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# FLAGYL (METRONIDAZOLE)*

BY

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We wish at the outset to thank our English colleagues—particularly Mr. King and Dr. Nicol—for the interest which they have taken in this anti-trichomonal drug originating in France. Our results continue to be good, but it is unnecessary to stress this. We should prefer to report on research work undertaken by our group.

## (A) Local or Systemic Administration?

In our opinion, in women, the best results are got by giving Flagyl concurrently orally and locally. Wishing, however, to compare the two methods of administration, we are studying two comparable groups of prostitutes.

Diagnosis is made from culture. Cultural tests are carried out at first at intervals of 7 to 10 days and later, after several negative reports, approximately every 4 weeks.

*Local Application.*—The patients were instructed to insert a 500-mg. pessary every evening, even during menstruation. A bland vaginal douche was also given once or twice a week. Eleven are still under observation after the first negative culture test and sixteen have been observed for periods ranging from 6 weeks to 9 months (five for 6 weeks, one for 2 months, two for 3 months, three for 4 months, four for 6 months, and one for 9 months).

Seven patients (two of them pregnant) became positive again after one or more negative cultures. These might be cases of re-infection, but it is wiser to regard them as failures. In six cases the trichomonas never disappeared. These thirteen failures give a rate of 32·5 per cent.

Eleven of the thirteen were re-treated, and in eight the trichomonas disappeared, giving a residue of three failures out of 38 treated (7·9 per cent.).

We conclude that the 10 days' course of local treatment is too short, and should be extended to 15 or 20 days.

*Oral Administration.*—The patients were told to take one 250-mg. tablet morning and evening for 10 days. This series was begun later than the first one, and the majority of the patients have only recently finished the course of treatment. Ten patients are still under observation after the first negative culture test and seven have been observed for from 3 weeks to 2 months (one for 3 weeks, five for 1 month, and one for 2 months. Three of the seven were patients in whom local treatment had failed.

This series contains six failures (26 per cent.). Two patients (one of them pregnant) became positive again in 1 to 3 months, and four (one of them pregnant) remained persistently positive. These six failures were then given local treatment and four are now negative, and two still being treated.

There may be no statistical difference between 32 and 26 per cent. in series of 38 and 23 patients, but it can be said that the oral treatment is at least as successful as topical application. *As far as we know, this is the first drug of which that can be said.*

A small number of these patients were pregnant (four in each group); it seems that failure is more frequent when the patient is pregnant.

After local application of the drug, yeasts were found in twelve women who had previously shown no evidence of them. This was noted only six times in those receiving the drug by mouth. The significance of this is uncertain, for it was not reported whether the fungi were saprophytic or *Candida albicans*.

Local treatment was well tolerated. Two of the women on oral administration complained of pain in the stomach; one of these was pregnant and vomited.

## (B) Urinary Excretion

We usually give one 250-mg. tablet night and morning. We wished to ascertain if in this dosage the drug was regularly excreted, or if some was retained in the body. It would have been more interesting if we could have studied blood-levels, but the method of estimation used with urine was not sufficiently sensitive for the blood levels.

**Method of Estimation.**—Metronidazole contains a nitro group which is readily reduced to an amine which may be diazotized and coupled to form a dyestuff; this allows a colorimetric determination analogous to that used for the sulphonamides. It is the technique used by Dubost and Devoize (personal communication). The product present in the urine is reduced by zinc and normal hydrochloric acid at room temperature: the amino derivative obtained is immediately afterwards coupled with Fourneau IV reagent†.

* Short paper read by Dr. P. Durel to M.S.S.V.D. on May 27, 1960.

† 0·1 per cent. aqueous solution of N, N–diethyl–N'–α–naphthyl propylenediamine hydrochloride.

The resulting azo compound is measured colorimetrically with a photometer.

Such an estimation after hydrolysis enables the conjugated drug to be determined. Estimation (without either hydrolysis or reduction) can also be made of the amino-substituted metabolite formed during the passage of Metronidazole through the body. Each sample, as well as the reference solutions, has been the subject of numerous examinations, and the average of these estimations is stated.

