LOCAL TREATMENT OF TRICHOMONAS VAGINITIS*

BY

R. D. CATTERALL and MARY WILLIAMSON

From the Whitechapel Clinic, The London Hospital

There is general agreement that the treatment of trichomonas vaginitis is unsatisfactory. Medicaments administered by mouth or parenterally have proved ineffective, and although the immediate response to some remedies applied locally is satisfactory, there is a marked tendency to relapse. There seems little doubt that the preparations which seem effective do no more than temporarily suppress the signs of infection in many cases. It is sometimes necessary to maintain suppressive treatment for many months before cure can be presumed and in some cases there are frequent relapses despite prolonged treatment of all kinds.

The value of local remedies must be assessed by the degree and speed with which the clinical effects of vaginal discharge, intertrigo, dyspareunia, and pelvic pain are abolished, and, in the course of observation and tests, by the proportion of cases in which the patients remain free from relapse. Assessment requires a considerable period of observation, and testing is complicated by the fact that many patients discontinue attendance when their symptoms are relieved, and that with out-patients there is no means of distinguishing between re-infection and relapse.

The necessity for prolonged treatment in many cases renders it imperative that remedies should be well tolerated and that patients should not readily become sensitized to them.

The standard preparation which has been used for a number of years is acetarsol. It has proved the most effective of the many remedies which have been tried and recommended, and in general it is well tolerated. It is, however, an arsenical preparation and cases of sensitization have been reported. Most of these, which occurred after prolonged treatment with acetarsol vaginal pessaries or powder used intravaginally, were manifested by a generalized exfoliative dermatitis, pyrexia, and malaise (Kesten, 1938; Doyle, 1952). Some patients had been previously sensitized by arsenical compounds for the treatment of syphilis and showed immediate symptoms of sensitization on beginning a subsequent course of acetarsol vaginal pessaries (Campbell,

1937; Orchard, 1951). Thus there is always the possibility that arsenical exfoliative dermatitis may develop, and patients who have been sensitized to the organic arsenicals in the past run an extremely grave risk if acetarsol is used. It is therefore desirable that an equally effective alternative drug belonging to some other chemical group should be available; such a drug may also prove effective in cases which prove resistant to acetarsol.

Present Investigation

The following compounds have been used:—

(1) **Acetarsol**.—This is a pentavalent arsenical compound, 3-acetamido-4-hydroxyphenylarsenic acid, containing 27 per cent. arsenic, with the following structural formula:

(2) **"Milibis"** (as marketed).—This compound is bismuthoxy-4-N-glycolylarsanilate; it contains approximately 15 per cent. arsenic and 42 per cent. bismuth, the structural formula being:

(3) **Milibis** contained in a more soluble base.

(4) **"Aroxine"**,* a pessary containing 100 mg. 2-formamido-5-nitrothiazole, which is about one hundred times more active *in vitro* than acetarsol (Bushby and Copp, 1955). The structural formula is:

* "Aroxine" is the trade name for the pessaries (Burroughs Wellcome Ltd.).

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(5) Pessaries containing 100 mg. 2-hexanamido-5-nitrothiazole, 40 C 53, an analogue of 2-formamido-5-nitrothiazole, with the structural formula :

(6) Pessaries containing 100 mg. of the higher homologue of 40 C 53, 2-heptanamido-5-nitrothiazole (41 C 53), with the structural formula :

During 1953, 215 patients with trichomonas vaginitis were divided into six groups, each of which was treated with one of the preparations enumerated. The immediate results of treatment were recorded and an attempt was made to follow these patients with frequent examinations and tests for at least 3 months. Many had first infections but some had relapsed after earlier treatment. In all but the last group, the method of treatment employed was to insert two tablets of the compound to be tested high into the vagina each day for periods varying from 7 to 14 days. On the first occasion the tablets were inserted by a member of the nursing staff and the patient was instructed in the technique of self-treatment. Thereafter the patients continued their own treatment without immediate supervision.

It was necessary to establish arbitrary criteria of cure, as follows :

(a) There must be no clinical evidence of vaginitis for at least 3 months after completion of course.

