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The effect of anti-amoebic drug therapy on the metabolism of butobarbitone

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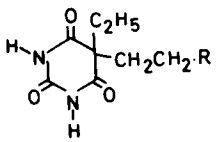
Metronidazole ('Flagyl') is a widely-used drug in the treatment of amoebiasis and related infections. It has also been investigated (e.g. Lehmann & Ban 1967) as a possible approach to the treatment of chronic alcoholism. The probable mode of action is that metronidazole inhibits alcohol dehydrogenase (Fried & Fried 1968) in a similar way to disulfiram (Antabuse), thus interfering with the normal metabolic elimination of ethanol, causing a build-up of the concentration of acetaldehyde in the body.



I $R=C_2H_5$
II $R=CH_2 \cdot COOH$
III $R=CH_2 \cdot CH_2OH$
IV $R=CH_2 \cdot CHO$

A significant urinary metabolite of butobarbitone (I) is the terminal carboxylic acid (II) (Gilbert & Powell 1974). It has recently been shown (Al Sharifi, submitted for publication) that the primary alcohol (III) is an intermediate in the metabolic production of the acid. If metronidazole does indeed interfere with one or both of the dehydrogenation steps involved in the metabolic conversion of a primary alcohol to the corresponding acid, it would seem likely that administration of butobarbitone following a course of treatment with metronidazole should result in a decreased output of the acid (II), accompanied by increased excretion of the primary alcohol (III), and/or the intermediate aldehyde (IV). Both (III) and (IV) are normally minor metabolites of butobarbitone.

As one of us had contracted amoebiasis during a recent visit to the Sudan, and had undergone a course of treatment involving diloxanide furoate (500 mg three times per day for 10 days) and, running concurrently for the second half of the above course, metronidazole (800 mg three times per day for 6 days), it seemed opportune to take a small therapeutic dose of butobarbitone (100 mg) on the final night of the anti-amoebic course, and to follow the urinary excretion of butobarbitone and its metabolites by the published method (Al Sharifi et al submitted for publication). As a control, the same volunteer took a further 100 mg of butobarbitone after eight weeks had elapsed, and its metabolism was followed in the usual way. The two sets of results are summarized in Table 1.

As can be seen, the overall recovery of butobarbitone plus phase 1 metabolites following metronidazole therapy (28·8%) is considerably lower than that (42·75%) of the control run, or of any previous butobarbitone run (e.g. Al Sharifi et al submitted for publication). This reduced overall yield results from approximately a 30% reduction in excretion of each of the four phase 1 metabolites. There is no sign of increase in the ratio of the output of the 4′-hydroxy derivative to that of the terminal acid. Thus there is no evidence that metronidazole plus diloxanide furoate cause any reduction in dehydrogenase activity; but there is clear evidence for a reduction in the initial hydroxylation processes. Since the $t_{1/2}$ for this run is similar to that for the control runs, the reduction in excretion of the four phase-1 metabolites would seem to be counteracted by an increase in some other metabolic pathway. A likely possibility would be that the anti-amoebic therapy caused a considerable increase in the formation of the *N*-glucoside, which has recently (Al Sharifi et al submitted for publication) been shown to be a major metabolite of butobarbitone.

It would be more convincing if the differences reported in this text were based on observations on several patients; but there are ethical problems in repeating this work. However, the conclusion that metronidazole plus diloxanide furoate significantly alter the metabolism of butobarbitone reinforces the reported (Kazmier 1976) interaction between metronidazole and warfarin, and makes it important to ensure that when metronidazole (assuming that the observed changes in the metabolism result from the effects of metronidazole, rather than of diloxanide furoate) is prescribed, the possibility of interference with the metabolism, and hence plasma levels, of concomitantly used drugs be covered.

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Table 1. Comparison of the urinary excretion of butobarbitone and its Phase 1 metabolites under normal circumstances, and immediately following a course of anti-amoebic chemotherapy.

	Parent			3′-Hydroxy			3′-Oxo			4′-Hydroxy			ω-Acid			Mean	Total
	%	$t_{1/2}$	Corr.	%	$t_{1/2}$	Corr.	%	$t_{1/2}$	Corr.	%	$t_{1/2}$	Corr.	%	$t_{1/2}$	Corr.	$t_{1/2}$	% rec.
After metronidazole and diolxanide furoate	5·1	29·9	0·97	14·0	35·6	0·90	5·6	32·7	0·95	0·6	23·7	0·90	3·5	41·9	0·87	32·7	28·8
Control run	6·6	37·4	0·99	22·4	32·1	0·97	7·6	24·5	0·86	0·95	33·2	0·97	5·2	32·2	0·99	31·9	42·75