(1) *Urinary Excretion after a Single Oral Dose of 1 g.*—Two individuals were used; the results are set out in Table I and Fig. 1. In these two cases some 40 per cent. of the drug (38 and 46 per cent.) was excreted in 24 hours, and the greater part was excreted in a free and unchanged form. In the course of 24 hours 12 per cent. in one case and 26 per cent. in the other was found in the conjugated form, with traces of the metabolized amino derivative.

Excretion seems to be quite rapid and continuous. In one subject it occurred mostly in the first twelve hours, in the other between the 12th and the 24th hour. One subject was observed for 4 days. By the third day 80 per cent. of the amount ingested had been excreted in the urine, and thereafter there was no more than a trace of the drug.

TABLE I

URINARY EXCRETION OF 1 G. GIVEN IN ONE ORAL DOSE

| Subject No. | Time (hrs) | Volume (ml.) | Amino+ Free Nitro | | Total | |
|---|---|---|---|---|---|---|
| | | | mg. | Per cent. | mg. | Per cent. |
| 2 | 0– 2 | 170 | 21·0 | 2·10 | 23·2 | 2·32 |
| | 2– 5 | 170 | 24·0 | 4·50 | 29·0 | 5·22 |
| | 5– 9 | 170 | 49·5 | 9·45 | 59·5 | 11·17 |
| | 9–12 | 400 | 185·0 | 28·50 | 207·0 | 31·87 |
| | 12–22 | 270 | 104·0 | 38·55 | 117·0 | 43·57 |
| | 22–24 | 244 | 26·0 | 40·10 | 33·0 | 46·87 |
| | 24–48 | 1,690 | 207·0 | 61·00 | 213·0 | 68·00 |
| | 48–72 | 1,890 | 84·0 | 80·00 | } No conjugates | |
| | 4th day | 1,390 | Traces | | | |
| 5 | 0– 2 | 270 | 5·5 | 0·55 | 6·5 | 0·65 |
| | 2– 4 | 200 | 34·7 | 4·02 | 50·0 | 5·65 |
| | 4– 7 | 575 | 40·0 | 8·02 | 40·0 | 9·65 |
| | 7–12 | 480 | 37·5 | 11·77 | 64·0 | 16·05 |
| | 12–24 | 560 | 158·0 | 27·57 | 217·0 | 37·75 |
| | 24–48 | 1,250 | 292·0 | 56·77 | No conjugates | |

