RESULTS OF CLINICAL TRIALS OF BAY-b 5097 FOR TRICHOMONAS VAGINALITIS

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We had the opportunity to carry out clinical trials of BAY-b 5097 vaginal suppository on patients with trichomonas vaginalitis, and found that we might significantly count upon the removing of subjective symptoms and trichomonas by of this drug.

Since Donne's discovery of trichomonas vaginalis in 1836 and since Hoene's statement in 1916 that vaginalitis complaining of intractable leucorrhea despite negative test for gonococcus is ascribable to trichomonas vaginalis, many subsequent studies have been performed as is well known.

In spite of the recent availability of Trichomycin and other superior therapeutic agents for the treatment of the above disease, erradiation of the disease is, unfortunately, often beyond hope, with relapse or resumed positive test too frequently observed.

Having recently been offered Bis-phenyl-(2-chlorophenyl)-1-imidazolyl-methane (BAY-b 5097), we used it for clinical trials on cases of trichomonas vaginalitis. Our experiences are reported hereunder.

MATERIALS AND METHODS

BAY-b 5097: This drug whose chemical name is Bis-phenyl-(2-chlorophenyl)-imidazolyl-methane, and its vaginal suppository used in our clinical

trials was supplied in a plastic container of 6 tablets.

Materials: Out of outpatients of the Department of Obstetrics and Gynecology of our University Hospital and our affiliated hospitals, 32 microscopically positive for trichomonas were given the drug. They are listed in Table 1.

The age distribution of the 32 cases is presented in Table 2: fifty percent or 16 cases were from 31 to 40 years of age; 3 of the patients in the 3rd decade of life were unmarried women.

TABLE 2
Age distribution

Age Case	~20	21~30	31~40	41~
32	1 (3.1%)	7 (21.9%)	16 (50%)	8 (25%)

Their presenting complaints are contained in Table 3. The majority, i.e. 90.6% of them, were complaining of leukorrhea. Thirtyseven and a half per cent had itching, too. Bleeding on touching was complained of in 9.4%.

TABLE 1
Patients list

Case No.	Age	Derivery	Chief Complaint			Local findings		Compli-cation	Remarks
			Leuco-rhea	Pruritus vulvae	Ontact bleeding	Mild redness	Erosion		
1	20	Unmarried	yes	yes	-	yes	-	-	-
2	31	1	yes	-	-	yes	-	-	-
3	24	1	yes	-	-	yes	-	-	-
4	46	5	yes	yes	-	yes	-	-	-
5	46	2	yes	-	-	yes	-	-	-
6	43	1	-	-	yes	yes	yes	-	-
7	42	3	yes	yes	-	-	-	Candidiasis	-
8	21	Unmarried	yes	yes	-	yes	-	-	-
9	30	3	yes	-	-	yes	-	-	-
10	35	1	yes	yes	-	yes	-	Candidiasis	-
11	39	4	-	yes	yes	-	yes	-	-
12	29	0	yes	-	-	yes	-	-	-
13	34	2	yes	yes	-	yes	-	-	-
14	29	2	yes	yes	-	yes	-	-	-
15	46	6	yes	yes	-	yes	-	-	Husband died
16	40	3	yes	-	-	yes	-	-	-
17	42	2	yes	-	-	yes	-	-	-
18	35	4	yes	yes	-	yes	-	-	-
19	35	2	yes	-	-	yes	-	-	-
20	30	0	yes	-	-	yes	-	-	-
21	35	3	yes	-	-	-	yes	-	-
22	32	1	yes	yes	-	yes	-	Candidiasis	-
23	25	Unmarried	yes	-	-	yes	-	-	-
24	31	1	yes	-	-	yes	-	-	-
25	39	3	yes	-	-	-	-	-	-
26	32	2	yes	-	-	yes	-	-	-
27	40	5	yes	-	-	yes	-	-	-
28	34	3	-	yes	yes	-	yes	-	-
29	45	3	yes	-	-	-	yes	-	-
30	34	1	yes	-	-	yes	-	-	-
31	41	3	yes	-	-	-	-	-	-
32	32	2	yes	-	-	yes	-	-	-

TABLE 3
Subjective symptoms

Case	Leucorrhea	Pruritus due to leucorrhea	Bleeding on contact and dyspareunia
32	29 (90.6%)	12 (37.5%)	3 (9.4%)

TABLE 4
Local findings

Case	Vaginal wall		Cervical erosion
	Mild redness	Erosion	
32	25 (78.1%)	5 (15.6%)	8 (25%)

The local findings are classified in Table 4. Mild redness of the vaginal wall was observed in 78.1%, and erosion in 15.6%. Though subjectively complaining of symptoms, there was nothing particularly abnormal in the local finding of the vaginal wall, with trichomonas demonstrated, however, in 2 cases. Eight cases were complicated by cervical erosion.

Complication by candidiasis, as a factor influencing the results of treatment, was noted in 3 cases as presented in Table 5. All the other cases were negative for candida.

TABLE 5
Complicated by candidiasis

Case	Yes	No
32	3 (9.4%)	29 (90.6%)

Whether or not treatment had been undergone previously, is shown in Table 6. Ten of the cases presented themselves for our medical attention having failed to obtain cure in spite of treatments received elsewhere. All the other were fresh cases, having undergone no treatment in the past.

