Drug points

Probable interaction between cyclosporin A and low dose ticlopidine

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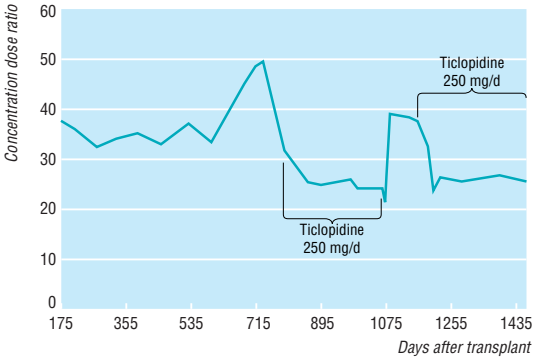
We report on a probable interaction between ticlopidine 250 mg once daily and cyclosporin A leading to a decrease in the trough concentration dose ratio—that is, concentration divided by daily dose per kilogram—of cyclosporin A.

A 64 year old woman had a stable renal graft. She was given ticlopidine 250 mg once daily owing to a left third cranial nerve palsy of new onset probably caused by ischaemia. Relevant medical history after the transplant included diabetes mellitus and angina precipitated by supraventricular tachycardia. The patient was taking frusemide (furosemide), digoxin, insulin, prednisone, azathioprine, and cyclosporin A throughout follow up. The patient was given pravastatin from 1132 to 1279 days after transplantation.

The dose of cyclosporin A was changed several times during the three year follow up (range 2.81-4.39 mg/kg daily). We therefore report the results as the concentration dose ratio, which gives an approximation of the clearance and bioavailability of the drug.

Monitoring of cyclosporin A concentration in whole blood by an enzyme multiplied immunoassay technique (EMIT 200, Behring Diagnostics, Cupertino, CA) showed a decrease in concentration dose ratio after ticlopidine was introduced. The median concentration dose ratios were 36 before and 25 after treatment with ticlopidine. The patient agreed to stop taking ticlopidine for three months, and aspirin 200 mg/day was simultaneously added to the treatment. The median concentration dose ratios were 38 and 26 after the discontinuation and reintroduction of ticlopidine (figure). No signs of graft rejection were observed.

We considered ticlopidine to be responsible for the observed changes because of both the observed temporal sequence, including the effects of reintroduction and withdrawal of ticlopidine, and the history of an interaction with ticlopidine 500 mg daily.[1 2]



Concentration dose ratio of cyclosporin A after exposure to ticlopidine

The only previous published report evaluating the potential interactions between ticlopidine and cyclosporin A, with half standard doses of ticlopidine for 14 days in 20 recipients of heart transplants, failed to show clear evidence of any pharmacokinetic modification.[3] We found that ticlopidine 250 mg once daily decreased the blood concentration of cyclosporin A in this patient, and we would therefore recommend close monitoring of such blood concentrations when introducing or withdrawing ticlopidine in patients taking cyclosporin A.

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Lithium toxicity after urinary diversion with ileal conduit

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A 71 year old woman underwent urinary diversion with ileal conduits for severe stress incontinence that had been refractory to previous treatments. She had longstanding bipolar affective disorder that was well controlled with lithium carbonate 600 mg daily. The lithium was discontinued preoperatively and recommenced at the original dose 48 hours postoperatively. Ten days later, after removal of the ureteric stents, she developed progressive confusion, dysarthria, nausea, and ataxia; her serum lithium concentration was increased at 2.1 mmol/l (treatment range 0.4-1.0 mmol/l). Lithium was discontinued and she made a full recovery with intravenous hydration alone. Subsequent dose titration required a reduction of lithium to 200 mg daily. This observation has been reported to the Committee on Safety of Medicines and the drug's manufacturer.

Metabolic complications (mainly hyperchloraemia and hypokalaemia) are well recognised after urinary diversion but infrequently require specific treatment.[1] Problems arising from drug reabsorption are rare but have been reported for phenytoin and methotrexate.[2 3] Lithium has a narrow treatment ratio, with toxicity occurring at only twice the upper limit of the treatment range. Steady serum concentrations occur as early as 2-5 days after starting treatment.[4] About 95% of lithium is eliminated unchanged in urine, and it is readily absorbed by enteral mucosa.

The delayed toxicity in this patient was probably related to the ureteric stents: on their removal all urine drained through the ileal conduit, resulting in reabsorption of lithium. We advise that such patients are discharged only after stable serum lithium concentrations are re-established after stent removal. Additionally, owing to the long term changes associated with urinary diversion,[5] continued vigilance is essential.

Any surgery resulting in exposure of bowel to urine should be taken into account when considering and monitoring pharmacotherapy, particularly of drugs excreted in a bioavailable form.

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