Effects of Azathioprine on Ciclosporin Metabolism

D.		Grekas
P.		Nikolaidis
M.		Karamouzis
P.	P	Alivanis
A.		Tourkantonis

Renal Unit, First Medical Department, University Hospital AHEPA, Thessaloniki, Greece

Dimitrios M. Grekas, MD, Ass. Professor in Nephrology, University Hospital AHEPA, GR-54636 Thessaloniki (Greece)

Dear Sir,

Ciclosporin (CS) is now established as a useful immunosuppressive drug in organ transplantation, and studies are currently being conducted in various autoimmune diseases. However, the fact that there are inter-individual differences in response to given doses means that an understanding of the kinetics and metabolism of the drug is necessary in designing optimal therapeutic regimens.

Plasma CS levels often rise sharply during antirejection treatment with high-dose methylprednisolone [1]. On the other hand observations reported by Öst [2] indicate that CS affects the metabolism of prednisolone reducing the clearance of this drug and therefore may potentiate the effect of prednisolone therapy in transplant patients.

Observations in our transplant patients suggest that azathioprine affects the metabolism of CS. The pharmacokinetics of CS has been studied in 5 renal transplant recipients given daily CS (4 mg/kg body weight) and methylprednisolone 8 mg (group A) and in 5 such patients treated daily with azathioprine (2 mg/kg body weight), methylprednisolone 8 mg and CS (4 mg/kg body weight; group B). A CS kinetics study was done in all patients 3-6 months after transplantation. After an overnight fast, each subject received a single oral dose of 600 mg of CS dissolved in 100 ml of milk, 8 mg of methylprednisolone and 50 mg of azathioprine concomitantly. Venous blood samples were drawn into heparinized tubes through an indwelling catheter at 0, 15, 30 and 60 min and 2, 3, 4, 6 and 8 h after the oral dose. Plasma samples were stored at -20°C until analyzed by the radioimmunoassay method (RIA Sandoz, Basel, Switzerland).

A pharmacokinetic analysis was carried out according to the two-compartment model. In both groups plasma CS levels increased progressively with time, but the mean peak plasma CS levels were attained by the second hour in group A ($1,737 \pm 882$ ng/ml) and the third hour in group B (675 ± 231 ng/ml, $p < 0.025$). The area under the curve was calculated from the concentration/time curve and was found at 7,533 and 3,635 ng/ml in groups A and B, respectively ($p < 0.001$).

Azathioprine is metabolized in the liver before it becomes active, but its biochemical effects are complex and not completely understood [3]. Since azathioprine is not metabolized by hepatic cytochrome P-450 which CS and prednisolone utilize for their metabolism, there

might not be competitive metabolic inhibition between these drugs. Azathioprine may decrease the plasma CS concentration not by enzyme induction but also by decreasing CS absorption and thereby bioavailability. Obviously this finding has important implications when triple drug regimens with CS, prednisolone and azathioprine are being applied.

References

Klintmalm, G.; Säwe, J.: High dose methylprednisolone increases plasma cyclosporin levels in renal transplant recipients. *Lancet* i: 731 (1984). Öst, L.: Effects of cyclosporin on prednisolone metabolism. *Lancet* i: 451 (1984). D'Apice, A.: Non-specific immunosuppression: Azathioprine and steroids; in Morris, Kidney 1984).

©1992 S.Karger AG, Basel
0028-2766/92/
0604-0489\$2.75/0