Pharmacodynamic Drug Interaction Study: Effect of Sertraline on the Hypoglycemic Action of Glibenclamide in Rats

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Abstract

The effect of sertraline on glibenclamide control of blood sugar level was determined in normoglycemic and alloxanised rats. Sertraline enhanced the hypoglycemic action in a non-dose dependent fashion in the normoglycaemic and alloxanised rats. Sertraline (40mg/kg body weight) was more effective in the enhancement of blood sugar lowering effect of glibenclamide than glibenclamide alone and glibeclamide-sertraline (80mg/kg body weight). Although sertraline enhanced the blood hypoglycemic activity of glibenclamide in rats the clinical significance of the study is not yet known.

Keywords: Normoglycaemic, Alloxanized, Sertraline and Glibenclamide.

Introduction

Diabetes mellitus is a metabolic disease caused by either a deficiency in pancreatic insulin secretion or impaired tissue responsiveness to insulin, or through both ways. It affects diverse organs producing its long-term complications. The patients are often prone to cardiovascular system disorders as micro and macro-angiopathies, atherosclerosis, congestive heart failure and hypertension (Yusuf et al, 1996) and neuropathy (Frier et al, 1999; Judd et al, 1999).

Most diabetic patients are depressed because of the constellation of complications, particularly the pains associated with neuropathy that increase with age and duration of diabetes (Joss, 1999;Hilz et al, 2000;Wilkinson, 2000): this neuropathy may cause decrease in pain perception that can lead to undetected trauma and subsequent infection that may warrant amputation to check the ulcer or gangrene spread in the patients system.

Treatment of diabetic neuropathy is aimed at relieving discomfort, depression and preventing further tissue damage by tight glycemic control since high blood glucose level and rapid glucose concentrations fluctuation may decrease the pain threshold (Joss, 1999). Discomfort, anxiety, social phobia and depression, associated with diabetes, as a chronic ailment, carry significant mortality rate because they predispose most patients to non-compliance to their therapy. The precipitated neuropathy and depression is commonly managed with antidepressants, both tricyclic and Selective Serotonin Re-uptake inhibitors (Ross, 1996; Martha and John 2000). The Selective Serotonin Re-uptake inhibitors group has become the most widely prescribed antidepressants for patients because of their safety and high tolerability.(Zongo et al,1994;Mycek et al,2000)

The effects of some tricyclic antidepressants and Selective Serotonin Re-uptake inhibitors on blood sugar level patients when used alone or in combination with sulphonylureas have been documented (John and Tiller, 1999;Kastrup, 1997). So far, no work on the effect of Sertraline, a Selective Serotonin Re-uptake inhibitor on blood sugar level when co-administered with sulphonylurea has been found in literature. This study, therefore, has been designed to understudy the effect of sertraline on glibenclamide control of blood sugar level using animal model.

Material and Methods

Drugs: Glibenclamide, 5 mg (Daonil® NGC Nigeria) tablets were weighed and crushed, and dissolved in distilled water (5mg/ml) and orally administered. Sertraline (Zoloft®, Pfizer, Paris) capsules were dissolved in distilled water (50mg/ml) and orally administered at 40mg/kg body weight and 80mg/kg body weight. These drugs solutions were administered immediately they were prepared to avoid degradation. Alloxan monohydrate (Sigma, USA), 400mg was dissolved in 5ml of normal saline and

Table 1: Effect of Sertraline on glibenclamide treated normoglycaemic rats

Group	Meaning fasting blood sugar level (mg%) (MFBSL)					% Max.
	0 h	1 h	3 h	6 h	10 h	Reduction
A	54.67±2.73	51.01±2.52	45.33±0.33	39.00±1.15	34.67±0.03	34.29
B	57.01±2.08	64.67±1.33	47.67±2.73	36.33±2.70*	44.32±3.21	36.30
C	50.00±1.01	53.67±4.91	49.01±1.53	40.01±1.76*	39.33±3.84*	24.73

*A, glibenclamide (2 mg/kg); B, glibenclamide (2 mg/kg) + sertraline (40 mg/kg); C, glibenclamide (2 mg/kg) + sertraline (80 mg/kg); Values are expressed in mean ± SEM. * P< 0.05 Vs 0 hr (n = 6)*

