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The effect of itraconazole on the pharmacokinetics and pharmacodynamics of oral prednisolone

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Abstract *Objective*: To examine the possible effect of itraconazole on the pharmacokinetics and pharmacodynamics of orally administered prednisolone.
Methods: In this double-blind, randomised, two-phase cross-over study, ten healthy subjects received either 200 mg itraconazole or placebo orally once a day for 4 days. On day 4, 20 mg prednisolone was given orally. Plasma concentrations of prednisolone, cortisol, itraconazole, and hydroxyitraconazole were determined by means of high-performance liquid chromatography up to 47 h.
Results: Itraconazole increased the total area under the plasma prednisolone concentration–time curve by 24% ($P < 0.001$) and the elimination half-life of prednisolone by 29% ($P < 0.001$) compared with placebo. The peak plasma concentration and time to the peak of prednisolone were not affected by itraconazole. The mean morning plasma cortisol concentration, measured 23 h after the ingestion of prednisolone, during the itraconazole phase was 73% of that during the placebo phase ($P < 0.001$).
Conclusions: The observed minor interaction between itraconazole and oral prednisolone is probably of limited clinical significance. The susceptibility of prednisolone to interact with CYP3A4 inhibitors is considerably smaller than that of methylprednisolone, and itraconazole and probably also other inhibitors of CYP3A4 can be used concomitantly with prednisolone without marked changes in the effects of this corticosteroid.

Key words Prednisolone · Itraconazole · Interaction

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Introduction

Prednisone, prednisolone and methylprednisolone are synthetic glucocorticoids. Prednisone is metabolised to prednisolone, which is the active form of the drug. Steroid hormones are thought to be metabolised, at least partly, by cytochrome P4503A4 (CYP3A4) [1, 2]. Itraconazole, a potent inhibitor of CYP3A4, considerably increases the plasma concentrations and decreases the clearance of methylprednisolone [3, 4], and concomitant use of itraconazole and methylprednisolone can increase the risk of glucocorticoid-related adverse effects [5].

Inhibition of the metabolism of prednisolone by other drugs may have clinical consequences, because decreased clearance of prednisolone is a risk factor for the development of corticosteroid adverse effects [6]. The aim of this study was to examine the effects of itraconazole on the pharmacokinetics and pharmacodynamics of orally administered prednisolone in healthy volunteers.

Materials and methods

Subjects

Written informed consent was obtained from five female and five male subjects (Table 1). They were considered to be healthy on the basis of medical history, physical examination and routine laboratory tests. None of the subjects was a smoker or used continuous medication (including oral contraceptive steroids). Grapefruit products were prohibited during the study period, starting 2 weeks before the first study day.

Study design

A randomised, double-blind, placebo-controlled cross-over study design with two phases, at an interval of 4 weeks, was used. The subjects took either 200 mg itraconazole (Sporanox 100-mg capsule, Janssen-Cilag, Beerse, Belgium) or placebo orally once daily for 4 days. On days 1–3, the medication was taken at 0730 hours with breakfast. On day 4, itraconazole or placebo was taken at the study site at 0800 hours after an overnight fast, and 20 mg prednisolone (Prednisolon 20-mg tablet, Leiras, Finland) was given

Table 1 Characteristics of the subjects and the area under the plasma concentration–time curve ($AUC_{0–23\ h}$) values of itraconazole and hydroxyitraconazole on day 4. AUC was calculated from the time of administration of prednisolone

Subject number	Gender	Age (years)	Weight (kg)	Itraconazole $AUC_{0–23\ h}$ (μg h/ml)	Hydroxyitraconazole $AUC_{0–23\ h}$ (μg h/ml)
1	Male	19	74	1.66	11.52
2	Male	21	68	6.55	12.97
3	Female	20	45	5.15	14.34
4	Male	22	78	2.65	7.42
5	Male	20	77	6.93	14.84
6	Female	30	61	1.66	5.03
7	Female	22	60	5.55	14.19
8	Male	25	90	3.80	10.25
9	Female	34	70	2.23	6.79
10	Female	22	65	3.50	9.86

with 150 ml water 1 h later. A light standard meal was served 2 h and 10 h and a standard lunch 6 h after prednisolone administration. The study protocol was approved by the Ethics Committee of the Department of Clinical Pharmacology, University of Helsinki (Helsinki, Finland) and the Finnish National Agency for Medicines.