TABLE 6
Treated in the past history

Case	Yes	No
32	10 (31.3%)	22 (68.7%)

What sort of treatment was undergone in the past could not be learned definitely, and the patients' informations in this connection are collectively quoted.

Methods: BAY-b 5097 was administered in doses of one tablet daily for

one week successively. When the patient was not available for administration because of a Sunday or holiday, they were made to insert the suppository by themselves so that the drug effect evaluation later could be in normal way.

The patients' male consorts were given no particular treatment. The patients, however, were given a full explanation of the disease and were persuaded to keep out of coitus until permission.

The drug effect was evaluated on the basis of the disappearance of subjective symptoms, improvements in local findings, and absence of trichomonas. This absence of trichomonas was regarded to be of the primary importance.

By the way, the examination for trichomonas was mainly by microscopic study. The negative cases were further examined by culture (cysteine bullion serum medium).

RESULTS

Improvements in subjective symptoms were judged by questioning the patients at 4 and 7 days after the institution of treatment. The results there by found out are presented in Table 7. Improvements in 4 days were observed in 37.5% of cases, and in 7 days in another 15 cases, too, i. e. in 46.9%. On completion of treatment, improvements were noted in 84.3% of all the cases treated.

TABLE 7
Improvement in subjective symptom by treatment

Case	In 4 days	In 7 days	On completion of treatment
32	12 (37.5%)	15 (46.9%)	27 (84.3%)

Changes in local findings are presented in Table 8. Disappearance of or decrease in the local abnormalities was noted in 21 (84%) of 25 cases that had, before treatment, mild redness of the vaginal wall and in 4 (80%) of 5 cases that had, before treatment, erosion. The 8 cases that had been complicated by cervical erosion all remained unchanged despite the treatment.

TABLE 8
*Improvement in local findings
on completion of treatment*

	Vaginal wall	
	Mild redness	Erosion
Case treated	25	5
Case improved	21 (84%)	4 (80%)

Tests for trichomonas vaginalis were done on the 4th and 7th days of treatment and in 1, 2 and 4 weeks after completion of treatment, by getting specimens from posterior vaginal fornix and cervical canal. During the insertion of the vaginal suppository, the patients

were told not to use any irrigation liquid. Even when menses occurred during treatment, the treatment was kept on, though the cases that seemed to make proper evaluation of the present treatment results difficult were left out the collective evaluation.

For the results, refer to Table 9 and Table 10. Examinations at 4 days after the start of treatment found 62.5 % negative for trichomonas vaginalis and at 7 days 84.4%. As for follow-up studies after completion of treatment, some cases were prevented by their own circumstances from reporting again for examination, and the number of cases that could be followed up had to be less than all those treated. Return to positive test for trichomonas vaginalis was noted in one week in 3 (12.5%) of 24 cases, in 2 weeks in 6 (30%) of 20 cases, and in 4 weeks in 7 (38.9%) of 18 cases.

TABLE 9
Removing Trichomonas

Case treated	after 4 days	after 7 days
32	20 (62.5%)	27 (84.4%)

TABLE 10
Follow-up studies

after 1 week			after 2 weeks			after 4 weeks		
Cases	Trichomonas positive	Relapse	Cases	Trichomonas positive	Relapse	Cases	Trichomonas positive	Relapse
24	3	12.5%	20	6	30%	18	7	38.9%

DISCUSSION

The therapeutic agents for trichomonas vaginalitis were at first corrosive sublimate, followed later by Yatren, Quinezol, Mercuro-chrome, etc. Today, better drugs are available thanks to progress in chemotherapy. Yet, even

those drugs supplied at present can hardly be considered satisfactory enough for erradiation of the disease. Unfortunately, the incidence of return to positive test is by no means low. That comes from the fact that trichomonas vaginalis not only parasitizes the vagina but also is present in the

bladder, skin glands, Bartholin's gland and even in the external genitalia. It furthermore parasitizes the male bladder, prostate, urinary tract and all the sexual organs. Local treatment alone can, therefore, not be expected to cure the disease. The current treatment, therefore, is three-fold-local treatment, general treatment and a simultaneous treatment of the male consort, most often. Good results obtained with this triple approach have been reported. The above concomitant treatment, however, is not feasible without the patient and her male consort' perfect understanding and cooperations, which, as a matter of fact, is known to be too often beyond hope. This situation makes treatment the more difficult.

BAY-b 5097 vaginal suppository used in our present clinical trials has been demonstrated, in *in-vitro* study and experimental infections, to be effective enough against candida. Its clinical results have been reported so far only A. Freis et al., who reported it excellent in 50 % and good in 35.1 % of 34 cases. No clinical report by Japanese workers has yet been published. So the effectiveness of this drug for the above purposes had been only suggestive.

We had the opportunity to try it clinically on 32 cases of trichomonas vaginalitis. The results of treatment were reasonably good: 7 days, treatment in succession improved subjective symptoms in 84.3% and produced negative test for trichomonas in 84.4%. However, that was result of the administration of its vaginal suppository to the patients themselves alone, without

treating their male consorts. There is no denying that the incidence of the return to positive test for trichomonas in the follow-up studies was somewhat high. The drug, however, should in no wise be considered inferior to the conventional preparations. We are counting upon the good results of further use of BAY-b 5097 on many more clinical cases of trichomonas vaginalitis.

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