INTERACTION OF TOLBUTAMIDE WITH PHENOTHIAZINES AND DIPHENHYDRAMINE

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Summary: The effect of concurrent administration of neuroleptics and diphenhydramine on the activity of tolbutamide was studied in rabbits and humans. Diphenhydramine did not modify the activity of tolbutamide. Chlorpromazine antagonised the hypoglycaemia produced by tolbutamide in rabbits as well as in humans without affecting the hypoglycaemia produced by insulin. It is likely that chlorpromazine inhibits the response of the pancreas to tolbutamide. This type of action is analogous to the action of the drug on other endocrine glands.

Key Words: hypoglycaemia neuroleptics diphenhydramine tolbutamide chlorpromazine—tolbutamide interaction

INTRODUCTION

The precipitation of hypoglycaemic coma in a patient who was on a combination of chlorpromazine and orphenadrine, an O-methly derivative of diphenhydramine has been reported (3). This combination potentiates the hypoglycaemic activity of tolbutamide and the potentiality of this combination to produce hypoglycaemia must be borne in mind (3). While the hypoglycaemic activity of orphenadrine could be shown, the investigation suggested chlorpromazine to have greater hypoglycaemic effect. Slade and Iosefa (13) reported a case of fatal hypoglycaemia due to tolbutamide and mentioned that one of the concurrently administered drugs had been diphenhydramine. Hypoglycaemia due to insulin is antagonized by the release of adrenaline from the adrenals. Such release is blocked by phenothiazines (1) suggesting that phenothiazines may potentiate the insulin hypoglycaemia. Diphenhydramine is an inhibitor of monoamine oxidase (14) and MAO inhibitors are known to potentiate antidiabetic agents (5, 16).

There is a variety of reports on the action of chlorpromazine on blood sugar and its interaction with hypoglycaemic agents. Bonacorsi *et al* (2) while reporting a hyperglycaemic response to chlorpromazine have reviewed the literature in several species wherein an increase (3, 9) or no change (4, 7, 11) has been reported.

Thus the literature on phenothiazines is conflicting and the reports on the influence of diphenhydramine on the activity of tolbutamide are not very convincing. A study was therefore undertaken to observe the effects of these drugs in different combinations on blood sugar of rabbits and humans.

MATERIALS AND METHODS

Adult rabbits weighing approximately, 1.5 kg starved for 48 hr were used for the experiments. Twelve rabbits were used for each drug or drug combination, an equal number serving as controls. Blood was withdrawn from the marginal ear vein just before drug administration and subsequently at specified intervals in fluoride-citrate tubes and concentration of glucose determined by Folin and Wu method (10). Human subjects constituted otherwise healthy mental patients admitted recently to Calicut Mental Hospital. They were in the age group of 25-35, weighed 48-52 kg, gave no previous history of drug administration, and were starved overnight before the study. All drugs were administered orally except insulin which was administered subcutaneously.

RESULTS

Administration of Chlorpromazine alone or combination of chlorpromazine with diphenhydramine did not significantly change the level of blood glucose in rabbits and humans.

TABLE I: Fall in blood sugar (mg% + S.E.M.) after the administration of insulin

Species	1 *hr*		2 *hr*		3 *hr*	
	Control	*Test*	*Control*	*Test*	*Control*	*Test*
Rabbits (12)						
Chlorpromazine 10 mg/kg+ 0.4 U Insulin	45 ±3.2	48 ±3.1	61 ±2.5	64 ±3.5	42 ±1.3	47 ±4.5
Humans (12)						
Chlorpromazine 250 mg+ 40 U insulin.			19 ±2.0	20.1 ±2.1		

At 4 hr the blood sugar values were not significantly different (P .05) from the initial values. (Controls received only insulin).

In rabbits neuroleptics antagonised tolbutamide (Table II). The same dose did not antagonise the insulin action (Table I). Diphenhydramine did not have any effect on the activity of tolbutamide (Table II).

DISCUSSION

The results indicate that diphenhydramine by itself as in rabbits or in combination with chlorpromazine as in rabbits and humans had no action on the blood glucose level. Further

TABLE II: Fall in blood glucose level (mg% ± S.E.M.) after the administration of some drugs or combinations thereof.

Drug	2 *hr*		4 *hr*		6 *hr*	
	Control	*Test*	*Control*	*Test*	*Control*	*Test*
			Humans			
Chlorpromazine 250 mg + Tolbutamide 1 g	19 ± 3.0	3.5 ± 4	26 ± 3.8	9 ± 3.7	25 ± 4.1	14 ± 4.0
	P<0.005		P<0.005		P<0.05	
Chlorpromazine 100 mg + Tolbutamide 1 g	15 ± 1.7	14 ± 2.3	22 ± 2.3	19 ± 2.1	20 ± 2.1	20 ± 2.3
Diphenhydramine 50 mg + Tolbutamide 1 g	10.5 ± 1.8	10 ± 1.8	15 ± 1.7	17 ± 2.0	13 ± 2.1	18 ± 2.3
Diphenhydramine 50 mg + Tolbutamide 1 g Chlorpromazine 250 mg	14.3 ± 2.6	4.1 ± 0.93	18.8 ± 2.5	6.8 ± 1.9	20.4 ± 3.65	10.6 ± 1.95
	P<0.003		P<0.003		P<0.04	
			Rabbits			
Chlorpromazine 10 mg/kg + Tolbutamide 100 mg/kg	15 ± 2.12	11 ± 2.0	40 ± 2.7	33 ± 2.4	42 ± 3.4	37 ± 2.4
Prochlorperazine 5 mg/Kg + Tolbitamide 100 mg/kg	23.5 ± 2.4	24 ± 2.8	39 ± 2.3	27 ± 2.7	45 ± 3.3	45 ± 3.2
Chlorprothixene 10 mg/kg + Tolbutamide 100 mg/kg	23 ± 1.3	23 ± 1.4	38 ± 1.8	39 ± 2.0	48 ± 2.1	49 ± 2.1
Diphenhydramine 10 mg/kg + Tolbutamide 100 mg/kg	16 ± 2.0	16 ± 1.0	29 ± 1.2	28 ± 1.3	41 ± 1.4	37 ± 1.4
azine 10 mg/kg + diphenhydramine 10 mg/kg mide 100 mg/kg	28 ± 2.3	20 ± 2.1	37 ± 2.1	32 ± 3.0	41 ± 2.5	35 ± 1.2

its received tolbutamide 100 mg/kg only.
mans received 1 g of tolbutamide only.
are given only when the differences are significant.

it did not modify the effect of tolbutamide. The antagonism of diphenhydramine-chlorpro zine combination on the activity of tolbutamide should be attributed to the chlorproma component.

Chlorpromazine appeared to block the response to tolbutamide at the level of be cells of Langerhans, since it did not interfere with the response of the pancreas to other stim like hyperglycaemia. Such dissociated antagonism by chlorpromazine on other endocri glands is also on record. For example, chlorpromazine blocks the response of the adre cortex to insulin hypoglycaemia, but not to ACTH (4). Chlorpromazine protects the pancr against the injurious effects of alloxan (12). The drug inhibits the release of antidiuret hormone in response to dehydration or various other stimuli (17) without interfering with t peripheral action of the hormone (8).

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