Trichomonal vaginitis treated with one dose of metronidazole

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Since its introduction in France, metronidazole (Flagyl) has become the standard treatment for trichomonal vaginitis (Durel, Roiron, Siboulet, and Borel, 1959). The course recommended at that time and continued ever since was 200 mg. three times daily for 7 days, giving a cure rate of 85 to 98 per cent. (Csonka, 1963; Evans and Catterall, 1970; Keighley, 1971). We have investigated the possibility of simplifying treatment by giving a single dose.

Patients and methods
The trial was carried out in 54 cases in women attending the clinics for sexually transmitted diseases at the Central Middlesex Hospital and Watford General Hospital. Most of them (87 per cent.) were aged between 15–28 years and 63 per cent. were single. Thirty were white and 24 coloured. The diagnosis was made by dark-ground examination of vaginal secretions and by culture in modified Bushby medium. Blood was taken from a proportion of the patients to estimate the metronidazole level 24 and sometimes 48 hours after taking the single dose and eighteen of the Trichomonas vaginalis isolates, mostly from cases in which the disease recurred, were tested for sensitivity to metronidazole in vitro. The vaginal flora of patients who failed to respond to this treatment was investigated for metronidazole-inhibiting organisms.

2 g. metronidazole were given in a single dose of five 400 mg. tablets under supervision at the clinics. The patients were seen again 24 hours later and again after 7 days, and then monthly for 3 months and at any time if symptoms recurred.

Concurrently, a reference group of 58 patients with trichomonial vaginitis was treated with the standard course of metronidazole (200 mg. three times a day for 7 days). The two groups were comparable in age, marital status, and racial composition.

The criteria for including patients in each treatment group were the same, namely the presence of Trichomonas vaginalis with clinical vaginitis but excluding known defaulters and visitors to the area. The treatments were given randomly.

Results
Of 54 patients treated with one dose of metronidazole, seven failed to return for further examination and are excluded from the trial; one other patient is excluded from the analysis of the therapeutic response as she vomited a few hours after taking the tablets on an empty stomach and may have retained too little metronidazole for it to be effective; her case is recorded when assessing tolerance. Of the remaining 46 cases, seven were considered to be treatment failures and ten to be cases of re-infection after resumption of intercourse.

Tolerance was good and apart from the patient already mentioned who vomited soon after taking the tablets, there was only one other patient who complained of some abdominal pain. There were no side-effects in the group given the 7-day course of metronidazole.

The results are set out in Table I. Although the 7-day course appeared to yield a higher cure rate than the single-dose treatment, statistically the difference was not significant. Comparison of probable treatment failure and re-infection shows a tendency for treatment failure to occur sooner than re-infection, but the main criterion for distinction was a history of resumption of intercourse or its denial (Table II). The mean serum metronidazole concentration in sixteen cases of the trial group after 24 hours was 16·0 μg./ml. (range 0·5 to 45·7) and after 48 hours it was 2·3 μg./ml. Eighteen strains of Trichomonas vaginalis, including most of the isolates from cases of recurrence, were tested for in vitro sensitivity and all strains were sensitive to 0·5 to 1·0 μg./ml. metronidazole.

In two of the seven cases of failure in the trial group, the vaginal flora was found to inactivate metronidazole and these two patients were successfully re-treated with a course of Ginetris vaginal tablets (chloramphenicol 250 mg.; myralact 10 mg.; cloponone 2·5 mg.); one tablet was inserted twice daily for 5 days and this was followed by a single
dose of 2 g. metronidazole. The same combination was tried in a third patient without success. Three other cases of failure were retreated with 2 g. metronidazole, but the parasite persisted in two cases which were finally treated with the standard 7-day course. In the seventh case of failure a very low serum

**TABLE I Results in two treatment groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total No. treated</th>
<th>Excluded from assessment</th>
<th>No.</th>
<th>Not assessable</th>
<th>Possible re-infection</th>
<th>No. assessed</th>
<th>Result</th>
<th>Cured</th>
<th>Failed</th>
<th>Defaulted</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single dose (2 g.)</td>
<td>54</td>
<td>7</td>
<td>1</td>
<td>10</td>
<td>36</td>
<td>20</td>
<td>82</td>
<td>7</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Standard dose (200 mg. three times a day for 7 days)</td>
<td>58</td>
<td>8</td>
<td>-</td>
<td>1</td>
<td>49</td>
<td>46</td>
<td>94</td>
<td>3</td>
<td>97</td>
<td></td>
</tr>
</tbody>
</table>

*Difference not significant

**TABLE II Diagnosis of recurrences after a single dose of metronidazole**

<table>
<thead>
<tr>
<th>Recurrences</th>
<th>Total no.</th>
<th>Positive test after treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presumed treatment failure</td>
<td>7</td>
<td>1st 2nd 3rd 4th 5th 6th or more</td>
</tr>
<tr>
<td>Presumed re-infection</td>
<td>10</td>
<td>- 1 4 3 1 1</td>
</tr>
</tbody>
</table>

metronidazole concentration (0.5 µg/ml) was reported shortly after the patient had been re-treated with the 2 g. dose; further treatment with the 7-day course was curative. The re-treatment results are given in Table III and show that patients in whom re-infection was suspected did better after a further single dose of 2 g. metronidazole than those believed to be treatment failures. Six of the seven treatment failures occurred in 'problem patients' with a long history of recurrent trichomoniasis and concurrent infections with Candida, gonorrhoea, or syphilis.

