Decreased Cyclosporine Levels during Gemfibrozil Treatment of Hyperlipidemia after Kidney Transplantation

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Dear Sir,

Hyperlipidemia following renal transplantation is a newly recognized problem, which may be associated with an increased risk of atherosclerosis as well as early graft loss [1]. However, the choice of treatment and advantages/disadvantages of treatment are not yet determined.

We performed a double-blind randomized study in kidney recipients with hyperlipidemia to determine whether atherosclerosis, measured by sonography in the carotid vessels, was changed by the treatment. Gemfibrozil was chosen as the hypolipidemic drug, since no interaction with cyclosporine had been reported and hyperlipidemia in kidney recipients is often combined. However, the trial was stopped after 6 months because of a suspected interaction between the study drug and cyclosporine. The cyclosporine whole blood concentrations were determined with a specific monoclonal radioimmunoassay (Incstar, cyclo-trac RIA). Altogether 19 patients (11 males and 8 females) with serum cholesterol levels of > 6.5 mmol/l after at least 3 months of diet were included. The dosage of gemfibrozil was 450 mg once when serum creatinine was > 200 μ mol/l and 450 mg twice when the serum creatinine level was < 200 μ mol/l. Fifteen patients were treated for > 3 months: 7 with gemfibrozil, and 8 with placebo. They all had severe hyperlipidemia, the mean pre-treatment values ($\pm$ SE) being 9.0 ± 0.46 mmol/l for cholesterol and 3.7 ± 0.3 mmol/l for triglycerides.

After 6 weeks of treatment, we found a significant decline in the 12-hour trough whole blood cyclosporine concentrations in the treatment group from 93 ± 8.5 to 76 ± 5.2 ng/ml ($p < 0.05$, Wilcoxon rank test). After 3 months, the mean cyclosporine level was 88 ± 9.3 ng/ml, adjusted by an increase in dosage in 3 of 7 patients. In the placebo group, the mean blood concentrations of cyclosporine were 99 ± 7.4 ng/ml at the start of treatment, 98 ± 19 after 6 weeks and 123 ± 17 ng/ml at 3 months (NS). The doses were not increased.

The mechanisms responsible for this phenomenon are not yet known, but the change in lipoprotein distribution during treatment may cause changes in the free fraction of cyclosporine [2]. A low free fraction has been associated with acute rejection [2]. In 2 patients there was a significant rise of serum creatinine requiring kidney biopsy. One biopsy showed chronic rejection and the other cyclosporine toxicity.

There is also a possibility that absorption of cyclosporine is diminished during therapy. In this case the new microemulsion of cyclosporine (neoral) might solve the problem.

Our observations of lowered cyclosporine concentrations during gemfibrozil treatment in these patients raises some concern about the appropriate pharmacological therapy in post-transplantation hyperlipidemia. Close monitoring of cyclosporine levels is recommended during pharmacological intervention in this clinically important situation.

References

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