

SINGLE DOSE ORAL THERAPY WITH FLAGYL (METRONIDAZOLE) FOR VAGINAL TRICHOMONIASIS

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Introduction

The introduction of Flagyl for systemic use in the treatment of urogenital trichomoniasis (Durel *et al* 1959, Cosar and Julou 1959) is considered a major therapeutic advance. The treatment is simple and limited to one tablet (200 mg.) three times daily for seven days to the patient as well as her male partner. This regimen has been giving cure rates ranging from 85 to 100 per cent, (McGill and Black 1962, Sohran and Kleinman 1962, K. Menon, 1962, Csonka 1963, Kishore and Dewan 1965, Evans and Catterall 1970 and Keighley 1971). Lately, Csonka (1971) and Woodcock (1972) aimed to reduce the treatment to a one-day course by giving a single oral dose of Flagyl 2 g. The cure rates obtained were comparable with those reported for the standard regimen, justifying the adoption of single dose therapy as an alternative form of treatment with Flagyl.

We present data from our comparative

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trial of single and standard dosage schedules of Flagyl in vaginal trichomoniasis.

Material and Methods

The trial was conducted in patients attending the outdoor department of Kamla Nehru Memorial Hospital, Allahabad. The patients were divided in two groups:

Group I

Test Group—165 patients.

(a) Flagyl in single dosage of 30 mg/kg.—75.

(b) Flagyl in single dosage of 35 mg/kg.—45.

(c) Flagyl in single dosage of 40 mg/kg.—35.

(d) Flagyl in single dosage of 2 g. Statim—10 pregnant patients.

Group II

Control Group—100 patients.

Flagyl one 200 mg. tablet three times a day for 7 days.

Male consorts of patients in both groups were given Flagyl either as a single dose (35 mg/kg.) or 400 mg. twice daily for five days.

Age and Body Weight

The patients ranged in age from 18 to 45 years.

The weight range was 42 to 78 kg.

Diagnosis

Vaginal secretions were obtained in the Out patient Department and examined microscopically. The finding of actively motile trichomonads led to confirmation of diagnosis.

Cervical cytology was carried out in

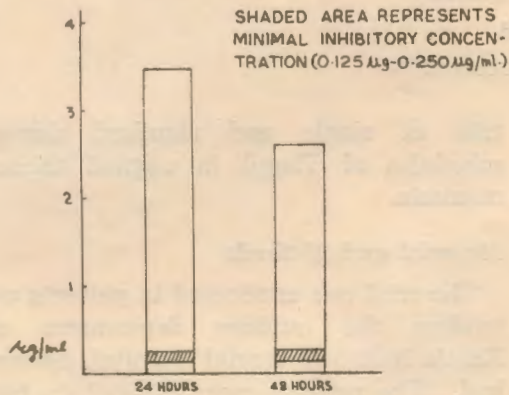


FIGURE 1. MEAN SERUM CONCENTRATIONS OF METRONIDAZOLE AFTER A SINGLE DOSE.

Fig. 1

89 cases of the trial group and 69 cases of the control group but this was not used as a diagnostic criterion. No culture of organism was done as microscopy is considered to be a reliable index for diagnosis (Woodcock 1972).

Drug Administration

Patients in the control group were advised to take the drug after meals but it was possible to administer the single doses under supervision. Male consorts were advised of the necessity for their treatment and put on one of the dosage schedules. Patients who had taken metronidazole for their ailment within the past three months, were excluded from the trial.

Follow-Up

The patients were re-examined and

vaginal secretions were obtained after 24 hours, one week, one month and thereafter once every month for at least three months. The patients were advised to report earlier if they had recurrence of symptoms.

Other Examinations

In 8 cases of the test group, vaginal secretions were collected every 2 hours for 24 hours after admission to the hospital. This was done with the specific aim of determining the exact time when the parasites disappear after a single dose of Flagyl. We also measured serum concentrations of metronidazole 24 hours and 48 hours after single dose medication.

Criteria of Assessment

Cure—Constant absence of the parasite from vaginal secretions for a minimum of 3 months.

Failure—Presence of the parasite on the first follow-up after medication.

Relapse—Absence of the parasite on one or more earlier follow-up but re-appearance upto 3 months.

Reinfection—Appearance of parasite after 3-months parasite free period.

