Unpredictable cyclosporin–fluconazole interaction in renal transplant recipients

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Abstract

Background. Cyclosporin (CsA) is metabolized primarily in the liver by cytochrome P-450 enzymes. Concomitant use of fluconazole can increase CsA concentrations by inhibiting this enzyme system and the effect seems to be dose dependent, with no interaction noted when fluconazole is used in a dose of 100 mg/day. Two previous investigations studying this interaction while using higher doses of fluconazole have provided inconsistent results. Recommendations advising an empirical 50% CsA dosage reduction in these patients have not been tested in a prospective trial.

Methods. We studied six renal transplant recipients on CsA immunosuppression in a prospective, unblinded, crossover trial. Baseline renal functions, CsA area under the curve (AUC), Cmax, Cmin, CsA clearance, and Tmax were compared with those 2, 4 and 7 days after starting fluconazole orally in a dose of 200 mg/day. From day 8 onwards, patients reduced CsA dose by 50% and the above parameters were repeated on day 14.

Results. CsA AUC increased from 2887±1729 ng.h/ml on day 0 to 3842±1975 ng.h/ml on day 2 (P<0.05), 4750±1718 ng.h/ml on day 4 (P<0.01) and then decreased to 4052±1687 ng.h/ml on day 7 (P<0.01). Following CsA dose reduction by 50%, the mean AUC decreased significantly to 2330±1602 ng.h/ml (P<0.01). The Cmax showed a significant increase from 701±345 ng/ml on day 0 to 941±326 ng/ml (P<0.01) on day 4 but decreased from 768±292 ng/ml on day 7 to 498±289 ng/ml on day 14, P<0.01. The mean Cmin increased from 207±138 ng/ml on day 0 to 274±168 ng/ml on day 4. No significant changes were observed in CsA clearance and Tmax. On repeated-measurement ANOVA, only the AUC and Cmax on day 4 of fluconazole were significantly higher than day 0 (P<0.001). There was a large interindividual variability in the degree of drug interaction between patients.

Conclusions. Fluconazole given orally in a dose of 200 mg/day is associated with significant increase in bioavailability of CsA. The maximum effect occurs on day 4 after starting fluconazole. Although repeated monitoring of CsA Cmin is convenient as opposed to repeated determination of AUC, changes in Cmin may not be sensitive enough to pick up this interaction. The increase in bioavailability of CsA is unpredictable in individual patients and all patients should be monitored with AUC near day 4 of treatment to guide CsA dosage reductions.

Key words: cyclosporin A; drug interaction; fluconazole; transplantation

Introduction

Cyclosporin (CsA), continues to be widely used in most immunosuppressive regimens to prevent allograft rejection in patients after solid organ transplantation. However this drug is bestowed with a narrow therapeutic range and there is marked inter-individual and intra-individual variability in terms of the blood levels achieved after a given dose [1,2]. The use of microemulsified preparation of the drug has minimized the intra-individual variability in absorption of the drug and linearity in bioavailability [3]. CsA is metabolized primarily in the liver by cytochrome P-450 group of enzymes, in particular the CYP3A4 [4]; drugs that stimulate or inhibit this enzyme system can significantly alter bioavailability of the drug.

Fungal infections are not uncommon after renal transplantation and systemic fungal infections are associated with a high mortality [5]. Current options for treating serious fungal infections include systemic amphotericin B, fluconazole or the imidazole group of anti-fungal agents which include ketoconazole, fluconazole and itraconazole. Although amphotericin B...
is the drug of choice for serious fungal infections, it requires weeks of intravenous administration and can cause serious nephrotoxic effects, especially when used in combination with CsA. These effects preclude its use in patients with less serious infections and in the maintenance phase of therapy. The imidazole group of drugs are appealing alternatives, but for their potential for inhibiting the hepatic cytochrome P-450 enzyme system and increasing CsA concentrations to toxic proportions. This group of drugs, in particular fluconazole, is routinely used for prophylaxis against fungal infections in many centres, especially after liver and bone marrow transplantation (BMT).

Fluconazole produces less marked inhibition of hepatic cytochrome P-450 enzyme CYP3A4 as compared to ketoconazole, at least in vitro [6,7]. The potential interaction of oral fluconazole 200 mg/day with CsA was systematically studied in a randomized double blind placebo controlled trial by Canafax et al. [8] who concluded that CsA trough levels almost doubled after 1 week and CsA clearance decreased by an average of 55%. However, because bioavailability of CsA is known to show a considerable inter-individual variation, the study design can be faulted and a cross-over design where the patient acts as his own control, would be preferable in this situation. Moreover, recent prospective trial on BMT patients receiving intravenous CsA and high dose intravenous fluconazole concluded that the drug interaction was not of any clinical significance [9]. The effect, if any, begins to appear between 3 (8) and 7 (10) days of starting fluconazole. Recommendations have been made to reduce CsA dose by 50% after starting fluconazole to avoid CsA toxicity [10,11], but this recommendation has not been tested in a prospective trial.

