Safety and tolerability of a microemulsion formulation of cyclosporin A in stable renal transplant patients: local experience

SL Lui, CSO Tang, TM Chan, IKP Cheng

The safety and tolerability of a microemulsion formulation of cyclosporin A (Sandimmun Neoral) in 20 post-renal transplant patients with stable allograft function was studied. The conventional formulation of cyclosporin A (Sandimmun) was converted to the microemulsion formulation using a ratio of 1:1. The patients were followed up for 12 weeks and their vital signs and safety parameters were monitored. After the conversion, there was no significant change in the mean cyclosporin dose given and mean cyclosporin levels (180 ± 54 ng/mL at week 0 vs 172 ± 42 ng/mL at week 12). Both serum creatinine and blood pressure remained stable (128 ± 18 μmol/L at week 0 vs 126 ± 20 μmol/L at week 12 and 99 ± 10 mm Hg at week 0 vs 98 ± 9 mm Hg at week 12). Only two adverse events were reported and no acute rejection episode was recorded. We believe that the conversion of the conventional formulation of cyclosporin A to the microemulsion formulation in stable renal transplant patients is both safe and well-tolerated.

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Introduction

Cyclosporin A is a very powerful immunosuppressive agent. Since its introduction in 1983, it has considerably improved the renal graft survival rate.[1] One of the main problems encountered with the use of cyclosporin A is the wide intra- and inter-patient pharmacokinetic variability found. Recently, a new microemulsion formulation of cyclosporin A (Sandimmun Neoral, Sandoz, Basel, Switzerland) has been developed. A number of clinical trials have demonstrated that the microemulsion formulation is superior to the conventional formulation in that it has a higher bioavailability and a more predicable pharmacokinetic profile.[2-4] This formulation of cyclosporin A has just been introduced into Hong Kong. The aim of the present study was to confirm the safety and tolerability of switching from the conventional formulation to the microemulsion formulation in stable renal transplant patients in our own locality.

Division of Nephrology, Department of Medicine, The University of Hong Kong, Queen Mary Hospital, Pokfulam, Hong Kong
SL Lui, MB, BS, MRCP
CSO Tang, BSc
TM Chan, MD, MRCP
IKP Cheng, PhD, FRACP

Correspondence to: Dr SL Lui

Subjects and methods

This was an open label study. Patients were eligible for inclusion in the study if their renal transplant had been performed more than six months previously, if they had stable renal function (serum creatinine < 200 μmol/L), and were receiving cyclosporin A as part of their immunosuppressive regimen. The study was carried out in the Renal Transplant Clinic in Queen Mary Hospital from November 1994 to March 1995. Written and informed consent was obtained from all patients and the study was approved by the University Ethics Committee.

On entering the study, demographic information and a relevant medical history of each patient was recorded. A physical examination that included measurement of blood pressure (Korotkoff sound V) and urinalysis by dip-stick (Ames Albustix, Bayer Diagnostics, Mulgrave, Victoria, Australia) was performed. Blood pressure measurement was performed by the same observer throughout the study using an automatic sphygmomanometer with the patient in the sitting position. Laboratory investigations included complete blood count, liver and renal function tests, and the determination of trough cyclosporin levels. Conventional cyclosporin A was converted to the microemulsion formulation accord-

ing to a 1:1 ratio. The soft gelatin capsule form of the microemulsion formulation of cyclosporin A (Sandimmun Neoral) was used for the study. Patients were followed up at weeks 0, 1, 2, 4, 8, and 12. Vital signs were recorded during each follow up. Laboratory evaluations included complete blood count, liver and renal function tests, and trough cyclosporin levels. Any adverse events observed by the investigators or reported by patients were recorded.

Statistics

Results are expressed as mean ± SD or median and range. The paired Student's *t* test was used to compare the differences between pre- and post-cyclosporin A conversion values for all clinical and laboratory parameters.

Results

Patients

Twenty post-renal transplant patients with stable graft function were enrolled in the study. All enrolled patients completed the study. There were 11 men and nine women and their mean age was 36 years (range, 25-54 years). All patients had had their renal transplants performed in Hong Kong. There were 12 cadaveric transplants, 6 living-related transplants, and 2 living non-related transplants. The mean interval between the time of the transplant and the commencement of the study was 29 months (range, 10-61 months).

