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Research Article

The effect of amlodipine on blood glucose level and its interaction with oral hypoglycemic drugs in albino rabbits

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ABSTRACT

Background: Amlodipine used as many cardiac conditions esp in hypertension. Diabetes affects cardiovascular system adversely. So this study was done to see effect of amlodipine on blood glucose level and its interaction with commonly used oral hypoglycemic agents in diabetic & non diabetic albino rabbits.
Methods: Rabbits were divided into nine groups of 6 rabbits in each group. I and II group were non-diabetic given normal saline and amlodipine respectively. Group III to IX were made diabetic by using alloxan monohydrate (150mg/kg i.p.) & given normal saline, glimepiride, metformin, pioglitazone, amlodipine + glimepiride, amlodipine + metformin and amlodipine + pioglitazone respectively. All drugs were given orally once daily for 7 day except group VII, VIII and IX in which glimepiride, metformin and pioglitazone were added on 7th day. After GTT blood glucose level were measured at 0, 1, 2 and 6 hours on 7th day in all groups by using spectrophotometer.
Results: After 7 days of treatment the amlodipine produced significant hyperglycemia in normal rabbits. Amlodipine on combination, causes significant decreased in hypoglycemic effect of glimepiride, significant increased the hypoglycemic effect of metformin, while no significant changes in hypoglycemic effects of pioglitazone in diabetic rabbits.
Conclusion: The present study shows that amlodipine causes hyperglycemia in normal rabbits. Amlodipine significantly altered hypoglycemic effect of glimepiride and metformin as compared to control group. If these finding are true to human beings then amlodipine should be use cautiously in diabetic patient on oral hypoglycemic drugs.

Keywords: Amlodipine, Diabetes**,** Hypoglycemia, Hyperglycemia

INTRODUCTION

Diabetes mellitus has emerged as a major public health problem in developing world. It is associated with many co-morbid conditions such as cardiovascular disorder e.g. hypertension, obesity, dyslipidemia and others. Many oral hypoglycemic drugs are used to treat type 2 diabetes mellitus. Concomitantly administered drugs to treat associate conditions may influence the hypoglycemia action of oral ant diabetic drugs.[1]

Nowadays, amlodipine is commonly used drug in treatment of hypertension. Also use in exertional angina in combination with other calcium channels blocker, heart failure, suppress the progression of mild atherosclerosis, symptomatic relief in Reynaud's disease.[2]

Glucose mediated stimulation of insulin secretion begins with its transport into β cell by GLUT-2 transporter. Further metabolism of glucose-6 phosphate via glycolysis generates ATP, which inhibit activity of ATP sensitive K^+ channels. Inhibition of these K^+ channels induce β cell membrane depolarization-which open voltage dependant calcium channels leading to influx of calcium and stimulate insulin release.[3]

Calcium ions play an important role in both the phase of glucose induced release of insulin from the β cells of pancreas.[4] Calcium channels blockers causes hyperglycemia by inhibiting insulin secretion directly.[5] So there is possibility that amlodipine, a calcium channel blocker, may influence the release of insulin and thereby glucose tolerance in normal and diabetic individuals.

Amlodipine is used for treatment of various cardiovascular complications in diabetic patients. There are some evidences that amlodipine causes hyperglycemia but there is paucity of information with regarding to its interaction with commonly used ant diabetic drugs.[6,7] The present study was done; to investigate the effect of amlodipine on blood glucose level in normal albino rabbits and to know interaction with various commonly use ant diabetic drugs in diabetic albino rabbits.

METHODS

The present study was undertaken in department of Pharmacology and Therapeutics, by using albino rabbits after obtaining approval from institutional animal ethics committee. Adult albino rabbits weighing approximately 1-1.5 kg were used for study.

Diabetes was induced by using single dose (150mg/kg, i.p) of freshly prepared solution of alloxan monohydrate 5% (dissolved in normal saline). Induction of diabetes was confirmed after 48 hour by blood glucose estimation and rabbits with fasting blood glucose level >200mg/dl were selected for study. Various drugs are procured from local market in tablets form. Doses of various drugs were calculated as per table from Paget and Barnes, 1964.[8] The animals were divided into nine groups of six animals in each group as below.

Group I- non diabetic rabbits treated with normal saline (1 ml).

