"FLAGYL" IN THE TREATMENT OF TRICHOMONIASIS.

by

M. K. KRISHNA MENON*, B.A., M.D.,

and

MARY WILLMOTT**, M.D.

It is 125 years since Alfred Donne reported his discovery of the Flagellate, now known as Trichomonas vaginalis, in the vaginal discharge of a woman suffering from vaginitis. A multiplicity of treatment, mostly local application, have been given and advocated during the decades succeeding the discovery. But the value of local therapy is, however, probably limited by the ability of trichomonas to persist in sites other than the vagina and also in the deeper layers of the vagina thus escaping contact with the drug. It could under such conditions reinvade the vagina when conditions there are again rendered favourable. Hence the poor response to local therapy.

It became obvious that a drug to become effective for trichomoniasis should be able to attack the organism at all sites which necessarily means a systemic trichomoniacide. Such a drug should be non-toxic to patient and capable of reaching all tissues of the urogenital tract.

Durel, Rovion, Siboulet, Borel (1959) initiated the study of 8823 R.P. ("Flagyl", May and Baker) in the treatment of trichomoniasis. This drug, metronidazole, is a derivative of nitro-imidazole. They gave "Flagyl" by mouth to a small number of men suffering from trichomonal urethritis with excellent results. They also treated women suffering from trichomonal vaginitis and reported very good results. Sylvestre, Gallai and Ethier (1959) reported very encouraging results with "Flagyl". By the middle of 1960 a number of papers were presented at a symposium in London praising the trichomoniacidal effects of the drug and the high cure rate in the treatment of this condition by oral therapy with "Flagyl".

In early 1961, "Flagyl" was made available to us for clinical trial and we gladly availed ourselves of this opportunity to study the results of treatment. The object of this study was to assess how far "Flagyl" was useful in the complete cure of trichomonal infections and to find out, if any toxic reactions followed the administration of the drug.

* *Director, Institute of Obsterics & Gynaecology, Govt. Hospital for Women and Children, Madras-8, and Professor of Obstetrics & Gynaecology, Madras Medical College.*

** *Research Assistant.*

Methods and Material

225 patients suffering from leucorrhoea form the subject of the study. Where an organic lesion was found in the genital tract to account

duration of treatment and if possible for three months.

The following investigations were done after the start of treatment.

(1) In all cases wet smears were repeated at the end of 48 hours of treatment.

(2) At the end of the week's treatment the clinical picture was reassessed by questioning regarding her symptoms and by gynaecological examination.

(3) The vaginal pH, wet smear, culture of the discharge for T.V. and monilia and blood counts were repeated. In some cases the vaginal smear was stained by Papanicolau technique.

(4) Patients were requested to report every fortnight for a period of 3 months. At each visit they were questioned about sexual activity, menstrual episodes and symptoms. Smears and cultures were repeated at each visit.

When trichomonas was found to persist or reappeared after being negative in culture once, the husbands of these patients were contacted for examination. Unfortunately, of 33 husbands so contacted, only 7 could be examined properly when all proved positive for T.V. 22 were not available for examination and the remainder refused a proper examination. This is indeed very unfortunate.

Observation and Results

Marked symptomatic relief was evident in the majority of cases within 72 hours of therapy and in all at the end of the treatment. Prior to treatment the wet smears showed very high infection with large numbers of leucocytes, pus cells, trichomonas and few epithelial cells. At the end of the treatment all smears were negative for trichomonas (by culture and wet smear). Thus there were no immediate treatment failures. The smears also showed a marked exfoliation of the superficial vaginal epithelial cells. Pus cells and leucocytes which were in plenty prior to treatment were now conspicuous by their absence and the smears had changed from a highly infected "dirty" smear to one with marked "clean" appearance. Within 48 hours of start of treatment in all cases the discharge was found to be negative for trichomonas on culture.

Papanicolau smears of the discharge prior to treatment were characterised by the presence of large number of pus cells and leucocytes. The vaginal cells were markedly acidophilic with autolysis of cell margins and perinuclear halos in several cells. The cells most commonly seen were the superficial vaginal cells. After treatment there was a considerable reduction in the number of acidophilic cells and the smears took on a clean appearance. Gram's staining prior to treatment revealed in addition to large number of pus cells and leucocytes, plenty of secondary organisms with few Doderlein's bacilli. After treatment there was considerable reduction in the number of organisms, leucocytes and pus cells and marked increase in the number of Doderlein's bacillus.

