

Long Term Trial of Metronidazole in Male Alcoholics

By RICHARD P. SWINSON

The use of metronidazole as an adjunct to treatment in alcoholism was first reported by Taylor (1964). Her study of 52 alcoholics led Taylor to suggest three effects of metronidazole in alcoholism—a reduction of craving for alcohol, a psychic aversion to alcohol, and in some cases an antabuse-like response.

Various authors (Lehmann, Ban and Naltchayan, 1966; Semer, Friedland, Vaisberg and Greenberg, 1966; Bonfiglio and Donadio, 1966) confirmed the initial reports but none of these studies used a control group.

Later authors (Goodwin, 1967; Linton and Hain, 1967; Gallant *et al.*, 1968; Gelder and Edwards, 1968; Merry and Westhead, 1968) failed to confirm the early findings, in trials of short term prognosis, of somatic and psychic effects of metronidazole-alcohol interaction. Lal (1969) reviewed the literature and reported a single-blind trial of two treatment groups and a control group which also failed to show any positive effect from metronidazole.

The majority of the studies quoted above were carried out over short periods of time, often of two months or less. Whilst this is legitimate in research into the alleged antabuse-like action of metronidazole, it is not a long enough period to study the effect of any factor on the prognosis of alcoholism. Davies, Shepherd and Myers (1956), in a two year follow-up of hospitalized alcoholics, found that the prognosis of any alcoholic for the remainder of the two years could be predicted with 88 per cent accuracy by the drinking behaviour occurring within the first six months after discharge from hospital. In view of the lack of studies on metronidazole which observed patients for any length of time, the present study of a twelve month treatment regime was initiated.

PROCEDURE

Sixty male alcoholics admitted to the addiction unit at Moston Hospital, Chester, during

July 1967 to August 1968, were studied. The majority were classified as gamma alcoholics (Jellinek, 1960), the rest being in the alpha or delta categories. The first 60 men discharged from the unit after the inception date, who were willing to enter the trial and who were likely to stay on Merseyside for at least twelve months, were randomly assigned by the hospital pharmacist to placebo or metronidazole groups. The code was broken only when the last patient assigned completed the treatment. In-patient treatment consisted of either drying out and a short stay or else a prolonged period of in-patient care with ten weeks group psychotherapy.

The active tablets, containing metronidazole 200 mgms, and identical bitter-tasting placebo tablets, were prescribed at the rate of 9 tablets (i.e. 1,800 mgms) daily for fourteen days, then 6 tablets for the next fourteen days and 3 tablets daily for the rest of the trial.

Assessment was carried out at weekly intervals for the first month and then at three monthly intervals. Wherever possible the alcoholic's spouse or next-of-kin was interviewed at each assessment interview. The alcoholic and his spouse were interviewed separately and then together and an estimate of the patient's abstinence was arrived at by means of these interviews. Where collaborative evidence of abstinence or otherwise was not available, the patient's own assessment of his drinking behaviour had to be used in the rating of his progress.

A five-point scale was devised which noted the patient's average daily consumption of alcohol prior to his admission to hospital, and the percentage of time of total abstinence during the year after entering the trial.

The scale was as follows:

0 = totally abstinent

1 = occasional drink but consumption greatly reduced

2 = still drinking heavily but some reduction
 3 = no change
 4 = default before end of trial.

In the final assessment points 0 and 1 were taken as 'improved' and 2, 3 and 4 as 'not improved'.

Patients who failed treatment in the first week were excluded from the trial. This rarely happened, since all patients were started on the medication whilst they were in-patients. Three patients, however, did so, and so the final number on the short term trial, up to four weeks, was 57.

RESULTS

1. Short term trial

TABLE I

	N	Score at four weeks				
		Improved		Not improved		
Metronidazole ..	28	0	1	2	3	4
Placebo ..	29	8	3	4	4	10

χ^2 (Yates' correction incorporated) = 1.41. Not significant.