Group II- non diabetic rabbits treated with amlodipine (0.35mg/kg/day).

Group III- alloxan induced diabetic rabbits treated with normal saline (1ml).

Group IV- alloxan induced diabetic rabbits treated with glimepiride (0.16mg/kg).

Group V- alloxan induced diabetic rabbits treated with metformin (81.8mg/kg).

Group VI- alloxan induced diabetic rabbits treated with pioglitazone (1.6mg/kg).

Group VII- alloxan induced diabetic rabbits treated with amlodipine and glimepiride.

Group VIII- alloxan induced diabetic rabbits treated with amlodipine and metformin.

Group IX- alloxan induced diabetic rabbits treated with amlodipine and pioglitazone.

All animals were maintained under standard animal house condition with free access to food and water ad libitum. Due care of animals were taken like house only 2 rabbits in each cage and using sterile instrument in experiment. All drugs were administered orally (using polyethylene tube) in single dose in morning. Group I (non diabetic group) serve as control for group II, group III (diabetic) serve as control for group IV, V and VI. Group VII, VIII and IX were given amlodipine for 7 days and on last day glimepiride (Glimcip, Cipla), metformin (Formin- Alkem) and pioglitazone (Pioglar- Ranbaxy CV) were added respectively and compared with group IV, V and VI respectively.

After overnight fasting GTT was done by giving 3.5 gm/kg/PO glucose dissolved in distilled water (5ml), blood glucose level were measured in all groups by using spectrophotometer (Techno) at predetermined intervals 0, 1, 2 and 6 hrs, by collecting blood sample (0.5ml) from marginal vein of ear in fluoride vials, under aseptic conditions.[9] Span diagnostic reagent kit (code no. is 93DP100-74) was used for estimation of blood glucose level.

All the data were expressed as mean ± SEM. Statistical analysis was carried out using unpaired Student's t test. $P < 0.05$ was considered to be statistically significant. Changes in blood glucose level by various drugs were determined in mg%.

RESULTS

Amlodipine treated non diabetic group (Group II) had significant increased in blood glucose level 10.30% and 19.15% and 19.24 at 1, 2 & 6 hours respectively in comparison to control group (group I) which is statistically significant (P<.01). There were significant (P<0.01) decreased in blood glucose level in diabetic rabbits treated with glimepiride (Group IV), metformin (group V) and with pioglitazone (group VI) at 1, 2 and 6 hours as compare to control group (group III). Amlodipine + glimepiride treated group (group-VII) had significant increased in blood glucose level (P<0.01) at 1, 2 and 6^{th} hr as compare to control group IV. Amlodipine + metformin (group VIII) had significant decreased in blood glucose level (P<0.05) at 1, 2 and 6 hr as compare to group V. Amlodipine + pioglitazone (group IX) had no significant changes in blood glucose level (P>0.05) at 1, 2 and 6 hr as compare to group VI (Table 1 and Figure 1).

DISCUSSION

Previous studies have shown that amlodipine causes hyperglycemia in non diabetic subjects but lack of much information on its interaction with oral hypoglycemia drugs.[10] This study also shows that the treatment of non-diabetic rabbits with amlodipine has significantly increased the blood glucose level as shown in result (10.30% and 19.15% and 19.24 at 1, 2 & 6 hours). This hyperglycemic effect by amlodipine could be due to decrease insulin release or by inhibition of GLUT-1 receptors by amlodipine.[6,7]

Table 1: Effect of amlodipine and different antidiabetic drugs on blood glucose level in various groups at 0, 1, 2 and 6 hours in albino rabbits.

Group	treated with	Mean blood glucose level (mg %) at			
		0hr	1hr	2hr	6 hr
I	Normal saline	88.17±2.26	126.17±1.94	106.7±1.90	86.67 ±3.23
II	Amlodipine	94.17±3.55	139.17.17±3.62@	126.5±4.46@	103.33±4.42@
III	Normal saline	307±5.22	398.17±7.22	345±4.98	315.5±5.21
IV	Glimepiride	302.33±3.95	300.83±3.24	219±3.99	186±4.34
V	Metformin	304.67±3.61	307±3.24	235.83±4.58	215.17±3.39
VI	Pioglitazone	305.33±4.20	313.5±4.11	256±5.19	199±3.64
VII	Amlodipine +Glimepiride	313.67±5.92	325±6.33@	242.83±6.33@	208±6.60@
VIII	Amlodipine + Metformin	310±5.28	292.5±5.14*	216.83±6.45*	196.67±6.77*
IX	Amlodipine + Pioglitazone	311.5±5.77	318.83±5.86	257±6.98	195.67±5.61

