No Clinically Significant Interaction between Ciclosporin and Isradipine

F.	Frank	Martinez ^a
Y.	Yves	Pirson ^a
P.	Pierre	Wallemacq ^b
C.v.Y	Charles van Ypersele	de Strihou ^a

Departments of ^aNephrology and ^bClinical Biochemistry, University of Louvain Medical School, Brussels, Belgium

Dr. Y. Pirson, Cliniques Universitaires St. Luc, Department of Nephrology, Avenue Hippocrate 10, B-1200 Brussels (Belgium)

Dear Sir,

Calcium channel blockers are increasingly used in kidney graft recipients not only to lower blood pressure but also to prevent or attenuate ischemia or ciclosporin (CS)-induced graft dysfunction [1–3].

Their usefulness however is limited by a potentially deleterious interaction with CS metabolism. Indeed increased CS trough levels with an attendant nephrotoxicity have been reported in transplant recipients given calcium channel blockers, probably as the result of an altered CS hepatic metabolism.

This effect is observed only with selected calcium channel blockers such as diltiazem [4, 5], verapamil [6] and nifedipine [7, 8] but not with others such as nifedipine [9] and nitrendipine [10]. Detailed information should thus be available for each new calcium channel blocker introduced in the treatment of patients receiving CS.

In this presentation we examine the potential interaction between CS and isradipine, a second-generation calcium channel blocker of the 1,4-dihydropyridine group [11] for which no such information is yet available.

After informed consent, 7 hypertensive transplant recipients with a stable graft function and a constant CS dosage were given isradipine 5 mg daily (in 2 doses) for at least 2 weeks. In 4, isradipine replaced nifedipine; in the other 3 no calcium channel blocker had been given. During the study, all other drugs remained unchanged. Serum creatinine, urea and CS trough levels were recorded before and 2 weeks after the initiation of isradipine treatment. CS was given daily in a single morning dose. Serum trough levels were measured by fluorescence-polarization immunoassay (nonspecific polyclonal antibody, Abbott) after 2 h equilibration of the blood sample at room temperature. As shown in table 1,

Table 1. CS dose, renal function and CS level before and after 2-week isradipine treatment (means $\pm$ SD)

CS dose	Serum creatinine	Serum urea	Serum CS trough level
mg/kg	mg/dl	mg/dl	ng/ml
Before	4.6 $\pm$ 1.2	1.26 $\pm$ 0.3	39 $\pm$ 13
			34.5 $\pm$ 21

On isradipine 4.6 ± 1 1.30 ± 0.3 41 ± 22 32.1 ± 12

No statistically significant difference was found.

Table 2. AUC₀₋₁₂ (CS serum concentrations versus time) in 2 patients before and after 1-week isradipine treatment

CS serum measurement	Patient Before isradipine	On isradipine
h ⁻¹ ng/ml	h ⁻¹ ng/ml	

Nonspecific 1	1,278	1,991 (+ 55%)
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2	2,614	3,378 (+ 30%)
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Specific 1	703	1,000 (+ 42%)
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2	1,360	1,642 (+ 20%)
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CS trough levels as well as serum creatinine and urea levels were not significantly modified by isradipine therapy, a finding suggesting the absence of a clinically relevant interaction.

A more detailed analysis of CS pharmacokinetics under isradipine was performed in 2 patients.

In order to detect an effect on both the parent drug and its metabolites, CS serum levels were measured by two methods: specific radioimmunoassay (monoclonal antibody, Inc-star) – identifying mainly unchanged CS – and nonspe-

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cific fluorescence-polarization immunoassay – recogniz- 2 ing in addition to CS a broad panel of its metabolites. Blood samples were collected 0, 1, 2, 3, 4, 6, 8, 10 and 12 h after oral CS administration (6.6 and 4.3 mg/kg for the first and second patient, respectively), before and after 1 week of isradipine treatment. CS levels at 12 h, both by specific and nonspecific methods, were not increased 4 under isradipine. The area under the time-versus-concentration curve (AUC) for

CS, calculated by the linear trapezoidal rule extrapolated to infinity, was unchanged under isradipine as well. Nevertheless, the pattern of the concentration curves seemed modified by isradipine in 6 the 2 patients: the first CS peak appeared earlier and tended to be higher under isradipine, resulting in an increase in the AUC₀₋₁₂ (table 2), which is suggestive of an enhanced CS bioavailability. Such an effect of a calcium 8 channel blocker has never been reported so far and should be confirmed in a larger group of CS-treated patients. Even if the finding is confirmed, enhanced bio- 9 vailability is clearly without clinical importance insofar as CS trough levels are not affected.

We conclude that isradipine at the dose of 5 mg daily 10 can be safely given to CS-treated patients.

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