Persistence of miconazole in vaginal secretions after single applications
Implications for the treatment of vaginal candidosis

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SUMMARY In vaginal secretions from 16 healthy women aged between 20 and 27 years miconazole persisted in biodetectable concentrations for at least 48 hours after insertion of a single miconazole vaginal pessary. This finding casts doubt on cure rates in vaginal candidosis determined soon after the end of treatment and suggests that current treatment courses with imidazole antifungal agents may be longer than their nominal three or five days.

Introduction

Imidazole antifungal agents, such as clotrimazole and miconazole, are widely used in the treatment of candidal vulvovaginitis. Initially, these drugs were usually given for 10 or 14 days, but the work of Masterton et al. led to the introduction of much shorter courses of treatment.

Retrospective analysis of cure rates in clinical trials of vaginal antifungal agents has suggested that the total dose applied topically has more effect on the outcome of therapy than the duration of treatment. There is no direct evidence, however, to determine for how long a single dose can remain active within the vagina. This paper reports the persistence of miconazole in vaginal secretions after single applications of miconazole pessaries.

Subjects and methods

Pessaries, each containing miconazole nitrate 100 mg (Janssen Pharmaceutical Ltd), were inserted intravaginally by 16 healthy non-pregnant female volunteers aged between 20 and 27 years.

COLLECTION OF SECRETIONS

Samples of vaginal secretions were collected by the volunteers themselves just before they inserted the pessaries and at intervals up to 48 hours afterwards.

The samples were collected with sterile polyester sponge swabs (2·5 x 2·5 x 0·6 cm), tied with cotton to wooden applicator sticks. The sponge portions of the swabs were placed in the barrels of 5-ml plastic syringes; 200 μl of phosphate-buffered saline (PBS) was added and fluid expressed from the swabs by pressure from the syringe plunger. A random sample of used and unused swabs was weighed and showed a mean weight gain of 0·45 g by the swabs. The addition of PBS was necessary because it proved difficult to obtain fluid from swabs taken one hour after insertion of the pessary.

ESTIMATION OF MICONAZOLE CONCENTRATIONS

Miconazole concentrations in vaginal fluid were measured by plate bioassay. An indicator strain of Candida albicans, grown for 18-24 hours at 37°C on peptone-glucose agar, was seeded to a concentration of 10⁶ yeasts per ml in agar containing yeast nitrogen base (Difco Laboratories (6·7 g/l and glucose 10 g/l), buffered at pH 7·0 with 0·02 mol/l citrate. The seeded agar was poured in 40-ml lots in 15-cm Petri dishes; 15 wells were cut, each 4 mm in diameter, and duplicate 12·5 μl samples of vaginal fluid and standard solutions of miconazole of 0·20, 0·63, 2·00, 6·30, and 20·00 μg/ml prepared in PBS from a stock solution in dimethyl sulphoxide were placed in the wells according to a randomisation scheme devised in advance. The dishes of agar were incubated at 37°C for 22-24 hours and miconazole concentrations determined from diameters of inhibition zones by reference to a standard curve of log miconazole concentration against zone diameter.
Persistence of miconazole in vaginal secretions after single applications

Results

Concentrations of miconazole in vaginal secretions were highest in the first post-dose sample and remained high for long periods (table). Although miconazole concentrations gradually fell, there was a concentration of at least 0.1 μg per ml in all 14 subjects that were tested as long as 48 hours after the miconazole pessary was inserted.

<table>
<thead>
<tr>
<th>Time after dose (h)</th>
<th>No of subjects tested</th>
<th>Miconazole (μg/ml)</th>
<th>Mean ± SEM</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>16</td>
<td>0.0±0.0</td>
<td>0.0±0.0</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>13</td>
<td>7.7±1.4</td>
<td>1.5±1.4</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>4.7±1.0</td>
<td>1.0±1.2</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>16</td>
<td>3.4±0.7</td>
<td>0.8±0.8</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>16</td>
<td>2.7±0.9</td>
<td>0.2±0.4</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>14</td>
<td>1.2±0.4</td>
<td>0.1±0.0</td>
<td></td>
</tr>
</tbody>
</table>

SEM = standard error of the mean

Discussion

It is clear that miconazole persists for a long time in an active form in samples from the vagina at concentrations well within the normal range of minimum inhibitory concentration of <0.01-2.0 μg/ml after a single dose of the drug.

That miconazole was still detectable in vaginal samples taken two days after insertion of the pessary was particularly notable. The fact that PBS was added to help in the removal of vaginal fluid from the swabs means that the data in the table are underestimates of the true miconazole concentrations in vaginal secretions.

The considerable persistence of miconazole in the vagina after a single topical dose has two clinical implications. Firstly the protocols for several clinical trials of imidazole antifungal agents in vaginal candidosis have included clinical and mycological follow-up examinations within 2-3 days after cessation of treatment.5-7 If other imidazole antifungal agents as well as miconazole remain active intravaginally for at least two days it follows that the scientific validity of high cure rates when patients are reassessed so soon after treatment is questionable. Secondly, since the persistent miconazole concentrations found in this study were measured after only a single topical dose, it is likely that the frequent multiple doses of imidazole antifungal agents currently recommended for short treatment regimens may give rise to inhibitory concentrations of antifungal that persist for even longer than 48 hours. This means that nominal three-day and five-day treatment courses may amount in practice to courses several days longer.

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References

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