Table 2: Effect of sertraline on glibenclamide treated alloxanized rats

	Meaning fasting blood sugar level (mg%) (MFBSL)					% Max.
Group	0 h	1 h	3 h	6 h	10 h	Reduction
A	124.33±2.01	129±6.30	121.67±3.22	114.60±9.02	106.56±8.4*	28.8
B	130.14±4.6	132.61±1.80	125.33±5.01	119.31±5.61	105.42±5.63*	35.9
C	109±1.78	113.1±1.21	107.27±2.67	89.01±2.52	92.33±2.80	31.7

A, glibenclamide (2 mg/kg); B, glibenclamide (2 mg/kg) + sertraline (40 mg/kg); C, glibenclamide (2 mg/kg) + sertraline (80 mg/kg); Values are expressed in mean ± SEM.; P< 0.05 Vs 0 hr (n = 6)*

administered (120mg/kg body weight) intra-peritoneally.

Animals: White albino rats of both sexes (113-150g, body weight) bred and housed in the animal house of Department of Pharmacology and Toxicology, University of Nigeria, Nsukka were used. The animals were kept to acclimatize with laboratory condition for 7 days with free access to water and food before the experiments.

Effect of sertraline on glibenclamide control of blood sugar level in normoglycaemic rats: Twelve Albino rats of 113-150g body weights were fasted for 12 h but had free access to water before and throughout the duration of the experiment. After the 12 h fasting period, blood sample was withdrawn from the tail vein of the rats and blood sugar level determined using the glucose and oxygen reaction in the presence of glucose oxidase principle (One Touch Glucose meter, Life scan®, USA).

The rats were divided into three groups of four rats per group. Group A received 2 mg/kg of glibenclamide only; Group B received sertraline, 40 mg/kg, and glibenclamide, 2 mg/kg, and Group C received Sertraline, 80 mg/kg, and glibenclamide, 2 mg/kg. The sertraline was administered 1 h before glibenclamide in all the combination therapy groups. All drugs were administered orally and blood samples withdrawn at 0, 1, 3, 6 and 10h from the rats and blood sugar levels determined accordingly (Obatomi et al, 1994).

Effects of Sertraline on glibenclamide control of blood sugar level in Alloxanized rats: Albino rats (113-150 g) from the normoglycemic group were fasted for 12 h but had free access to water, after 4 weeks of recovery from the previous experiment. Their blood samples were obtained and blood sugar levels determined and those rats with blood sugar levels of 60-80 mg% after 12 h of fasting were used for the experiment.

The rats were made diabetic by injecting alloxan monohydrate 120mg/kg intraperitoneally. The animals were fed for 7 days. On the day 8 the rats were fasted for 12 h and their blood sugar levels determined as before. The animals were divided into three groups of four animals per group and dosed as in normoglycemic animal experiment though the treatment was given on the day 9. The blood samples were collected at intervals 0, 1, 3, 6 and 10 h and blood sugar level determined as above. These were continued on weekly interval for 3 weeks according to (Obatomi et al, 1994).

Statistical Analysis: Mean blood sugar levels were expressed in mean SEM, and the significance of difference between the blood sugar levels at Zero time and other time intervals in each treatment group, and the Sertraline treated groups and the glibenclamide alone were analyzed using student's t-test ($p < 0.05$).

Results

From the effect of the different doses of sertraline on the glibenclamide control of

mean fasting blood sugar levels of both normal and alloxanized rats, the glibenclamide-sertraline (40 mg/kg) combination had higher maximal percentage reduction of 36.30% in normoglycemic and 35.9% in hyperglycemic than glibenclamide – sertraline (80 mg/kg) combination of 24.73% in normaglycemic and 31.7% in hyperglycemic rats.

In normoglycaemic rats, the glibenclamide-sertraline (40 mg/kg) combination caused a significant ($P< 0.05$) lowering of mean fasting blood sugar level from 57.01 mg/dl at zero time to 36.33 mg/dl after 6 h while the glibenclamide-sertraline (80 mg/kg) combination caused lowering of mean fasting blood sugar level from 50.0 mg/dl at zero time to 39.33 mg/dl at 10 h. (Table 1).

