Interaction between Ciclosporin and Ciprofloxacin

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Dear Sir,

We report two cases in which the concomitant oral administration of ciprofloxacin (CP) and ciclosporin (Cs) increased whole blood levels of the latter and caused a decrease in renal function in one of the patients.

Case 1. L.W. is a 29-year-old man with cystic fibrosis, who received a heart-lung transplant in January 1989. The patient was admitted to Georgetown University Hospital in August 1989, with shaking chills, fever of 103 °F and purulent sputum production. His medications included Cs 700 mg twice a day, vitamins, dipyridamole 100 mg twice a day, vitamin C 500 mg once a day, pancreatic enzymes, salicylic acid, chlorzoxazone and acetaminophen. He was started on oral CP 500 mg thrice a day, and gentamicin 80 mg thrice a day by aerosol inhalation. Two weeks prior to admission Cs blood levels, measured by radioimmunoassay, were in the range of 478–538 ng/ml. Twenty-eight hours after initiation of CP, Cs blood level was 1,613 ng/ml and 52 h later 1,711 ng/ml. Plasma creatinine increased from 1.6 to 2.2 mg/dl (143–200 µm/l). CP was discontinued and Cs dosage was decreased. Cs blood level decreased to 803 ng/ml within 24 h. There was no evidence of any abnormality in liver function during this admission.

Case 2. T.N. is a 26-year-old man with history of insulin-dependent diabetes mellitus, who received a cadaveric renal transplant in January 1988 for end-stage diabetic nephropathy. He was maintained on prednisone 10 mg once a day, Cs 250 mg twice a day, vitamins, azathioprine 75 mg once a day, dipyridamole 75 mg/day, and insulin. His usual serum creatinine was 1.4 mg/dl (123 µm/l). He was started on oral CP 500 mg thrice a day for an infected foot ulcer. Routine Cs blood level was found to be 1,032 ng/ml 4 weeks after initiation of CP treatment, while his usual levels ranged between 456 and 497 ng/ml. CP was discontinued and Cs was held for 1 day and within 2 days Cs blood level decreased to 267

ng/ml. Plasma CP was not measured in either case. Cs has been reported to interact with various drugs. Drugs which increase Cs blood level are corticosteroid, dantrolene, diltiazem, ketoconazole and metoclopramide [1, 2] and drugs that decrease Cs blood levels include pheno-barbital, phenytoin, rifampicin, and intravenous trimethoprim [1, 2]. Other drugs which increase the risk of Cs nephrotoxicity without increasing Cs blood levels are gentamicin, amphotericin, melphalan, sulfonamide/ cotrimoxazole, trimethoprim and lately ciprofloxacin [1–4].

Various side effects have been reported with quinolones including nausea/vomiting, dizziness, tremors and restlessness (especially when combined with theophylline), elevation of liver enzymes, eosinophilia, hematuria and acute renal failure (the latter in less than 1% of the patients) [5–7]. Crystalluria without any change in renal function has also been reported [7]. The quinolones have been reported to interact with various drugs [3–5, 8–13]. As far as interactions with Cs are concerned, there are two case reports in the literature of enhanced Cs nephrotoxicity without any increase in Cs blood levels [3, 4]. These interactions were labelled as pharmacodynamic. The acute renal failure that developed in these two cases was presumed to be due to Cs nephrotoxicity that occurred when CP and Cs were used together. However, in 1 of the cases it seems that the Cs level increased to 754 ng/ml after 4 days of therapy [3] (usual levels ranged between 160 and 603 ng/ml). Although it was not addressed in the discussion, this increase in blood Cs level might have been due to an interaction between CP and Cs. CP by itself has been reported to cause interstitial nephritis, nonspecific nephritis, and acute renal failure of unknown etiology [5, 7]. In one of the reported cases mentioned above, the increase in plasma creatinine from a baseline of 1.6 to 2.2 mg/dl (143–200 $\mu\text{m/l}$) was attributed to Cs toxicity because of the biopsy findings [4].

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Our two cases demonstrate that concomitant use of CP and Cs can lead to an increase in blood levels of Cs. Neither of our patients showed any evidence of liver dysfunction that could account for the increase in Cs blood levels. This is in contrast to the demonstration of no pharmacokinetic interaction between Cs and CP in a group of healthy volunteers, as well as in a small group of postrenal transplant patients [11, 14]. We have no other explanation for the increase of blood Cs levels in our patients, but for the addition of CP to their regular therapeutic regimen. These discrepancies between our cases and the previous reports may represent individual differences in the metabolism of both CP and Cs. It may be that some patients are more susceptible than others to an increase of Cs blood levels when CP is used concomitantly.

In conclusion, we caution simultaneous use of these two drugs. We believe that blood Cs levels should be carefully monitored in these patients, if such a combination is therapeutically desirable.

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