RESEARCH ARTICLE

Effect of buspirone on blood glucose levels in rats

Nisharani Jadhav[1], Anita Deshpande[2], Ravikumar Baradol[3]

[1]Department of Pharmacology, Al-Ameen Medical College, Vijayapur, Karnataka, India, [2]Department of Physiology, Al-Ameen Medical College, Vijayapur, Karnataka, India, [3]Department of Paediatrics, Shri B. M. Patil Medical College, Vijayapur, Karnataka, India

Correspondence to: Anita Deshpande, E-mail: dranitavijay@yahoo.com

ABSTRACT

Background: Buspirone is commonly used as an anti-anxiety drug. There is controversy over the dysglycemic effects of buspirone in various clinical and animal studies. **Aims and Objectives:** This study aims to evaluate the effect of buspirone on blood sugar level in rats at three different doses. **Materials and Methods:** Rats were treated with three doses of buspirone orally, namely, 3 mg/kg, 5 mg/kg, and 10 mg/kg and control group received distilled water orally for 14 days. Blood was collected by tail prick method at 0 h (fasting), at ½ h, 1 h, 1½ h, 2 h, and 4 h after drug administration on day 1. On days 7 and 14, the blood glucose levels were estimated at baseline (0 h) and at 1 h after the drug administration. Blood glucose levels were estimated using the glucometer. **Results:** On day 1, mean blood glucose values were found to be significantly ($P < 0.001$) low in control group and in buspirone 3 mg/kg and 5 mg/kg groups at various time intervals as compared to baseline value at 0 h in respective group. In buspirone 10 mg/kg group, mean blood glucose levels at all-time intervals were found to be significantly high ($P < 0.01$) as compared to baseline value at 0 h. On days 7 and 14, a significant increase in the blood glucose level was observed immediately within 30 min of drug administration and reach maximum value at the end of 1 h only in buspirone 10 mg/kg group. This rise in blood glucose level was not seen in groups receiving buspirone 3 mg/kg and 5 mg/kg. **Conclusion:** Buspirone 3 mg/kg and 5 mg/kg does not have any effect on blood glucose levels, while in a high dose of 10 mg/kg causes a significant transient increase in the blood glucose level.

KEY WORDS: Buspirone; Blood Glucose; Rats

INTRODUCTION

In our society, anxiety disorders are the most prevalent psychiatric disorders. It has proven that one-third of the population is affected by an anxiety disorder during their lifetime.[1,2] Anxiety is a psychological and physiological state characterized by somatic, emotional, cognitive, and behavioral components.[3,4] As compared to general people, diabetic patients are more prone to the development of anxiety. The prevalence of anxiety in diabetic patients is 15.7% as compared to 5.3% in normal persons.[5,6]

Several anxiolytics are available for the treatment of anxiety. They are mainly sedatives, hypnotics, antidepressants, antihistaminics, beta-blockers, antipsychotic, and azapirones group of drugs.[7,8] Recently, azapirones group of drugs is used as anxiolytics. Azaspirones group consists of drugs such as ipsapirone, buspirone, alnespirone, and gepirone.[9,10] The best known is buspirone, which has anti-anxiety and antidepressant[11] property. Adverse effects are minimal with dizziness, nervousness, and headache.

Buspirone is a serotonin receptor (5-hydroxytryptamine 1A [$5HT_{1A}$]) agonist. Due to this mechanism of action, it is used as an anxiolytic drug.[8] There are many studies

available which have highlighted the effects of serotonin (5HT), serotonin receptor agonists, antagonists, and selective serotonin reuptake inhibitors on blood glucose levels.[12-16]

Buspirone is uniquely associated with increased risk of both hypoglycemia and hyperglycemia. The dysglycemic effects of buspirone have been seen in animal studies, healthy volunteers, and case report studies. These studies show conflicting conclusions regarding the effects of buspirone on blood glucose levels.[17-23]

As there is controversy over the dysglycemic effects of buspirone, the present study was undertaken to clarify and reconfirm the conflicting dysglycemic effects of buspirone at three different doses. This study was started with the study objectives as follows:

- To evaluate the effect of buspirone on blood glucose levels in rats on acute administration at three different doses of 3 mg/kg, 5 mg/kg, and 10 mg/kg
- To evaluate the effect of buspirone on blood glucose levels in rats on daily administration over a period of 14 days.

MATERIALS AND METHODS

The protocol of the experiment was approved by our institutional animal ethical committee as per the guidelines of the committee for the purpose of control and supervision of experiments on animals; the study was performed in the experimental laboratory in the department of pharmacology in a tertiary care hospital.

