

## Systemic absorption of ketoconazole from vaginal pessaries

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Eight healthy female subjects were each given (a) ketoconazole 400 mg orally, (b) ketoconazole 400 mg as a single vaginal pessary, (c) ketoconazole 800 mg as two vaginal pessaries, and (d) ketoconazole 1200 mg as three vaginal pessaries. The area under the plasma concentration time curve (AUC) after the oral dose was  $51.41 \pm 10.99$  mg l<sup>-1</sup> h (mean  $\pm$  s.d.) and the half-life of ketoconazole was  $2.98 \pm 1.41$  h. The AUCs after vaginal administration were  $0.27 \pm 0.14$ ,  $0.52 \pm 0.25$ , and  $0.43 \pm 0.22$  mg<sup>-1</sup> l h following the 400, 800 and 1200 mg pessaries respectively. Systemic absorption of single doses of vaginally administered ketoconazole appears to be negligible in the absence of vaginal infection. There were no local or systemic side effects related to ketoconazole in these healthy volunteers.

**Keywords** ketoconazole vaginal pessaries absorption

### Introduction

Ketoconazole is a new oral imidazole derivative which is active against both superficial and deep fungal infections. Its pharmacokinetics after oral dosing have been examined in normal subjects (Daneshmend *et al.*, 1981, 1983; Gascoigne *et al.*, 1981; Mannisto *et al.*, 1982), in patients with different fungal infections (Brass *et al.*, 1982; Gascoigne *et al.*, 1981) and in immunocompromised patients (Hann *et al.*, 1982; Maksymiuk *et al.*, 1982). In view of the dysmorphogenic effects of ketoconazole noted in animals (Heel *et al.*, 1982), the use of ketoconazole by the oral route in pregnancy is contraindicated. In the treatment of vaginal candidiasis this risk could be lessened in pregnancy if ketoconazole were given by the vaginal route, provided that absorption of the drug was low from this site. However the vaginal absorption of ketoconazole has not previously been determined in humans. In this study we examined the systemic absorption of single doses of ketoconazole vaginal pessaries in normal healthy females and compared this to an oral dose.

### Methods

Eight healthy female volunteers (age range 21–25 years, weight range 53–58 kg) gave informed consent to this study which was approved by the hospital ethical committee. All subjects were on the oral contraceptive pill, and treatments were given only in the second and third weeks of each menstrual period. Each subject received the following treatments in random order (a) ketoconazole 400 mg orally, as two 200 mg tablets, (b) one ketoconazole 400 mg vaginal pessary, (c) two ketoconazole 400 mg vaginal pessaries, and (d) three ketoconazole 400 mg vaginal pessaries. Treatments were given after breakfast. Following pessary insertion, subjects rested supine for 2 h. Venous blood samples were collected before and at 1, 2, 3, 4, 6, 8, 12, 24, 36, 48 and 72 h after each dose. Plasma was separated and frozen for later analysis of ketoconazole by h.p.l.c.

#### *H.p.l.c. assay*

Ketoconazole in plasma samples was measured

by Dr R. Woestenborghs, Department of Drug Metabolism and Pharmacokinetics, Janssen Pharmaceutica, Beerse, Belgium, by the following method. Plasma samples were spiked with internal standard (terconazole), alkalised by 0.1 N sodium hydroxide and extracted twice with a heptane-isoamyl alcohol mixture. The combined organic layers were back extracted with 0.05 M sulphuric acid. The organic layers were discarded and the acid phase made alkaline with concentrated ammonia, then extracted twice with more of the heptane-isoamyl alcohol mixture (95:5, v/v). These combined organic layers were evaporated to dryness and the residue dissolved in the mobile phase for h.p.l.c. [water-acetonitrile-diethylamine (50: 50: 0.05)]. These were injected onto a RSIL C18HL reversed phase column (particle size 5  $\mu$ m) attached to a Hewlett-Packard 1084B h.p.l.c. The flow rate of the mobile phase was 0.5 ml/min. Detection was at 254 nm. Peak area ratios were used for quantitation. The detection limit of ketoconazole in plasma was 2 ng/ml. The recovery of the plasma extraction procedure was 88%, and the mean coefficient of variation for the assay was 4.5%. There was no interference from ketoconazole metabolites.

A full blood count, plasma urea and electrolyte concentrations and standard liver function tests were performed before and 3 days after each treatment. The area under the plasma concentration time profile (AUC) was calculated by the trapezoidal rule. The plasma half-life of ketoconazole was calculated from least squares regression analysis of the log serum concentration-time profile.