Blood sampling and determination of plasma drug and cortisol concentrations

A forearm vein was cannulated during the morning of day 4. Timed blood samples (10 ml each) were drawn into tubes that contained ethylene diamine tetraacetic acid (EDTA) before prednisolone administration and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 23 and 47 h later. Plasma was separated within 30 min and stored at −40 °C until analysis. Plasma prednisolone and cortisol concentrations were determined by means of high-performance liquid chromatography (HPLC) using dexamethasone as an internal standard [7]. The quantification limit was 5 ng/ml for prednisolone and 2 ng/ml for cortisol. The interday coefficient of variation (CV) for prednisolone was 8.5% at 11 ng/ml ($n = 6$), 2.8% at 49 ng/ml ($n = 6$) and 3.8% at 227 ng/ml ($n = 6$). The interday CV for cortisol was 3.7% at 12 ng/ml ($n = 6$), 3.3% at 50 ng/ml ($n = 6$) and 3.2% at 230 ng/ml ($n = 6$). Itraconazole and hydroxyitraconazole concentrations were determined by HPLC [8] in samples taken 1, 5, 9 and 24 h after the fourth dose of itraconazole (i.e. just before prednisolone administration and 4, 8 and 23 h later). The quantification limit was 10 ng/ml for both compounds.

Pharmacokinetics

The pharmacokinetics of prednisolone were characterised by peak concentration in plasma (C_{max}), time to C_{max} (t_{max}), area under the prednisolone plasma concentration–time curve ($AUC_{0-\infty}$), and elimination half-life ($t_{1/2}$) [9]. The C_{max} and t_{max} were obtained directly from the data. The prednisolone elimination rate constant (k_{el}) was calculated using linear regression analysis of the log-linear part of the plasma concentration–time curve. The AUC was calculated using the linear trapezoidal rule, with extrapolation to infinity by dividing the last measured concentration by k_{el}. The $t_{1/2}$ was calculated from the equation, $t_{1/2} = \ln 2/k_{el}$. The $AUC_{0–23\ h}$ values for itraconazole and hydroxyitraconazole refer to the time between 0 h and 23 h after the intake of prednisolone, that is, 1 h and 24 h after the last dose of itraconazole.

Pharmacodynamics

The effect of prednisolone on endogenous cortisol secretion was evaluated by measuring the morning plasma cortisol concentration (normal range in the morning, 50–250 ng/ml) at 0800 hours on the fourth pretreatment day (i.e. 1 h before the intake of prednisolone) and on the following 2 days (i.e. 23 h and 47 h after the administration of prednisolone).

Statistical analysis

Results are expressed as mean values (±SD) (SEM in Fig. 1), except for t_{max} which is presented as median with range. The pharmacokinetic variables and 23-h and 47-h plasma cortisol concentrations between the phases were compared using a paired (two-tailed) *t*-test. The Wilcoxon test was used for analysis of t_{max}. Pearson's correlation coefficient was used to evaluate the correlation between the changes in the pharmacokinetic variables of prednisolone and the $AUC_{0–23\ h}$ of itraconazole and hydroxyitraconazole. The data were analysed using the statistical program Systat for Windows, version 6.0.1 (SPSS Inc., Chicago, Ill.). The level of significance was $P < 0.05$.

Results

Prednisolone

Itraconazole slightly increased the plasma concentrations of prednisolone (Fig. 1). Itraconazole increased the $AUC_{0-\infty}$ of prednisolone by 24% (range 9–50%; $P < 0.001$) and the $t_{1/2}$ by 29% (range 16–54%; $P < 0.001$) compared with placebo (Fig. 1, Table 2). An increase in the $AUC_{0-\infty}$ and the $t_{1/2}$ of prednisolone after itraconazole was seen in all the subjects. The C_{max} and t_{max} values of prednisolone were not affected by itraconazole.

