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LETTER TO THE EDITOR

EFFECT OF DANAZOL ON CYCLOSPORINE PHARMACOKINETICS[1]

Danazol, a derivative of ethisterone is an inhibitor of pituitary gonadotrophins and a weak androgen. It is increasingly used in endometriosis and fibrocystic mastopathy. There has been only a single report of its effect on cyclosporine (CsA*) pharmacokinetics in a kidney transplant recipient in the literature in English (*1*).

One of our patients, a 47-year-old woman with primary biliary cirrhosis, received an orthotopic liver transplant in January 1986. The patient began having irregular heavy vaginal bleeding in April 1986. At this time, she was taking CsA 150 mg p.o. b.i.d.; prednisone 10 mg q.d., azathioprine 25 mg q.d., and lasix 40 mg q.d. She was placed on intermittent norethindrone (Norlutate) 15 mg p.o. q.d. This did not have any effect on her vaginal bleeding, cyclosporine levels, or liver functions over a period of 3 months. The patient was eventually started on danazol 200 mg p.o. q.i.d. Within days of starting danazol her CsA levels increased, along with a rise in transaminase values. There was no change in bilirubin and alkaline phosphatase levels (Table 1). After stopping danazol, CsA, transaminases, and creatinine levels reached previous values.

The rise in CsA levels could reflect increased intestinal absorption or decreased breakdown in the liver. There have been reports of inhibition by some sex steroids of hepatic microsomal enzyme systems (*2*) that increases CsA levels. It is more than likely that the rise in CsA levels seen in our patient is a result of a decrease in CsA breakdown by the liver rather than increased absorption. In a series of nontransplant patients danazol has been reported to cause elevation of hepatic transaminases in a small minority of cases when given in doses of 800 mg/day (*3*). The other possibility, that hepatic transaminase elevations in our patient are secondary to CsA hepatotoxicity, is unlikely because of the absence of changes in bilirubin and alkaline phosphatase (*4*). The progestational agent norethindrone did not affect the CsA levels or liver functions when given intermittently. Hence caution is indicated when starting patients taking CsA on danazol or other sex steroids. CsA levels should be measured and liver function tests performed frequently.

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* Abbreviations used: CsA, cyclosporine; SGOT, serum glutamic oxaloacetic transaminase; RIA, radioimmunoassay; SGPT, serum glutamic pyruvic transaminase.

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TABLE 1. Cyclosporine levels, liver functions, and creatinine values before, during, and after danazol therapy

Date	CsA level (RIA) (ng/ml)	Total bilirubin (mg/dl)	SGPT/SGOT (U/L)	Alkaline phosphatase (U/L)	Creatinine (mg/dl)
3/23/87	305	0.7	4/9	68	2.2
4/13/87	319	0.8	10/15	58	2.2
5/14/87	238	0.6	11/11	65	2.2 Norethindrone given intermittently
6/1/87	224	0.6	8/5	60	2.1 Danazol 200 mg q.i.d. 7/31/87
8/11/87	812				
8/14/87	724				
8/25/87	1034	0.7	253/111	62	2.9 Danazol stopped
8/27/87	734	0.6	249/90	52	2.6 CsA dose to 125 mg b.i.d.
8/31/87	595	0.5	122/29	55	2.3
9/21/87	269	0.6	21/10	68	2.3
10/5/87	287	0.5	21/17	71	2.3