**Subjects and methods**

Six renal transplant recipients on CsA immunosuppression with stable graft functions for at least 2 weeks (defined as a change in serum creatinine of <20%) were studied in a prospective, unblinded, crossover trial. All patients had evidence of systemic candidiasis requiring anti-fungal treatment. Only patients on microemulsified preparation of CsA (Sandimmun Neoral, Novartis Pharma AG, Basel, Switzerland), who had not had any alteration in CsA dosages in the previous 2 weeks were included. Patients having received in the previous 2 weeks any drug known to potentiate the nephrotoxicity of CsA or those with planned co-administration of any other drug known to interfere with CsA pharmacokinetics were excluded. Patients with histories of acute/chronic liver disease and women of childbearing potential who were likely to get pregnant or were lactating were also excluded.

Baseline laboratory data were checked within 72 h of starting the trial and included a haemogram, liver function tests, serum creatinine, and calculation of CsA area under the curve (AUC). For the latter, patients were asked to take their usual morning CsA dose. Blood for estimating CsA concentration was drawn just prior to ingestion of the dose and subsequently at 1, 2, 4, 6 and 8 h after the dose. Patients were started on fluconazole (Flumycin, Pfizer Amboise, France) orally in a dose of 200 mg/day (day 1). All investigations including CsA levels were repeated on days 2, 4 and 7. From day 8 onwards, patients were instructed to reduce the CsA dose by 50% of their original dose and all investigations, including calculation of CsA AUC and CsA clearance were repeated on day 14. For estimating CsA concentrations, 3 ml of blood was collected in EDTA vials and refrigerated at 2–8°C. The whole-blood CsA levels were analysed using Cyclo-Trac SP (Incstar Corporation, Stillwater, Minnesota, USA) radioimmunoassay kit, which utilizes mouse monoclonal antibodies specific against the parent CsA molecule. The mean inter-assay and intra-assay coefficients of variation using this kit at our laboratory are 6.8% and 4.3% respectively.

Routine CsA trough level monitoring is not practised at this centre because of financial constraints and this is only performed when clinically indicated. Patients exhibiting a rise in serum creatinine more than 20% above their baseline value during the course of the study were required to be removed from the study protocol and undergo a graft biopsy. The results of CsA blood levels in these patients were to be made available to the treating clinician on request. In the absence of any graft dysfunction, the results of CsA blood levels were available to the clinician only after completion of the study protocol. Based on available literature, before the study was planned, it had been the practice at this centre to reduce CsA dose by 50% after a week of treatment with 200 mg or more of oral fluconazole a day. All patients were enrolled after obtaining informed consent, and had the option to withdraw from the study protocol whenever they desired. The study protocol had the sanction of the Ethics Committee of the Institute.

**Statistical and pharmacokinetic analysis**

AUC were calculated using the Microcal Origin (version 2.94) computer software program after plotting each patient’s CsA blood levels at 0, 1, 2, 4, 6 and 8 h of ingestion of the drug. The maximum blood concentration (Cmax) was determined by observation of each patient’s data; and Tmax was the time that Cmax first occurred. Cmin was the concentration of CsA in blood drawn just before ingestion of the CsA dose. CsA clearance was calculated using the formula:

$$\text{Clearance (ml/m/kg)} = \frac{\text{CsA dose (ng)} \times 1440 \text{min}}{\text{Cmin (ng/ml)} \times \text{Ideal body weight (kg)}}$$

Paired t test was used to assess the differences in serum creatinines, CsA AUC, Cmax, Cmin, CsA clearance, and Tmax with and without fluconazole and after 50% CsA dose reduction. Factorial analysis was done using the SPSS (version 6) computer software program to test any interaction between CsA AUC, Cmax, Cmin and CsA clearance with time. Repeated measurement ANOVA was performed to test for intra-individual variability in these parameters with time. Only P values <0.05 were considered significant.

**Results**

Six renal transplant recipients aged 39.2 ± 12.7 years (range 19–53 years) and 8.3 ± 6.2 months (range 3–19 months) after transplantation receiving the microemulsified preparation of CsA (Sandimmun Neoral) in a dose of 3–6 mg/kg/day were included. Patients weighed 59.8 ± 5.8 kg (range 57–69 kg). Three patients...
had oesophageal candidiasis and no other apparent cause for fever; two patients had pulmonary candidiasis, and one had cryptococcal meningitis. The mean serum creatinine, CsA AUC, \( C_{\text{max}} \), \( C_{\text{min}} \), CsA clearance, and \( T_{\text{max}} \) are shown in Table 1.