(b) Smears from the vaginal secretion must be negative for *Trichomonas vaginalis* during the same time, which must extend over three menstrual periods.

At the end of this time patients were discharged provided that they were free from associated infections such as gonorrhoea or syphilis.

The patients treated included married women and single women, of whom some were prostitutes and others of promiscuous sexual habits. If no condition other than trichomonas vaginitis was found they were informed that they were not suffering from a venereal disease but were urged to regard the condition seriously. This policy of reassurance, which was ethically correct, affected the investigation adversely, for many took a light-hearted view of their disease and either did not follow instructions conscientiously or failed to continue attendance. Some patients were of low intelligence, so that occasionally tablets were not properly inserted and were found lying between the labia. Two patients inserted the tablets into the rectum and four even

took the tablets by mouth. No distinction was possible between patients who relapsed and those who were re-infected, and therefore all who showed evidence of infection after treatment were included among those who were considered to have relapsed. All those who ceased to attend received two letters renewing their appointments but the response to correspondence was uniformly poor throughout the series. All these factors added to the difficulties of assessment.

Results

1. Acetarsol and Aroxine.—Of fourteen patients, all of whom had experienced relapse after various remedies, four received acetarsol and ten Aroxine. The method of treatment was to insert two tablets vaginally each night for 7 nights.

All four patients who received acetarsol and five who received Aroxine defaulted. The remaining five patients made an immediate satisfactory clinical response and microscopic tests for *T. vaginalis* became negative. Two relapsed, however, after 1 month and three after 2 months. These results suggested that Aroxine was an effective remedy but probably required to be used for more than 1 week.

(2) Aroxine.—All of 39 patients who had been treated with acetarsol and had subsequently relapsed were treated with Aroxine by vaginal insertion of two tablets each night for 14 successive nights.

Sixteen patients defaulted and seven relapsed within 1 week of the cessation of treatment. Four patients relapsed after 1 month, five after 2 months, and three after 3 months. Three patients were cured. In one case treatment was discontinued because of vulval irritation (see Table I).

TABLE I
RESULTS IN SERIES 2

Results						Aroxine
Defaulted	..	..	..	..	..	16
Cured	..	..	..	..	..	3
Relapsed after 1 week	..	..	..	..	..	7
Relapsed after 1 month	..	..	..	..	..	4
Relapsed after 2 months	..	..	..	..	..	5
Relapsed after 3 months	..	..	..	..	..	3
Treatment discontinued	..	..	..	..	..	1
Total Patients	..	..	..	..	..	39

One of the five patients who relapsed after 2 months developed acute bilateral salpingitis but the gonococcus was not found in the secretions. Two patients who relapsed were subsequently cured by further administration of acetarsol.

In view of the evidence that the immediate effect of Aroxine seemed to be as satisfactory as that of

acetarsol, it was decided to institute a comparison between these drugs in a larger number of cases.

(3) **Aroxine and Acetarsol Compared.**—The investigation was limited to patients in whose secretions trichomonads were discovered for the first time. All had recently come under observation and were, as far as could be judged, cases of fresh infection. Alternate patients were treated with Aroxine and acetarsol by the intravaginal insertion of two tablets each night for 14 successive nights. Of the 99 patients treated, 23 of those receiving Aroxine and 26 receiving acetarsol defaulted. Five cures were obtained with Aroxine and six with acetarsol. Five patients relapsed within 1 week of the course of Aroxine while only one relapsed in a similar period after acetarsol. Of patients who relapsed after 1 month, seven had received Aroxine and six acetarsol; at 2 months eight relapsed after Aroxine and eight after acetarsol; at 3 months, one relapsed after Aroxine and two after acetarsol. One of the patients who received acetarsol had the treatment discontinued because of local soreness and irritation (Table II).

TABLE II
RESULTS IN SERIES 3

Results	Drug		
	Aroxine	Acetarsol	Total
Defaulted	23	26	49
Cured	5	6	11
Relapsed after 1 week ..	5	1	6
Relapsed after 1 month ..	7	6	13
Relapsed after 2 months ..	8	8	16
Relapsed after 3 months ..	1	2	3
Treatment discontinued ..	—	1	1
Total Patients	49	50	99

Three of the patients who relapsed after treatment with Aroxine were subsequently cured by the administration of acetarsol.

