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Influence of losartan on the hypoglycemic activity of glimepiride in normal and diabetic rats

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Abstract

Background: The influence of losartan on the hypoglycemic effect of glimepiride was studied in normal and diabetic rats.

Method: Losartan and glimepiride were studied at a dose of 4.5 and 0.09 mg/kg and in normal and diabetic rats, respectively. The blood samples were collected at 0, 1, 2, 3, 4, 6, 8, 10, 12, and 16 hours and analyzed for glucose levels using a glucometer.

Results: Glimepiride exhibited a maximum reduction of blood glucose levels at the 4th hour in normal and diabetic rats. The maximum hypoglycemic effect was observed at the 6th hour in normal rats treated with losartan. In normal rats, losartan did not have any significant effect on the hypoglycemic activity of glimepiride in either the single- or multiple-dose interaction study. In the case of diabetic rats, losartan did not have any significant effect on the hypoglycemic activity of glimepiride in the single-dose interaction study, but a significant change was observed in the multiple-dose study of diabetic rats. Hence, the interaction was found to be pharmacodynamic.

Conclusions: The study indicates that chronic losartan pretreatment elevates the hypoglycemic effect of glimepiride by a possible rise in insulin sensitivity and improving insulin homeostasis or may be due to the inhibition of CYP2C9. The study also suggests that caution may be recommended concerning combined use of losartan and an oral hypoglycemic agent, glimepiride.

Keywords: glimepiride, losartan, hypoglycemia, drug interactions

Introduction

Diabetes mellitus is described as a metabolic disorder characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects of insulin production or action or both [Murthy *et al*. 2008; Swami *et al*. 2005; Bastaki, 2005; Satyanarayana *et al*. 1998]. A study of the literature reveals that diabetes and hypertension are interrelated and strongly predispose an individual to atherosclerotic vascular disease [James and Epstein, 1995]. Patients with such comorbid diseases are often treated with more than one drug. There is then a possibility of interactions between drugs, resulting in either reduced or enhanced effects of any of the drugs. Therefore, monitoring and readjustment of the dose(s) is often necessary to optimize treatment. Hence, the present study was planned to assess the interaction between losartan, an angiotensin II receptor antagonist, and glimepiride, an oral antidiabetic agent [Groop, 1992; Lebovitz, 1994]. Glimepiride is a sulfonylurea derivative and is metabolized by cytochrome P-450 (CYP2C9). Losartan is a substrate of CYP2C9, which is metabolized by CYP3A4 [Iwamura *et al*. 2011; Yasar *et al*. 2001]. Therefore, it is hypothesized that losartan may influence the pharmacological activity of glimepiride by any one of the above mechanisms. Maekawa and colleagues studied substrate-dependent functional alterations of seven CYP2C9 variants in Japanese subjects and suggested the necessity for careful administration of losartan and glimepiride to patients bearing CYP2C9.3, CYP2C9.13,

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CYP2C9.26, CYP2C9.33, CYP2C9.28 and CYP2C9.30 alleles [Maekawa *et al*. 2009].

Materials and methods

Drugs and chemicals

Glimepiride and losartan were obtained from Zydus Cadila, Ahmedabad and Radiant Research Pvt. Ltd, Bangalore, India, respectively. Alloxan monohydrate was obtained from Sigma Chemicals, India. A glucometer for blood glucose estimation was obtained from Roche Diagnostics, Germany.

Animals

As rats are mammals and the physiology and biology of them are easier to monitor and more likely to resemble the human condition, we have selected rats for testing in the present interaction study. Adult Wistar rats of either sex, weighing 150–250 g, obtained from the animal house of Bapatla College of Pharmacy (1032/ac/07/CPCSEA), Bapatla, were maintained at a constant temperature of 22 ± 3°C and humidity 60–70% with 12 h light/dark cycles, throughout the experiments. The animals were fed with commercial rat feed (Rayan's Biotechnologies Pvt Ltd, Hyderabad, India) and sterile water was given *ad libitum*. The protocol was approved by the Institutional Animal Ethics Committee, in accordance with the guidelines of the Committee for the purpose of control and supervision of experimentation on animals (IAEC/IV/03/BCOP/2012).