The mean serum creatinine increased from \( 139.0 \pm 30.4 \, \mu\text{mol/l} \) to \( 154.7 \pm 36.1 \, \mu\text{mol/l} \) on day 4 \( (P < 0.01) \) and \( 156.4 \pm 35.6 \, \mu\text{mol/l} \) on day 7 \( (P < 0.01) \). There was a significant decrease in serum creatinine to \( 147.8 \pm 30.4 \, \mu\text{mol/l} \) \( (P < 0.05) \) on day 14 of treatment. CsA AUC increased from \( 2887.8 \pm 1729.7 \, \text{ng.h/ml} \) on day 0 to \( 3842.3 \pm 1975.8 \, \text{ng.h/ml} \) on day 2 \( (P < 0.05) \), \( 4750.5 \pm 1718.4 \, \text{ng.h/ml} \) on day 4 \( (P < 0.01) \) and declined to \( 4052.0 \pm 1687.9 \, \text{ng.h/ml} \) on day 7 \( (P < 0.01) \). Following CsA dose reduction by 50%, the mean AUC decreased significantly to \( 2330.8 \pm 1602.9 \, \text{ng.h/ml} \ \( (P < 0.01) \) and there was no significant difference between the mean AUC on day 0 and day 14. The \( C_{\text{max}} \) showed a significant increase from \( 701.8 \pm 345.1 \, \text{ng/ml} \) on day 0 to \( 941.5 \pm 326.6 \, \text{ng/ml} \ \( (P < 0.01) \) on day 4. After CsA dose reduction by 50%, the \( C_{\text{max}} \) decreased from \( 768.0 \pm 292.0 \, \text{ng/ml} \) on day 7 to \( 498.0 \pm 289.0 \, \text{ng/ml} \) on day 14, \( P < 0.05 \). The mean \( C_{\text{min}} \) on day 14 was significantly lower as compared to the mean \( C_{\text{max}} \) on day 0 \( (P < 0.05) \). The mean \( C_{\text{min}} \) increased from \( 207.7 \pm 138.3 \, \text{ng/ml} \) on day 0 to \( 274.0 \pm 168.8 \, \text{ng/ml} \) on day 4. The \( C_{\text{min}} \) on day 14 \( (174.7 \pm 123.3 \, \text{ng/ml}) \) was significantly lower than that on day 0 \( (P < 0.05) \). The mean CsA clearances on day 2 \( (18.3 \pm 4.2 \, \text{ml/min/kg}) \) and day 4 \( (13.1 \pm 4.2 \, \text{ml/min/kg}) \) were not significantly different from those on day 0 \( (16.9 \pm 5.2 \, \text{ml/min/kg}) \); however, the reduction in CsA clearance on day 7 \( (12.0 \pm 3.7 \, \text{ml/min/kg}) \) approached statistical significance \( (P = 0.08) \). There were no significant changes observed in \( T_{\text{max}} \). The changes in AUC in individual patients during the study period are shown in Figure 1.

The percentage changes in AUC, \( C_{\text{max}} \), \( C_{\text{min}} \) and CsA clearance on days 2, 4, 7 and 14 as compared to day 0 are shown in Table 2. The AUC on day 2 showed an increase of 40.95 ± 33.82% over day 0; however, the percentage increase varied over 10-fold (7.1–86.6%) in individual patients. The AUC were higher by 87.48 ± 77.65% \( (\text{range} \, 24.8–233.5\%) \) on day 4 and 56.1 ± 49.93% \( (\text{range} \, 3.5–143.3\%) \) on day 7 as compared to day 0. After 50% reduction in CsA dosage, the AUC on day 14 were \( -15.70 \pm 48.29 \% \) \( (\text{range} \, -78.9 \% \text{to} \, 50.0\%) \) different from the AUC on day 0. Similar inter-individual variability in percentage changes in \( C_{\text{max}} \), \( C_{\text{min}} \) and CsA clearance were seen during the study period (Table 2). On factorial analysis to test for any interaction between patients with time, a significant interaction was seen in AUC, \( C_{\text{max}} \) and \( C_{\text{min}} \) \( (P < 0.001) \), suggesting thereby that each patient was behaving differently over time. Assuming an insignificant interaction with time, the main effect model was used and a significant difference was observed in changes in AUC and \( C_{\text{max}} \) during the study period \( (P < 0.001) \), but changes in \( C_{\text{min}} \) and CsA clearance did not reach statistical significance \( (P > 0.05) \). On repeated measurement ANOVA, which controls for intra-individual variabilities, only the AUC at day 4 of fluconazole were higher from day 0 levels \( (P < 0.001) \). In addition, \( C_{\text{max}} \) on day 4 were also significantly higher than those on day 0 \( (P < 0.01) \). Changes in \( C_{\text{min}} \) and CsA clearance over time were not found to be significantly different. None of the patients developed alterations in liver function tests or graft dysfunction necessitating withdrawal from study protocol.

