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Cyclosporin A blood levels during use of cyclosporin as oral solution or in capsules: comparison of pharmacokinetic parameters

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Abstract. Recently cyclosporin A (CsA) capsules have been introduced to meet a number of disadvantages associated with the use of the oral solution. We compared the pharmacokinetics of the oral solution and the capsules in a group of nine renal transplant patients during the first 3 weeks after transplantation. After a morning dose of CsA, whole blood concentrations were measured at regular intervals for 12 h. Subsequently, a cross-over was made to the alternative form of administration, and 3 or 4 days later a second pharmacokinetic profile was obtained. Comparison of the trough level, the maximum concentration, the time to reach the maximal concentration and the area under the blood concentration curve, showed no significant differences. Our findings thus suggest a similar bioavailability of CsA administered as oral solution or in capsules in the early post-transplant period.

Key words: Cyclosporin A, capsules – Pharmacokinetics, cyclosporin A – Capsules, cyclosporin A

Cyclosporin A (CsA) is a potent immunosuppressive drug, widely used in organ transplantation. Traditionally CsA has been administered as an oral solution, but soft gelatine capsules of CsA have been developed (Sandoz, Basel, Switzerland), mainly because the oily solution has an unpleasant taste, and exact dosing is difficult for patients with visual impairment. The two forms differ slightly in their inactive constituents. We compared the pharmacokinetics of the oral solution and the capsules in renal transplant patients in the early post-transplant period.

Patients and methods

Pharmacokinetic profiles were obtained for five female and four male renal transplant patients of mean age 43 years (range 23–57). All patients received the same immunosuppressive therapy consisting of CsA and corticosteroids. CsA was given via constant-rate intravenous infusion (3 mg/kg per day) for the first 3 days after transplantation. The initial oral dosage was 12 mg/kg per day given in two divided doses as oral solution (Sandimmun 100 mg/ml) or as capsules (Sandimmun 25 and 100 mg). The dosage was decreased when CsA-induced renal dysfunction was suspected.

All patients underwent a first 12-h pharmacokinetic assessment 5–18 (mean 9) days after transplantation. They had been on the same CsA dosage and preparation for at least 3 days. On the initial study day, seven patients used the capsules and two patients the oral solution. After the first assessment a cross-over was made to the alternative administration form in the same dosage. A second pharmacokinetic study was carried out 3 or 4 days later. Meanwhile the accompanying drug management remained unchanged and no patient received drugs with known interactions with CsA. Transplantation had been successful in all patients and none of them required dialysis at the time of the study. CsA was given at 9.00 a. m. The oral solution was mixed in a glass with 50–100 ml chocolate milk and ingested immediately after mixing. The capsules were swallowed with an equal volume of water. Standard hospital meals were served 1–2 h before and 3 and 8 h after taking the drug.

Peripheral venous blood samples were collected in EDTA tubes immediately before drug administration and 0.5, 1, 1.5, 2, 3, 4, 8, and 12 h thereafter. The whole blood samples were stored at −20 °C until analysis. The CsA concentrations (ng/ml) in the whole blood samples were determined using the Sandoz monoclonal radioimmunoassay (RIA) kit which measures specifically the parent molecule of CsA. The maximum concentration of CsA (c_{max}) and the time to reach the maximal concentration (t_{max}) were directly taken from the measured CsA blood levels. The area under the blood concentration versus time curve (AUC) for 0–12 h was obtained by use of the linear trapezoidal rule.

Comparisons between the pharmacokinetic parameters were performed with the paired t-test. Statistical significance was defined as $P < 0.05$.

