

## EFFECT OF MIANSERIN ON BLOOD GLUCOSE LEVEL IN RABBITS

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**Abstract :** Blood glucose level was estimated in 18 h fasted albino rabbits following acute feeding of graded doses of mianserin. Mianserin (6.0 mg/kg) produced a gradually increasing hyperglycemic effect which became significant ( $P < 0.01$ ) at 10 h and onwards. This appears to be due to increased turnover and release of noradrenaline by the drug. The same dose of mianserin also produced glucose intolerance during early hours probably by interfering with gastrin functions.

**Key words :** antidepressant drugs mianserin blood glucose level glucose tolerance test

### INTRODUCTION

Mianserin is a tetracyclic antidepressant. The exact mechanism of its antidepressant action is not well understood. Magnus (1) observed rise in blood sugar levels in 22 out of 28 patients given mianserin as a single dose at bed time. We, therefore, planned this study to observe the effect of mianserin *per se* on glucose homeostasis.

### METHODS

Albino rabbits of either sex, weighing between 1-2 kg were divided in groups of 6-8 animals each, containing equal number of males and females. They were maintained on controlled laboratory conditions and fed on commercial diet ("Gold Mohur", M/s Lipton India Ltd.). All the animals were fasted for 18 h before administering test drug while water was allowed *ad libitum*. Blood samples were collected for blood glucose estimation (2) from the marginal ear vein, before and at 0.5, 1, 2, 3 and 4 h following mianserin administration which was given in doses of 1.5, 3.0 and 6.0 mg/kg to rabbits in group I, II and III respectively through intragastric tube. The saline fed group served as control. In another set of experiment blood samples were collected upto 24 h after administering mianserin (6.0 mg/kg). For glucose

tolerance test (GTT) mianserin (6.0 mg/kg) was administered in close succession to glucose (1.0 g/kg orally as 20% solution) and blood samples were collected before and at 0.5 h intervals for 3 h. Animal data where one or more blood samples could not be collected/estimated for any reason, were excluded from the analysis. The fasting blood glucose level (BGL) of each rabbit served its own control and was taken as 100. The change in BGL after the administration of drugs was then expressed as percent BGL. The area under the percent BGL-time-curve (AUC) for the blood glucose data of each animal in each experiment was calculated by trapezoid integration. The statistical significance was calculated with the help of unpaired student's 't' test.

### RESULTS

The blood glucose level (BGL) in the control animals remained fairly constant without any significant alteration during the observation period of 4 h. The fasting BGL in rabbits of all the groups of this study ranged between 46.43 to 91.43 mg%. Feeding of mianserin (1.5 mg/kg) produced mild hypoglycemia which was significant ( $P < 0.5$ ) at 2 h with a peak at 3 h and was followed by a tendency towards recovery. On the other hand 3.0 mg/kg dose of mianserin produced hyperglycemia ( $P > 0.05$ ) at 2 h which was

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preceded as well as followed by hypoglycemia. However, 6.0 mg/kg dose produced a persistent hyperglycemia. Since  $AUC_{0-4}$  with none of the doses employed was significantly different from that of control group ( $P > 0.05$ ; Fig. 1) highest dose of mianserin was selected to study the *per se* effect on BGL for 24 h as well as to observe any alteration in GTT.

The animals of control group ( $n = 6$ ) exhibited mild hypoglycemia which was maximum at 10 h during the 24 h observation period while mianserin ( $n = 5$ ) produced a gradually increasing hyperglycemic effect

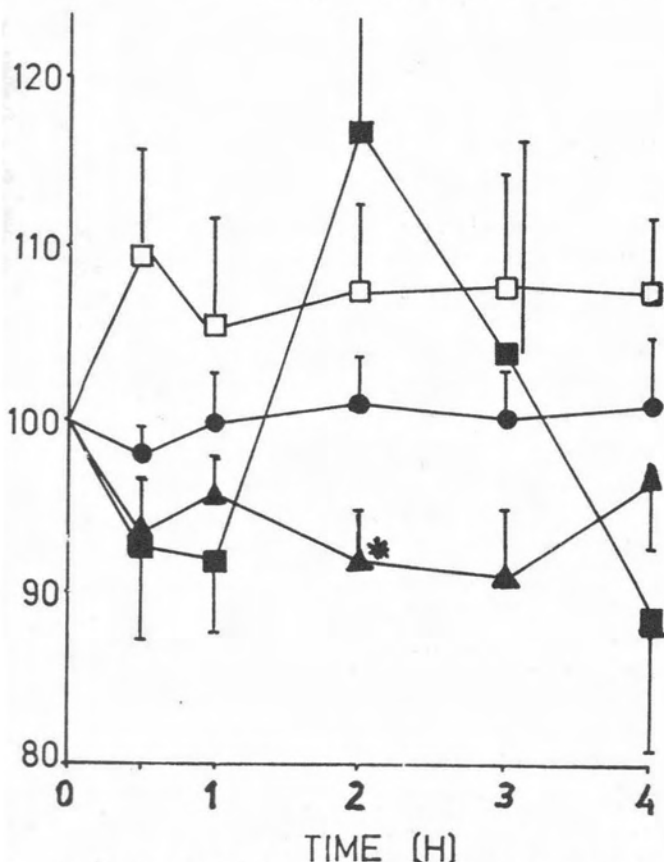


Fig. 1: Effect of graded doses of mianserin (po) on blood glucose level (BGL) in rabbits. BGL of each animal before drug administration was taken as 100%. Points are mean values, with their standard errors represented by vertical bars. Filled circles = saline fed control group ( $n = 8$ ,  $AUC_{0-4} = 400.4 \pm 9.2$ ); Filled triangles = mianserin 1.5 mg/kg ( $n = 6$ ,  $AUC_{0-4} = 374.5 \pm 7.6$ ); Filled squares = mianserin 3.0 mg/kg ( $n = 6$ ,  $AUC_{0-4} = 405.6 \pm 28.7$ ); Empty squares = mianserin 6.0 mg/kg ( $n = 6$ ,  $AUC_{0-4} = 426.8 \pm 13.9$ ). \* $P < 0.05$  in comparison to control group.