Twenty-four albino Wistar rats of either sex (12 males and 12 females) weighing 150–170 g of age 6–8 weeks were used for the experiment. The rats kept in polypropylene cages with grill on top. Food, water, and bedding of clean paddy husk were provided. The rats were allowed 1 week period of acclimatization in the institutional animal house. Temperature was maintained between 18°C and 29°C. Relative humidity was maintained between 30% and 70%. Animals were fed on standard pellet diet. Food and water were given *ad libitum*.

This is a parallel-group, four-arm experimental study. There were a total of four groups in the study. Six rats were included per group.

Blood Sample Collection

Blood collected from rat distal caudal vein by tail prick method using 23G sterile needle. Blood glucose levels were estimated using the Johnson and Johnson One Touch Horizon glucometer and glucose strips. The sensitivity of this glucometer is 20–600 mg/dl.

Baseline blood glucose values at 0 h before the drug administration were estimated in the rats. Buspirone powder

dissolved in distilled water and buspirone suspension was made. This suspension was fed through an oral feeding tube to each rat. The dose of each rat was calculated depending on the weight of the rat. After this, the rats received an oral dose of distilled water or buspirone as per the group as follows:

- Group I: Control (distilled water) p.o. 1 ml for 14 days
- Group II: Buspirone 3 mg/kg p.o. for 14 days
- Group III: Buspirone 5 mg/kg p.o. for 14 days
- Group IV: Buspirone 10 mg/kg p.o. for 14 days.

Blood glucose levels were then estimated using the glucometer and glucose strips at ½ h, 1 h, 1½ h, 2 h, and 4 h after drug administration on day 1. After collection of the 4th h blood sample, the rats were placed back in their respective cages and put on standard pellet diet. On days 7 and 14, the same procedure was followed, but the blood glucose levels were estimated only twice, i.e., at baseline (0 h) and at 1 h after the drug administration.

Statistical Analysis

The significance of the difference between the mean blood glucose levels at various time intervals within the group was estimated using repeated measures ANOVA and between different groups was estimated using one-way ANOVA. "Paired *t*-test" (two tailed) was used to compare mean blood glucose levels before and after the administration of drug on days 7 and 14. $P < 0.05$ was considered statistically significant. GraphPad Prism version 5.03 was used. Data displayed as mean ± SD.

RESULTS

On day 1, the baseline blood glucose levels of the four groups were compared [Figure 1]. The differences in the values were not significant ($P > 0.05$).

Mean blood glucose values were found to be significantly ($P < 0.001$) low in Groups I, II, and III, at various time intervals as compared to baseline value at 0 h in respective
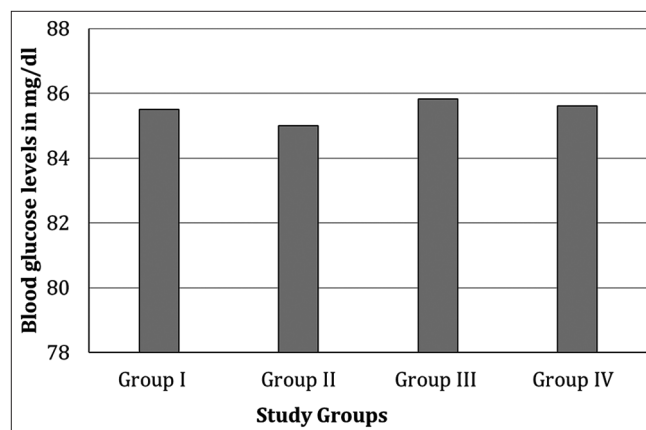
Figure 1: Comparison of mean blood glucose levels at 0 h in all study groups on day 1

group, except at baseline (0 h) and ½ h. In Group IV, mean blood glucose levels at all-time intervals were found to be significantly high ($P < 0.01$) as compared to baseline value at 0 h, except at baseline (0 h) and 4 h. The maximum rise in blood glucose level was seen at the end of 1 h after drug administration [Figure 2]. Hence, it was decided that to estimate the blood glucose levels at 0 and 1 h in all the groups on days 7 and 14.

On day 7, mean blood glucose levels at 0 h in Groups II, III, and IV with Group I, it was seen that the blood glucose levels were not significantly different from each other ($P > 0.05$). The mean blood glucose levels at 1 h in Groups II and III were not statistically different from Group I ($P > 0.05$). The mean blood glucose levels at 1 h were significantly low as compared to 0 h ($P < 0.001$) in Groups I, II, and III, while the mean blood glucose level in the Group IV at 1 h was significantly high ($P < 0.0001$) as compared to 0 h [Figure 3].