**Discussion**

The majority of reports describing an interaction between fluconazole and CsA are published as case reports. Initial reports on this potential interaction concluded that fluconazole given orally in a dose of 100 mg/day did not have any significant interaction with CsA \([12–15]\). Subsequently case reports describing an interaction with doses ranging from 100 mg \([16]\) to 200 mg \([17,18]\) started appearing. A recent large prospective randomized trial using fluconazole in a dose of 100 mg/day for prophylaxis against candida infections in liver-transplant recipients failed to show

| Table 1. Changes in serum creatinine and cyclosporin bioavailability parameters during the study |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Se creatinine (\( \mu\text{mol/l} \)) | 139.0 ± 30.4 | 144.1 ± 35.7 | 154.7 ± 36.1 | 156.4 ± 35.6 | 147.8 ± 30.4 |
| AUC (\text{ng.h/ml}) | 2887.8 ± 1729.7 | 3842.3 ± 1975.8 | 4750.5 ± 1718.4 | 4052.0 ± 1687.9 | 2230.8 ± 1602.9 |
| \( C_{\text{max}} \) (\text{ng/ml}) | 701.8 ± 345.1 | 821.8 ± 226.4 | 941.5 ± 362.6 | 786.8 ± 292.0 | 498.0 ± 289.0 |
| \( C_{\text{min}} \) (\text{ng/ml}) | 207.7 ± 138.3 | 291.5 ± 170.6 | 274.0 ± 168.8 | 293.2 ± 171.2 | 174.7 ± 123.3 |
| CsA clearance (\text{ml/min/kg}) | 16.9 ± 5.2 | 18.3 ± 9.4 | 13.1 ± 4.2 | 12.0 ± 3.7 | 30.3 ± 32.7 |
| \( T_{\text{max}} \) (h) | 3.0 ± 1.1 | 2.8 ± 1.3 | 2.0 ± 1.1 | 2.5 ± 1.2 | 3.0 ± 1.1 |

All values have been expressed as means ± 2SD.

\( ^{1}P < 0.05 \) when compared with day 0;

\( ^{2}P < 0.01 \) when compared with day 0;

\( ^{3}P < 0.05 \) when compared with day 4;

\( ^{4}P < 0.01 \) when compared with day 4;

\( ^{5}P < 0.05 \) when compared with day 7;

\( ^{6}P < 0.01 \) when compared with day 7.
any significant interaction with CsA [19]. One of the two published studies confirming this interaction used oral fluconazole in a dose of 200 mg/day [8] but can be faulted for its study design, as it randomized patients to receive either fluconazole or placebo. This study was done in patients receiving a non-emulsified preparation of CsA, which is known to possess marked inter-individual and intra-individual variability in gastrointestinal absorption and systemic bioavailability of the drug [1]. These drawbacks were overcome in this study by selecting patients receiving only the micro-emulsified preparation of CsA (Sandimmun Neoral) and employing a crossover study design, where patients acted as their own controls.

In our study, we showed that mean CsA AUC increased from day 2 onwards and peaked on day 4 of starting 200 mg of oral fluconazole. There was a reduction in AUC on day 7 as compared to day 4, thereby raising the possibility of autoinduction of the hepatic P-450 enzyme system. Fifty per cent reduction in CsA dose resulted in a fall in AUC to levels not significantly different from the baseline values. The mean $C_{\text{max}}$ also increased and peaked on day 4 of fluconazole. There was a reduction in mean $C_{\text{max}}$ on day 7, although this was not statistically significant. Moreover the mean $C_{\text{max}}$ on day 14 were significantly lower than those on day 0. The mean $C_{\text{min}}$ increased from day 0 to day 4 and the $C_{\text{min}}$ on day 14 were significantly lower than those on day 0. Apart from reduction in CsA clearance on day 7 of treatment with fluconazole that approached statistical significance, no changes in this parameter were observed with time. In addition, no significant changes in $T_{\text{max}}$ were seen during the course of the study. Although the mean serum creatinine increased on day 4 and day 7 as compared to day 0, none of the patients had an increase of more than 20% from baseline necessitating withdrawal from study protocol. There was a significant decrease in serum creatinine after 50% reduction in the CsA dosage. None of the patients developed alterations in liver function tests.

