Interaction between Ciclosporin A and Sintrom

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Sir,

Several clinically important interactions during treatment with ciclosporin (CsA) have been reported [1]. However, interaction between CsA and warfarin have been observed just once before and with a reciprocal negative effect [2]. Recently, a patient with a mitral prosthesis valve (Bjork-Shiley) treated with Sintrom (Acenocoumarol) came to our unit for cadaveric kidney transplantation, and was successfully treated with CsA. The interaction between CsA and Sintrom in our patient was opposed to one objective by Snyder [2] and we consider of interest to describe it.

The patient, a 35-year-old white man, was affected by chronic renal failure secondary to idiopathic diffuse crescentic glomerulonephritis, and was on maintenance he-modialysis from 1977. In January 1987, a mitral valve replacement was performed by a mechanical prosthesis (Bjork-Shiley) because of a double rheumatic lesion. Sintrom was started as an anticoagulant at a dose of 3–4 mg/day and prothrombin activity was stable between 60 and 75%. In September 1987 he underwent heterotopic cadaveric kidney transplantation, treated with CsA (14 mg/kg/day) as immunosuppressive therapy. Twenty days after renal transplant a rejection episode was evident and a methylprednisone bolus (1 g × 3) was introduced. The patient recovered renal function and was discharged from hospital on the 25th day. The prothrombin activity decreased progressively (20–30%) and Sintrom dose had to be decreased (2–2.5 mg/day). The CsA blood level rose to 680 ng/ml and CsA dose was progressively reduced (fig. 1). Hepatic function was strictly normal. Twelve months after kidney transplant the patient was in good health, with normal renal function (serum creatinine 1.4 mg/dl); the Sintrom dose is 1.5 mg/day with a prothrombin activity between 20 and 25%, and CsA dose is 7 mg/kg/day.

Yours

P.S.

75
50

25

14-
12 10-
8-
6
4

(7 mg/kg)

o 7/8 o E

Kidney transplant

Fig. 1. Interaction between CsA and Sintrom after renal transplantation. Note the progressive decrease in prothrombin activity after the introduction of CsA.

CsA has proven to be a useful immunosuppressive agent and has resulted in improvement allograft survival and diminished morbidity or mortality in renal, hepatic, and cardiac transplantation [3–5]. However, its clinical use is limited by the occurrence of CsA-induced nephrotoxicity, on functional and anatomical damage [6–8]. Although early studies indicated that this nephrotoxicity was dose-dependent and reversible, recent studies have indicated that long-term administration induces irreversible renal damage [7, 8]. Therapeutic ranges for dosage and blood concentrations have been described, but the lowest effective maintenance dose has not yet been defined.

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CsA is metabolized by the liver and excreted via the bile into the feces, and many factors may influence CsA absorption and metabolism. CsA blood levels are increased by drugs that inhibit CsA active transport into the bile or biotransformation in the liver, such as cimetidine, erythromycin or josamycin [3]. On the other hand, CsA blood levels are decreased by compounds that induce or enhance P450 activity, such as phenobarbital, rifampicin or diphenylhydantoin. On Snyder's patient [2], interaction between CsA and warfarin was on the way of enhanced P450 activity by enzymatic induction, requiring increased doses of both drugs. In our patient the effect was opposed: when CsA was introduced, the prothrombin activity decreased and the dose of Sintrom had to be decreased, and accompanying it the CsA dose was also slightly decreased. In this case, it seems that CsA inhibited the biotransformation of Sintrom reinforcing the coagulant effect.

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