Dosage of the microemulsion formulation and trough cyclosporin levels

The mean dose of the microemulsion formulation given on entry to the study was 105 ± 22.36 mg/day. There was no significant change in this dose during the study period. Only one patient needed dosage adjustment (decrease from 100 mg twice daily to 75 mg twice daily) during the study period. Her dose was reduced because she was hypertensive at week 4 and as the attending physician thought that the microemulsion formulation could have contributed to this, the dose of the microemulsion formulation was reduced. Her cyclosporin level was within the therapeutic range. No significant change in mean trough cyclosporin levels was observed during the study period (Table). The percentage of patients with cyclosporin levels within the predefined therapeutic range (100-250 ng/mL) increased from 80% at week 0 to 90% at week 12. This difference did not reach statistical significance, probably because of the small sample size.

Stability of clinical and laboratory parameters and frequency of adverse events

Serum creatinine levels remained stable in all patients throughout the study period. Systolic, diastolic, and mean arterial blood pressures also remained stable in the majority of the patients (Table). Only two patients required adjustment of their anti-hypertensive medications. Two minor adverse events were reported; one patient noticed increased gingival swelling at week 2 and another developed mild intermittent headache at week 4. Neither required discontinuation of the microemulsion formulation and no acute rejection episode was recorded.

Table. Laboratory parameters and blood pressure measurements in 20 stable renal transplant patients following conversion from the conventional formulation to the microemulsion formulation of cyclosporin A

Parameter	Week 0	Week 1	Week 2	Week 4	Week 8	Week 12
Trough CyA* level (ng/mL)	180±54	175±42	168±43	178±53	171±41	172±42
Creatinine level (μmol/L)	128±18	127±20	124±15	127±18	124±19	126±20
Systolic BP† (mm Hg)	130±13	127±10	127±13	127±13	131±12	130±13
Diastolic BP (mm Hg)	84±10	84±10	85±7	82±7	85±10	82±8
Mean BP (mm Hg)	99±10	98±9	99±8	97±8	100±10	98±9

All data are presented as the arithmetic mean ± standard deviation
*CyA cycolosporin A
†BP blood pressure

Discussion

The microemulsion formulation of cyclosporin A is self-emulsifying and will form a transparent microemulsion on contact with aqueous fluids, making it more readily available for absorption.[5] As a result, its absorption is less dependent on bile flow, pancreatic juice, or concomitant food intake.[6,7] The microemulsion formulation offers significant advantages over the conventional one in that it has better bioavailability, a more stable pharmacokinetic profile, and a better correlation between trough cyclosporin levels and total drug exposure.[8-11]

Previous studies in predominantly Caucasian populations have shown that many patients given the microemulsion formulation require a reduction in dosage because of a rise in their trough cyclosporin levels.[4] We were unable to observe this in the patients we studied. In all patients, trough cyclosporin levels were unchanged after conversion, and remained so for the three months of the observation period. Only one patient needed to have the microemulsion formulation dosage reduced. In this patient, however, the dosage reduction was made by the attending physician who felt that the improved bioavailability of the microemulsion formulation might have contributed to the patient's increased blood pressure—not because of any increase in the drug serum level.

The increased bioavailability of the microemulsion formulation did not result in greater clinical toxicity. Serum creatinine levels remained unchanged after conversion. Blood pressure increases were observed in two of 20 patients after conversion, necessitating a dosage reduction in one patient. Increased gum hypertrophy was noticed in only one patient and the relationship between headaches and drug conversion in another patient was undetermined. More importantly, no patient developed acute rejection after the change in drug delivery.

The reason for the relative stability of trough cyclosporin levels following conversion in our patient population when compared with the populations in previous studies is unclear. A study conducted in another hospital (using an identical protocol to ours), showed no significant change in trough cyclosporin levels after the conversion (WK Tsang, unpublished observations). It is possible that the small number of patients studied may have masked the presence of a significant change (type II error). Alternatively, it could also be due to a distinct ethnic difference in the metabolism of the drug. A detailed pharmacokinetic study involving a larger number of patients is required to clarify the issue.

From this study, we conclude that a 1:1 conversion from the conventional formulation of cyclosporin A to the microemulsion formulation is both safe and well-tolerated in stable renal transplant patients in our locality.

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