Canafax et al. [8] in their study measured CsA trough levels daily during treatment with 200 mg of oral fluconazole. AUC were done as baseline and after 2 weeks of fluconazole. They found that the trough levels started increasing by day 3 and the trough levels after a week of treatment were significantly higher than baseline values. In addition, the AUC after 2 weeks of fluconazole were significantly higher than the baseline. We believe that it is possible that bioavailability (and AUC) of CsA had increased before 7 days of treatment in the patients studied by Canafax et al., because trough levels are a poor indicator of total bioavailability of the drug especially when a non-emulsified preparation of CsA is used [1]. This could only have been confirmed if AUC estimations were performed more frequently in their study. A recent study on high dose (400 mg/day) intravenous fluconazole in six BMT recipients receiving intravenous CsA found a 21% increase in CsA steady-state levels after about 1 week of treatment [9]. However, the authors believe that this increase in CsA levels was not of clinical significance as they did not observe any ‘adverse effects’ on renal functions during the study period. The threshold for diagnosing renal toxicity in this study was a minimum rise in serum creatinine more than twice the baseline value. Although this much increase in serum creatinine may be ‘acceptable’ in BMT patients, in renal transplant recipients a much smaller rise in serum creatinine is of considerable concern to the treating physician. In our study, a slight but statistically significant increase in serum creatinine levels was observed on days 4 and 7 of treatment with fluconazole, coinciding with the increments in AUC and $C_{\text{max}}$ of CsA.

![Fig. 1. Cyclosporin AUC during treatment with fluconazole.](image-url)
Similar alterations in renal functions during concomitant use of CsA and fluconazole were reported by Canafax et al. [8] and others [14,20].

The degree of interaction between fluconazole and CsA was different and unpredictable in individual patients. The peak increase in AUC over baseline varied 10–40 fold during the study period. Moreover the AUC achieved after 7 days of CsA dosage reduction by half resulted in AUC which ranged from 78.9% below the baseline to 50% above the baseline. Similar inter-individual variability in percentage changes were seen in C\text{max}, C\text{min}, and CsA clearance also. This inter-individual variability in changes in AUC, C\text{max} and C\text{min} was confirmed on factorial analysis. We have also shown that in individual patients (regardless of the inter-individual variability), CsA trough levels are poor indicators of any ongoing changes in bioavailability of the drug due to an interaction with fluconazole. In this situation changes in AUC and C\text{max} are more likely to be apparent. Moreover, on repeated measurement ANOVA, which controls for intra-individual variabilities, only the AUC at day 4 of fluconazole were different from those on day 0 levels. Although bioavailability of fluconazole exceeds 90% after oral administration and is unaffected by food or gastric pH, it would have been ideal to measure fluconazole levels to control for any inter-individual variations in bioavailability of this antifungal agent. In this study, we took patients receiving only the microemulsified preparation of CsA, which possesses much less intra-individual variation in the pharmacokinetics of the drug.

Our findings support observations that CsA bioavailability has marked inter-individual variability. In addition, we believe that alterations in CsA pharmacokinetics with fluconazole also possesses marked inter-individual variations. Similar inter-individual variability in sensitivity of CsA metabolism to inhibition by fluconazole was reported in an in vitro study on human liver substrates recently [7]. Therefore, no firm recommendations can be made on empirical CsA dosage reduction when CsA treatment is combined with fluconazole in a dose of 200 mg/day. The possibility of any interaction with lower doses of fluconazole was not evaluated in the present study. Moreover, whether fluconazole used in doses more than 200 mg/day will have a greater degree of effect on CsA bioavailability was also not evaluated in this study.

We conclude that oral fluconazole given in a dose of 200 mg/day is associated with significant increase in bioavailability of CsA. The maximum effect occurs on day 4 after starting fluconazole. Changes in CsA trough levels are not sensitive enough to pick up this interaction. The increase in bioavailability of CsA is unpredictable in individual patients and no firm recommendations can be made regarding empirical dosage reduction of CsA when used in combination with fluconazole. All patients on CsA requiring fluconazole for treatment of systemic fungal infections should be monitored with AUC near day 4 of treatment to guide CsA dosage reductions.

### Table 2. Changes in AUC, C\text{max}, C\text{min} and CsA clearance from baseline values at day 0

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<th>%change at day 7</th>
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<td>AUC</td>
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