**TABLE III Results of re-treatment of probable treatment failures and re-infections**

<table>
<thead>
<tr>
<th>Reason for re-treatment</th>
<th>Re-treatment given</th>
<th>Total no. of cases</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment failure (7)</td>
<td>Metronidazole 2 g.</td>
<td>3</td>
<td>Cleared</td>
</tr>
<tr>
<td></td>
<td>2 g. then 4.2 g.</td>
<td>1</td>
<td>Failed</td>
</tr>
<tr>
<td></td>
<td>Ginetris vag. tablets followed by metronidazole 2 g.</td>
<td>3</td>
<td>Defaulted</td>
</tr>
<tr>
<td>Re-infection (10)</td>
<td>Metronidazole 2 g.</td>
<td>9</td>
<td>Cleared</td>
</tr>
<tr>
<td></td>
<td>Naxogin 7-day</td>
<td>1</td>
<td>Failed</td>
</tr>
</tbody>
</table>

**Discussion**

One of the treatment failures after 2 g. metronidazole was probably due to inadequate absorption, but in the rest of this group the mean serum concentration of metronidazole was higher after 24 hours than at any time during the standard 7-day course as reported by Rodin, King, Nicol, and Barrow (1960) and Wilkinson, Rodin, McFadzean, and Squires (1967). Thus the question is not whether a high enough serum concentration is reached after a single dose of 2 g. but whether it is sustained long enough to be effective. The clinical results in this series suggest that this is so in the majority of cases.

Inactivation of metronidazole by the vaginal flora is another possible cause of treatment failure; this was first reported by Nicol, Evans, McFadzean, and Squires (1966) and further investigated by McFadzean, Pugh, Squires, and Whelan (1966) who found that 28 per cent. of the vaginal flora in a random sample of 84 inocula was capable of inactivating metronidazole. Of six cases adequately observed, only one appeared to be a treatment failure, thus the significance of inactivating vaginal organisms remained uncertain. In our two patients with metranidazole-inactivating bacteria the treatment response to a combination of metronidazole and Ginetris tablets, which rendered the vagina at least temporarily bacteria-free, favours the view that on occasions an inimical vaginal flora may be the cause of treatment failure.

The continuing high sensitivity of strains of
T. vaginalis to metronidazole as found in this study is remarkable and agrees with the observation of McFadzean and others (1969) that there is still no evidence of the development of resistance after widespread use of the compound for the past 10 years.

It is probable that a number of those at present regarded as treatment failures are in reality either re-infections or cases in which the full course of the drug was not taken. This would explain the unequalled good results reported by Keighley (1971) who obtained 98.3 per cent. cures in the closed community of a prison where re-infection was unlikely and the administration of the drug was supervised. For this reason the results in the open community could be expected to improve if the consorts of patients could be induced to attend for investigation and treatment under supervision, possibly with a single dose of 2 g. metronidazole.

Summary
A single dose of 2 g. metronidazole (Flagyl) was compared with the standard 7-day course of 200 mg. three times a day in the treatment of trichomonal vaginitis. Of 36 patients treated with 2 g. and adequately observed, 82 per cent. were cured compared with 94 per cent. of 49 patients treated with 4:2 g. given over a period of 7 days. The difference is not statistically significant. The drug was well tolerated in both groups. Some factors possibly related to treatment failure are discussed. The results of this trial show the remarkable activity of metronidazole in trichomonal vaginitis and suggest that the single-dose treatment is a practical and acceptable alternative to the longer conventional course.

I am grateful to Mr. S. L. Squires of the Research Laboratories, May and Baker Ltd., and Mrs. O. Sheldon of the Medical Trials Division, May and Baker Ltd., for their unfailing help in the preparation of this paper.

References
Keighley, E. E. (1971) Ibid., 1, 207

Traitement de la vaginite à Trichomonas par une dose unique de métronidazole

SOMMAIRE

On a comparé l'action thérapeutique, dans la vaginite à Trichomonas, d'une dose de 2 g. de métronidazole (Flagyl) avec celle de la série habituelle de 7 jours, à 3 comprimés de 200 mg. par jour. Parmi 36 femmes traitées avec 2 g. et correctement suivies, 82 pour cent furent guéries, alors que 94 pour cent des 49 malades traitées avec 4,2 g. en sept jours furent guéries ; la différence n'est pas statistiquement significative. Le médicament fut bien toléré dans les deux groupes. On discute de quelques facteurs pouvant avoir un rôle dans les échecs. Les résultats de cet essai montrent l'activité remarquable du métronidazole dans la vaginite à Trichomonas et suggèrent qu'un traitement par dose unique peut remplacer d'une manière pratique et acceptable la série plus longue habituelle.
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doi: 10.1136/sti.47.6.456

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