On day 14, the mean blood glucose levels at 1 h were significantly low as compared to 0 h ($P < 0.001$) in Groups I, II, and III, while the mean blood glucose level in the Group IV at 1 h was significantly high ($P < 0.0001$) as compared to 0 h [Figure 4].
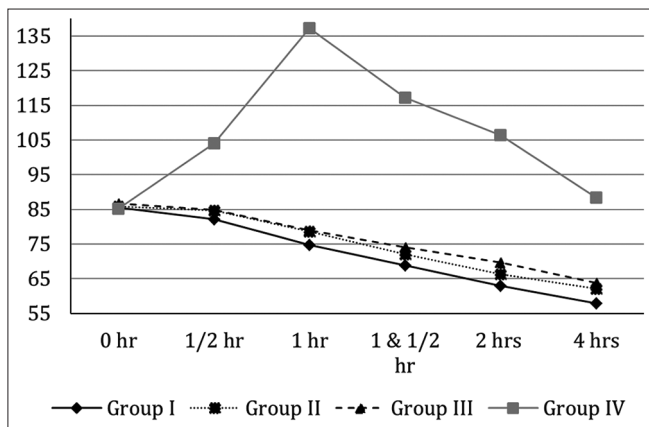
Thus, a significant increase in the blood glucose level was observed only in Group IV, i.e., at a high dose of buspirone 10 mg/kg. This rise in the blood glucose level was seen immediately within 30 min of drug administration and reach maximum value at the end of 1 h only in Group IV on days 1, 7, and 14. This rise in blood glucose level was not seen in Groups II and III, where buspirone was administered in a low dose of 3 mg/kg and 5 mg/kg, respectively.

As it was necessary to ascertain, whether there was any statistically significant difference in the above findings on all days, percentage change in blood glucose levels from 0 to 1 h was calculated only in Group IV on days 1, 7, and 14 using the following formula:

Percentage change from 0 to 1 h =([Blood glucose value at 1 h − Blood glucose value at 0 h] × 100)/(Blood glucose value at 0 h).

The percentage change at the end of 1 h from 0 h blood glucose level was found to be statistically non-significant ($P > 0.05$) on various days within the Group IV [Figure 5].

Figure 2: Mean blood glucose levels in all the study groups on day 1 at various time intervals
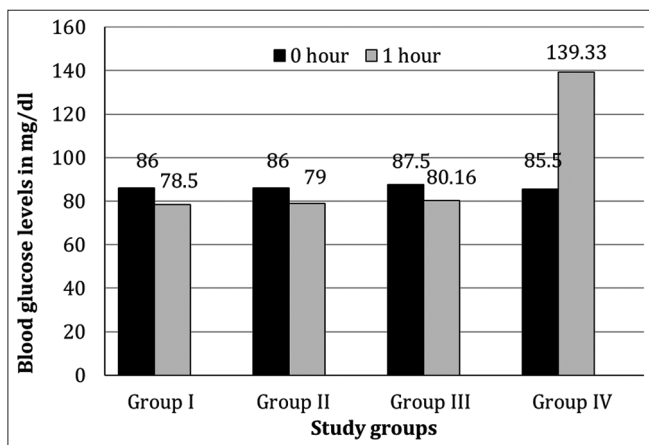
Figure 3: Mean blood glucose levels in all study groups at 0 h and 1 h on day 7
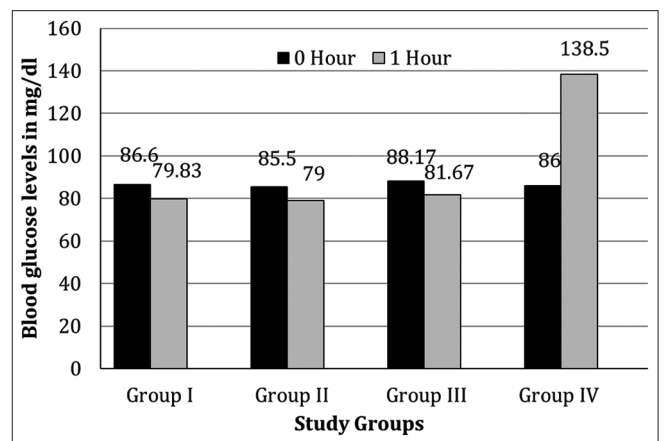

