Relative bioavailability of a new oral form of cyclosporin A in patients with rheumatoid arthritis

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The relative bioavailability of cyclosporin A (CsA) from a new microemulsion oral formulation (NEO) and the currently used soft gelatine capsule (SGC) was determined at steady state in 12 patients with rheumatoid arthritis. The AUC(0,12 h) values of cyclosporin A were significantly greater after NEO than SGC (2873 ± 848 ng ml⁻¹ h (mean ± s.d.) vs 2355 ± 1128 ng ml⁻¹ h; P = 0.02, 95% CI (confidence interval of the difference: 81 to 955 ng ml⁻¹ h). Cmax values were significantly higher after NEO than after SGC (811 ± 244 ng ml⁻¹ vs 495 ± 291 ng ml⁻¹, P < 0.0001, 95% CI of the difference: 209 to 422 ng ml⁻¹).

Keywords pharmacokinetics cyclosporin A rheumatoid arthritis

Introduction

The currently used oral formulation of cyclosporin A (CsA) is a soft gelatine capsule (SGC) in which the drug is dissolved in alcohol and maize oil [1]. Absorption of CsA from SGC is incomplete and highly variable [2], resulting in substantial inter- and intrasubject variability of plasma and whole blood drug concentrations [3–5]. The ‘therapeutic window’ is generally considered to be small [6], although in patients with rheumatoid arthritis (RA) and other autoimmune diseases the relationships between drug concentration and efficacy and toxicity are poorly defined [7].

A new liquid microemulsion oral formulation of CsA has been developed recently based on an oil in water microemulsion (NEO). Kovarik et al. [8] have shown that inter- and intra-individual variation in Cmax, tmax, AUC and t½ values was significantly less following administration of single doses of CsA in NEO compared with SGC in healthy subjects. Furthermore, Müller et al. [9] showed in a single dose crossover study in healthy males that the influence of a fat-rich meal on the absorption of CsA from NEO was less pronounced when compared with SGC. Under steady state conditions in renal transplant patients, Kovarik et al. [10] showed that CsA was 30% more bioavailable from NEO compared with SGC, independent of food intake.

In the present study we have determined the relative bioavailability of CsA from NEO and SGC in patients with RA at steady state. Data on efficacy, tolerability and safety of NEO and SGC were also collected.

Keywords pharmacokinetics cyclosporin A rheumatoid arthritis

Methods

Formulations

The standard oral formulation of CsA (SGC = Sandimmune®), contains the drug dissolved in alcohol and maize oil within a soft gelatine capsule [1]. Available doses are 25 mg and 100 mg.

A new oral formulation NEO = Sandimmune Neoral® incorporates the drug in a microemulsion preconcentrate containing a surfactant, lipophilic and hydrophilic solvents and ethanol within a hard gelatine capsule [10]. Available doses are 25 mg and 100 mg.

Both formulations were kindly supplied by Sandoz Pharma Ltd, Basle, Switzerland.

Protocol

The study protocol was approved by the Human Ethics Committee of the Wever Hospital, Heerlen, The Netherlands. Written informed consent was obtained from all patients and the study was carried out according to the European Guidelines for good clinical practice [11]. Though a randomised design is preferable, for practical reasons a non-randomised, open label study in which each patient served as his/her own control was used. The patients were seen at the outpatient clinic every 2 weeks (days –14 (screening visit), 0, 14, 28 and 42).

Twelve patients with RA according to the 1987 ARA criteria [12] were recruited. All had participated in an open label study in which CsA (SGC) had been
given as an investigational drug to assess its efficacy and tolerability [13]. For entry to the present study CsA (SGC) had to have been used for at least 3 months. The drug was given twice daily at 12 h intervals (09.00 h and 21.00 h) and the dosage regimen was stable for at least 2 weeks prior to the study.

At entry (day 0) SGC was changed to NEO at the same dose. All patients were provided with alarm watches and were instructed to take their medication at strict 12 h intervals.