Because of the large proportion of defaulters it was not possible to draw conclusions from this comparison, but as far as the evidence went there appeared to be no great difference between the effects of the two drugs, although the higher proportion of immediate relapses after Aroxine is perhaps worthy of note.

(4) **Pessaries containing Analogues of 2-formamido-5-nitrothiazole.**—These were used for trial in cases which had previously relapsed. These substances are less soluble than 2-formamido-5-nitrothiazole and were tried in the hope that the antitrichomonal activity would be more prolonged.

(i) Fourteen patients were given Aroxine: seven relapsed within 2 months, three defaulted, and four were cured.

(ii) Eleven patients were given 40 C 53: four relapsed within 2 months, six defaulted, and one was cured.

(iii) Eleven patients were treated with 41 C 53: six relapsed within 2 months, four defaulted, and one was cured.

The results were inconclusive but it seems that these analogues had no particular advantages over the original (Table III).

TABLE III
RESULTS IN SERIES 4

Results	Drug		
	Aroxine	40 C 53	41 C 53
Defaulted	3	6	4
Cured	4	1	1
Relapsed after 1 or 2 months	7	4	6
Total Patients	14	11	11

(5) **Milibis.**—Twelve patients were treated by the vaginal insertion of two tablets of Milibis nightly on ten consecutive occasions. The results showed that no patient was cured, three relapsed after the first month, seven showed trichomonads in the secretions during the course of treatment with no evidence of clinical improvement and two defaulted (Table IV).

All these patients complained of dryness, soreness, and vulval and vaginal irritation. They also complained of difficulty in inserting the tablets which were so insoluble that on examining patients the vagina was found to contain undissolved tablets. In view of the lack of an immediate satisfactory effect and the local reactions which the majority of patients experienced, it seemed clear that this preparation was unsatisfactory.

The makers then supplied a preparation contained in a more soluble base, and this was used in the treatment of ten patients who received a similar course lasting 10 days. Results showed again that no patient was cured, three relapsed in 1 month and two showed relapse within a week. Five patients defaulted (Table IV).

TABLE IV
RESULTS IN SERIES 5

Results	Drug	
	Milibis	Modified Milibis
Defaulted	2	5
Cured	0	0
Relapsed during treatment ..	7	—
Relapsed after 1 month ..	3	3
Relapsed in 1 week ..	—	2
Total Patients	12	10

The modified preparation did appear to dissolve in the vagina more satisfactorily, but dried residue was found on routine examination in most patients. Only three patients showed evidence of clinical

improvement and all three relapsed and showed positive smears at the end of the first month. These three patients were subsequently cured with acetarsol. There seemed no indication to pursue investigation of this preparation.

(6) Irrigation and Local Application.—The unsatisfactory results which followed these forms of local treatment might be due to the fact that the trichomonocidal agent which was applied in the form of small vaginal tablets did not reach all the folds and rugae of a canal which, on distension, is fairly voluminous. Another possible source of error was that reliance had to be placed upon the patient for proper insertion of the tablets. The effect was therefore tried of using a single treatment in which the vagina was thoroughly irrigated with 0.2 per cent. solution of 2-formamido-5-nitrothiazole followed by the application to the vaginal walls of paste containing 1 per cent. of the drug.

Technique

The patient was placed in a modified Trendelenberg position and the vaginal wall was stretched by means of a Cusco's bivalve speculum of appropriate size. The solution was injected into the vagina with a Ritchie's bladder syringe. After three successive irrigations by which the walls and fornices of the vagina were exposed to the solution, the cavity was filled with the fluid which was left in position for 20 minutes. Previously it had been ascertained that the application of this solution in a similar concentration *in vitro* was lethal to the organism in 20 minutes. The vagina was then emptied and the paste liberally applied to the vaginal wall. The patient was subsequently allowed to go home.

It was hoped that such thorough treatment given on one occasion would remove the responsibility of further treatment from the patient. Five patients were so treated with satisfactory immediate response, but unfortunately all relapsed within one week. Thus this form of local treatment also proved unsuccessful.