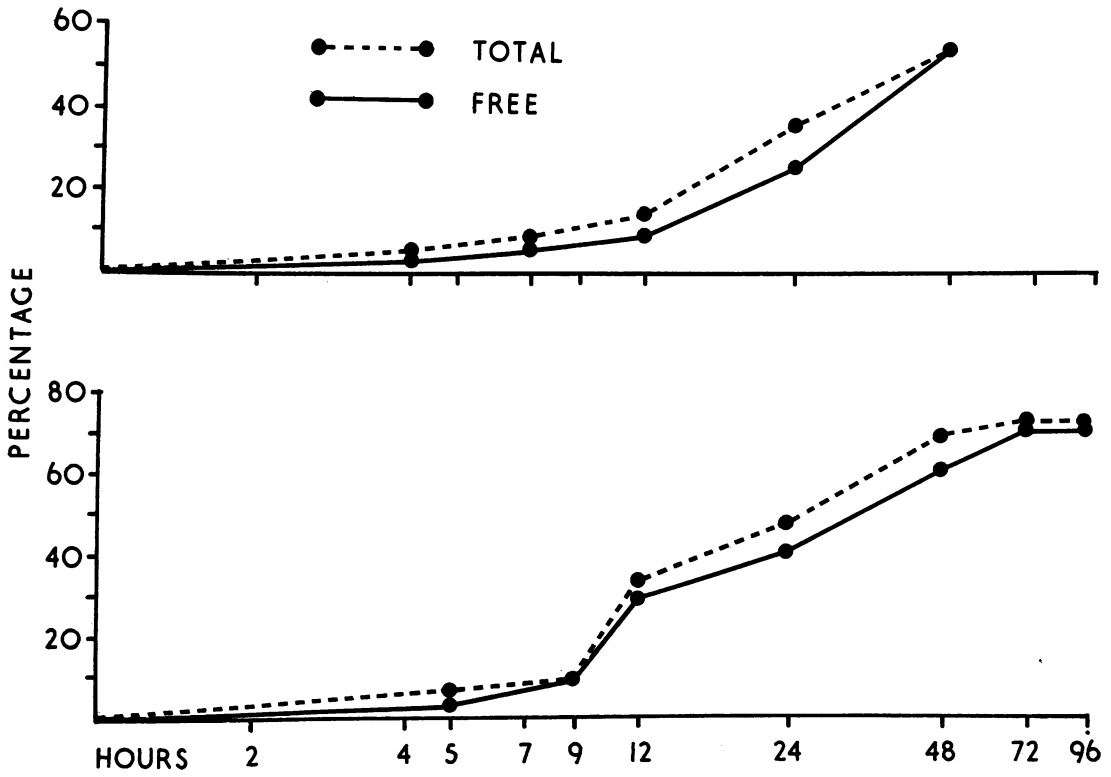


Fig. 1.—Cumulative excretion of 1 g. Flagyl given in one oral dose in two subjects.

(2) *Urinary Excretion with Different Types of Administration.*—Table II gives the figures for the three types of dosage: 250 mg. morning and evening, 250 mg. once a day, and 100 mg. morning and evening. With the first of these there is some tendency for the drug to accumulate in the body, as is shown in Fig. 2, which gives the percentages for Subject 2, but this accumulation is minimal.

TABLE II
URINARY EXCRETION WITH DIFFERENT TYPES OF ADMINISTRATION

| Dose .. | 250 mg. Twice Daily | | | | | | 250 mg. Once Daily | | | | | | | | | | | | 100 mg. Twice Daily | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subject No. | 1 | | | 2 | | | 2 | | | 1 | | | 3 | | | 4 | | | 2 | | |
| Days of Treatment | vol. | mg. | Per cent. | vol. | mg. | Per cent. | vol. | mg. | Per cent. | vol. | mg. | Per cent. | vol. | mg. | Per cent. | vol. | mg. | Per cent. | vol. | mg. | Per cent. |
| 1st a.m. | 290 | 87·5 | 35 | 720 | 52 | 21 | 475 | 59·5 | 23 | 275 | 88·5 | 35 | 575 | 47·5 | 19 | 200 | 54 | 21 | 545 | 45·5 | 45 |
| p.m. | 275 | 174 | 52 | 680 | 72 | 25 | 285 | 52·5 | 45 | 420 | 67 | 62 | 360 | 54 | 40 | 210 | 130 | 73 | 350 | 33·5 | 39 |
| 2nd a.m. | 420 | 234 | 65 | 590 | 121 | 33 | 485 | 101 | 42 | 240 | 96 | 50 | 695 | 114 | 43 | 230 | 158 | 68 | 555 | 82 | 54 |
| p.m. | 630 | 216 | 70 | 1000 | 122 | 36 | 400 | 80 | 58 | 455 | 86 | 67 | 400 | 54·7 | 54 | 190 | 71 | 82 | 330 | 80 | 60 |
| 3rd a.m. | 450 | 214 | 73 | 600 | 164 | 42 | 615 | 136 | 57 | 260 | 162 | 66 | 645 | 84 | 47 | 200 | 166 | 77 | 525 | 95 | 67 |
| p.m. | 270 | 198 | 74 | | | | 710 | 92 | 70 | 165 | 107 | 81 | 505 | 60 | 55 | 240 | 71 | 87 | 500 | 70 | 68 |
| 4th a.m. | | | | | | | 630 | 148 | 67 | 315 | 163 | 76 | 315 | 86 | 50 | 80 | 65 | 71 | 580 | 87 | 70 |
| p.m. | | | | | | | 410 | 95 | 76 | 275 | 57 | 82 | 1355 | 90 | 59 | 240 | 177 | 89 | 320 | 35 | 66 |
| 5th a.m. | | | | | | | 725 | 140 | 72 | 375 | 91 | 73 | | | | 70 | 51 | 75 | 750 | 73·5 | 67 |
| p.m. | | | | | | | 765 | 68 | 78 | 852 | 61 | 78 | | | | 295 | 165 | 89 | 800 | 73·5 | 68 |
| Treatment Stopped | | | | | | | | | | | | | | | | | | | | | |
| 6th .. | | | | | | | | | | 900 | 42·5 | 81 | | | | | | | | | |
| 7th .. | | | | | | | | | | Traces | | | | | | | | | | | |