Group I and II-non diabetic, groups III to IX were diabetic, n=6, * P<0.05,@-P<0.01

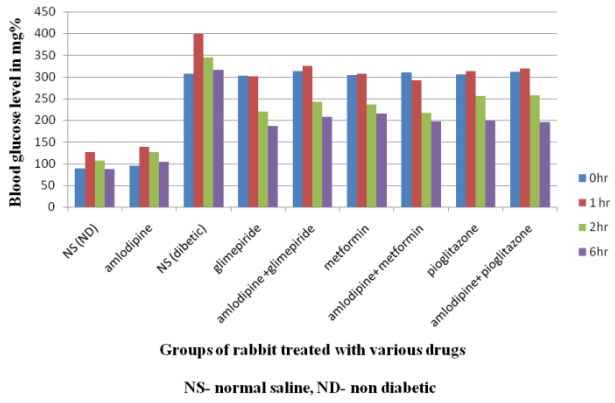

Figure 1: Comparative effects of amlodipine and antidiabetic drugs on blood glucose level in various groups 0, 1, 2 and 6 in albino rabbits.

The combination of amlodipine and glimepiride in diabetic rabbits shows that amlodipine reduced hypoglycemic effect of glimepiride. This antagonizing effect can be explained by the result which shows significant hypoglycemia (24.45% at 1 hr, 36.52 at 2hr and 41.05% at 6hr) with glimepiride alone, whereas after addition of amlodipine with glimepiride, the hypoglycemia effect of glimepiride was less (18.34% at 1 hr, 29.61% at 2 hr and 34.01% at 6 hr) in diabetic rabbits. This decreasing hypoglycemic effect of glimepiride by amlodipine could be due to inhibition of insulin release.[11,12]

The combination of amlodipine with metformin showed beneficial interaction. Amlodipine increased the hypoglycemia effect of metformin. This beneficial effect can be explained by results which shows significant hypoglycemia (22.90%, 31.64% and 33.80% at 1, 2 and 6 hr respectively) with metformin, after combination of amlodipine with metformin the hypoglycemia effect of metformin was increased (26.54%, 37.15% and 37.66% at 1, 2 and 6 hr respectively). Similar results that amlodipine cause significant increase in blood glucose level lowering effect of glimepiride in combination, compare to glimepiride alone in diabetic rabbits were also found in other studies.[13]

Pioglitazone alone cause significant hypoglycemia in diabetic rabbits (21.26%, 25.80% and 36.93% at 1, 2 and 6 hr respectively). Amlodipine with pioglitazone show no significant change in blood glucose level as shown in results (19.93%, 25.51% and 37.98% at 1, 2 and 6 hr respectively) as compare to pioglitazone alone in diabetic rabbits. Similar results that amlodipine cause no significant changes in blood glucose level lowering effect of pioglitazone in combination, compare to pioglitazone alone in diabetic rabbits were also found in other studies.[14]

Nowadays, amlodipine is commonly used drug in treatment of hypertension. Also use in exertional angina in combination with other calcium channels blocker, heart failure, suppresses the progression of mild atherosclerosis, symptomatic relief in Reynaud's disease.

Thus in any situation where amlodipine is used in a diabetic patient who is on various oral antidiabetic drugs, there is a possibility of interaction leading to the decrease hypoglycemic effect of glimepiride and increase the hypoglycemic effect of metformin while no changes in hypoglycemia effect of pioglitazone.

CONCLUSION

Amlodipine causes increase blood glucose level in normal albino rabbits. It reduces the hypoglycemia effect of glimepiride while increase hypoglycemic effect of metformin and there is no changes in hypoglycemic effect of pioglitazone in diabetic albino rabbits. If these finding are true to human beings, amlodipine should not be used in diabetic patients on glimepiride and metformin therapy as it may lead to reduce hypoglycemic effect of glimepiride while increase hypoglycemic effect of metformin.

Further studies are required to understand the exact mechanism of this interaction and its clinical implications.

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Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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