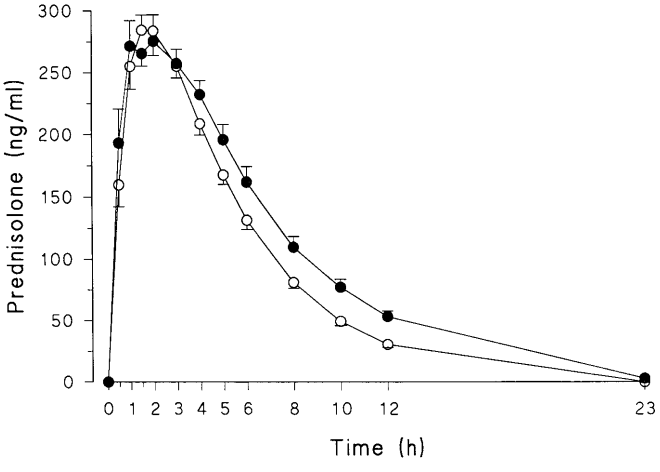

Fig. 1 Plasma concentrations of prednisolone in ten subjects (mean ± SEM) after 20 mg oral prednisolone, following pretreatment with 200 mg itraconazole or placebo once daily for 4 days. *Solid circles* after itraconazole; *open circles* after placebo

Table 2 The pharmacokinetic variables of 20 mg oral prednisolone in ten subjects after placebo or 200 mg itraconazole once a day for 4 days. Data are given as mean ± SD values. t_{max} is given as median (range)

Variable	Placebo phase (control)	Itraconazole phase
C_{max} (ng/ml)	303 ± 44	312 ± 31
% of Control (95% CI)	100	104 (95–114)
t_{max} (h)	1.5 (1.0, 3.0)	1.5 (1.0, 4.0)
$t_{1/2}$ (h)	2.8 ± 0.4	3.6 ± 0.4*
% of Control (95% CI)	100	129 (121–138)
$AUC_{0-\infty}$ (ng h/ml)	1810 ± 242	2240 ± 353*
% of Control (95% CI)	100	124 (115–133)

*$P < 0.001$ versus placebo phase

Cortisol

The morning plasma cortisol concentration measured 23 h after the administration of 20 mg prednisolone was significantly ($P < 0.001$) lower during the itraconazole phase than during the placebo phase (104 ± 39 ng/ml versus 141 ± 33 ng/ml; Fig. 2). After the administration of prednisolone, the morning plasma cortisol was below the lower limit of the normal range in one subject during the itraconazole phase (Fig. 2). There was no significant difference in the morning plasma cortisol between the itraconazole and placebo phases on day 4 (just before ingestion of prednisolone) or 47 h after the administration of prednisolone.

Itraconazole and hydroxyitraconazole

The $AUC_{0-23\ h}$ of itraconazole and hydroxyitraconazole ranged from 1.66 μg h/ml to 6.93 μg h/ml and from 5.03 μg h/ml to 14.8 μg h/ml, respectively (Table 1). There were no significant correlations between the changes in the pharmacokinetic variables of prednisolone and the $AUC_{0-23\ h}$ of itraconazole or hydroxyitraconazole.

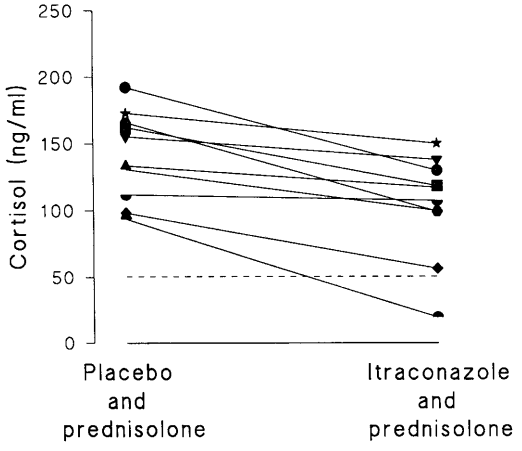

Fig. 2 The individual plasma cortisol concentrations measured 23 h after the intake of 20 mg prednisolone during the placebo and itraconazole phases in ten subjects. The *broken line* indicates the lower limit of the normal range of the morning plasma cortisol concentration

Discussion

In the present study, the use of itraconazole for 4 days resulted in minor, although statistically significant increases in the $AUC_{0-\infty}$ and $t_{1/2}$ of oral prednisolone. In addition, the mean morning plasma cortisol concentration, measured 23 h after the intake of prednisolone, was decreased by about 25% during the itraconazole phase.