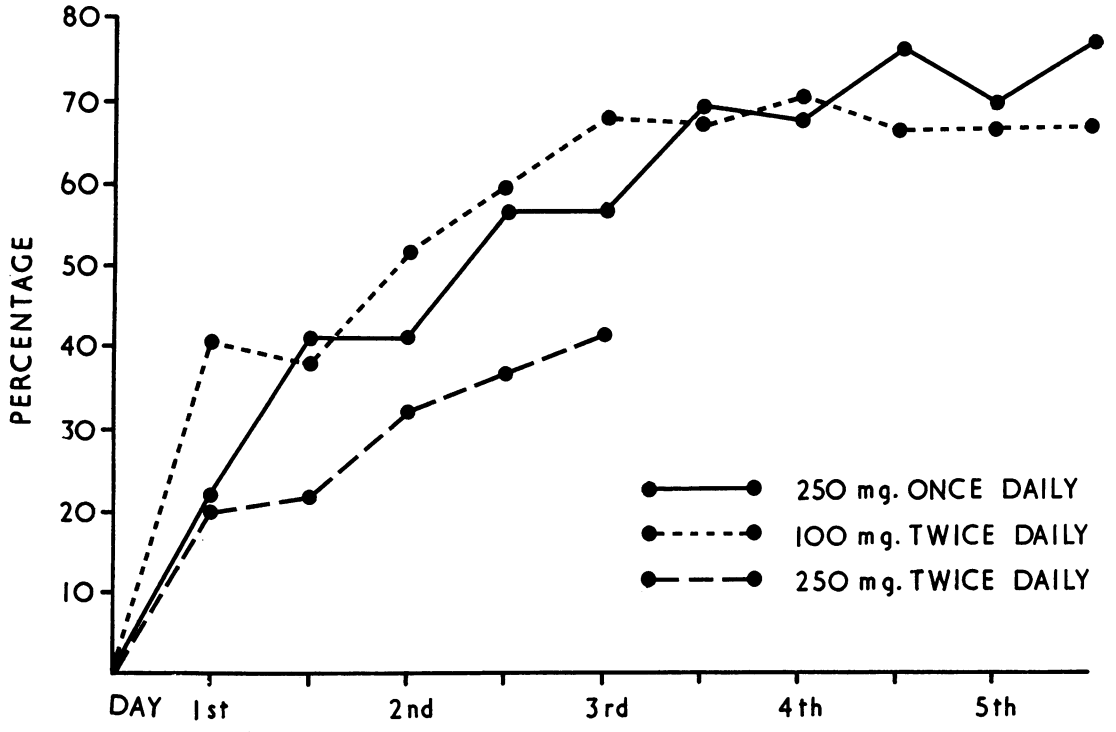


Fig. 2.—Percentage Flagyl excreted by one subject after three different dosage schedules.

(C) Absence of Action of Flagyl on Reproductive System in the Rat

As trichomonal infestation is common in pregnant women, it is of interest to know what effect, if any, Flagyl has on the reproductive system and offspring. Such animal studies are time-consuming, and they give us only partial information on what may happen in man, but they may serve as a pointer.

