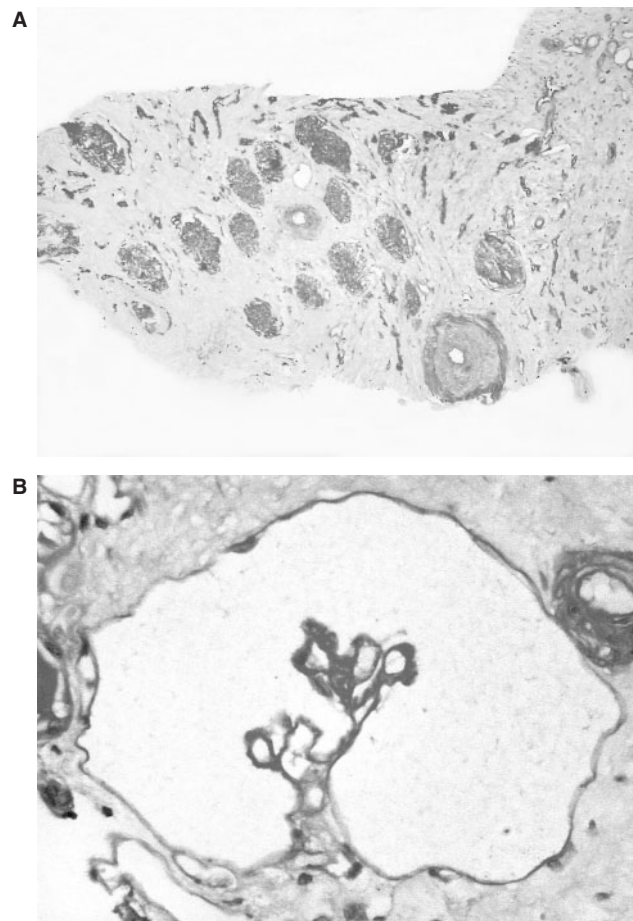


Fig. 2. (A) This is renal biopsy specimens obtained from the patient on both tacrolimus and zolmitriptan. On light microscopy, ischaemic cortical scar with obsolescent glomeruli, interstitial fibrosis, tubular atrophy and arteriosclerosis are observed on this specimen (PAS, $\times 50$). (B) This is renal biopsy specimens obtained from the patient on both tacrolimus and zolmitriptan. At higher magnification, ischaemic injury is characterized by corrugation of the glomerular basement membranes and retraction of the glomerular tuft (PAS, $\times 200$).

been yet described in human renal artery, but a recent case report suggests its presence [5]. Indeed, one case of renal infarction was reported in a 34-year-old man after one dose of 2.5 mg of zolmitriptan [5]. This case report demonstrates that renal graft can also be exposed to ischaemic injuries secondary to the vasoconstrictive properties of zolmitriptan.

Of importance, this patient was also under tacrolimus therapy, which may have enhanced the ischaemic injuries induced by zolmitriptan. The calcineurin inhibitors cyclosporine and tacrolimus are known to elicit vasoconstriction in different vascular beds [10]. Acute nephrotoxicity secondary to vasoconstriction is well described with tacrolimus. The incidence of headache as an adverse event is higher among tacrolimus-treated patients than in cyclosporine-treated patients [11]. There is a recent case report of a transient ischaemic attack after rizatriptan administration in a liver transplant recipient, who developed migraine while on tacrolimus therapy, suggesting that

this association leads to an excessive risk of cerebral vasospasm [4]. Several mechanisms are involved in the vasoconstrictive action of tacrolimus. Among them, endothelial cell dysfunction is a major mechanism, including deficiency in NO-vasodilatory effect, increase in peroxynitrite production and increase in endothelin release [10]. In addition, adenosine, a renal vasoconstrictor mediator, has been shown to be elevated by tacrolimus administration [12]. However, it does not seem that tacrolimus vasoconstrictive action is mediated by 5-HT receptors. Thus, we suggest that both drugs act synergistically to enhance vasoconstriction in the renal graft, which might lead to severe ischaemic lesions. The deleterious role of zolmitriptan is further confirmed in this case report by the improvement of renal function after its discontinuation, whereas tacrolimus therapy was maintained. Thus, in the presence of migraines in a kidney recipient under calcineurin inhibitors, agents specific for migraine, such as the various triptans, should be used with extreme caution. Indeed, the combination of zolmitriptan or other triptans and tacrolimus (or cyclosporine) can increase the risk of acute or subacute ischaemic injuries of the kidney graft and we advise strongly against it.

Conflict of interest statement. None declared.

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