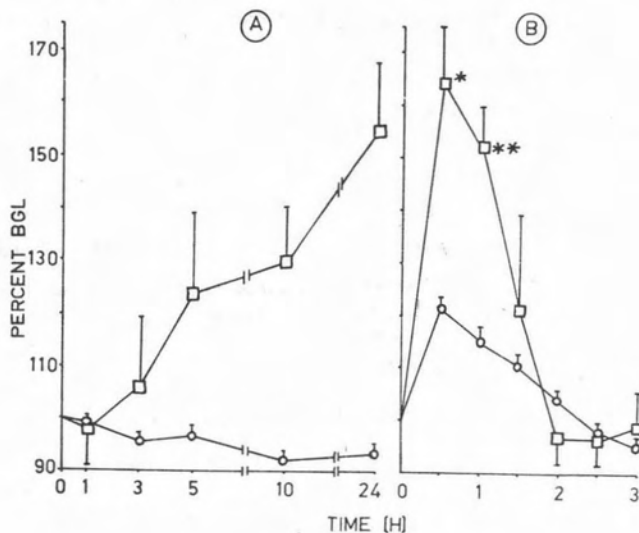


Fig. 2: Effect of mianserin (6.0 mg/kg, po) on (A) blood glucose level (BGL) for 24 h, and (B) oral glucose tolerance (1.0 g/kg), in rabbits. BGL of each animal before drug administration was taken as 100%. Points are mean values, with their standard errors represented by vertical bars. Filled circles = control group; Filled squares = mianserin treated group, \* $P < 0.01$ ; \*\* $P < 0.001$  in comparison to control group.

which became significant at 10 h and onwards ( $P < 0.01$ ). The  $AUC_{0-24}$  of this group ( $3161.3 \pm 242.0$ ) also significantly ( $P < 0.01$ ) differed from that of control group ( $AUC_{0-24} = 2253.2 \pm 34.4$ ; Fig. 2A).

The animals of the control group ( $n = 7$ ) exhibited an immediate rise in BGL following glucose administration with peak at 0.5 h followed by a gradual recovery towards basal level within next 2 h. Feeding of mianserin ( $n = 6$ ) in close succession to glucose resulted in significant enhancement of hyperglycemia at 0.5 ( $P < 0.01$ ) and 1 h ( $P < 0.001$ ) followed by recovery to normal value within the next 1 h. However, the  $AUC_{0-3}$  ( $351.6 \pm 20.1$ ) was not much different ( $P > 0.05$ ) from that of control GTT ( $AUC_{0-3} = 322.7 \pm 4.8$ ; Fig. 2 B).

## DISCUSSION

Mianserin (1.5 mg/kg) had no significant effect on BGL as judged by  $AUC_{0-4}$  inspite of significant hypoglycemia at 2 h. However, a significant hyperglycemia was observed with 6.0 mg/kg dose beginning after 5 h and persisting even upto 24 h. This observation is in accordance with Magnus (1) who reported a rise in BGL in 22 out of 28 patients following a single bed time dose of mianserin.

Mianserin can produce hyperglycemia by inhibiting presynaptic  $\alpha_2$ -adrenoceptors which regulate noradrenaline release (3), antagonising 5-HT receptors in peripheral tissues that may release a 'serotonergic brake' on noradrenergic neurones leading to an increased noradrenaline turnover and availability (4), and by inhibiting dopaminergic mechanisms, since dopaminergic mechanism has been implicated in the release of insulin from pancreatic  $\beta$ -cells (5, 6).

The rise and fall of blood glucose during glucose tolerance test (GTT) is determined by the effect of glucose on insulin secretion due to the presence of

anticipatory signals (incretins) from the gastrointestinal tract to the pancreas (7), several gastrointestinal hormones, including gastrin, stimulate insulin secretion (7). Mianserin (8) has been shown to inhibit pentagastrin stimulated gastric acid secretion. Since pentagastrin possesses full spectrum of gastrin-like activity including stimulation of pancreatic secretion (9), it is not unreasonable to speculate that the observed intolerance to oral glucose in initial hours by mianserin is due to some interference in the efficacy of gastrin as an incretin. This may result in inhibition of initial burst of insulin secretion from  $\beta$ -cells of pancreas leading to an undue hyperglycemic response to usual dose of glucose.

Thus it may be concluded that mianserin disturbs glucose homeostasis and produces glucose intolerance. However, further work is essential to delineate the exact mechanism of such alterations in BGL.

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## METHODS

Twenty one patients of ischemic stroke aged 42-68 years, 14 males and 7 females, were included in the study. Each patient with a history suggestive of