Dosage and drug administration

In clinical practice, losartan and glimepiride are administered orally. Hence, their human therapeutic doses were extrapolated to rats based on the body weight and were used and administered orally for the study [Ramachandra *et al*. 2005].

Pharmacodynamic interaction studies in normal rats and diabetic rats

Normal rats

Effect of losartan and glimepiride on blood glucose levels in normal rats. Adult Wistar rats were divided into three groups of six animals each. The animals were fasted for a period of 18 h prior to the experimentation and water was supplied *ad libitum* [Rosenstock *et al*. 1996]. Group I served as the control and received distilled water, group II received glimepiride 0.09 mg/kg, and group III received losartan 4.5 mg/kg, administered once after the 18 h fasting period. The blood samples were collected by the tail vein method at 0, 1, 2, 3, 4, 6, 8, 10, 12, and 16 h of drug treatment and were analyzed for blood glucose levels using a glucometer [Shim, *et al*., 2003] to evaluate the onset, duration and maximum activity of the individual drugs.

Single-dose interaction study in normal rats. Single-dose interaction studies were carried out on group II animals to evaluate the effects of a single dose of losartan on the hypoglycemic activity of glimepiride after a brief washout period of 1 week, as it is necessary to consider that the elimination period should be at least five times the terminal half-life (of the active ingredient or its metabolites, or of the acute pharmacological effect, etc.). The animals were fasted for 18 h prior to experimentation and water supplied *ad libitum*. The animals were administered once with the interacting drug losartan 4.5 mg/kg followed by glimepiride 0.09 mg/kgafter 30 minutes. The blood samples were collected before and after administration of drug at the predetermined time intervals and subjected to glucose estimation, as mentioned previously.

Multiple-dose interaction study in normal rats. As single-dose interaction study results cannot be extrapolated to chronic use effects, the study was extended to include a multiple-dose interaction study to evaluate the effect of chronic use of losartan on the hypoglycemic activity of glimepiride. The group II animals were administered with losartan 4.5 mg/kg, for the following 7 consecutive days after the single-dose interaction study. During this period, the animals had free access to food and water. On the 7th day of the study food was withdrawn 6 h after the losartan administration, but water was supplied *ad libitum*. On the 8th day, glimepiride 0.09 mg/kg was given 30 minutes after losartan administration and the blood samples were collected at the predetermined intervals and were analyzed for glucose levels using a glucometer.

Diabetic rats

Induction of diabetes

Experimental diabetes in rats was induced by injecting alloxan monohydrate intraperitoneally

at a dose of 150 mg/kg in ice-cold normal saline. After 72 h, samples were collected by the tail vein method and analyzed for glucose levels. Rats with blood glucose levels of 200 mg/dl and above were considered as diabetic and selected for the study [Ghosh, 2005; Murthy and Mayuren, 2008].

Single-/multiple-dose interaction studies in diabetic rats

The effects of single and multiple doses of losartan on the antihyperglycemic activity of glimepiride were studied to report the effect of losartan on the blood glucose lowering effect of glimepiride. The diabetic rats were divided into two groups of six animals each. The animals were fasted for a period of 18 h prior to experimentation and water supplied *ad libitum*. Group I was treated with the vehicle and group II administered with glimepiride 0.09 mg/kg. After a brief washout period of 1 week, the animals of group II were used for the interaction study. An experimental protocol similar to that of earlier studies in normal rats was followed for the single- and multiple-dose interaction studies in diabetic rats [Lawrence and Bacharach, 1964].

Statistical analysis

The hypoglycemic activity of glimepiride at any time t was calculated as the percentage blood glucose change at that time with respect to initial blood glucose level according to the formula [Satyanarayana *et al.* 1998].

$$\text{Percentage blood glucose reduction at time } t = [(a - b)/a] \times 100$$

where a is the initial blood glucose level and b is the blood glucose level at time t.

The significance of the observed difference in the pharmacodynamic parameters of glimepiride was assessed by one-way analysis of variance (ANOVA), followed by Dunnett's multiple comparison tests. A value of $p < 0.05$ was considered to be statistically significant.

