Interaction between Ciclosporin and Ceftriaxone

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Dear Sir,

Ciclosporin (CS) is an immunosuppressive drug metabolized in the liver, by means of a P-450 cytochrome isoenzyme. Pharmacokinetic interactions resulting in both induction and inhibition of its metabolism have been described [1]. Therefore, those interactions may induce the appearance of CS subtherapeutic or toxic levels.

Among the group of antibiotics, both inductors as rifampin [2], intravenous sulfadimidine [3] or nafcillin [4], and inhibitors as erythromycin [5] or josamycin [6] have been described.

We present two kidney-transplanted patients in whom an increase in CS levels was noted after administration of ceftriaxone (CTX). CS levels returned to normal when the antibiotic was withdrawn.

The first patient was a 30-year-old female in whom a renal transplant was performed using an immunosuppressive treatment with CS (250 mg b.i.d.), azathioprine (AZA; 100 mg/day) and prednisone (PRED; 20 mg b.i.d.). The clinical outcome was successful with stable graft function, supporting therapeutic levels of CS until the 12th week after transplantation, at which time she was admitted to our hospital because of a pneumonia. At that time she was taking CS (125 mg b.i.d.), AZA (100 mg/day) and PRED (10 mg b.i.d.).

Treatment with CTX (1 g b.i.d.) was initiated. Two days later, an increase in the CS parent and CS parent plus metabolites levels were observed, reaching a toxic level and remaining elevated while CTX was administered. Nine days after the withdrawal of CTX, the CS levels had diminished to a therapeutic range (fig. 1a).

The second kidney-transplant was a 64-year-old female in whom CS (250 mg b.i.d.), AZA (75 mg/day) and PRED (10 mg b.i.d.) were being administered. Three weeks later, a *Streptococcus faecalis* & c-teremia was diagnosed, so she was treated with gentamicin (40 mg b.i.d.) plus CTX (1 g b.i.d.).

Three days after initiating the antibiotic treatment, an increase in CS levels was noted, reaching the toxic range and remaining there while CTX was being administered. Twelve days after the withdrawal of CTX, the CS levels were in a therapeutic range (fig. 1b).

Fig. 1. Relation between the dose of CS administered (mg/kg/ day) and CS parent levels (ng/ml), and also the CS parent plus metabolites levels (ng/ml), before, during and after the administration of CTX. The values of total bilirubin in plasma during the episodes ($\mu\text{mol/l}$) are shown.

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The remaining treatment in both patients was not changed while they had the infection (except for a reduction in the dosage of AZA (50 mg/day) in the first patient). The liver biochemical tests had not changed, so a decrease in the hepatic metabolic capacity was not likely. Poor cardiac output was never probed.

The levels of CS were measured in whole blood and always in the trough, 12 h after the last intake, the CS plus metabolites by fluorescence polarization immunoassays utilizing the TDx system (Abbott Laboratories) with a between-run coefficient of variation of 7% and CS by radioimmunoassay (RIA), utilizing a commercially available kit (Sandoz ^3H monoclonal) with a between-run coefficient of variation of 9%.

CTX is an antibiotic belonging to third-generation cephalosporins, which is stable to β -lactamases. It has a broad spectrum that covers gram-negative bacteria and most gram-positive cocci, except *S. faecalis*.

CTX is unique because of its prolonged serum half-life, which permits once or twice-daily dosing. CTX is not metabolized in the body; 40–50% of a parenterally administered dose is excreted in the urine as the active drug, and the remainder appears to be excreted unchanged in the bile [7].

There are no reports about the possibility that CTX could be an enzymatic inhibitor of the hepatic oxidative metabolism (P-450 cytochrome), nor have pharmacokinetic interactions between CTX and other drugs been described. But we think that in our patients the mechanism responsible for the increase in the CS whole blood levels may be the use of CTX. CTX could produce a pharmacokinetic interaction, either by inhibiting the hepatic metabolism of CS (inhibiting means of a P-450 cytochrome isoenzyme) or by competing with the bile excretion of its metabolites.

These facts would explain the increase in CS levels few days after CTX administration, the high CS levels during CTX administration, and their decrease to basal levels after CTX withdrawal.

The fast onset of the inhibitory action suggests that CTX joins to the cytochrome P-450 system working as an alternate substrate and producing a competitive inhibition, since the inhibitory effect will be delayed when the inhibitor acts by decreasing the biosynthesis of the enzyme, whereas substrate binding remains normal, producing a noncompetitive inhibition [8].

Other factors that could explain this increase in CS levels, as the existence of hemodynamic alterations or hepatic failure, could reasonably be excluded. The patients were not taking any other drugs that inhibit the

hepatic oxidative metabolism. Further there was no evidence of changes in the patients' volume of distribution.

Although both patients had an acute bacterial infection, there is no evidence that it could produce disturbances in the metabolic hepatic capacity, except when there are complications (septic shock, congestive heart failure or hepatic failure) [9], but our patients did not have these problems.

In conclusion, since an interaction between CTX and CS is possible, it would be necessary to closely watch CS levels when both drugs are administered jointly.

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