Bile and Blood Ratios of Cyclosporin and its Metabolites in Patients on Continuous Infusion During the First Three Weeks after Liver Transplantation

D. Debruyne, D. Samba, J. Lacotte, J. Tarière, J.P. Deshayes, Ph. Segol, H. Bricard and M. Moulin

Laboratory of Pharmacology and Department of Anaesthesiology, University Hospital Centre of Caen, Caen, France

Summary

Ten patients with orthotopic liver transplants were investigated during routine therapeutic monitoring to study the relationship between the concentrations of cyclosporin and its metabolites in blood, bile and urine, and whether this information can provide early signs of severe hepatic disorders post-transplantation. Cyclosporin (Sandimmun®) was administered by continuous infusion at a constant rate of 5 mg/kg/day, modified to keep the blood cyclosporin concentration within the target range (400 to 500 μg/L). The concentrations of cyclosporin and combined cyclosporin-metabolites in blood, bile and urine were assayed daily during the 3 post-transplantation weeks that the patients spent in intensive care.

All patients developed cholestatis and cytolysis during the first week. The severity of these liver transplant disorders increased in 5 patients and decreased in the other 5 in the second week. The pharmacokinetics of cyclosporin differed in the 2 groups: in patients without severe hepatic disorders, the blood metabolites/cyclosporin ratio (M/C) stabilised at 1.2 ± 0.4 in week 2 and at 0.8 ± 0.2 in week 3, bile cyclosporin/blood cyclosporin (bile C/blood C) fluctuated around 13.5 (13.5 ± 9.5 in week 2 and 13.5 ± 9.0 in week 3) and the bile metabolite/blood metabolite (bile M/blood M) ratio was very high and variable (131 ± 86 in week 2 and 159 ± 116 in week 3). Metabolites significantly accumulated in the blood of patients with severe hepatic disorders (M/C = 2.8 ± 0.6 in week 2 and 3.5 ± 1.0 in week 3); bile C/blood C (2.6 ± 2.1 in week 2 and 3.4 ± 1.1 in week 3) and bile M/blood M (11.9 ± 7.8 in week 2 and 12.5 ± 7.9 in week 3) significantly decreased and showed less interindividual variability.

Blood cyclosporin is usually monitored to help optimise the dosage. However, if this was extended to include the monitoring of metabolites in the blood, and cyclosporin and metabolites in the bile, it could provide an early indication of severe hepatic disorders in patients with transplanted livers.
Cyclosporin is a potent immunosuppressive agent that is widely used to prevent rejection of transplanted organs. It selectively inhibits the interleukin-2 driven proliferation of activated T lymphocytes, thus suppressing cell-mediated immunity and perturbing the development of self-tolerance.\(^1\) Cyclosporin is extensively metabolised in the liver by the mixed-function oxygenases related to the cytochrome P450 3A system, and the major pathway by which cyclosporin and its metabolites\(^2\) is eliminated is via the bile. The pharmacokinetics of cyclosporin vary greatly between individuals, and depend on factors such as age, type of organ transplant and concomitant medication.\(^3\)

Cyclosporin has a narrow therapeutic range and causes a variety of toxic effects that are mostly concentration dependent.\(^4\) Trough blood or plasma concentrations of cyclosporin are usually measured frequently after the initiation of drug therapy, then once a month.\(^5\) The most widely used procedure is an immunoassay with monoclonal antibodies for cyclosporin, as this molecule is considered to be responsible for 80 to 90% of the immunosuppressive activity in vitro.\(^6\) Monitoring the cyclosporin blood concentration, in conjunction with other laboratory and clinical data, provides a rational basis for establishing appropriate therapeutic regimens for individual patients that achieve optimal efficacy with minimal toxicity.\(^4,7\)

The present study was carried out to determine the relationships between the concentrations of cyclosporin and its metabolites in blood, bile and urine, during routine therapeutic monitoring after liver transplantation. These parameters were then analysed to identify any that might provide an early sign of disorder in the newly implanted liver. Monitoring of immunosuppressive therapy may thus be an additional factor with which to evaluate hepatic function.

**Patients and Methods**

**Patients**

This open, nonrandomised study included 10 orthotopic liver transplantations conducted in 9 patients (5 men, 4 women) aged 15 to 58 years. Patient demographic details are given in table I.

All the patients underwent orthotopic liver transplantation for posthepatic cirrhosis of viral, alcoholic or toxic origin, or for hepatocarcinoma. One patient underwent 2 successive liver transplantations within 2 weeks. Patients with heart or multiviscera failure were excluded.

The patients were monitored for the time they spent in the hospital intensive care unit (generally 3 weeks). Since all samples for routine therapeutic monitoring were taken in the intensive care unit, no informed consent or ethical approval was needed.