In alloxanized rats, glibenclamide-sertraline (40 mg/kg) combination lowered the mean fasting blood sugar level from 130.14 mg/dl at zero time to 105.42 mg/dl at 10 h while glibenclamide-sertraline (80 mg/kg) lowered the sugar level from 109mg/dl to 89.01 mg/dl at 6 h. (Table 2). Both dose combinations of glibenclamide-sertraline had higher percentage maximal reduction of mean fasting blood sugar than the glibenclamide alone.

From Fig. 1, the continual administration of the dose combinations of sertraline and glibenclamide for 3 weeks did not show much difference on the mean fasting blood sugar level at the 21st day of daily treatment with the drugs.

Discussion

Glibenclamide, a sulphonylurea, has both pancreatic and extra-pancreatic ways of lowering blood sugar level especially in patients with viable Beta cells (Wilkinson, 2000; Zongo et al, 1994; Obatomi et al, 1994). In the normoglycaemic rats, the Beta cells were viable and glibenclamide showed significant percentage maximal reduction of blood sugar level when compared to the alloxanized rats on the same dose of glibenclamide. The enhanced blood sugar reduction by glibenclamide when co-administered with sertraline showed a degree of drug interaction though was not dose related.

Alloxan is known to permanently destroy the Beta-cells of the pancreaticcells (Yusuf *et al*, 1996; Esimone *et al*, 2000) but in the alloxanized rats, glibenclamide caused decrease in mean fasting blood sugar level, which is indicative of extra-pancreatic mode of action (Yusuf *et al* 1996; Obatomi *et al* 1994)

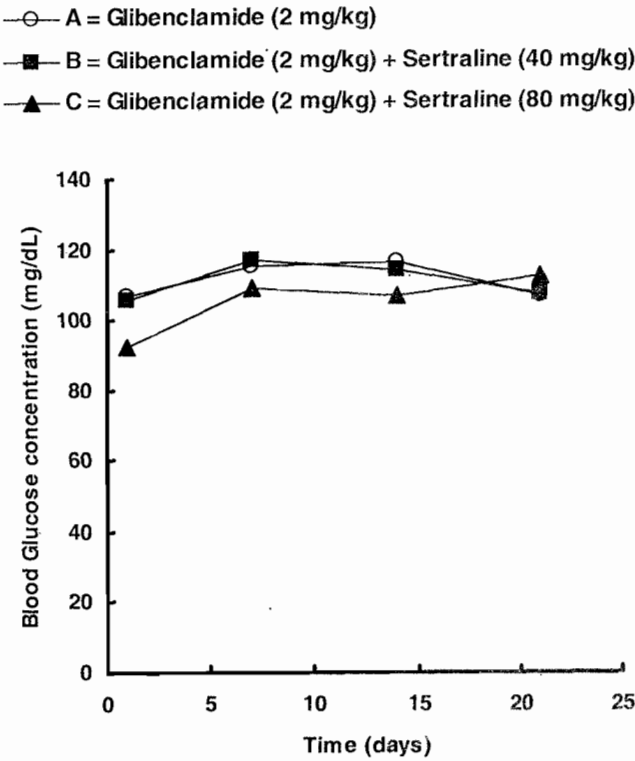

Fig. 1: Long-term effect of sertraline on glibenclamide blood sugar level control in hyperglycemic rats

The percentage maximal reduction of blood sugar levels by glibenclamide in the alloxanized rats were enhanced by sertraline in both doses. Sertraline enhances the accumulation of serotonin, which is known to decrease blood sugar level (Yusuf *et al*, 1996; Heidi *et al*, 2000). Thus, the enhancement of the glibenclamide percentage maximal reduction of blood sugar levels may have resulted from serotonin increment in the blood of the alloxanized rats, inhibition of glibenclamide metabolism and clearance by sertraline (Zongo *et al* 1994;John and Tiller, 1999) or through the displacement of glibenclamide from the protein-binding site (Winteri, 1992). All these ways may have enhanced the extra-pancreatic effect of the glibenclamide. This enhancement effect of the sertraline on glibenclamide hypoglycemic activity may not be continual hence the combination may be good enough to treat depressed non-insulin

dependent diabetics without fear of excessive hypoglycemic effect.

This study has shown that sertraline enhance the hypoglycemic effect of glibenclamide. The clinical significance of this interaction has not been determined but precaution needs to be taken when the need to use these drugs together arises.

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