SINGLE DOSE THERAPY FOR TRICHOMONAL VAGINITIS WITH SATRANIDAZOLE (Go. 10213)—PHASE 2 STUDY WITH A NEW ANTI-PROTOZOAL AGENT

by

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SUMMARY

Three groups of patients were administered a single dose of Go. 10213, 300 mgm (22 subjects), 450 mgm (10 subjects), and 600 mgm (32 subjects). There was 100% cure with 600 mgm single dose of Go. 10213 and 95.5% and 90% in 300 mg and 450 mg. respectively. The tolerability of the drug was excellent.

Introduction

Satranidazole (Go. 10213)*, a new potent nitroimidazole was discovered and developed (Nagarajan *et al* 1982) at the Research Centre of Hindustan CIBA-GEIGY Limited. It has the chemical structure shown in Fig. 1. Satranidazole

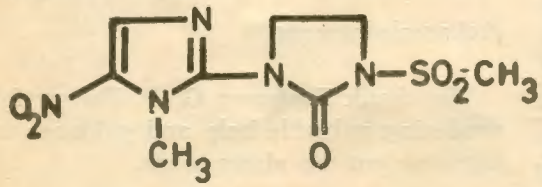

Fig. 1
Satranidazole-1-methylsulphonyl-3-(1-methyl-5-nitroimidazolyl)-2-imidazolidinone.

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induced complete cure of *Trichomonas vaginalis* infection, in mice, at a dose of 10 mg/kg p.o. x 4. In this model with a subcutaneous infection, satranidazole is approximately four times more potent than metronidazole (Ray *et al* 1982). In acute, subacute and chronic toxicity and teratogenicity studies in several species of animals, the compound was found to have an acceptable tolerability profile. Satranidazole was well tolerated in volunteers and patients with intestinal amoebiasis (Vaidya *et al* 1983).

Trichomoniasis is a sexually transmitted disease that is prevalent worldwide. The incidence in India has been reported to vary from 20 to as high as 40 per cent of the women (Narvekar 1959, and Sakia *et al*, 1971). Single dose treatment of trichomoniasis with different nitroimidazoles has been reported by several investigators

with cure rates ranging from 70 to 100% (Czonka 1971; Panjabi *et al* 1975; Thin *et al* 1979 and Gabriel *et al* 1982).

In the present study, satranidazole was studied in single doses in women with vaginal trichomoniasis to assess the anti-trichomonal activity, optimal dose and tolerability of the compound.

Material and Methods

Sixty-four women with vaginal trichomoniasis attending the outpatient gynaecological department of the K.E.M. Hospital in Bombay were studied. Their spouses were also treated with satranidazole. The criteria for selection were:

1. adult women of 18 to 50 years of age;
2. complaints of leucorrhoea, itching and other vaginal symptoms; and
3. the presence of actively motile *T. vaginalis* in vaginal discharge.

Those women who did not report for follow-up and those who were pregnant were excluded from the study. Women with vaginal smears positive for gonococci or candida were excluded. An informed consent was obtained from the women and their spouses.

Examination and Investigations

All patients underwent thorough history, general physical and pelvic examinations. Blood pressure and heart rate were recorded in supine and standing positions. The symptoms of leucorrhoea, pruritus, dyspareunia and the signs of discharge, erythema, excoriation, etc. were graded basally and during the follow-up visits as absent = 0, mild = 1, moderate = 2 and severe = 3. A check list of 26 baseline symptoms, including the reported side-effects of metronidazole was used initially and after treatment (Vaidya, *et al* 1973). Any other side-effects reported by patients were recorded.

The vaginal discharge was collected with a Pasteur pipette, under direct vision. A hanging drop preparation in normal saline was immediately made on a slide and examined microscopically for *T. vaginalis* using x 40 objective. Random samples were inoculated into trichomonas culture medium (Johson *et al* 1943) cross-checking the negative results. The examination for *T. vaginalis* was repeated at each follow-up visit. Laboratory investigations to monitor organ functions were carried out only basally to avoid poor patient compliance in this outpatient study. The investigations included routine blood counts, serum proteins, transaminases, alkaline phosphatase, electrolytes, BUN, blood sugar and urine analysis.