In the short term trial it can be seen that there was a trend towards greater improvement by the metronidazole group, but this did not reach statistical significance.

Eighteen patients were scored as 'default' on the short term trial; of these only five defaulted because of continued heavy drinking. Four patients left the district within the first four weeks after discharge. Four stopped their tablets because of side effects; of these patients two were taking metronidazole and two the inert preparation. A further two patients also stopped taking the tablets, one because he preferred Antabuse, and the other because he felt the taking of tablets was incompatible with continued attendance at Alcoholics Anonymous. Three patients refused to attend the out-patient follow-up clinic.

In addition to the 18 patients above, seven patients who had restarted drinking heavily during the four weeks after discharge failed to take their medication with any regularity

and were excluded from the long term trial. Only two of these patients were taking metronidazole and both had had short stay in-patient care; of the other five patients two had short stay care and three prolonged group psychotherapy.

2. Long term trial

Thirty-two patients progressed to the long-term trial, 18 in the metronidazole group and 14 in the control group.

TABLE II
Six months assessment

	Metronidazole	Placebo	Total
Improved (0 and 1) ..	10	3	13
Not improved (2, 3 and 4) ..	8	11	19

$\chi^2 = 2.5191$ (Yates' correction).

The trend noticed at the end of the short-term trial was again evident, but the difference in the ratings of the metronidazole group compared with the placebo group just failed to reach statistical significance.

At twelve months the trend was even more marked, and the final assessment showed metronidazole to be associated with a good prognosis significantly more often than placebo (Table III).

TABLE III
Twelve months assessment

	Metronidazole	Placebo	Total
Improved ..	9	1	10
Not improved ..	9	13*	22

$\chi^2 = 4.8854$ (Yates' correction) $p < 0.05$.

* Of the patients proceeding to the long term trial, one in the placebo group was excluded from the trial and classified as 'not improved' after he demonstrated dependence on the inert tablets. He would take a fortnight's supply of these tablets in two days and reported feeling elated after taking them. At 20 years, he was the youngest of the whole group and was further distinguished by being addicted to mead; in fact although classified as not improved he remained abstinent beyond the twelve month trial period.

The long-term assessment may be criticized for failing to take into account the total number of patients initially admitted to the trial. However, if all the patients are included the metronidazole group shows an even greater difference from the placebo group than seen in Table III. In Table IV one patient in the metronidazole group has been classified as 'not improved' because he stopped taking the tablets at 46 weeks. In fact he remained abstinent for twelve months, and his inclusion as improved produces an χ^2 value of 7.5638 (Yates correction incorporated) $p < 0.01$.

TABLE IV

	Metronidazole	Placebo	Total
Improved ..	9	1	10
Not improved ..	19	28	47
Total	28	29	57

$\chi^2 = 6.2460$ (Yates' correction) $p < .025$.

In order not to influence the patient's expectancy of the effects of tablets too greatly each patient was told that he might expect to feel less like drinking alcohol when taking the medication than he had done previously. The investigator did not ask directly about the effects of the medication, but the side-effects spontaneously reported were as follows:

TABLE V

	Metronidazole	Placebo
Vomiting (once) ..	0	1
Indigestion	2	1
Indigestion and peculiar taste	0	1
Nausea	1	0
Sedation	1	2
Sedation and indigestion	1	1
Sedation and reduced potency	1	0
Foul taste	2	0
Foul taste and sedation	1	0
Foul taste, nausea and lethargy	1	0
Blurring of vision ..	0	1
Impotence and anorexia	1	0
Headaches and depression	1	0

DISCUSSION

The early reports of trials of metronidazole quoted above in the treatment of alcoholism all suffered from the disadvantage of being non-blind trials.

Goodwin (1967) intended to carry out a blind trial, but before starting the proposed study he administered metronidazole to a group of twelve 'good prognosis' alcoholics. The study was supposed to last for four months, but within six weeks ten of the twelve had stopped taking the medication and had resumed drinking. The other two were unable to distinguish between the effects of metronidazole and placebo. The fact that such a large proportion of a 'good prognosis' group resumed drinking so quickly suggests that the investigator may have conveyed his doubts about the efficacy of the preparation to the patients involved.

