LETTER TO THE EDITOR

GLIBENCLAMIDE HYPOGLYCAEMIA: EFFECT OF β-ADRENOCEPTOR ANTAGONISTS

Sir,

(Received on May 25, 1982)

Ischaemic heart disease (angina and infarction) is common in patients of long standing diabetes and therefore concomitant use of antianginal/antiarrhythmic agent like a β-adrenoceptor blocker with oral hypoglycaemics is not unlikely. β-adrenoceptor blockers have been shown to enhance insulin hypoglycaemia in experimental animals (5,6,14) and in man (2). However, the effect of propranolol on sulfonylurea hypoglycaemia is less clear (9) and the probability of dampening of hypoglycaemia has been suggested on the basis of interactions with insulin (1,4,10).

Glibenclamide, a sulfonylurea, is now being used in the management of maturity onset diabetes, but has not yet been studied for an interaction with β-blockers. Our observations on such an interaction are reported here.

Rabbits weighing 1.5-2.0 *kg* were divided in groups of 10 each, containing 5 male and 5 female rabbits, fasted for 18 hr but allowed water *ad libitum*. Blood sugar level was estimated by the micromethod (13) using ear-vein blood samples obtained before and at various times after giving saline or drug by a stomach tube. The following drugs were used : glibenclamide (25 *μg/kg*; suspended in 2% gum acacia), propranolol (15 *mg/kg*), atenolol (6 *mg/kg*), oxprenolol (1.2 *mg/kg*), sotalol (6 *mg/kg*), pindolol (0.5 *mg/kg*) or labetalol (15 *mg/kg*). The drugs were either given alone of in combination with glibenclamide to observe modification of the effect of glibenclamide on blood sugar level.

The fasting blood sugar level in rabbits ranged between 75-85 *mg*/100 *ml* during 5 hr of the study. Following glibenclamide administration hypoglycaemia was observed at 2 hr which persisted for 5 hr. The maximum fall in blood sugar level was observed in 3 hr (Table I). On the other hand none of the β-adrenoceptor blocking agent had

any significant effect on blood sugar during 5 hr of the study. All β-adrenoceptor blocking agents significantly hastened and intensified the hypolglycaemic response to glibenclamide.

TABLE I : Effect of glibenclamide (Gli) and beta adrenoceptor antagonists on blood sugar level (expressed as % of control) in fasting rabbits.

Drug (mg/kg)	*% Control (before drug) value, Blood Sugar level mean±S.E.M*				
	1 hr	*2 hr*	*3 hr*	*4 hr*	*5 hr*
Saline	99.8±3.28	99.1±1.69	99.2±2.76	100.6±1.73	95.5±3.97
Glibenclamide (0.025)	99.3±1.87	62.3±2.19***	60.3±3.09***	66.2±3.55***	73.6±2.48***
Gli+Propranolol (15.0)	85.5±0.75***	66.2±2.38	48.9±0.84**	63.8±0.72	87.4±1.62***
Gli+Labetalol (15.0)	94.0±1.1*	88.7±6.43**	48.8±2.18**	56.5±1.62*	65.5±1.76*
Gli+Atenolol (6.0)	84.6±1.86***	57.2±6.41	54.2±13.46	51.4±0.9***	65.4±1.1**
Gli+Oxprenolol (1.2)	75.3±2.79***	46.0±1.59***	47.5±0.8***	58.2±1.0*	70.1±1.99
Gli+Pindolol (0.5)	73.8±1.52***	50.5±0.97***	53.6±0.9*	67.3±4.0	77.6±3.5
Gli+Sotalol (6.0)	85.6±1.12***	60.2±5.42	59.0±3.24	51.4±1.2***	68.0±0.82*

Value significantly differs from glibenclamide group (*$P<0.05$, **$P<0.01$, ***$P<0.001$; t test) except that the glibenclamide group itself was compared with saline group.

β-adrenoceptor blocking agents have been reported to exert a variable influence on blood sugar level. Grasi *et al.* (8) have reported an increase while Berk *et al.* (3) noticed a fall in blood sugar level with propranolol in rabbit. That none of the β-adrenergic blockers was found to alter the blood sugar level significantly by itself, corroborates with the findings of Byers and Friedman (6) and Nash and Smith (12). β-adrenergic receptors are known to be involved in glycogenolysis as well as in insulin secretion (15). β-adrenoceptor blockade, hence, may inhibit not only the insulin secretion but also the possible hypoglycaemia due to glycogenolysis. This might account for the lack of any major effect of β-adrenergic blocking agents on blood sugar level.

Propranolol has been reported to prevent exercise (4), stress and/or glucose feeding (7) induced hyperglycaemia. Propranolol (2,5,10) as well as the other β-blockers (14) have been found to potentiate insulin induced hypoglycaemia. In this study also all the β-blocking agents hastened and augmented the hypoglycaemia induced by glibenclamide. It is hence possible that the response to glibenclamide which primarily acts by releasing insulin is augmented by the β-blockers. It is known that hypoglycaemia consequent to insulin release leads to liberation of catecholamines (11,15) and glucagon

(11). β-adrenoceptor blockade may also counteract hyperglycaemic effect of adrenaline (1,15) or glucagon and augment the hypoglycaemia.

The present study offers a convincing evidence of an interaction between glibenclamide and the widely employed β-adrenoceptor blocking agents in rabbit. It would be of interest to look for such an interaction in man.

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