not be used for dialysis anticoagulation in patients with a past diagnosis of atheroembolic disease. When a patient with a past history of cholesterol crystal embolization needs extrarenal epuration, peritoneal dialysis or haemodialysis without anticoagulation should be used.

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An exploratory study examining the influence of religion on attitudes towards organ donation among the Asian population in Luton, UK

Sir,

I would agree with G. Randhawa [1] that Moslems view organ donation in the light of religious teachings and ethics. Indeed a Moslem’s deeds are, or should be, greatly governed by the teachings of Islam. I wish to make the following comments in the light of our experience in the Kingdom of Saudi Arabia.

We would not have had a successful cadaveric programme in the Kingdom of Saudi Arabia without first obtaining religious leaders opinion (Fatwa) that Islam does not object to organ donation. We are now probably the leading Islamic country in transplantation from cadaveric donors (380 kidneys, 215 hearts (or heart valves) and 165 livers have been transplanted so far).

Saudis, before donating, always ask whether a fatwa has been passed to allow them donating their next of kins organs. Even when we assure them of this, they often seek the advice of a prominent religious person, whom they trust to seek his counsel.

Many fatwas have been passed by the Islamic Jurisprudence Council, which is made up of prominent religious scholars from all over the Islamic world allowing cadaveric organ donation, brain death and even xenotransplantation. Furthermore, they always, of course, stipulate that there is no harm done to the donor or desecration of his body, the chance of success outweighs failure and no other alternative is available. They also stress willingness for donation by involved parties and refuse commercialism.

It may therefore be useful, in order to encourage Moslems in the west to donate organs, to have an intensive media campaign to inform them of its permissibility in Islam, to educate local Mosque Imams to support the campaign (since they will always be referred to for counselling) and also highlight to them that in many Moslem countries, especially Saudi Arabia where the sacred mosques exist and where Islamic Jurisprudence is applied as a way of life, that cadaveric organ donations is practiced routinely.

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Marked elevation of blood cyclosporin and tacrolimus levels due to concurrent metronidazole therapy

Sir,

Cyclosporin and tacrolimus (FK506) are both potent immunosuppressive agents which are characterized by a narrow range between blood concentrations that produce therapeutic efficacy and those which produce potentially serious side effects, such as nephrotoxicity, neurotoxicity, fluid retention and hypertension [1,2]. Since both drugs are extensively metabolized by the hepatic and intestinal cytochrome P-450 system, circulating levels may be greatly increased by inhibitors of these microsomal enzymes, including ketoconazole, cimetidine, erythromycin, danazol, methyl-prednisolone, diltiazem and verapamil [1,2]. We present two cases which suggest that metronidazole should also be added to this list.

Case 1: a 69-year-old man underwent cadaveric renal allograft transplantation in March 1998 for end-stage renal failure secondary to hypertensive nephrosclerosis. There was no prior history of other significant comorbid illnesses and he was on no medications, apart from calcitriol, calcium acetate, erythropoietin and nifedipine. His initial immunosuppressive therapy consisted of a combination of cyclosporin, prednisolone and sirolimus. On day 18, he developed acute vascular rejection, which responded promptly to 3 days treatment with intravenous methylprednisolone, followed by conversion of cyclosporin to tacrolimus and sirolimus to mycophenolate. The plasma creatinine stabilized at 0.21 mmol/l and mean ± SD trough tacrolimus levels in the country in transplantation from cadaveric donors (980 blood were 10.4 ± 1.6 μg/l on a daily dose of 5 mg (3 mg mane, 2 mg nocte). Two months after transplantation, he developed profuse, watery diarrhoea complicated by orthotonic hypotension. Stool cultures yielded Clostridium difficile and he was treated with a 2-week course of 400 mg of metronidazole three times daily per os. The patient’s diarrhoea settled after 2 days, but tacrolimus levels progressively rose from an initial value of 9.0–17.9 μg/l after 9 days (Figure 1). This was accompanied by an increase in plasma creatinine from 0.15 mmol/l to 0.21 mmol/l. His tacrolimus dosage was reduced accordingly to 1 mg twice daily, resulting in a fall in tacrolimus and creatinine concentrations over the next few days to 8.1 μg/l and 0.16 mmol/l, respectively. When his metronidazole was ceased at the completion of the 2-week treatment course, tacrolimus concentrations promptly fell further to a nadir of 5.2 μg/l. The dosage of tacrolimus was subsequently doubled to 2 mg b.d. to achieve a level of 8.8 μg/l, which has remained stable thereafter.

