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A scheduled dosage regimen for cyclosporine based on the effect of active infection on cytochrome P450-mediated metabolism

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By

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Abstract

Background. Drug-infection interaction should be considered in drug prescribing, as infections downregulate CYP activities and thus may alter drug disposition, especially for narrow therapeutic index drugs. Cyclosporine, still used for the prevention of allograft rejection in renal transplant recipients in Egypt, seems to be affected based on random clinical observations. In the present study, the effects of bacterial and fungal infection on cyclosporine metabolism were studied in renal transplant patients (the Clinical study) and the effects of Candida and e-coli infections separately, and fluconazole administration were tested on cyclosporine metabolism in rabbits (the Animal study). Possible nephrotoxicity was also monitored.

Methods. **The Clinical study:** Twenty renal transplant patients, diagnosed with fungal or bacterial infection, were recruited from the Renal Transplantation Outpatient Clinic in Alexandria University Hospitals. Cyclosporine trough levels and/or serum creatinine concentrations were measured pre-infection, during infection and/or, in many cases, post-infection. No dose adjustment in cyclosporine was performed at least one week before the onset of infection. Exclusion criteria were acute or chronic unstable liver disease, elderly patients and concomitant drugs affecting cyclosporine metabolism.

The Animal study: Three study designs were carried out, crossover Single-dose-Fluconazole-Cyclosporine study which tested fluconazole-cyclosporine interaction, Multi-Candida-Fluconazole-Cyclosporine and Multi-Escherichia coli-Cyclosporine study designs involved each rabbit acting as its own control; cyclosporine was given daily for the whole period of the experiment in both studies. Candida and e-coli infections were inoculated on day 5 of each

experiment. In the Multi-Candida-Flu-CyA; fluconazole-cyclosporine interaction was also considered.

For both studies, cyclosporine trough levels and serum creatinine concentrations were measured by Immunoassays and enzymatic assay respectively, pre-infection, during infection and/or, in many cases, post-infection.

Results. **The Clinical study:** Cyclosporine trough levels and serum creatinine concentrations increased significantly during the infection ($P<0.001$), and ($P = 0.002$) respectively. Eighty seven percent of the patients experienced a concomitant rise in cyclosporine trough level and serum creatinine concentrations. No significant difference between pre-infection and post-infection levels of cyclosporine trough and serum creatinine was found.

The Animal study: Both infections resulted in significant rise in cyclosporine trough level ($P=0.018$) and ($P=0.005$); in fungal and bacterial studies respectively. The median rise of the CyA level reached 52% (range 9-426%) in the Candida infection and mean 60% with the e coli infection. Fluconazole also increased cyclosporine trough levels in the single study by 70.3% and the concomitant rise in the multi study reached median 76% (range 22-665%) (n=6). Post-infection s.creatinine concentrations were not statistically different from baseline.

Conclusion. Cyclosporine trough levels increased during bacterial and fungal infections and returned to pre-infection levels once the infection was resolved in patients and rabbits. Serum creatinine levels increased during bacterial and fungal infections in patients but not in rabbits. Fluconazole, given in inhibitory doses, exerted an additive effect to the Candida CYP inhibitory action (n=4 in rabbits) and (n=2 in patients). Type of infection and inoculum size affect differently CyA levels. The data generated stress the importance of monitoring

cyclosporine levels during episodes of infection. Our recommendations concerning cyclosporine dose adjustment differ according to severity and duration of infection.

Keyword: infection, cyclosporine, disease-interaction, CYP-450, renal transplant, Candida, e-coli, rabbits, cyclosporine-nephrotoxicity.