Drug Interaction of Chloroquine with Ciclosporin

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Dear Sir,

One of the major difficulties in using Ciclosporin (CS) in clinical practice are its wide-ranging interactions with drugs that may have to be often used simultaneously. Interaction of chloroquine with CS has not yet been reported in the English medical literature to the best of our knowledge. A 51-year-old male with end-stage renal disease due to chronic pyelonephritis underwent living donor kidney transplantation on February 2, 1988 in India. He was on immunosuppression with prednisolone 17.5 mg, CS 3.4 mg/kg body weight and azathioprine 0.5 mg/kg body weight daily. He had normal renal and liver functions. On July 1, 1988, he presented with a history of fever of 10 days' duration. The fever used to occur every 48-72 h, last for 3-4 h and terminate with marked sweating. He denied any history of malaria or tuberculosis in the past. A detailed physical examination was non-contributory. Routine urine analysis, hemogram and blood chemistry, search for bacterial, viral, fungal and tuberculous infection in urine, CSF and bronchial lavage were negative. Further examinations which included chest X-ray, abdominal ultrasound, barium studies, abdominal CT and echocardiogram were all normal. Since he had recently returned from a malaria-endemic country and because of the pattern of fever, he was given a therapeutic trial of the antimalarial drug chloroquine. The CS dose remained unchanged but the blood level was monitored every day by a radioimmunoassay method. Within 48 h of starting chloroquine (900 mg), the CS level rose to three times (420 ng/ml) the basal value (148 ng/ml). This was associated with a rise in the serum creatinine level to 140 $\mu\text{mol/l}$ from the basal level of 95 $\mu\text{mol/l}$. However, the chloroquine course was continued for a total of 3 days as in the WHO recommendation for the treatment of malaria [1]. CS blood level remained elevated during the days of chloroquine administration. On discontinuation of chloroquine, serum CS and creatinine levels returned back to the basal levels (140 ng/ml and 85 $\mu\text{mol/l}$, respectively) by the 10th day, i.e., 7 days after stopping chloroquine (fig. 1). The fever, however, did not respond to anti-malarial treatment. Subsequently, histological examination of a needle biopsy specimen of the liver revealed features of tuberculous hepatitis with several granulomas. He responded to triple drug antituberculous treatment and became afebrile in 6 weeks' time.

Biotransformation of CS to metabolites is known to occur in the liver. Metabolism of CS occurs by hydroxylation and N-demethylation in the liver through a cytochrome-P-450 dependent monooxygenase polyezyme system. Thus, enzyme induction or inhibition by other drugs can alter the metabolism of CS leading to decrease or increase in CS blood levels. It is also known

that competition for enzyme exists between CS and other drugs [4]. Chloroquine is known to be extensively localized in tissue where it concentrates in lysosomes, particularly in such cells as those of the liver parenchyma [2]. Aminoquinolines, to which chloroquine belongs, have also been demonstrated to have the effect of stabilizing the lysosomal membrane [3]. It could thus be postulated that chloroquine decreases CS

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Fig. 1. Relationship of serum creatinine and cyclosporin levels to chloroquine. O = Serum creatinine, $\mu\text{mol/l}$; $\cdot$ = CS blood level, ng/ml; ■ = CS dose, 3.4 mg/kg.

metabolism either by inhibiting the hepatic enzymes directly, by enzyme competition or by reduced enzyme release from lysosomes. Similar mechanisms have been proposed for drugs like ketoconazole and erythromycin interacting with CS [5,6].

In our patient, the introduction of chloroquine was followed by a sudden increase in the serum CS level without a concomitant change in CS dosage or addition of any other drug. Notably, the patient also showed transient nephrotoxicity when CS levels were high. Chloroquine is not known to be nephro-toxic [7]. The temporal relationship between chloroquine administration, blood levels of CS and nephrotoxicity clearly indicate drug interaction between CS and chloroquine. Thus, close monitoring of serum levels of CS is recommended when the two drugs are administered concomitantly.

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