Figure 4: Mean blood glucose levels in all study groups at 0 and 1 h on day 14
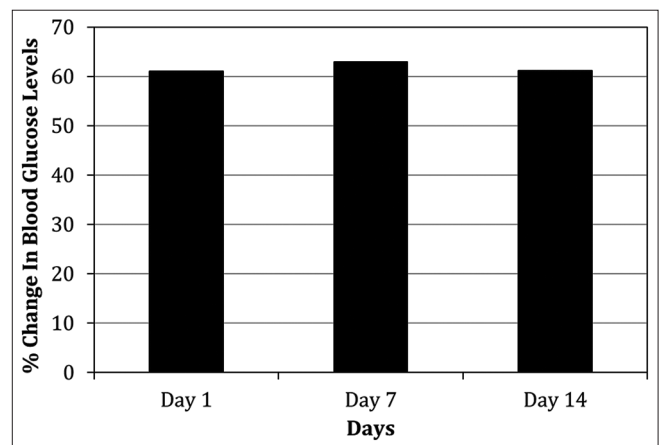

Figure 5: Percentage change in mean blood glucose level in Group IV on days 1, 7, and 14

DISCUSSION

Buspirone is one of the best known anxiolytic drugs among azapirones.[9] Buspirone is uniquely associated with an increased risk of both hypoglycemia and hyperglycemia. These dysglycemic effects of buspirone have been observed in animal studies, healthy volunteers, and case reports. These studies show conflicting results regarding the dysglycemic effects of buspirone.[15-23]

In the present study, oral administration of buspirone in low and moderate doses of 3 mg/kg and 5 mg/kg, respectively, did not show any effect on the blood glucose levels. Oral administration of buspirone in a high dose of 10 mg/kg caused a significant increase in the blood glucose level at the end of 1 h after buspirone administration. This hyperglycemia caused by a high dose of buspirone 10 mg/kg was transient.

These findings are similar to the previous rat study, in which the rats were treated with s.c. buspirone in the doses of 1 mg/kg, 5 mg/kg, 10 mg/kg, and 20 mg/kg as a single dose.[15] The investigators found that rats treated with buspirone 1 mg/kg and 5 mg/kg did not show a significant change in plasma glucose levels at any time interval. Buspirone at both dose levels, i.e., at 10 mg/kg and 20 mg/kg induced increase in plasma glucagon levels. The authors then investigated the effects of buspirone at a dose of 20 mg/kg on plasma glucose and glucagon levels in adrenodemedullated rats. It had been observed that both hyperglycemia and hyperglucagonemia elicited by buspirone were not seen in adrenomedullated rats. The investigators also found that buspirone significantly increases the level of plasma adrenaline. It is postulated that adrenaline release is responsible for hyperglycemia induced by buspirone. [24,25]

Meltzer and Maes evaluated the cortisol levels in healthy as well as in depressive patients.[20] The study results revealed that the administration of buspirone causes increase in cortisol levels in humans. Corticosteroid is a known cause of hyperglycemia.

Contrary to our findings, Ojha *et al*. presented the results of a randomized, double-blind placebo-controlled, crossover trial of the effect of buspirone on blood glucose levels in humans.[21] The authors reported that administration of buspirone (10 mg) produced a significant fall in postprandial blood glucose level (at 0.5 h after oral glucose load in comparison with placebo). In this study, investigators also found that there is no effect on plasma insulin level. Similar to our study, Coulie *et al*. studied the effect of 5-HT$_1$ activation on endocrinal pancreatic secretion.[26] The investigators concluded from the study that administration of buspirone inhibits fasting and postprandial endocrine pancreatic secretion in humans, probably through activation of the presynaptic 5-HT$_1$ receptor.

Administration of buspirone causes a dose-dependent increase in both epinephrine and cortisol levels, which ultimately leads to an increase in blood glucose level. Furthermore, with increasing doses of buspirone, there is probably much higher rise in epinephrine levels than insulin levels, thereby resulting in hyperglycemia which is seen at higher doses as against no effect at low and moderate doses of buspirone decreases serum glucagon-like peptide-1 levels, leading to an increase in glucagon levels.[19] Buspirone through its 5-HT$_{1A}$ agonistic activity causes inhibition of pancreatic insulin secretion, leading to hyperglycemia.[26] Buspirone causes increase in hepatic glucose output.[27]

From our study, it is clear that buspirone in low to moderate doses (10–45 mg in humans) does not affect the blood glucose levels. Our study had considered multiple doses of buspirone. Hence, from our study, it is clear that buspirone can be safely used at therapeutic doses by physicians for the treatment of anxiety disorders. However, they should be aware of the risk of acute transient hyperglycemia occurring at high dose of buspirone (96 mg in humans). However, our study failed to prove the chronic effect of buspirone on blood glucose levels. Hence, further animal studies and prospective randomized controlled trials of longer duration with buspirone need to be done to confirm our findings.

CONCLUSION

Our study concludes that buspirone in therapeutic doses does not have an effect on the blood glucose levels, while high dose causes acute significant transient hyperglycemia.

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