Corr. = correlation. Rec. = recovery

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Some autonomic blocking properties of zetidoline (DL 308-IT), a novel potential anti-psychotic drug

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Zetidoline [DL 308-IT (1-(3-chlorophenyl)-3-[-2-(3,3-dimethyl-1-azetidinyl ethyl]imidazolidin-2-one hydrochloride)] is a novel centrally acting dopamine antagonist, which inhibits apomorphine-induced emesis and stereotypy in the dog, amphetamine stereotypy in the rat, prevents conditioned avoidance responses and increases the turnover of dopamine in rat brain (see Szabadi et al 1980; Barone et al 1982). In healthy volunteers both DL 308-IT and thioridazine displayed sedative properties, caused miosis, hypotension and a decrease in salivation although in equisedative doses DL 308-IT had a smaller influence on autonomic functions than thioridazine (Szabadi et al 1980). Szabadi et al (1980) considered that DL 308-IT (10, 20 mg) caused miosis possibly through an α-adrenoceptor antagonist action although with the smaller of the two doses used they noted an increase in sweating and heart rate which they considered to be a sympathomimetic action of the drug. The decrease in salivation was considered to indicate an anti-acetylcholine effect. It was of interest therefore to identify the peripheral autonomic blocking properties of the new drug on isolated organ preparations in vitro.

Cumulative dose-contractile response curves were made for phenylephrine on the rabbit and guinea-pig aortic spiral preparations and repeated after 30 min incubation with different concentrations of DL 308-IT (1, 10, 40 and 100 μM).

On the rabbit aorta, increasing concentrations of DL 308-IT displaced the log dose-response line of phenylephrine to the right in a parallel manner indicating competitive antagonism of postsynaptic α_1-adrenoceptors. The antagonism was quantified by the method of Arunlakshana & Schild (1959) to give a pA_2 value of 5·99 (slope function −0·93; pA_2–pA_{10} 1·02). Similar results were obtained for DL 308 IT against phenylephrine on the guinea-pig aorta (pA_2 5·82; slope function −1·11; pA_2–pA_{10} 0·85; Fig. 1).

Dose-response curves to the cardioaccelerator effect of isoprenaline were constructed on guinea-pig isolated spontaneously-beating atria in the absence and presence of DL 308-IT (100 μM). DL 308-IT did not antagonize this effect of isoprenaline suggesting that the drug has no affinity for β_1-adrenoceptors. Cumulative dose-response curves to the relaxant effect of isoprenaline on the inherent tone of the guinea-pig isolated tracheal spiral preparation were similarly unaffected by DL 308-IT.

On the longitudinal muscle of the guinea-pig isolated ileum dose-contractile response curves to histamine were displaced to the right by increasing concentrations of DL 308-IT (1, 2, 4 and 10 μM). DL 308-IT appeared to be a weak competitive antagonist of histamine H_1-receptors on this preparation (pA_2 5·6; slope function −0·92; pA_2–pA_{10} 1·03). It has previously been reported that the contractile responses of the guinea-pig ileum to acetylcholine were antagonized in a non-competitive manner by DL 308-IT (Fosbraey et al 1980) in concentrations greater than 1 μM.

The drug proved to be a powerful antagonist of the morphine-induced inhibition of the twitch response of the guinea-pig ileum to transmural electrical stimulation (0·2 Hz; 0·5 ms; 7–8 V). The antagonism did not appear to be competitive despite an apparent parallel displacement of log dose-response curves with concentrations less than 8 μM (Fig. 2). This property of DL 308-IT was also shared by metoclopramide (Fosbraey et al 1980).

DL 308-IT in concentrations of 0·1–1·0 μM potentiated the twitch response of the guinea-pig ileum to transmural electrical stimulation, an effect that has

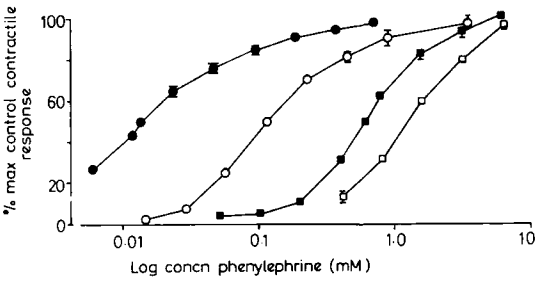

FIG. 1. Effect of increasing concentrations of DL 308-IT on the contractile responses of the guinea-pig aortic spiral preparation to phenylephrine. The results are expressed as mean % maximal contraction in the absence (●) and presence of the antagonist (○ = 10 μM, n = 7; ■ = 40 μM, n = 4; □ = 100 μM, n = 5). Vertical bars indicate s.e.m. except where the error falls within the bounds of the symbol.

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