Results and discussion

Pharmacodynamic interaction studies in normal rats

Glimepiride at the dose of 0.09 mg/kg was studied in normal rats. The onset of action was observed at the first hour and was observed to last until the 16th hour. Glimepiride produced hypoglycemia in normal rats, with peak activity at the 4th hour (blood glucose 63.83 ± 0.79 mg/dl, decrease in blood glucose 31.36 ± 0.26%), which may be due to the rapid release of insulin [Deininger *et al.* 2001] by glimepiride, and to the ability of glimepiride to increase the sensitivity of pancreatic β cells to glucose. Losartan at a dose of 4.5 mg/kg exhibited a peak hypoglycemic effect at the 6th hour (blood glucose 66.83 ± 2.49 mg/dl, decrease in blood glucose 27.42 ± 0.82%).

Single-dose interaction study

The study was conducted in normal rats by the administration of glimepiride 0.09 mg/kg and losartan 4.5 mg/kg. Blood glucose levels at various time intervals were subjected to statistical comparison with initial blood glucose of the same group and with that of the glimepiride alone group. There was a significant change in the blood glucose values when compared with their 0 hour blood glucose values but the percentage change (decrease) in blood glucose values are insignificant when compared with that of treatment with glimepiride alone, revealing that there is no significant effect of losartan in normal rats in this single-dose interaction study. The peak hypoglycemic effect in the single-dose interaction study was observed at the 4th hour as 62.67 ± 2.29 mg/dl and the decrease in blood glucose was found to be 31.7 ± 1.21% (Table 1).

Multiple-dose interaction study

The study was conducted by the administration of losartan 4.5 mg/kg daily followed by glimepiride 0.09 mg/kg on the 8th day of the study. There was a significant change in the blood glucose values when compared with their initial 0 hour blood glucose values but the percentage decrease in blood glucose levels was insignificant when compared with that of glimepiride alone and with that of values observed in single-dose interaction study, which reveals that there was no significant effect of losartan in normal rats in the multiple-dose interaction study.

Pharmacodynamic interaction studies in diabetic rats: single- and multiple-dose interaction study

In the case of diabetic rats, glimepiride and losartan were studied at doses of 0.09 and 4.5 mg/kg

Table 1. Mean percentage blood glucose change (mean glucose levels in parentheses) in normal rats (n = 6) with different treatments.

Time (h)	Control	Glimepiride	Losartan	Single-dose study	Multiple-dose study
0	(83.14 ± 1.08)	(93.0 ± 0.96)	(92.16 ± 2.46)	(91.67 ± 1.76)	(94.0 ± 1.41)
0.5	−2.14 ± 0.51 (84.54 ± 0.96)	7.53 ± 0.07 (86.0 ± 0.96)	−4.34 ± 0.2 (96.16 ± 2.67)	7.8 ± 0.41 a^{ns} (84.5 ± 1.92)	10.43 ± 0.35 a*** b** (84.17 ± 1.42)
1	−7.2 ± 1.24 (88.94 ± 1.01)	16.14 ± 0.38 (78.0 ± 1.09)	−1.45 ± 0.21 (93.5 ± 2.6)	11.28 ± 0.75 a** (81.33 ± 2.17)	12.22 ± 0.32 a*** b^{ns} (82.5 ± 1.47)
2	−3.3 ± 0.81 (85.71 ± 0.79)	23.11 ± 0.23 (71.5 ± 0.56)	14.2 ± 0.58 (79.0 ± 2.59)	21.67 ± 0.96 a^{ns} (71.83 ± 2.22)	23.43 ± 0.74 $a^{ns}b^{ns}$ (72.0 ± 1.75)
3	−2.83 ± 0.76 (84.93 ± 0.85)	24.16 ± 0.08 (70.5 ± 0.76)	17.8 ± 0.67 (75.62 ± 2.6)	24.62 ± 1.25 a^{ns} (69.17 ± 2.44)	27.63 ± 0.61 $a^{*}b^{ns}$ (68.0 ± 1.59)
4	−3.89 ± 0.92 (86.23 ± 1.35)	31.36 ± 0.26 (63.83 ± 0.79)	20.65 ± 0.57 (73.16 ± 2.46)	31.7 ± 1.21 a^{ns} (62.67 ± 2.29)	33.52 ± 0.75 $a^{ns}b^{ns}$ (62.5 ± 1.6)
6	−5.77 ± 0.9 (87.80 ± 1.39)	26.52 ± 0.19 (68.17 ± 0.6)	27.42 ± 0.82 (66.83 ± 2.49)	25.38 ± 1.6 a^{ns} (68.5 ± 2.77)	28.52 ± 0.51 $a^{ns}b^{ns}$ (67.17 ± 1.4)
8	−5.08 ± 0.83 (84.36 ± 0.87)	19.53 ± 0.17 (74.83 ± 0.7)	23.6 ± 0.58 (70.3 ± 2.39)	21.32 ± 1.15 a^{ns} (72.17 ± 2.41)	22.88 ± 0.69 $a^{*}b^{ns}$ (72.5 ± 1.7)
10	−1.85 ± 0.62 (85.53 ± 0.86)	14.51 ± 0.11 (79.5 ± 0.76)	21.15 ± 0.6 (72.16 ± 2.39)	14.07 ± 1.27 a^{ns} (78.83 ± 2.65)	16.3 ± 0.6 $a^{ns}b^{ns}$ (78.67 ± 1.64)
12	−1.02 ± 0.39 (83.84 ± 0.93)	10.57 ± 0.14 (83.17 ± 0.87)	16.4 ± 0.43 (77.0 ± 2.2)	11.67 ± 1.0 a^{ns} (81.0 ± 2.42)	12.77 ± 0.71 $a^{ns}b^{ns}$ (82.0 ± 1.78)
16	2.13 ± 0.6 (81.24 ± 1.38)	3.22 ± 0.03 (90.0 ± 0.96)	12.62 ± 0.29 (80.52 ± 2.17)	8.95 ± 0.94 a** (83.5 ± 2.43)	10.45 ± 0.44 a*** b^{ns} (84.17 ± 1.62)