On day 14 blood samples were taken into EDTA coated polypropylene tubes before the morning dosage and at 0.5, 1, 2, 3, 4, 5, 7, and 12 h thereafter. The samples were then stored at −20°C.

From day 14 to day 28 patients continued NEO twice daily at the same dose. On day 28 NEO was replaced by the same dose of SGC. On day 42 blood samples for CsA measurements were obtained as on day 14.

No dietary restrictions were made during the study period. Dietary habits were held constant for all patients on days 14 and 42, when the blood samples were obtained. No patient was taking drugs known to affect the metabolism of CsA.

**Drug assay**

All samples were assayed simultaneously and in duplicate for whole blood CsA concentrations, using a specific monoclonal antibody 125I-tracer (Incstar Cyclo-Trac SP) radioimmunoassay kit (Incstar Corp., Stillwater MN, USA) [14]. The limit of quantification was 28 ng ml⁻¹. At concentrations of 112 and 360 ng ml⁻¹, the respective interassay (n = 3) coefficients of variation were 2.75% and 3.50%.

**Pharmacokinetic analysis**

Morning pre-dose trough concentration (Cmin(1)), 12 h post-morning dose concentration (Cmin(2)), Cmax and tmax values were noted directly from the data. Values of AUC(0,12 h) were calculated using the linear trapezoidal rule.

**Assessment of efficacy and tolerability**

The following efficacy parameters were determined on day 0 (efficacy of SGC) and on day 28 (efficacy of NEO): the Ritchie articular index (RAI) (15), number of tender joints (TJC), and the number of swollen joints (NSJ). On day 42 (after switching NEO back to SGC) both patient and investigator assessed overall efficacy using a three point scale (‘SGC superior’, ‘NEO superior’ or ‘no difference’).

At each visit body weight, blood pressure, pulse rate and serum values of creatinine were determined. Tolerability was scored on a 5 point scale (1: very good, 2: good, 3: moderate, 4: poor, 5: very poor) by both the patient and the investigator on days 0 and 28.

**Statistics**

After checking for normal distribution, differences in AUC(0,12 h) and Cmax values between formulations were tested for significance by Student's t-test for paired observations, and 95% confidence limits for differences were estimated.

The normally distributed efficacy and safety parameters were tested for significance by analysis of variance (ANOVA) and differences between formulations characterized by Student’s t-test for paired observations and 95% confidence limits.

**Results**

**Patients and dosage schedule**

The mean (± s.d.) age and weight of the 12 RA patients (three male, nine female) was 58 ± 7 years and 71 ± 11 kg, respectively, and the mean disease duration was 15 ± 12 years. The patients had used CsA (SGC) for 20 ± 7 months before entering the study.

Two patients (3 and 9) received CsA (SGC) without having been previously treated with a disease modifying anti-rheumatic drug. Before entry to the present study, five patients had a reduction of CsA (SGC) dose because of an increased value of serum creatinine (patients 1, 6, 8, 10 and 11). Four patients needed a dose reduction because of other adverse events (patients 3, 7, 9 and 12). The mean CsA maintenance dose was 2.5 mg kg⁻¹ day⁻¹ (range 1.7 to 3.9 mg kg⁻¹ day⁻¹) (Table 1).

**Relative bioavailability**

Mean and individual pharmacokinetic parameters are shown in Table 1. The Cmax and AUC(0,12 h) values were significantly higher after NEO than SGC by about 20%.

**Efficacy and safety**

The mean RAI was 8.2 ± 5.9 on day 0 and 9.3 ± 8.4 on day 28 (P = 0.48; 95% CI of the difference: −4.8 to +2.4). The mean TJC was 6.7 ± 4.1 on day 0 and 6.9 ± 5.7 on day 28 (P = 0.91; 95% CI of the difference: −3.5 to +3.1). The mean NSJ was 3.8 ± 1.9 on day 0 and 4.1 ± 1.8 on day 28 (P = 0.65; 95% CI of the difference: −1.6 to +1.0). The investigator scored no difference in efficacy between NEO and SGC in 83% (10/12) of the patients and a superiority for NEO in 17% (2/12). The patients scored no difference between NEO and SGC in six cases (50%) and a superiority of NEO or SGC in three (25%) each.

