Acute effect of cyclosporin on renal function following the initial changeover to a microemulsion formulation in stable kidney transplant patients

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Abstract Potential differences in the acute effect of cyclosporin on renal function when dosed orally as the current market formulation or following a milligram-to-milligram conversion to a new microemulsion formulation were investigated in 14 stable kidney transplant patients. The study consisted of three sequential periods of 2 weeks duration each. Patients entered (period I) and completed (period III) the investigation with the market formulation and received the microemulsion formulation in period II; individualized cyclosporin doses remained unchanged throughout the study. Over one steady-state dosing interval at the end of each study period, whole blood cyclosporin pharmacokinetic profiles were assessed in parallel with endogenous creatinine clearances over sequential 1- to 2-h intervals. The rate and extent of cyclosporin absorption were significantly greater (P < 0.01) from the microemulsion formulation with average increases of 73% in peak concentration and 44% in area under the curve compared to the market formulation. Sequential creatinine clearances exhibited a transient decrease with the nadir occurring on average between 4 and 6 h post dose followed by a rapid return to baseline. Specifically in period I on the market formulation, clearances decreased from a baseline of 71.7 ± 20.6 to a minimum of 51.1 ± 17.9 ml/min per 1.73 m² (similar values in period III) and from 76.8 ± 24.8 to 53.5 ± 17.5 ml/min per 1.73 m² in period II on the microemulsion. Neither the baseline nor minimum clearances were significantly different among the study periods. Hence, the pharmacokinetic differences between the formulations did not acutely influence the pattern of glomerular filtration rate following the initial milligram-to-milligram changeover in stable renal transplant patients.

Key words Cyclosporin, renal transplantation, microemulsion · Renal transplantation, cyclosporin, microemulsion · Microemulsion, cyclosporin, renal transplantation

Introduction

A new microemulsion formulation of cyclosporin (Sandimmune Neoral, Sandoz Pharma) has recently been introduced in the clinical management of immunosuppression. The initial changeover from the original oral formulation (Sandimmune) to the microemulsion is generally based on a milligram-to-milligram conversion [5, 9, 12]. While for the majority of stable renal transplant patients trough concentrations remain in the target therapeutic range following the changeover, exposure to cyclosporin (area under the concentration curve; AUC) is increased on average by 30% and peak concentrations by 60% due to between-formulation dif-
Ferences in cyclosporin absorption [5]. These increases have given rise to concern of a possible adverse influence on renal function. However, 3-month follow-up data in over 450 stable renal transplant patients who have changed over to the microemulsion formulation have not revealed any significant changes in serum creatinine or blood urea nitrogen (BUN) [12].

In recognition of the limitations in using serum creatinine to register possible alterations in glomerular filtration rate (GFR), the present crossover study was undertaken to focus on the early postconversion period with a more specific index of glomerular filtration. To accommodate the study to a clinic setting and allow a sufficient number of patients to be assessed, we opted to perform sequential endogenous creatinine clearance (CLcr) measurements in parallel with pharmacokinetic sampling over a steady-state dosing interval on an outpatient basis. The method chosen could be easily applied in this setting while being sufficiently sensitive to reproducibly detect the transient decrease in GFR and its return to baseline, which has been previously described in renal transplant patients receiving Sandimmune [10].

Materials and methods

Study design

The protocol was approved by a local medical ethics committee and the study was performed in accordance with the Declaration of Helsinki and with current European Community and U.S. Food and Drug Administration guidelines for good clinical practice. All subjects gave written informed consent for participation in the study. The 6-week investigation consisted of three sequential periods. In period I (study weeks 1–2), stable renal transplant patients were enrolled and continued to receive their individualized dose of the reference formulation (Sandimmune soft gelatin capsules) with the total daily dose divided into two equal doses administered every 12 h. In period II (study weeks 3–4), patients were changed over to the microemulsion formulation (Sandimmune Neoral soft gelatin capsules) at the same dose as in period I. Based on trough concentration monitoring, the dose could subsequently be adjusted if necessary. In period III (study weeks 5–6) the reference formulation was reinstituted at the same dose as at study initiation.

