Effect of Carbamazepine on Ciclosporin Blood Level

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Dear Sir,

Ciclosporin (CsA) is an immunosuppressive drug currently used in the prevention of the rejection of human allogenic transplants as well as in the treatment of several autoimmune diseases.

CsA is metabolized in the liver by means of a P-450 cytochrome isoenzyme. Pharmacokinetic interactions resulting in both the induction and inhibition of its metabolism have been described. These interactions may induce the appearance of subtherapeutic or toxic CsA levels.

Among the anticonvulsive drugs, the inductor effects of phenytoin [1] and phenobarbital [2] are well documented, while the action of carbamazepine (CBZ) is not so clear, although an inductor effect has been suggested. We have found only one case in the literature [3].

Herein, we report a kidney-transplanted patient in whom an important decrease in CsA level was noted after introducing CBZ; the CsA level returned to normal when CBZ was withdrawn.

The patient was a 53-year-old male treated with immunosuppressive drugs: CsA (300 mg b.i.d.), prednisone (PRED) (20 mg b.i.d.), and azathioprine (AZA) (100 mg/day); the clinical outcome was successful, with stable graft function during the first 8 months. He was taking chronically CsA (100 mg b.i.d.), AZA (100 mg/day), PRED (10 mg b.i.d.), insulin NPH (40 units/day), propranolol (100 mg/day) and hydralazine (50 mg/day).

He was admitted to our Hospital because of acute bacterial meningitis which was treated with ampicillin intravenously (1 g q.i.d.); AZA was withdrawn, and the other drugs were not changed. Eight days later, he presented generalized tonic-clonic seizures, so CBZ was initiated (400 mg b.i.d.); the other drugs were not modified.

Fig. 1. Relation between the dose of CsA administered (mg/kg/day) and measured CsA (ng/ml; $\square$), and CsA plus metabolite (M) levels (ng/ml; $\triangle$), before, during, and after introducing CBZ.

Three days after beginning CBZ, his CsA level decreased notably to a subtherapeutic range, remaining low while CBZ was being administered (serum level: 23.26 μ mol/l; fig. 1).

Because of the favorable outcome, CBZ and ampicillin were withdrawn 13 days later, and the patient was discharged taking the same doses of CsA, PRED, insulin, propranolol, and hydralazine.

After the suppression of CBZ, the patient's CsA level rose slowly, 4 months later being similar to the level obtained before CBZ was introduced. Hepatic and renal functions remained stable during the whole time, without

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

The inductor effect of CBZ on the hepatic oxidative metabolism of some drugs is well described [4]. It is produced by an increase in the synthesis rate of cytochrome P-450 isoenzymes. This action is observed in the first 48–72 h after its introduction, although the more severe effect is delayed several days, keeping up after its suppression.

It is probable that in our patient, CBZ was responsible for the changes in CsA metabolic pattern, because the CsA level decreased after initiating CBZ, the inductor pattern was similar to that previously described (with CsA levels returning to normal when CBZ was withdrawn) and, with the rest of the drugs that he was taking chronically, there are no reports about inductor effects. Because of this possible inductor effect of CBZ, when CsA and CBZ are administered simultaneously, it is necessary to monitor CsA concentrations in order to avoid a subtherapeutic range and the possible appearance of an acute rejection episode.

References

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