ns, nonsignificant;* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
[a]When compared with glimepiride alone treatment results.
[b]When compared with single-dose interaction study results.

respectively. Glimepiride produced antihyperglycemic activity in diabetic rats with peak activity at the 4th hour (blood glucose 129.7 ± 2.74 mg/dl, decrease in blood glucose 38.23 ± 0.44%). Losartan produced antihyperglycemic activity in diabetic rats with peak activity at the 6th hour (blood glucose 163.3 ± 1.7 mg/dl, increase in blood glucose 22.38 ± 0.29%). In the single-dose interaction study the blood glucose levels (Table 2) decreased significantly when compared with their 0 hour blood glucose values but the percentage decrease in blood glucose levels was insignificant when compared with that of blood glucose levels observed in rats treated with glimepiride alone, which shows that there was no significant effect of losartan in diabetic rats on single-dose administration. A multiple-dose interaction study was conducted as in diabetic rats and a significant difference was observed when compared with single-dose interaction studies. The maximum change in blood glucose at the 4th hour was observed as 124.2 ± 2.74 mg/dl and the change was calculated as 41.5 ± 0.46%, which may be due to the blockade of angiotensin I receptor [Shinozaki *et al.* 2004], as insulin resistance induced upregulation of AT1 receptors. This might explain the association of insulin resistance with endothelial dysfunction and hypertension [Onuchin *et al.* 2008] or may be due to inhibition of hepatic glucose output [Srivastava, 2009]. Losartan is used to treat hypertension and to help protect the kidneys from damage due to diabetes. It has been concluded that short-term treatment with losartan slightly attenuates symptomatic and hormonal responses to hypoglycemia in humans [Deininger *et al.* 2001]. Losartan-mediated improvement in insulin sensitivity is mainly due to an increase in non-oxidative glucose metabolism and blood flow in insulin-resistant hypertensive patients [Schupp, *et al.*, 2004]. Chu and colleagues reported that AT1 receptor antagonism improves β-cell function and glucose tolerance in young type 2 diabetic mice [Chu *et al.* 2006]. In addition, administration of losartan orally to diabetic rats was observed to improve insulin sensitivity to reduce elevations in fasting and fed glucose concentrations [Murali and Goyal, 2001]. Past studies reveal that losartan increases sensitivity and enhances β-cell responsiveness to glucose and enhances glucose

Table 2. Mean percentage blood glucose change (mean glucose levels in parentheses) in diabetic rats (n = 6) with different treatments.

