Interaction of Josamycin with Cyclosporin A

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Dear Sir,

Cyclosporin A (CyA), a hydrophobic cyclic undecapeptide, belongs to a new generation of immunosuppressive drugs which has greatly improved the survival rate in organ transplantation, and more recently has demonstrated effectiveness in the treatment of autoimmune diseases. CyA is metabolized by isoenzymes of the hepatic cytochrome P-450, so that coadministration of drugs that interact with the cytochrome P-450 system may effect CyA metabolism. Several drug interactions have been reported; cytochrome P-450 inhibitors that increase CyA plasma levels include ketoconazole, fluconazole, oral contraceptives, diltiazem and erythromycin whereas the coadministration of phenytoin and rifampicin decreases CyA blood levels [1].

Josamycin is a macrolide antibiotic produced by *Streptomyces narbonensis* subsp. *josamyceticus*. Its spectrum of bacteriostatic activity is similar to that of erythromycin, although josamycin inhibits most of the ery-thromycin-resistant staphylococci and, unlike erythromycin, it does not induce macrolide resistance in these strains. Also josamycin is better tolerated in fasting subjects than erythromycin stearate [2]. Josamycin provides comparable blood and urine concentrations as erythromycin and is metabolized rapidly in the liver to an inactive form and excreted primarily in the bile. However, josamycin does not induce microsomal enzymes, neither form cytochrome P-450-metabolite complexes and does not inhibit cytochrome P-450 activity [3]. This may indicate that josamycin might be preferred to other macrolides in patients receiving CyA.

We report 5 cases of renal transplant recipients in whom josamycin interacted with CyA, which resulted in a rapid and high increase in CyA blood levels. The present 5

Fig. 1. Changes in CyA blood levels after 1g/12h of josamycin therapy without CyA dose modification (patients 1 and 3).

Fig. 2. Changes in CyA blood levels after 1 g/12 h of josamycin therapy with consecutive CyA dose decrease (patients 2, 4 and 5).

Patient 3

CyA blood level (ng/mL)

Days of Josamycin therapy

-1 ■ r

4 DAYS 5

CyA blood level

Patient 4

CyA blood level (ng/mL)

300

100-

CyA dose (mg/Kg/day)

5,0

4,5

-4,0

3,5

3,0

CyA dose

CyA dose (mg/Kg/day)

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cases confirm that the interaction between CyA and josamycin takes place in a similar way and intensity as with erythromycin.

Case 1. A 66-year-old woman with chronic renal failure secondary to membranoproliferative glomerulonephritis type I received a cadaveric renal transplant in April 1991. Ten months after the kidney transplantation with normal renal function (serum creatinine 1.1 mg%) and CyA blood levels of 163 ng/mL (RIA monoclonal specific), josamycin (1 g/12 h) was introduced for suspicion of a Legionella pneumonia. CyA dose (4 mg/kg/day) was not modified. Four days after the introduction of josamycin, CyA blood levels increased to 382 ng/mL. After suppression of josamycin, CyA blood levels decreased to 123 ng/mL (fig. 1).

Case 2. A 65-year-old man with chronic renal failure secondary to urinary tract obstruction received a cadaveric renal transplant in March 1991. Seven months after the kidney transplantation with normal renal function (serum creatinine 0.9 mg%) and CyA blood levels of 111 ng/mL, josamycin (1 g/12 h) was introduced for suspicion of a Legionella pneumonia. CyA dose (1.5 mg/kg/day) was not modified. Three days after the introduction of josamycin, CyA blood levels increased to 334 ng/mL. After reduction of the CyA dose to 1 mg/kg/day, CyA blood levels decreased to 246 ng/mL. After suppression of josamycin and increase of the CyA dose to 1.5 mg/kg/day, CyA blood levels decreased to 110 ng/mL (fig. 2).

Case 3. A 55-year-old man with chronic renal failure of unknown etiology received a cadaveric renal transplant in August 1988. Twenty-two months after the kidney transplantation with normal renal function (serum creatinine 1.4 mg%) and CyA blood levels of 143 ng/mL, josamycin (1 g/12 h) was introduced for suspicion of a Legionella pneumonia. CyA dose (4 mg/kg/day) was not modified. Four days after the introduction of josamycin, CyA blood levels increased to 419 ng/mL. After suppression of josamycin, CyA blood levels decreased to 123 ng/mL (fig. 1).

Case 4. A 35-year-old man with chronic renal failure secondary to chronic glomerulonephritis received a cadaveric renal transplant in August 1988. Forty-two months after the kidney transplantation with a serum creatinine of 3 mg% and CyA blood levels of 79 ng/mL, josamycin (1 g/12 h) was introduced for suspicion of Legionella pneumonia. The CyA dose (3 mg/kg/day) was not modified. Four days after the introduction of josamycin, CyA blood levels increased to 325 ng/mL. After a progressive reduction of the CyA dose to 2.5 mg/kg/day, CyA blood levels decreased to 281 ng/mL. After reduction of the CyA dose to 2 mg/kg/day, CyA blood levels

decreased to 223 ng/ml. Lastly, after withdrawal of josamycin and increased CyA dose to 3 mg/kg/day, CyA blood levels decreased to 115 ng/ml (fig. 2).

Case 5. A 58-year-old man with chronic renal failure secondary to polycystic kidney disease received a cadaveric renal transplant in June 1988. Thirty months after the kidney transplantation with normal renal function (serum creatinine 1.3 mg%) and CyA blood levels of 149 ng/ml, josamycin (1 g/12 h) was

introduced for suspicion of a Legionella pneumonia. CyA dose (2 mg/kg/day) was not modified. Five days after the introduction of josamycin, CyA blood levels increased to 437 ng/ml. After reduction of the CyA dose to 1 mg/kg/day, CyA blood levels decreased to 251 ng/ml. After suppression of josamycin and an increased CyA dose to 2 mg/kg/day, CyA blood levels decreased to 147 ng/ml (fig. 3).

Interaction of CyA with erythromycin is well known and has been reported several times in the literature. However, only two cases of josamycin and CyA interaction have been described in the literature [4, 5].

Macrolides, with more than 14 carbon atoms, do not inhibit cytochrome P-450 activity and do not interfere with other drug metabolism [1, 6]. Azanza et al. [4] and Kreft et al. [5] suggested that the inhibition of cytochrome P-450 may be produced when the dose of josamycin is high, although in the present cases, josamycin doses were normal.

Our data indicate that the administration of josamycin inhibits the hepatic metabolism of CyA, increasing CyA blood levels in a similar way as erythromycin.

Nevertheless, we recommended that josamycin must be used with caution in patients receiving CyA. Careful and frequent monitoring of blood CyA levels are necessary to adjust CyA doses.

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