Vaginal pH

Before treatment the vaginal discharge was more alkaline, after treatment there was an increase in

the vaginal acidity as shown in table below:

TABLE IV

pH of vagina	Before treatment No. of cases	After treatment No. of cases
4—5	16	33
5—6	46	56
Over 6	38	11

Blood Counts

In 47 patients there was a drop in the total white cell counts. The range of fall varied from 200-6400 per c.mm. In no case did the total white cell count drop below 2,600 per c.mm. The haemoglobin level was unaffected in all cases.

Toxic Effects

Apart from mild gastro-intestinal disturbances in 15 patients, no toxic or side effects were noticed. Three patients complained of a furred tongue with acid taste in the mouth.

Effect on Pregnancy

Eighteen of the patients were pregnant. No untoward symptoms were noticed. Two patients aborted giving an incidence of 11.1% which is the same as the over-all incidence of abortion in normal pregnancies. The drug was found to have no contraceptive effect as 3 patients conceived while under observation after treatment.

Results of Treatment

In presenting the final results of treatment we experienced certain difficulties. All are agreed that to obtain best results both male and female partners should be treated. We have been unable to get at the male partner for investigation and treatment in all cases. Even in those wherein the trichomonas reappeared after being negative on culture at the end of the treatment we have not been able to get the male partner for investigation and treatment except in a small number. In 33 of the 100 patients, while under observation, the trichomonas reappeared. Thirty of these patients admitted coitus and they could be considered as cases of reinfection. Only 7 of the 33 male partners were available for investigation and they were all found to be positive for trichomonas. In giving out our final results we have therefore adopted the simpler method of finding out the incidence of failure at the end of treatment and observation period irrespective of the fact whether they are cases of reinfection or not. The table below gives the number of cases treated and followed up, the duration of follow-up and results on culture.

TABLE V

Duration of follow-up	Less than 1 month	1 - 2 months	2 - 3 months	Over 3 months	Total
No. of cases	11	15	3	71	100
Reappearance of trichomonas	Nil	Nil	2	31	33
Monilia	2	3	Nil	28	33
Yeast	Nil	6	Nil	18	24

Thus out of 71 cases which were followed up for a period of three months and over after treatment, 33 showed a return of symptoms with positive culture for trichomonas. The gross success rate is 56.3%. We admit as stated above that majority could be cases of reinfection and not true relapses. However, there is evidence that 3 patients with recurrence denied coitus and these must be considered as treatment failures. In these 3 patients the trichomonas reappeared at the end of 6, 9 and 12 weeks respectively. All cases became negative after a second course of treatment.

One of the most interesting findings was the growth of monilia and yeast like organisms during the follow-up period in these patients. Thirty-three patients, who did not have monilia infection prior to start of treatment, on examination during the observation period showed that the persistent discharge was due to candida infection as proved by culture. These patients were negative for trichomonas and treatment with Mycostatin vaginal tablets cured them completely. Monilial infection was observed at any time after treatment, in some cases within a month and in one case as long as 5 months later. It is observed that in our series there has been no immediate treatment failures. The gross cure rate has been 56.3% and in nearly 33% of cases monilial infection occurred when the trichomonas infection was cured. Our results as compared to those of other workers are given in the tabular statement below.

TABLE VI

Name of authors	No. of cases	No. of cases followed upto 3 months	Success		Failure	
			No.	Per cent	No.	Per cent
Rodie et al	82	52	43	83.0	9	17.0
Watt and Jennison	44	31	25	56.8	6	12.0
King A. J.	82	52	43	83.0	9	17.0
Wilcox	34	34	29	85.3	5	14.7
Nicol et al	122	57	40	70.1	17	29.9
G. W. Csonka	37	37	34	91.9	3	8.1
Menon and Willmot	100	71	40	56.3	31	43.7

Comment

A survey of literature shows that "Flagyl" is a very reliable oral trichomonacide. Rodie et al reported resolution of symptoms in most patients within a few days of start of treatment. In 25% of cases in our series clinical symptoms persisted at the end of treatment though the vaginal discharge did not reveal trichomonas even on culture. A follow-up of these patients showed that later 17 developed candida infection and in 4 trichomonas reappeared.

Failure of response to treatment as evinced by persistence of the organism in the first post-treatment smear may be due to either the drug being taken irregularly, inadequate absorption of the drug, or resistant strains of organism. Rodie et al re-

ported 5% immediate treatment failures, Nicol and associates 4% and Wilcox 5.9% immediate treatment failures. In our series there were no immediate treatment failures. Durel and his associates advocate a combined local and oral treatment with Flagyl for better results.