Time (h)	Control	Glimepiride	Losartan	Single-dose study	Multiple-dose study
0	(208.9 ± 2.15)	(210.0 ± 3.06)	(210.5 ± 2.14)	(209.5 ± 2.17)	(212.0 ± 3.06)
0.5	−1.78 ± 0.57 (212.6 ± 1.98)	7.33 ± 0.14 (194.5 ± 2.93)	2.71 ± 0.13 (204.7 ± 1.99)	6.88 ± 0.36 a^{ns} (195.2 ± 2.12)	14.6 ± 0.17 a*** b*** (181.2 ± 2.65)
1	−9.41 ± 1.74 (231.5 ± 1.69)	15.75 ± 0.30 (176.8 ± 3.01)	3.81 ± 0.07 (202.3 ± 2.07)	16.48 ± 0.44 a^{ns} (174.8 ± 1.42)	19.38 ± 0.08 a*** b** (170.8 ± 2.6)
2	−8.55 ± 1.11 (226.8 ± 3.8)	24.5 ± 0.31 (158.5 ± 2.93)	11.52 ± 0.22 (186.2 ± 1.72)	23.67 ± 0.36 a^{ns} (159.8 ± 1.4)	27.48 ± 0.33 a*** b** (153.7 ± 2.8)
3	−8.21 ± 1.12 (226.1 ± 3.95)	27.18 ± 0.39 (152.8 ± 2.79)	13.82 ± 0.2 (181.3 ± 1.47)	28.61 ± 0.44 a^{ns} (149.5 ± 1.78)	30.57 ± 0.36 a*** b^{ns} (147.2 ± 2.89)
4	−1.06 ± 0.41 (211.1 ± 2.23)	38.23 ± 0.44 (129.7 ± 2.74)	18.47 ± 0.32 (171.5 ± 1.64)	37.73 ± 0.25 a^{ns} (130.3 ± 1.47)	41.5 ± 0.46 a*** b** (124.2 ± 2.74)
6	−1.76 ± 0.49 (212.4 ± 1.93)	27.57 ± 0.19 (152.0 ± 2.79)	22.38 ± 0.29 (163.3 ± 1.7)	28.05 ± 0.1 a^{ns} (150.7 ± 1.62)	29.98 ± 0.23 a*** b^{***} (148.3 ± 2.3)
8	5.54 ± 1.09 (197.3 ± 2.01)	22.33 ± 0.36 (163.0 ± 2.64)	19.87 ± 0.19 (168.2 ± 2.12)	22.09 ± 0.18 a^{ns} (163.2 ± 1.99)	26.5 ± 0.13 a*** b*** (155.7 ± 2.33)
10	9.55 ± 1.18 (188.9 ± 1.95)	17.72 ± 0.24 (172.7 ± 2.47)	18.82 ± 0.37 (170.3 ± 2.12)	18.33 ± 0.25 a^{ns} (171.2 ± 2.08)	21.65 ± 0.09 a*** b*** (166.0 ± 2.26)
12	9.27 ± 1.34 (189.41 ± 1.54)	15.45 ± 0.31 (177.5 ± 2.71)	13.61 ± 0.43 (176.2 ± 2.35)	16.42 ± 0.19 a^{ns} (175.0 ± 2.2)	18.48 ± 0.17 a*** b*** (172.7 ± 2.36)
16	9.98 ± 1.07 (188.0 ± 1.95)	12.40 ± 0.15 (183.8 ± 2.52)	16.27 ± 0.42 (181.8 ± 2.33)	13.48 ± 0.25 a^{*} (181.2 ± 2.31)	15.27 ± 0.2 a*** b** (179.5 ± 2.46)

ns, nonsignificant;* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.
[a]When compared with glimepiride alone treatment results.
[b]When compared with single-dose interaction study results.

homeostasis [Fang and Huang, 1998] in subjects with type 2 diabetes and nephropathy [Henriksen *et al.* 2001; Jin and Pan, 2007].

Conclusion

In conclusion, on the basis of the available evidence, the co-administration of losartan with glimepiride results in alteration of the hypoglycemic activity of glimepiride and was more pronounced in the multiple-dose interaction study in diabetic rats. Although the combination was well tolerated and did not induce any hypoglycemic shock in diabetic rats, this study should be extended to humans to investigate any possible interaction.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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