SHORT COMMUNICATION

INFLUENCE OF METRONIDAZOLE AND CHLORAL HYDRATE ON THE ACTIVITY OF OTHER DRUGS

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Summary: Chloral hydrate and metronidazcle were investigated for their effect on the hypoglycaemic activity of tolbutamide. Metronidazole was investigated for its ability to potentiate phenytoin. Chloral hydarte potentiated tolbutamide and metronidazole potentiated phenytoin.

Key words: chloral hydrate metronidazole phenytoin tolbutamide drug interaction

INTRODUCTION

The hypoglycaemic action of tolbutamide is potentiated by disulphiram (15). Chloramphenicol and phenylbutazone which produce a disulphiram-like effect (11) also potentiate tolbutamide (2,5). Tolbutamide is metabolised by xanthine oxidase and aldehyde dehydrogenase (12). Presumably, drugs which produce a disulphiram-like effect inhibit these enzymes (7). Chloral hydrate and metronidazole produce a disulphiram-like effect (4,17) and metronidazole inhibits alcohol dehydrogenase and other alcohol oxidising enzymes (20). Hence, a study of the effect of metronidazole and chloral hydrate on the hypoglycaemic activity of tolbutamide is indicated. Furthermore, drugs like chloramphenicol, disulphiram and phenylbutazone which sensitize to alcohol potentiate phenytoin (13). Hence, the effect of metronidazole on the activity of phenytoin also merits investigation.

MATERIALS AND METHODS

Adult rabbits weighing approximately 2 *kg* were starved for 48 hr and used for the hypoglycaemic studies. Test rabbits were primed with metronidazole, 50 *mg/kg* or chloral hydrate, 400 *mg/kg*. Control rabbits received saline. All rabbits were challenged with tolbutamide, 200 *mg/kg*, 1 hr after durg or saline. Blood was drawn from the ear veins before the addminstration of tolbutamide and at 2,4 and 6 hr after its administration. Blood glucose was estimated by the method of Folin and Wu (10). All drugs were administered orally. Metronidazole and chloral hydrate were also investigated for any effect of their own on blood glucose levels.

Male albino rats weighing about 200 g and showing a tonic extensor response to an electric shock (150 mA, 0.2 sec, ear clip electrodes; Techno Model Convulsiometer) were selected for

the study. The times for tonic flexor phase (F) and tonic extensor phase (E) of the convulsion were measured with a stop watch correct to 0.1 sec. Only those rats showing a F/E ratio of about 0.3 were selected for the study. Test rats received metronidazole, 50 *mg/kg* while control rats received saline. After hr all rats were administered phenytonin. Shocks were given at 1, 2 3 and 5 hr and the F/E ratio of the convulsions was calculated (14)

Groups of 10 rats were administered phenytoin at various dose levels, The ED50 of phenytoin was calculated 3 hr after its administration in control rats receiving saline and test rats receiving metronidazole, 1 hr prior to the administration of phenytoin. Metronidazole, was investigated for any anticonvulsant effect of its own.

RESULTS

Chloral hydrate potentiated the hypoglycaemic activity of tolbutamide in rabbits (Table I). Metronidazole was without any effect on the hypoglycaemic activity of tolbutamide (Table I). Chloral hydrate and metronidazole did not have any effect of their own on the blood glucose levels.

TABLE I : Modification of the hypoglycaemic effect of tolbutamide (200 *mg/kg* orally) by metronidazole and chloral hydrate.

Treatment		*Fall in blood glucose mg/se*		
		2 hr	*4 hr*	*6 hr*
Tolbutamide alone (Control)	(12)	17.0±2.7	28.0±2.7	30.0±2.4
Metronidazole 50 *mg/kg* orally + tolbutamide	(12)	21.0±3.0 P>0.05	27.0±2.9 P>0.05	26.0±3.0 P>0.05
Chloral hydrate 400 *mg/kg* orally + tolbutamide	(12)	30.0±3.5 P<0.01	39.0±3.0 P<0.01	42.0±2.5 P<0.01

Figures in parentheses indicate the number of animals.

Metronidazole had no effect on the F/E ratio, but potentiated the F/E ratios observed with pehnytoin (Table II).

TABLE II: Ratio of flexion time/extension time (F/E)* of rats treated with phenytoin (1 *mg/kg* i.p. alone; after controls) and with metronidazole (50 *mg/kg* i.p.) and phenytoin (1 *mg/kg* i.p. test).

Group	*F/E ratio ± SE*			
	Before	*1hr After 2hr*	*3 hr*	*5 hr*
Control	33.21 ±1.18(31)	46.76 ±1.92(28)	60.19 ±5.0(23)	61.36 ±3.1(25)	79.81 ±3.0(24)
Test	32.07 ±1.57(34)	72.92 ±4.0(27) P<0.001	84.48 ±3.64(24) P<0.001	80.29 ±2.6(27) P<0.001	72.79 ±2.9(26) P>0.05

Figures in parentheses indicate the number of observations.

* For the case of calculations the data on F.E. ratios was multiplied by 100.

The ED_{50} of phenytoin alone was 10.0 ± 0.52 *mg/kg*. With prior administration of metronidazole the ED_{50} was 5.0 ± 0.40 (*mg/kg*). The potentiation was statistically significant ($P < 0.01$). Metronidazole had no anticonvulsant activity.

DISCUSSION

Chloral hydrate is metabolised to trichlorethanol by alcohol dehydrogenase (6) which is also involved in the metabolism of tolbutamide (12). Possibly, chloral hydrate saturates this enzyme and makes it non-available for metabolising tolbutamide, resulting in the potentiation of tolbutamice, analogous to pra-amino-salicylic acid potentiating isoniazid by competing for the acetylation enzyme (1). Another enzyme, metabolising tolbutamide is aldehyde dehydrogenase (12). The disulphiram-like effect of chloral hydrate (4) suggests interference with aldehyde dehydrogenase (7). This may be another mechanism of potentiation by chloral hydrate of tolbutamide. It may be of interest that drugs which potentiate warfarin also potentiate tolbutamide. Chloramphenicol, phenylbutazone and phenyramidol potentiate warfarin as well as tolbutamide (2,8) . Chloral hydrate also potentiates warfarin. Displacement from sites of protein binding and thus an increase in the free dialysable concentration of warfarin has been cited as the mechanism of such potentiation (16). But it is doubtful whether such mechanism operates for tolbutamide since although sulphaphenzol potentiates tolbutamide and increases the free dialysable concentration of tolbutamide, sulphadimethoxine increases the free dialysable concentration of tolbutamide by displacing it from sites of protein binding, but does not potentiate tolbutamide (3).

Tedeschi *et al.* (18) have reported that the administration of phenytoin decreases the extension time, increases the flexion time and increases the F/E ratio (18). Other workers have also measured the increase of F/E ratio as an index of anticonvulsant activity (14,22). Our unpublished studies also confirmed that dose-related increase in the F/E ratio occured consistently after the administration of phenytoin. Inhibition by metronidazole of enzymes metabolising phenytoin, is a possibility. Metronidazole also potentiates narcosis produced by alcohol (21). The exact mechanism of potentiation requires further study. Metronidazole should be considered as an addition to the long list of drugs potentiating phenytoin (19, 9).

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