Male Contacts.—Ninety-seven males who were known to be contacts of the 215 women suffering from trichomonas vaginitis were examined. In only four were trichomonads found in urethral smears or in specimens of urine after centrifuging; 62 of the male contacts, however, showed evidence of gonococcal urethritis and 32 of "non-specific" urethritis. Five male contacts showed no evidence of urethritis although two of them had urethral strictures.

Discussion

The methods used in these cases were unsatisfactory, like all other forms of treatment for trichomonas vaginitis. Even the better preparations

produced only symptomatic relief during treatment, with cure in a very small proportion of cases. Subsequent relapse occurred in the majority of those who remained under observation.

Within these limitations, acetarsol, in the course of long experience, has proved its comparative efficacy and has caused few toxic reactions. The disease, however, is a chronic one and the likelihood of repeated relapse is considerable. Therefore it is desirable that alternative drugs should be available if they can be shown to be reasonably effective. Aroxine appears to be effective and non-toxic. Only three patients out of 103 who were treated with this drug complained of toxic effects; two of these noticed local irritation and one experienced a more severe reaction which was apparently due to sensitization. This patient complained of a burning sensation on the vulva on the fourth day of treatment and was found to have oedema of the labia. Intradermal and patch tests with Aroxine proved negative and the condition subsided when the drug was discontinued and antihistamines were given by mouth. Aroxine has the advantage that it is not an arsenical. Acetarsol, which is an arsenical, has produced few sensitization effects, but the fear remains that, with long-continued use, these effects may occur and prove severe and even fatal. Those patients who have in the past become sensitized to the arsenical drugs run considerable risk if acetarsol is used for this very common infection without knowledge or appreciation of the significance of the earlier history. From present experience it cannot be said that Aroxine is a better preparation than acetarsol or even as good in view of the high proportion of patients showing early relapse after its use; nevertheless it did give symptomatic relief to almost all the patients and must be regarded as a useful substitute.

The number of cures obtained after using each drug was not insignificant and the proportion was increased by prolonging treatment and by changing from one drug to the other. So little is known about the fundamental pathology of the disease that it would be difficult to draw conclusions from these facts. It is possible that there is more than one strain of the parasite or that in certain circumstances the parasite is not susceptible to a single drug. Some patients are resistant to all treatment and show immediate relapse after any drug. A case in point was a patient who was kept in hospital for 3 months to exclude the possibility of re-infection, and was treated with acetarsol, Milibis, acetic acid, Aroxine and its analogues, and solution of Aroxine followed by the application of paste containing the drug. In spite of continuous therapy negative

results to smears were never obtained for a longer period than 1 week. There are no special features which enable such cases to be recognized before treatment and the cause of resistance remains obscure.

Results with Milibis were unsatisfactory. There was no relief from symptoms in the majority of patients and no regression of clinical signs. The tablets failed to dissolve and caused discomfort and irritation. The preparation was deficient in trichomonocidal power, for on more than one occasion vaginal smears showed active trichomonads among the crystals. The modification of Milibis which dissolved more satisfactorily showed no greater efficacy.

Summary

The treatment of trichomonas vaginitis is unsatisfactory. No medicament is effective systemically, and although some forms of local treatment are immediately effective the condition is prone to relapse. The assessment of any form of treatment is difficult because so many patients discontinue attendance and because there is no means of distinguishing between relapse and re-infection. The standard remedy, acetarsol, is an arsenical and

its use occasionally results in sensitization which may be dangerous. It is desirable that an equally effective non-arsenical preparation should be available as an alternative.

Clinical results obtained in the treatment of 215 cases of trichomonas vaginitis with acetarsol, Milibis, Aroxine, and some modifications are described.

Milibis proved ineffective. Aroxine (2-formamido-5-nitrothiazole) applied locally produced results which were comparable with, although possibly slightly inferior to, those obtained with acetarsol. Analogues of 2-formamido-5-nitrothiazole had no particular advantages.

The results of investigations in the cases of 97 male contacts of women suffering from trichomonas vaginitis are described.

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