Results

There were 16 drop-outs in the test group and 11 in the control group. Hence the results were assessed from 149 cases and 89 cases respectively. The results from cervical cytology carried out in 89 and 64 cases in the two groups respectively are shown in Table I.

The parasite was identified in 79.3 and 79.7% cases in the two groups respectively. The results of treatment on the cases followed up for 3 months or longer are presented in Table II.

TABLE I
Cervical Cytology in Test and Control Groups of Patients with Trichomoniasis (Percentage in Parenthesis)

| Group | No. of cases | Cytology done | T. Vag positive | T. Vag. negative |
|-----------------------------|--------------|---------------|-----------------|------------------|
| Group I (Test Group) | 165 | 89 | 68 (79.3) | 21 (20.7) |
| Group II (Control Group) | 100 | 64 | 51 (79.7) | 13 (20.3) |

TABLE II
Results of Treatment (Percentage in Parenthesis)

| Groups | No. of cases | No. of cases follow-up | Cure | Failure/relapse | Re-infection |
|-----------------------------|--------------|------------------------|---------------|-----------------|--------------|
| Group I (Test Group) | | | | | |
| (a) 30 mg./kg. | 75 | 66 | 61 (92.4) | 5 (7.5) | 13 (19.7) |
| (b) 35 mg./kg. | 45 | 41 | 37 (91.0) | 4 (9.9) | 5 (12.1) |
| (c) 40 mg./kg. | 35 | 33 | 31 (94.0) | 2 (6.0) | 4 (12.1) |
| (d) 2 g. stat. | 10 | 9 | 8 (88.9) | 1 (11.1) | 1 (11.1) |
| Total | 165 | 149 | 137 (92.0) | 12 (8.0) | 23 (15.4) |
| Group II (Control Group) | 100 | 89 | 85 (95.6) | 4 (4.5) | 14 (15.7) |

An average cure rate of 92% with single dose treatment and 96.5% with standard treatment was obtained. Twelve cases (8%) of the test group were considered treatment failures as they showed either persistence of parasites or relapse during the three month follow-up period. In the control group, 4 cases (4.5%) were treatment failures.

During the follow-up beyond 3 months, 23 cases (15.4%) in the test group and 14 cases (15.7%) in the control group show-

ed re-infection at different phase of follow-up.

The differences between the test and control groups on cure, failure/relapse rates were statistically not significant. All the four single dose schedules were found equally effective.

The co-operation from the male consorts for their treatment was not entirely satisfactory as 127 in the test group and 73 in the control group took the therapy as advised.

TABLE III
Incidence of Re-infection After Treatment

| Groups | No. of cases | Evidence of T.V. in vaginal smear | | | | | Total |
|------------------------------------|--------------|-----------------------------------|---------|---------|---------|----------------|-------|
| | | 3 mths. | 4 mths. | 5 mths. | 6 mths. | Beyond 6 mths. | |
| Group I (Test Group) | | | | | | | |
| (a) 30 mg./kg. | 75 | — | 4 | 5 | — | 4 | 13 |
| (b) 35 mg./kg. | 45 | — | 1 | 1 | — | 3 | 5 |
| (c) 40 mg./kg. | 35 | — | 1 | 3 | — | — | 4 |
| (d) 2 g. stat. | 10 | — | — | — | — | 1 | 1 |
| Total | 165 | — | 6 | 9 | — | 8 | 23 |
| Group II (Control Group) | | | | | | | |
| | 100 | — | 4 | 4 | 3 | 3 | 14 |

Side-Effects

Excellent tolerance was experienced by patients in both groups. In the test group, 9 patients had nausea or general malaise (8 had received Flagyl in a dosage of 40 mg/kg. or 2 g. statim, whereas only one had had the 30/35 mg./kg. dosage). Four patients of the control group had nausea and general malaise. Thus the tolerance of single dose treatment was found to be excellent and in no way hindrance to treatment.

Disappearance of Parasite from the Vaginal Secretion

Vaginal secretions were tested every 2 hours. In 2 patients, parasites were absent after 2 hours, 4 were negative after 6 hours and the remaining 2 were negative after 8 hours.

Serum Concentrations of Metronidazole

The mean serum metronidazole concentrations estimated by the method advocated by Populaire, Decouvelaere, Lebreton and Pascal (1968) were found to be 8.5/ μ g./ml. after 24 hours and 2.6/ μ g./ml. after 48 hours (See Figure 1).