The results of treatment should be judged only after a long period of follow-up. Most workers have adopted a period of three months in assessing the results of treatment and in conformity with them we have also adopted the same standard to assess the results. The reappearance of trichomonas in smears while under observation could be due to reinfection from the male partner and it is herein where our troubles lay in assessing correctly the value of the drug. Of 71 cases followed up for 3 months the organism reapeared in smears at varying periods in 31 cases, i.e. 43.7%. Twenty-eight of these patients admitted coitus and of 7 husbands who were available for investigation in this group of 31 all were positive for trichomonas. Our gross cure rate is thus lower than any reported as shown in table.

The appearance of monilia in 33 patients who did not have the infection prior to treatment with Flagyl is interesting. It suggests that perhaps the effect of the drug was to render the vagina more prone to candida infection. One is reminded of the tendency for vaginal moniliasis during and after intensive antibiotic therapy. Moffett and McGill reported 3 cases of monilial infection in 42 cases following therapy with Flagyl. Scott Gray noted the development of yeast infection in 25% of 23 cases treated by her while in control series 10.2% were found infected. Even though Rodie et al found monilia in culture in 4 patients after treatment, Csnoka in 4 and Rues in 9 out of his 38 patients after treatment they concluded that there was no evidence to suggest that "Flagyl" favoured or inhibited the growth of candida. Lang in his study had found that monilia infection may appear when severe trichomonas infection is brought under control.

We were struck by the high incidence of monilia and yeast infection (33%) following "Flagyl" therapy and what is more, the patients had really distressing symptoms, mainly vaginal discharge and pruritus. It appeared that while bacteriologically the patient was cured of trichomonas infection, clinically, as far as she was concerned, her troubles were not relieved (whatever be the organism). However, a course of treatment with vaginal Mycostatin tablets for a fortnight cured them of this infection.

One feature of this drug is its extremely low toxicity. Mild reactions, such as gastrointestinal upset and acid taste in the mouth, have been noted in a few cases. Almost all workers have reported low toxicity rates. Its effect on the haemopoetic system was in the nature of a temporary leucopaenia in 47% of cases but in no case did the count fall to alarmingly low levels. It had no effect on haemoglobin level. From our trials we conclude that "Flagyl" is a very valuable oral trichomonacide. Our results would certainly have been better if only we had the male partner's co-operation in treatment and in stating that the gross cure rate is 56.3% this factor has to be taken into consideration.

Summary and Conclusions

1. "Flagyl" 200 mgms. orally three times a day was administered to 100 women suffering from trichomonas infection of the vagina. All cases were submitted to culture of the vaginal discharge for T.V. and monilia, determination of vaginal pH, haemoglobin estimation and leucocyte count, Gram's and Pappanicolau staining of the discharge before and after treatment. Cases were followed up fortnightly for three months with examination and culture of the vaginal discharge. The final assessment was made at the end of 3 months.

2. There were no immediate treatment failures.

3. Seventy one cases were followed up for 3 months in 31 trichomonas reappeared which was cured by a second course of "Flagyl". Twenty-eight admitted intercourse and of the 7 husbands available for investigations all were found positive for trichomonas in this group. These could be cases of re-infection. However, we put down our gross cure rate as 56.39 per cent.

4. Thirty-three of the 100 cases developed monilia infection when trichomonal infection had been cured. It is observed that suppression of trichomonas infection by "Flagyl" may bring forth infection by monilia Monilial infection was cured by Mycostatin vaginal tablets.

5. There was only very low incidence of even mild toxicity due to drug in this series. In no case did the total white cell count fall below 2500 and the haemoglobin level was maintained at the original level.

We are very grateful to Messrs. May and Baker Ltd. for having placed at our disposal generous supplies of "Flagyl" and culture media for this work.

References

1. Acta Obstetrica et gynaecologica Scandinavia; vol. XXXIX, Fasc.
2. Brit. Med. Jour. of Venereal Disease; 157, 1960.
3. Durel P. et al: Brit. Med. Jour. of Venereal Disease; 154, 1960.
4. King A. J.: Practitioner; 808, 1960.
5. Lang W. R.: J.A.M.A.; 174, 1814, 1960.
6. Moffett M. and McGill: Brit. Med. Jour.; 910, 1960.
7. Nicol C. A., Barrow J. and Redmond A.: Brit. Med. Jour. of Venereal Disease; 152, 1960.
8. Rees E: Brit. Med. Jour.; 906, 1960.
9. Rodie P., King A. J., Nicol C. S. and Barrow J.: Brit. Jour. of Venereal Disease; 147, 1960.
10. Watt L., Jennison R. F.: Brit. Med. Jour.; 902, 1960.
11. Wilcox R. R.: Brit. Med. Jour. of Venereal Diseases; 175, 1960.