Results

The mean daily CsA dose in the nine patients was 11.6 mg/kg (range 8.7–12.9), half of which was given as a morning dose at 9.00 a. m. The mean blood concentrations of CsA before and after administration of oral solution and capsules are illustrated in Fig. 1. Table 1 summarizes

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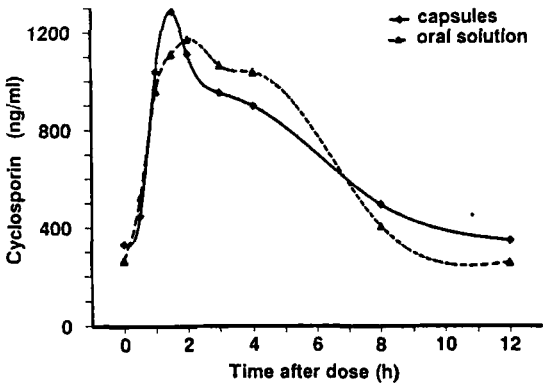

Fig. 1. Mean whole blood concentrations of CsA (RIA) after oral administration of *oral solution* or *capsules* ($n = 9$)

Table 1. Cyclosporin pharmacokinetic parameters. Administration as oral solution vs. capsules. Values are expressed as mean ± SD. Differences between groups are not significant

Parameter	CsA solution	CsA capsules
Trough level (ng/ml)	266 ± 103	332 ± 136
c_{max} (ng/ml)	1452 ± 385	1461 ± 902
t_{max} (h)	1.8 ± 0.8	2.5 ± 1.3
AUC (ng/h/ml)	8002 ± 2109	8046 ± 3631

the pharmacokinetic data. There were no significant differences between CsA oral solution and capsules in any pharmacokinetic variable. A double-peaked concentration versus time curve could be demonstrated in some subjects on one or both occasions.

Discussion

Cyclosporin is a widely used drug in the field of organ transplantation and autoimmune diseases. Recently CsA capsules have been introduced to meet a number of disadvantages associated with the use of the oral solution. The generally disliked, oily taste of the solution necessitates mixing with a beverage. The mixing has to take place in glass because binding of cyclosporin to plastic materials has been demonstrated [1, 12]. As a consequence, the oral solution is inconvenient to take during activities outdoors. In addition, especially for patients with visual impairment, exact dosing of the oral solution is difficult. Because the capsules are much easier to handle than the oral solution, compliance can be expected to improve. Didlake et al. drew attention to the clinical importance of patient compliance by demonstrating that non-compliance was a major cause of late graft failure in CsA-treated renal transplant patients [2].

There are two reports on the pharmacokinetic properties of CsA capsules in renal transplant patients [7, 13], but these patients were at least 4 months after transplantation, had a good graft function and received relatively low doses of CsA (mean dosage 4.8 mg/kg and 3.9 mg/kg). Improvement of CsA absorption during the first months after transplantation has repeatedly been demonstrated when the oral solution was used [4, 5, 10, 11]. Kahan et al. reported decreased absorption of CsA in patients with acute tubular necrosis or on dialysis, while CsA-induced renal dysfunction was associated with increased drug absorption [5]. This implies that pharmacokinetic data following the administration of CsA may change with time after transplantation. The aim of our study, therefore, was to compare the pharmacokinetics of CsA oral solution and capsules, given at higher dosages during the first 3 weeks after transplantation. CsA levels were determined with a monoclonal RIA kit specific for the parent CsA [9]. With the use of a non-specific RIA method, which measures cross-reactive metabolites in addition to the parent molecule of CsA, pharmacokinetic data are more difficult to interpret.

Since possible differences between oral solution and capsules might especially be expected in the absorption phase, we measured the maximum concentration, time to reach maximal concentration, AUC and trough levels after at least 3 days use of each form of administration. Our findings suggest that the previously demonstrated bioequivalence of oral solution and capsules also applies in the early post-transplant period.

In interpreting the data one has to keep in mind the marked interpatient variability in absorption and elimination of CsA [3, 5, 8, 10]. Moreover, Lindholm et al. found an intraindividual variation up to two-fold in the AUC of CsA after administration of CsA as oral solution under strictly standardized conditions in healthy men [6]. The large variability within and between subjects in the bioavailability of oral CsA may make it difficult to detect any differences in the bioavailability of oral solution and capsules without the use of a very large sample size.

In conclusion, we found no differences in terms of bioavailability between CsA administered as oral solution or as capsules in renal transplant patients in the early post-transplant period. The easier handling of the capsules favours their use as it may contribute to a better compliance.

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