Discussion

The efficacy of Flagyl in urogenital trichomoniasis has been well documented and high cure rates have been achieved by various workers (*loc. cit.*); Keighley (1962) obtained a 100 per cent cure rate in women in prison. Its efficacy as reported by Kishore and Diwan (1965) is 90 per cent in the initial stages and 75 per cent after 3 months, following cessation of the treatment. Menon (1962) quotes cure rate with Flagyl as 56.3 per cent after 3 months.

A single dosage schedule was suggested by the finding of Powell *et al* (1969) that a single large dose of Flagyl was as effective as divided doses given for five days in the treatment of amoebic liver abscess. In our trial, the cure rate obtained with a single dose was comparable with that of the standard schedule. The different levels in the single dose schedule gave similar results and as such the lower dosages of 30-35 mg./kg. are recommended. No adverse effects have been reported with the use of Flagyl in pregnant women (Perl 1965, Peterson *et al* 1967, Scott Gray 1964, Woodcock 1972) and

our small group of 10 pregnant patients delivered normally at full term and had normal babies.

The failure and relapse rates with treatment, though minimal and within our acceptable range, could possibly be related to unsatisfactory co-operation from the male consorts, some of whom did not take treatment as advised. The drug may sometimes be inactivated by intestinal micro-organisms (McFadzean 1968).

Serum metronidazole concentration after a single dose continued to be much higher for 24-48 hours than the minimal inhibitory concentration as demonstrated by Jennison, Stenton and Watt (1961).

Summary

A comparative trial of single (30-40 mg./kg.) and standard (200 mg. t.d.s. x 7 days) dosage schedules of Flagyl has been carried out in 165 and 100 cases of vaginal trichomoniasis respectively. Cure rates of 92% and 95.5% were obtained in the two groups (the difference was statistically insignificant). The parasite had disappeared from the vagina within 8 hours of the administration of a single dose in 8 patients and their mean serum drug level for 24-48 hours was much higher than the minimum inhibitory concentration of metronidazole against *T. vaginalis*. The single dose treatment was well tolerated and is considered to be a practicable and acceptable alternative to the standard schedule.

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References

1. Cosar, C. and Julou, L.: *Annales de l'Institut Pasteur*, 96: 238, 1959.
2. Csonka, G. W.: *Brit. J. of Venereal Diseases*, 39: 259, 1963.
3. Csonka, G. W.: *Brit. J. of Venereal Diseases*, 47: 456, 1971.
4. Durel, P., Peiron, V., Siboulet, A. and Borel, L. J.: *Compte Rendu de la Society Francaise de Gynecologie*, 29: 36, 1959.
5. Evans, B. A. and Catterall, R. D.: *Brit. Med. Jour.*, 2: 335, 1970.
6. Kieghley, E. E.: *Brit. Med. Jour.*, 2: 93, 1962.
7. Keighley, E. E.: *Brit. Med. Jour.*, 1: 107, 1971.
8. Kishore, N. and Dewan, P.: *J. Obst. & Gynec. Brit. Cwlth.*, 83: 1280, 1965.
9. McFadzean, J. A.: *Indian Practitioner*, 21: 618, 1968.
10. McGill, M. I. and Black, M. D.: *Am. J. Obst. & Gynec.* 83: 1280, 1962.
11. Menon, M. K. K. and Willmott, M.: *J. Obst. & Gynec. India*, 12: 333, 1962.
12. Perl, G.: *Obst. & Gynec.* 25: 273, 1965.
13. Peterson, W. F., Hansen, F. W., Stauch, J. E. and Ryder, C. D.: *Am. J. Obst. & Gynec.* 97: 472, 1967.
14. Populaire, P., Decouvelaere, B., Lebreton, G. and Pascal, S.: *Annales Pharmaceutiques Francaise*, 26: 549, 1968.
15. Powell, S. J., Wilmot, A. J. and Elsdon, Dew, R.: *Annals of Tropical Medicine and Parasitology*, 61: 511, 1969.
16. Schram, N. and Kleimann, H.: *Am. J. Obstet. & Gynec.* 83: 1284, 1962.
17. Scott Gray, M.: *J. Obst. & Gynec. Brit. Cwlth.* 71: 82, 1964.
18. Woodcock, K. R.: *Brit. J. of Venereal Diseases*, 48: 65, 1972.