Treatment

Three groups of patients were administered a single dose of satranidazole p.o. 300 mg (22 patients), 450 mg (10 patients) and 600 mg (32 patients). Uncoated tablets of 150 mg of satranidazole were employed and these were swallowed both by the patient and her husband in the presence of a physician. No other local or systemic trichomonicidal agents were permitted before or during the follow-up.

Follow-up Assessment

Patients were asked to report on day 1, 4, 7, 14, 21, 28, 35 and 42 after treatment. The vaginal symptoms and signs, baseline symptoms and the presence of *T. vaginalis* were assessed. The total severity score of individual symptoms and signs was evaluated. The persistent disappearance of *T. vaginalis* in the discharge signified a cure of the infection. The women, whose

consorts were untreated, showed a reappearance of *T. vaginalis* after a later sexual contact and it was considered as a reinfection. A failure was defined as presence of *T. vaginalis* at follow-up visits in patients, whose husbands were also treated.

Results

Efficacy

The cure rates with different single doses are shown in Table I. With 600 mg single dose, there was 100% cure as judged by the disappearance of *T. vaginalis*. There were two failures—one each with 450 mg and 300 mg. Reinfection was noticed in one patient on 300 mg and another on 450 mg, in the fifth week. Among women on 600 mg, one patient was reinfected in the fourth week. The patient's husband who was not treated was out of station and there was a history of sexual intercourse after his return. The two patients on 450 mg—one failure and one reinfection—were retreated with 450 mg dose; the former responded and the latter did not. The reinfected patient in the group on 600 mg dose was not retreated.

TABLE I

Cure Rate with Safranidazole

Dose p.o.	Cured/n	Percentage	
		Cured	Failure
300 mg	21/22	95.5	4.5
450 mg	9/10	90	10.0
600 mg	32/32	100.0	0

The number of patients with positive symptoms and signs before and after the treatment are shown in Table II for all the three dose groups. The major complaint of leucorrhoea was completely controlled in 30 out of 32 patients, after a single oral dose of 600 mg of satranidazole. One patient had mild leucorrhoea despite the disappearance of *T. vaginalis*. The other patient showed a reinfection by husband, who was not treated, as he was out of station. With 300 mg and 450 mg the number of patients who were relieved of leucorrhoea was less. However, erythema, excoriation and erosions were relieved with all the doses. Figure 2 shows graphically the decline in the mean severity score of leucorrhoea in all the three groups. The objective rating of the vaginal discharge as shown in Figure 3 also confirms the symptomatic relief.

TABLE II

Number of Patients With Positive Findings Before and at the End of the Follow-up

Symptoms/Signs	300 mg		450 mg		600 mg		All doses	
	Before	After	Before	After	Before	After	Before	After
Leucorrhoea	22	10	10	4	32	2	64	16
Pruritus	17	6	6	1	19	1	32	8
Dyspareunia	3	1	3	2	6	1	12	4
Discharge	22	12	10	4	32	8	64	24
Erythema	3	0	0	0	8	0	11	0
Excoriation	0	0	2	0	7	0	9	0
Erosion	3	0	2	0	10	0	15	0

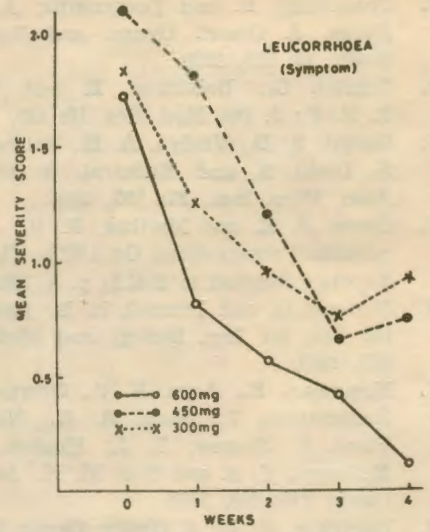

Fig. 2
The decrease in mean severity score of leucorrhoea.

