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MODIFICATION OF GLYBENCLAMIDE HYPOGLYCAEMIA BY VERAPAMIL IN RABBITS

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Abstract : The study was designed to demonstrate the interaction between varapamil and glybenclamide on blood glucose in rabbits. Glybenclamide (0.05 mg/kg, po) induced hypoglycaemia was observed 1 h after treatment and persisted till 3 h. Verapamil (8 mg/kg, sc) *per se* produced hyperglycaemia which lasted for 2½ hr. Concurrent administration of verapamil was found to impair significantly the hypoglycaemic response of glybenclamide.

Key words : glybenclamide verapamil blood glucose

INTRODUCTION

The calcium channel blockers are commonly used in the management of cardiovascular disorders such as ischemic heart diseases and hypertension. Occurence of such cardiovascular disorders is known to be much higher in diabetic patients (1). Hence, simultaneous administration of calcium channel blockers and antidiabetic agents in such patients becomes inevitable.

While it is certain that calcium channel blockers influence blood sugar level, controversy still exists regarding their effect on blood sugar level. Some workers have reported calcium channel blockers to be hyperglycemic in clinical (2, 3) as well as in experimental studies (4, 5). On the other hand Jain et al. (6) reported verapamil not only to cause hypoglycemia in rabbits but also potentiation of glybenclamide induced hypoglycemia. In view of such controversial reports, the present study was undertaken to study the effect of verapamil and its interaction with glybenclamide on blood in rabbits.

METHODS

The study was conducted on 36 rabbits of either sex, (1.0-2.0 kg). The animals were kept under controlled conditions and fed on commercial pellet diet (Lipton India Ltd.). The animals were divided into six groups of six animals each. They were fasted for 24 hr and each group was administered with one of the following agents verapamil (2, 4 or 8 mg/kg, sc); glybenclamide (0.05 mg/kg, po); or verapamil (8 mg/kg, sc) + glybenclamide (0.05 mg/kg, po). Matching volume of normal saline was administered orally to the animals of control group. Blood samples for glucose estimation (7) were collected from the marginal ear vein before treatment and at 1/2 hr intervals for 3 hr and at 4 hr after treatment. Results were analysed by employing Student's 't' test.

RESULTS

Blood glucose level in saline treated animals ranged from 73.7±3.3 mg/dl to 79.5±3.8 mg/dl. Verapamil in the dose of 2, 4 and 8 mg/kg produced hyperglycemia which lasted for 2 hr. Rise in blood sugar was noted at 1 hr with 2 and 4 mg of verapamil while 8 mg dose exhibited rise at 1/2 hr. Glybenclamide induced hypoglycemia began at 1 hr and lasted for 2½ hr. It reverted to control values at 3 hr. When verapamil (8 mg/kg) was

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TABLE I : Effect of various doses of verapamil on blood glucose level in rabbit and its interaction with glybenclamide (6 animals in each group).

Treatment (mg/kg)	*Blood glucose (mg/dl), Mean ± SEM*							
	Time (hr)							
	0	$\frac{1}{2}$	1	$1\frac{1}{2}$	2	$2\frac{1}{2}$	3	4
Saline	75.6	74.6	73.7	79.5	73.8	75.3	77.2	74.6
	±3.8	±4.6	±3.3	±3.8	±2.6	±3.4	±3.6	±3.9
Verapamil (sc)	78.5	80.4	95.4**	101.1	91.6**	80.2	83.3	80.1
(2)	±4.2	±3.4	±5.4	±4.1	±3.2	±3.8	±3.5	±2.5
(4)	80.7	84.3	102.0**	114.0***	97.2**	88.0	81.7	81.4
	±3.5	±4.7	±5.3	±6.5	±4.7	±5.4	±5.0	±4.2
(8)	74.8	90.3*	108.5***	121.3***	111.8***	87.9	78.5	76.6
	±5.1	±5.2	±6.3	±6.6	±4.5	±6.8	±5.8	±4.2
Glybenclamide (0,05, po)	81.3	66.0	44.1***	40.2***	38.4***	50.1***	69.3	77.7
	±3.3	±4.6	±3.8	±4.1	±3.9	±4.2	±4.1	±3.8
Glybencalmide (0,05, po) + Verapamil (8, sc)	76.9	98.8++	77.55++	63.5++	69.7+++	75.5++	83.5+	77.8
	±2.9	±6.8	±3.6	± 5.2	±4.8	±3.9	±4.6	±5.1

*P <0.05; **P<0.01; ***P<0.001; in comparison to saline treatment
+ P<0.05; ++P<0.01; +++P<0.001; in comparison to glybenclamide treatment
sc = subcutaneous; p.o. = per oral.

given in conjunction with glybenclamide, the blood glucose remained significantly at higher level till 3 hr in comparison to the treatment with glybenclamide alone (Table I).

DISCUSSION

Sulphonylureas viz. glybenclamide are known to produce hypoglycemia by increasing the release of insulin from the beta cells of islets of Langerhans (8). Any agent which affects this release of insulin is, therefore, bound to impair the hypoglycemic response of glybenclamide. Verapamil, on account of its impairing the calcium channels, has been shown to attenuate drastically the insulin release from islets of Langerhans (9). Hence, it is not unreasonable to believe that this inhibitory effect of verapamil on insulin release could impair the effect of glybenclamide on blood glucose level as observed in the present study. However, more direct studies are required to establish the mechanism of this interaction.

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