Interventions

Tolerability and safety were monitored at clinic visits during each study period and at study completion. At these visits weight, blood pressure, pulse rate, routine laboratory chemistries/urinalysis and fasting total cholesterol, total triglycerides and glucose were assessed. A 12-lead ECG was performed at study entry and completion. A morning predose cyclosporin concentration was assessed weekly throughout the study.

Pharmacokinetic and CLcr assessments were performed over a morning dosing interval within the last 3 days of each study period. On these days patients reported to the study center after an overnight fast. They received their morning dose followed immediately by a continental breakfast. Because of a possible influence of circadian rhythm on GFR [3], the administration time for the morning dose was identical for each subject on all three assessment occasions. Additional standardized meals were served at 4, 8, and 10 h after the dose administration. Venous blood samples for the determination of cyclosporin in whole blood were obtained predose and then 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 10, and 12 h thereafter. Samples were collected in EDTA-containing tubes, gently inverted several times, and frozen at −20°C. GFR was assessed by sequential endogenous creatinine clearances. Subjects were instructed to ingest 300 ml tap water upon awakening and an additional 10 ml/kg were given upon arrival at the clinic. A continuous, intravenous 250-ml/h infusion of isotonic saline solution was started at least 30 min before the first urine collection and was maintained over the 12-h dosing interval with rate adjustments as necessary to maintain a roughly constant urine flow.

Urine samples were collected by spontaneous voiding over nine collection intervals: 0–2, 2–3, 3–4, 4–5, 5–6, 6–7, 7–8, 8–10, and 10–12 h after dose administration. Blood samples for serum creatinine determinations were taken before dose administration and every 2 h over the dosing interval. Creatinine in serum and urine was analyzed via a validated, automated, enzymatic colorimetric test.

Bioanalytical methods

Concentrations of cyclosporin in whole blood were assayed using the commercially available radioimmunoassay kit (Sandoz, Basel, Switzerland), which is based on the use of a monoclonal antibody specific for the parent compound [11]. At quality control concentrations of 6.25, 12.5, 100, 400, and 1600 ng/ml, the respective accuracies were −3.0%, 0.4%, −12.3%, −6.4%, 1.4%; the intra-assay coefficients of variation were 32.8%, 17.7%, 5.2%, 3.0%, and 6.8% and the interassay coefficients of variation were 14.5%, 6.9%, 4.1%, 5.8%, and 5.8%. The overall detection limit calculated from the mean ± SD concentration corresponding to 95% binding was 5.0 ± 0.6 ng/ml (n = 9). The quantification limit (intra-assay coefficient of variation ≤ 30%) was set at 12.5 ng/ml.

Pharmacokinetic and CLcr evaluations

Whole blood steady-state cyclosporin concentration-time data were analyzed by standard noncompartmental methods. The highest measured blood (b) concentration and the corresponding sampling time were defined as Cmax,b and tmax, respectively. The measured blood concentration 12 h after the profiled dose was defined as Cmin,b. The AUC0–b was calculated from 0 to 12 h using the trapezoidal rule. The average steady-state concentration Css,b was calculated as AUC0–bs/ss, where v is the dosing interval, and the percent peak-trough fluctuation (%PTF) was calculated as [(Cmax,b−Cmin,b)/Css,b]·100. CLcr for each sampling interval was calculated as the product of urine creatinine concentration and urine volume divided by the serum creatinine concentration. CLcr was normalized to 1.73 m² body surface area [4]. The minimal clearance over the dosing interval was designated as CLmin. Because the study was conducted at steady state, the baseline clearance (CLcrbaseline) was chosen as the clearance from the 10–12 h interval since, at this time, cyclosporin concentrations are reaching trough levels with little change over this 2-h interval.

Statistical evaluation

Pharmacokinetic parameters and clearances were compared by ANOVA with subjects and treatments as sources of variation after...