The work undertaken on this subject by those who carried out the early experiment with this compound is to be published at a later stage. The preliminary results obtained by Julou, Ganter, and Cosar (personal communication) are of considerable interest.

(*a*) Female rats received daily by mouth 50 or 100 mg./kg. Flagyl for 40 days. 10 days after starting treatment they were placed for 10 days along with untreated male rats, and for 20 days they were in individual cages. Each lot has the same proportion of pregnant rats as of untreated control animals. The average percentage increase in weight, and the average number in the litters were the same in all three groups.

(*b*) Male rats received daily by mouth 100 mg./kg. Flagyl for one month. At the end of that time they were placed for 10 days with untreated females. Thereafter they were killed and histological investigations were made of the genital system (to be reported later). Six out of nine females mated with treated males were impregnated, and among the controls six out of ten. It appears, therefore, that Flagyl has no effect on the fertility of rats, male or female.

(D) Blood Examinations

We continued, as a precaution, to check the blood picture in patients receiving Flagyl by mouth. We have already reported (Durel, Roiron, Siboulet, and Borel, 1960) the average counts before and after treatment in ten cases. Our observations now cover thirty patients, and no alteration has been noted.

Summary

(1) In two groups of women vaginal and oral administration have been compared. Given by mouth alone the drug is at least as active as when applied locally. Local treatment should probably be continued for more than 10 days.

(2) Flagyl (given orally) is recovered from the urine mostly in the free form. When the total daily dose is 500 mg., there is a tendency to accumulation which is not noted with lower dosages.

(3) In the rat the drug, given by mouth in high dosages, has had no effect on fecundity.

(4) No alteration of the blood picture, in either number or type of cell, was observed in a new group of patients who received the drug by mouth.

REFERENCE

Durel, P., Roiron, V., Siboulet, A., and Borel, L. J., (1960). *Brit. J. vener. Dis.*, **36**, 21.

**Flagyl**

**Résumé**

Le Flagyl (8823 R.P.) est efficace par voie générale comme ceci fut démontré, dès le début, par les succès observés chez l'homme. Chez la femme, le traitement mixte, oral et vaginal, donne les meilleurs résultats mais, *pour comparer les deux modes d'administration*, deux séries de femmes furent traitées: l'une par la seule voie locale, l'autre par la seule voie orale (500 mg. par jour pendant 10 jours, dans les deux cas).

Il y eut 13 échecs sur 40 (=32,5%) dans la première série, 6 sur 23 (=26%) dans la seconde; le traitement général est donc au moins aussi actif que le traitement local.

*L'élimination urinaire* du Flagyl, administré oralement, fut étudiée chez des volontaires. L'élimination est assez rapide et continue. La majeure partie du produit s'élimine à l'état nitré libre. Si les doses sont de 500 mg par jour, il y a a une légère tendance à l'accumulation.

Des études sont en cours concernant un éventuel retentissement du traitement sur les *fonctions génitales du rat*. Jusqu'ici, on peut dire que le produit est sans action ni sur la gestation, ni sur l'embryogénèse de la rate, ni sur la fécondité du rat mâle.

Il n'a pas été noté d'altération de la *numération* ou des *formules sanguines* sur une nouvelle série de 20 malades soumis au traitement buccal.

## DISCUSSION

Dr. G. W. Csonka (*St. Mary's Hospital, London*) said that his experience of Flagyl was the result of a double-blind controlled trial undertaken at the Central Middlesex Hospital and St. Mary's Hospital, Paddington, by Dr. Rosedale, Miss Bigby, and himself. The patients concerned were 66 females with clinical vaginitis in whom *trichomonas vaginalis* had been demonstrated by microscopy of a wet film of vaginal discharge. Pregnant women were excluded from the trial but otherwise the patients were unselected. Treatment consisted of 200-mg. tablets of Flagyl taken three times a day by mouth for 10 days. No local treatment was given. Dummy tablets (prepared by May & Baker