Case 2: a 50-year-old man received a left iliac fossa cadaveric renal allograft in February 1997 for end-stage renal failure secondary to glomerulonephritis. His post-operative course was uncomplicated and he remained well for 14 months. His immunosuppressive regime consisted of cyclosporin, azathioprine and prednisolone. During the second year post-transplantation, his cyclosporin dosage and trough whole blood levels had remained stable at 125 mg twice daily and 130–150 μg/l, respectively. On July 1 1998, he was admitted to hospital with a 3-day history of vomiting and diarrhoea associated with right iliac fossa tenderness. His serum creatinine was unchanged at 0.17 mmol/l and com-
Computed tomography of the abdomen revealed bowel wall thickening consistent with a terminal ileitis. Stool cultures subsequently isolated Campylobacter coli for which he was treated with oral metronidazole 400 mg three times a day for 1 week. The patient’s illness resolved over the next 3 days. During this time period however, cyclosporin levels progressively increased from 134 μg/l to 264 μg/l and were accompanied by a modest elevation in serum creatinine to 0.19 mmol/l. Metronidazole was ceased after 1 week and the cyclosporin concentration subsequently fell to 120 μg/l. Renal function returned to baseline levels. Apart from the metronidazole treatment course, no other changes had been made at any time to the patient’s medication regimen (including cyclosporin dosage).

The administration of metronidazole in these cases was closely temporally associated with a marked increase in blood tacrolimus and cyclosporin levels of 99% and 97%, respectively. The augmented levels occurred in the absence of any other medication changes and could not be explained on the basis of variable compliance or laboratory error. Altered gastrointestinal absorption is also unlikely to account for the increased tacrolimus concentration in the first patient since the latter coincided with the zenith in diarrhoea severity. Moreover, in both patients, the dosage requirement of tacrolimus and cyclosporin rose again shortly following cessation of metronidazole.

Both tacrolimus and cyclosporin are known to be metabolized extensively by demethylation and hydroxylation to a large number of inactive or marginally active metabolites via the hepatic mixed-function oxidase system [3,4]. A common clearance mechanism for these drugs is suggested by their identical interactions with a large number of drugs in vivo [1,2] and by the fact that they mutually inhibit each others metabolism in vitro [5]. Moreover, the primary isozyme felt to be responsible for their metabolism is CYP3A4, also known as P450NF (nifedipine oxidase) [3,4,6]. Metronidazole, like other imidazole derivatives, has been shown in vitro to inhibit CYP3A and other mixed function oxidases to a variable extent [7,8]. However, clinically important interactions with metronidazole have only been reported twice in the literature for cyclosporin (83–127% increase in trough concentrations) [9,10] and have not been previously identified for tacrolimus.

The two cases presented in this report indicate that metronidazole should be added to the list of medications that can produce clinically important increases in circulating concentrations of both cyclosporin and tacrolimus to toxic levels. Clinicians should monitor drug trough concentrations and renal function closely when patients receive cyclosporin or tacrolimus concurrently with metronidazole.

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Omeprazole-induced agranulocytosis in a kidney transplant recipient

Sir,

Drug-induced agranulocytosis is a very rare complication in non-cytotoxic pharmacotherapy. The incidence is estimated to be 3 per million per year in the general population [1]. Omeprazole is a well tolerated drug often prescribed in the early post-transplant period as peptic ulcer prophylaxis. Blood dyscrasias occur in rare cases with this drug and only one case of omeprazole-induced agranulocytosis has been reported in the literature [2]. We report a case of agranulocytosis in a renal allograft recipient during omeprazole treatment. The activity of the S-mephenytoin hydroxylase, an isoenzyme of the CytP450 that metabolizes omeprazole, was normal. This is evidence against a pharmacokinetic cause. Thus, this is the first case of omeprazole-induced blood dyscrasias in which an unaltered activity of the S-mephenytoin hydroxylase is demonstrated.