Statistical comparisons were made using Student's *t*-test for paired data. Significance was assumed at  $2P < 0.05$ .

## Results

The AUCs after oral and vaginal administration are shown in Table 1. Compared to the 400 mg oral dose, the systemic absorption of ketoconazole given by the vaginal route was 1% or less at all three doses given. Vaginal absorption of ketoconazole was significantly greater after

the 800 mg and 1200 mg doses when compared to the 400 mg vaginal dose.

The plasma ketoconazole half-life after the 400 mg oral dose was  $2.98 \pm 1.41$  h (mean  $\pm$  s.d.). Peak ketoconazole concentration after the oral dose was  $8.53 \pm 2.99$  mg/l, and occurred 3 h post-dose. Peak plasma ketoconazole concentrations following the vaginal doses of 400 mg, 800 mg and 1200 mg were  $0.012 \pm 0.004$  mg/l,  $0.013 \pm 0.003$  mg/l, and  $0.015 \pm 0.003$  mg/l, and occurred at 6 h, 6 h and 4 h respectively.

Plasma ketoconazole concentration 24 h after the oral dose was  $0.043 \pm 0.037$  mg/l and had fallen to  $0.013 \pm 0.005$  mg/l by 48 h. Plasma ketoconazole concentrations 24 h after the 400 mg, 800 mg and 1200 mg vaginal doses were  $0.007 \pm 0.003$  mg/l,  $0.009 \pm 0.003$  mg/l and  $0.009 \pm 0.004$  mg/l respectively; by 48 h these had decreased to  $0.003 \pm 0.001$  mg/l,  $0.008 \pm 0.005$  mg/l and  $0.006 \pm 0.002$  mg/l respectively.

There were no side effects to oral or vaginal ketoconazole. No abnormalities were noted in haematological or biochemical indices after any of the doses of ketoconazole.

## Discussion

This study shows that ketoconazole is poorly absorbed into the systemic circulation following vaginal administration in healthy female subjects. The plasma ketoconazole concentrations were extremely low and would have been undetectable by microbiological or other assay methods with a lower limit of sensitivity of 0.02 mg/l. The lower mean AUC of ketoconazole with the 1200 mg vaginal dose may have been due to inadequate retention of the pessary material after it had melted.

The poor vaginal absorption of ketoconazole may in part be due to the physicochemical properties of the drug. Ketoconazole is a weak dibasic compound ( $pK_{a1} = 6.51$ ;  $pK_{a2} = 2.94$ ) and is almost insoluble in water except at a pH lower than 3. Thus the normal vaginal pH of about 4.5 would tend to hinder the solubility and absorption of ketoconazole. The possibility exists of greater amounts of ketoconazole being

**Table 1** The area under the plasma concentration time profile in eight healthy female subjects following a single oral dose of ketoconazole and three different doses of ketoconazole by the vaginal route. Mean  $\pm$  s.d.

Dose/route	400 mg oral	400 mg vaginal	800 mg vaginal	1200 mg vaginal
AUC (mg l <sup>-1</sup> h)	$51.41 \pm 10.99$	$0.27 \pm 0.14$	$0.52 \pm 0.25^*$	$0.43 \pm 0.22$

\*400 mg vaginal vs 800 mg vaginal  $2P < 0.01$ .

absorbed in the presence of vaginal candidiasis, if this infection were to significantly lower vaginal pH.

The AUC and half-life after oral administration seen in this study are similar to those observed by us in other studies in normal subjects (Daneshmend *et al.*, 1981, 1983). The plasma ketoconazole concentrations after both oral and vaginal administration were extremely low after 24 h and decreased still further by 48 h. The data after vaginal administration did not allow calculation of half-life. The delay of 4 to 6 h in reaching peak plasma concentrations after vaginal doses suggested slow dissolution and gradual systemic absorption of small amounts of ketoconazole.

In pregnant rats, high doses of ketoconazole (80 and 160 mg ketoconazole/100 mg of food)

have resulted in dysmorphogenic effects in pups (Heel *et al.*, 1982). In addition, tritiated ketoconazole when given to pregnant rats leads to radioactivity in the placenta, but foetal tissue levels were much lower than maternal tissue levels (Heel *et al.*, 1982). However, the present study shows that less than 1% of the vaginal dose disperses into the systemic circulation in healthy adult females. Therefore most of the drug would be present in the vagina for the treatment of local fungal infections such as vaginal candidiasis. If clinical trials show ketoconazole pessaries to be effective in such infections, then vaginal administration may be safer than oral administration in pregnancy.

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