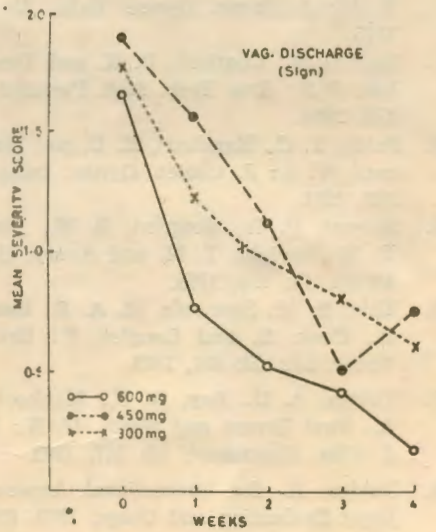

Fig. 3
The decrease in mean severity score of vaginal discharge.

Tolerability

The tolerability of the single doses of 300, 450 and 600 mg of satranidazole was excellent; only one patient on 300 mg complained of metallic taste, 24 hours and 4 days after the drug, which disappeared later. Most of the baseline symptoms were mild and disappeared after the treatment in majority of patients. Backache, diminished appetite, abdominal pain and tiredness were observed basally in 15, 10, 10 and 8 patients respectively in the group of 32 patients of 600 mg. The symptom of diminished appetite persisted only in 2, whereas backache persisted in all the 15 patients. Among the 450 mg group, only itching was reported in one patient basally. Baseline symptoms of itching, dysuria and headache were observed in 7, 3 and 2 patients respectively and one patient each complained of abdominal pain, anorexia, giddiness and tiredness, in 300 mg group. There was no aggravation of the baseline symptoms after satranidazole. The husbands too tolerated well the single doses of satranidazole.

Discussion

Satranidazole in a single oral dose of 600 mg, cured 100% of the patients with vaginal trichomoniasis. With 2 g single doses of metronidazole and tinidazole, the cure rates obtained were 97.5% and 95.3% in a study on 40 and 42 patients respectively (Gabriel *et al* 1982). In a review (Sawyer 1976) has cited cure rates of 81-100% wihh tinidazole in trichomoniasis. In a previous study, it was observed that cure rates are almost 100% with a 8 g single dose of metronidazole (Panjabi *et al* 1975). Satranidazole, as shown by the present study, appears to be 3 to 4 times more effective than metronidazole and tinidazole, as judged from the reported doses in literature (Chaudhuri and Drogandojik 1980). Earlier, comparable cure rates have been reported with 2 g single doses of metronidazole and tinidazole (Zaremba *et al* 1980).

The side-effects with a single dose of metronidazole have been reported to be 15% with a 2 g dose; nausea/vomiting was observed in 10 patients out of 72 (Panjabi *et al* 1975). Particularly, the asymptomatic husbands or sexual partners would not like diarrhoea and nausea reported due to metronidazole (Novira 1978). The spectrum of side-effects due to tinidazole has been reported to be similar to metronidazole (Vakil *et al* 1983). Satranidazole, in the present study, showed excellent tolerability in patients and husbands. In another study, the side-effects with a similar dose of satranidazole were reported to be in 7.7% of patients, as compared to 29.8 and 25.7% of patients receiving 2 g of metronidazole and tinidazole respectively (Gupta *et al* 1983).

The absence of disulfiram type of interaction with alcohol with satranidazole may be an added advantage over metronidazole for the treatment of husband who may not like to follow beverage restrictions (Gadgil *et al* 1983). Satranidazole in a single dose of 600 mg appears to be a very potent and well tolerated trichomonacidal agent.

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