Body weight, systolic and diastolic blood pressure, pulse rate and serum values of creatinine did not change during the study (data not shown).

The tolerability of SGC was assessed as ‘very good’ in 75% (9/12) and as ‘good’ in 25% (3/12) of the patients. The tolerability of NEO was assessed as ‘very good’ in 33% (4/12), ‘good’ in 50% (6/12), ‘moderate’ in 8% (1/12) and ‘poor’ in 8% (1/12) of the patients. The investigator assessed the tolerability of SGC as ‘very good’ in 58% of the patients (7/12), ‘good’ in 33% (4/12) and ‘moderate’ in 8% (1/12). The tolerability of NEO was assessed by the investiga-
Table 1 Pharmacokinetic parameters of CsA in 12 rheumatoid arthritis patients after administration of two different oral formulations

<table>
<thead>
<tr>
<th>Patient number</th>
<th>CsA (mg kg⁻¹ day⁻¹)</th>
<th>Cₘₙ₁ (ng ml⁻¹) NEO*</th>
<th>Cₘₙ₁ (ng ml⁻¹) SGC**</th>
<th>Cₘ₉ (ng ml⁻¹) NEO</th>
<th>Cₘ₉ (ng ml⁻¹) SGC</th>
<th>tₘ₉ (h)</th>
<th>AUC(0,12 h) (ng ml⁻¹ h) NEO</th>
<th>AUC(0,12 h) (ng ml⁻¹ h) SGC</th>
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<tr>
<td>1</td>
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<td>71</td>
<td>81</td>
<td>70</td>
<td>101</td>
<td>0.05</td>
<td>1879</td>
<td>984</td>
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<tr>
<td>2</td>
<td>2.5</td>
<td>64</td>
<td>88</td>
<td>54</td>
<td>58</td>
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<td>1692</td>
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<tr>
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<td>142</td>
<td>123</td>
<td>132</td>
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<td>Mean</td>
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<td>109</td>
<td>105</td>
<td>157</td>
<td>1.0</td>
<td>2873</td>
<td>2355</td>
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<tr>
<td>± s.d.</td>
<td>± 0.6</td>
<td>± 58</td>
<td>± 37</td>
<td>± 47</td>
<td>± 15</td>
<td>±  ±</td>
<td>± (0.5–1.0)</td>
<td>± (1.0–2.0)</td>
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<td>95% CI of difference</td>
<td>−9 to 26</td>
<td>−128 to 23</td>
<td>209 to 422</td>
<td>−3 to 1</td>
<td>81 to 955</td>
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<td>0.15</td>
<td>&lt;0.001</td>
<td>0.22</td>
<td>0.02</td>
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</table>

Cₘₙ₁(1) = morning pre-dose minimum whole blood drug concentration (= trough level); Cₘₙ₁(2) = 12 h post morning dose minimum whole blood drug concentration; Cₘ₉ = maximum whole blood drug concentration; tₘ₉ = time to maximum whole blood drug concentration; AUC(0,12 h) = area under the blood drug concentration-time curve from 0–12 h. *New oral formulation as oily solution or capsule. Artzeit-Forsch/Drug Res 1990; 40: 62–64.

Discussion

We conclude that the relative bioavailability of CsA from NEO is about 20% greater than from SGC, although trough drug concentrations are similar. The results of the present study are in accordance with the results of the single dose study with NEO in healthy volunteers and the steady state study in renal transplant patients by Kovarik et al. [8, 10].

Neither overall efficacy nor tolerability assessments disclosed differences.

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References


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