Egan and Goetz (1968) treated 46 'Skid Row' alcoholics in a double-blind trial of metronidazole for periods of up to six months. The results for the two groups were equally poor, only one patient in each group remaining abstinent for the duration of the trial. The prognosis for such a group is known to be extremely poor, and treatment which influences prognosis with more socially integrated groups has been found to have little influence on the Skid Row patient. It is not surprising, therefore, that a regime involving a considerable degree of patient's co-operation, in the taking of tablets and attending follow-up clinic, should fail in such a group.

Two studies (Linton and Hain, 1967; and Lal, 1969), although both double-blind in design, lasted for too short a period, ten weeks and twelve weeks respectively, to be of value. In neither of these studies was there found to be any difference between the active preparation and placebo groups.

Gallant *et al.* (1968), comparing the efficacy of metronidazole and chlordiazepoxide, found the two preparations to be equally effective up to six months, but neither treatment was considered to be any more effective than the usual regime of treatment—about which no detail was given. A similar study on alcoholics living in a hostel was carried out by Merry

and Westhead (1968), who concluded that metronidazole was as effective as, but not superior to, other treatments of chronic alcoholism. Two treatment periods with metronidazole were observed, but each period lasted only 30 days.

A different approach to the elucidation of the possible role metronidazole might play in alcoholism was adopted by Gelder and Edwards (1968). Ten alcoholics were given metronidazole 500 mgms. q.i.d. for ten days and a placebo for ten days in randomized order, and one alcohol test was carried out at the end of each ten day period. No evidence of an Antabuse-like property was discovered, but patients reported feeling calmer after metronidazole, and there was some interference with the usual taste of the drink. It was considered, however, that these effects were not sufficiently marked to lead to any therapeutic effect.

In the present study none of the patients reported symptoms resembling an Antabuse-alcohol response, but more of the patients taking metronidazole reported side effects than did patients taking placebo. In the long-term trial the patients who improved with metronidazole complained of side-effects more often than those who did not improve with the drug, although this trend was not statistically significant (Table VI). As Gelder and Edwards pointed out, it is probable that the 'side-effects' are the main effects of the drug in relation to its success in treating alcoholism.

TABLE VI
Incidence of side-effects in metronidazole group

1 year rating	Side-effects reported	No side-effects reported
0 and 1	8	1
2, 3 and 4	4	5

(Tocher's modification of Fisher's exact probability test) $p = 0.0656$.

Differences in the random selection of patients for the two groups could have been responsible for the differences in treatment outcome. No statistically significant differences were found between the short-term/long-term: metronidazole/placebo groups. The Straus-Bacon Score

was not found to have any predictive value on treatment outcome. Belonging to Social Class I or II predicted continuance on to the long-term trial, but there was no significant difference between the social class proportions in the two groups on the long term trial. ($\chi^2 = 2.7428$, Yates' correction.) Social class did not predict outcome within the active and placebo groups ($.20 > p > .10$ F.E.P.). There was no evidence that the treatment in the unit prior to the trial had any influence on the results. (Short stay vs. long stay: $\chi^2 = 0.0307$ Yates' correction.)

It seems likely that the effects of metronidazole in alcoholism are due to sedation and a change in taste sensation, in view of the frequency of reported side-effects in the metronidazole group; which, contrary to Gelder and Edwards expectations, led to a therapeutic effect.

The results, however, have to be interpreted with the proviso in mind that a group of alcoholics who agree to take medication for a year are not likely to be typical of alcoholics in general.

SUMMARY

A long-term double blind trial of metronidazole in alcoholism is described. In the short term trial, up to four weeks, there was a trend to greater improvement in the metronidazole group, but this trend only reached statistically significant levels ($p < 0.025$) at twelve month follow-up. Possible methods of action of the drug are discussed.

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