Case: A 32-year-old man with diabetic nephropathy and end-stage renal failure was treated with omeprazole (Antra®) 20 mg/day as peptic ulcer prophylaxis after he received a renal allograft. Seventeen weeks after an uneventful kidney transplantation, agranulocytosis was noticed in a routine laboratory investigation. The patient’s current medication was prednisone 20 mg/day, cyclosporin A (Sandimmun Neoral®) 450 mg/day, mycophenolate mofetil (CellCept®) 1500 mg/day and insulin according to capillary glycaemias. The total white blood cell (WBC) count was 2.4 × 10^9/l and the neutrophil count was <0.1 × 10^9/l. A bone marrow aspirate showed myeloid hypoplasia with a shift towards premature forms. The CMV early-antigen in urine and blood was negative. The patient was asymptomatic, presented no evidence for infection and therefore was not admitted to the hospital. A toxic-pharmacological or immunological drug-related mechanism was suspected and omeprazole was immediately withdrawn. The WBC and neutrophil counts increased to 8.4 × 10^9/l and 5.0 × 10^9/l, respectively, 14 days after omeprazole was withdrawn (Figure 1). The patient was not exposed to the drug again, immunosuppressive drugs were continued and peptic ulcer prophylaxis was not re-installed.

One possible explanation for this adverse event could be a decreased metabolism of omeprazole. Slow hydroxylators are at increased risk for a variety of adverse reactions to drugs like phenytoin, captopril and certain beta blockers [3]. Therefore, we analysed the activity of the CytP450 isoform S-mephenytoin hydroxylase, the hepatic microsomal enzyme responsible for the metabolism of omeprazole [4]. Briefly, the ratio of mephenytoin to hydroxymephenytoin was determined chromatographically in an early morning 8-h urine sample after oral ingestion of one dose of mephenytoin 100 mg at 10.00 PM the night before [3]. The urinary ratio of mephenytoin to hydroxymephenytoin in the index case was within normal range.

Comment: To date few haematological adverse effects like erythroptenia, leukopenia, or thrombocytopenia, suspected to be related to omeprazole have been reported to the pharmacovigilance centres, but none of these cases has been confirmed by drug rechallenge or re-exposure [5]. The incidence of haematological adverse events, as estimated from spontaneous reports is very low, with 1/80000 for a 4-week treatment [5]. Nevertheless, this agranulocytosis-related complication is mentioned in the current precautions.

Toxicological studies in rats and mice found only minor changes in erythrocyte count, haematocrit and haemoglobin [6]. To date only one report of agranulocytosis has been published [2]. Between 62 and 72% of all cases of agranulocytosis observed in clinical practice are due to drugs, while xenobiotics are responsible for observed aplastic anaemias in only 2–27% of cases [7]. Therefore, the likely cause of the agranulocytosis in this patient was the medication. Moreover, the probability for drug-induced agranulocytosis is very high if the granulocyte count normalizes after withdrawing the causative agent, even without a rechallenge test, as it was observed in our patient. A rechallenge with omeprazole was considered to be ethically unacceptable.

Two major pathogenetic mechanisms may be implicated with a drug-induced agranulocytosis. On one hand, an immunologic reaction can be hypothesized and on the other hand, a toxic reaction to the drug itself or one of its metabolites, probably in conjunction with an individual susceptibility of the bone marrow deserves consideration. In cases of immune mediated agranulocytosis the onset of neutropenia is usually abrupt. In the present case the WBC decreased over a period of 2 weeks (Figure 1) after the patient had been on omeprazole for more than 4 months. In the other reported cases none of the subjects were receiving immunsuppressive therapy, while in our patient the immunsuppression with cyclosporine, mycophenolate mofetil and prednisone might have played a protective role rather than a predisposing factor for an immunologic drug reaction. Therefore, a toxic-metabolic mechanism of this patient’s agranulocytosis seems more likely. Omeprazole is a potent proton pump inhibitor, metabolized by the S-mephenytoin hydroxylase P450 isoform [4]. Approximately 3% of Caucasians metabolize the compound slowly, which can lead to plasma concentrations about 5-fold higher than normal. Nevertheless, a clear dose-relationship of other adverse reactions has not been established in the dose range of 10–60 mg omeprazole per day in more than 1.2 million patient treatments [8]. For prevention of post-transplant peptic ulcers we dispose principally of two alternative groups of antacid drugs: (i) H2-receptor antagonists and (ii) the prostaglandin E1