The oral bioavailability of prednisolone is high, about 80%, suggesting only a limited role of presystemic metabolism in its pharmacokinetics [10]. Considering the minor increases in the $AUC_{0-\infty}$ and $t_{1/2}$ of prednisolone by itraconazole and the fact that itraconazole is a potent inhibitor of CYP3A4 in vivo [11, 12], this enzyme probably plays only a small role in the metabolism of prednisolone. However, the present results suggest that the systemic clearance of prednisolone was slightly decreased by itraconazole, assuming that the volume of distribution of prednisolone was not altered by itraconazole.

Previous interaction studies with prednisone or prednisolone and CYP3A4 inhibitors have found somewhat discrepant results. In the study of Zürcher et al. [13], ketoconazole (200 mg/day) increased plasma concentrations of prednisolone by about 50% following oral prednisone or i.v. prednisolone administration. Two other studies failed to find any effect with 200 mg/day ketoconazole on either the pharmacokinetics or pharmacodynamics of prednisolone [14, 15]. Furthermore, the clearance of prednisolone was not affected by troleandomycin [16], and grapefruit juice did not affect the AUC or C_{max} of prednisolone after oral administration of prednisone [17]. However, diltiazem was reported to increase the AUC of prednisolone by about 20% after ingestion of prednisone [18]. In the present study, itraconazole, which in vitro is about tenfold less potent an inhibitor of CYP3A4 than ketoconazole [19], had a consistent although small effect on the AUC and $t_{1/2}$ of orally administered prednisolone.

The small effect of itraconazole on prednisolone pharmacokinetics contrasts with the results of our previous study, in which the $AUC_{0-\infty}$, C_{max} and $t_{1/2}$ of orally administered methylprednisolone were considerably increased by itraconazole (3.9-fold, 1.9-fold and 2.4-fold, respectively) [3]. In another study, the systemic clearance of i.v. administered methylprednisolone was decreased by 60% and the $t_{1/2}$ increased 2.6-fold by itraconazole [4].

Itraconazole inhibits P-glycoprotein [20], a transmembrane efflux pump present in many tissues with excretory function, such as in the kidney and liver [21]. Inhibition of P-glycoprotein-mediated biliary or renal elimination might explain the effects of itraconazole on the pharmacokinetics of prednisolone. However, a recent study suggested that prednisolone, unlike methylprednisolone, is not a substrate for intestinal P-glycoprotein [22].

The normal endogenous cortisol synthesis shows a diurnal variation, with peak cortisol concentrations occurring early in the morning. The minor changes in

the pharmacokinetics of prednisolone caused by itraconazole were associated with a mean decrease of 27% in the morning plasma cortisol concentration measured 23 h after intake of 20 mg prednisolone. Although the morning plasma cortisol concentration remained within the normal range in nine of the ten subjects, it was clearly below the lower limit in one subject during the itraconazole phase. Thus, it is probable that itraconazole in a dose of 200 mg/day can slightly extend the adrenal-suppressant effect of prednisolone. This effect, however, is considerably smaller than the potentiation of the adrenal-suppressant effect of oral methylprednisolone by the same dose of itraconazole [3].

In conclusion, itraconazole for 4 days only slightly increased the $AUC_{0-\infty}$ and $t_{1/2}$ of oral prednisolone and its effect on morning plasma cortisol. Importantly, the susceptibility of prednisolone to interact with CYP3A4 inhibitors is considerably smaller than that of methylprednisolone. The observed minor interaction is of limited clinical significance only. Thus, itraconazole and probably also other inhibitors of CYP3A4 can be used concomitantly with prednisolone without marked changes in the effects of this corticosteroid.

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