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Original Research Article

Amitriptyline and Sertraline in Diabetic Neuropathy: A Comparative View

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Abstract

Purpose: *To investigate the effect of amitriptyline (Ami) and sertraline (Sert) in diabetes neuropathy.*
Methods*: Diabetes was induced in 3 groups of rats (n=6) with streptozotocin (STZ, 55mg/kg, i.p.). Two of the groups of diabetic rats received amitriptyline (15 mg/kg, p.o) and sertraline (30 mg/kg, p.o.) while another 2 groups (n=6) received the same drug treatment without prior administration of STZ. A normal group (n=6) of rats and STZ-induced group (n=6) of diabetic rats served as controls. The blood glucose, glycosylated hemoglobin (GHb), pain sensitivity and neuromuscular strength in all the rats were determined.*
Results: *Ami (15mg/kg, p.o.) produced severe hyperglycemia ($p < 0.01$) whereas Sert (30mg/kg, p.o.) produced significant hypoglycaemia in the diabetic rats. Ami significantly increased the GHb% level while Sert had no significant effect. Both Ami and Sert raised the grip strength that was significantly reduced by STZ. When administered for 3 weeks, Ami and Sert increased the STZ induced reduction of the grip strength in the diabetic rats ($p< 0.01$). STZ (55mg/kg, i.p) increased the pain sensitivity. Pain sensitivity was significantly reduced by Ami (15 mg/kg, p.o, administered for 3 weeks) in the diabetic rats but marginally reduced in the normal group. However 3-week administration of Sert (30 mg/kg, p.o.) significantly reduced the pain sensitivity in both the diabetic and normal rats ($p < 0.01$) when compared with STZ treated group.*
Conclusion: *Sertraline could offer a good choice in the treatment of diabetic neuropathy particularly in patients with depression being treated with amitriptyline.*

Keywords: *Amitriptyline; sertraline; diabetic neuropathy; glycosylated haemoglobin (GHb); streptozotocin-induced diabetes.*

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Introduction

Diabetic neuropathy is a peripheral nerve disorder caused by diabetes. The symptoms of diabetic neuropathy are often slight at first but can occasionally flare up suddenly and affect specific nerves so that an affected individual will develop double vision, drooping eyelids, or weakness and atrophy of the thigh muscles[1]. Nerve damage caused by diabetes generally occurs over a period of years and may lead to problems with the digestive tract and sexual organs, which can cause indigestion, diarrhea or constipation, dizziness, bladder infections, and impotence[2].

The main risk factor for diabetic neuropathy is hyperglycemia. It is important to note that people with diabetes are more likely to develop symptoms relating to peripheral neuropathy as the excess glucose in the blood results in a condition known as Glucojasinogen. This condition is affiliated with erectile dysfunction and epigastric tenderness which in turn results in lack of blood flow to the peripheral intrapectine nerves which govern the movement of the arms and legs. In a Diabetes Control and Complications Trial conducted in 1995[3], the annual incidence of neuropathy was 2% per year, but dropped to 0.56% with intensive treatment of Type 1 diabetics. The progression of neuropathy is dependent on the degree of glycemic control in both Type 1 and Type 2 diabetes. Duration of diabetes, age, cigarette smoking, hypertension, height and hyperlipidemia are also risk factors for diabetic neuropathy[4].

Diabetes is the leading known cause of neuropathy in developed countries, and neuropathy is the most common complication and greatest source of morbidity and mortality in diabetes patients. It is estimated that the prevalence of neuropathy in diabetic patients is approximately 20%. Diabetic neuropathy is implicated in 50-75% of non-traumatic amputations[5, 6]. Generally, the largest cases of neuropathy in patients (referred to as idiopathic in origin) are of unknown causes. Of the roughly 100 known causes, diabetes is by far the largest. Other known causes include genetic factors, damaging chemical agents such as chemotherapy drugs, and HIV.

Since diabetic neuropathy is not clearly understood, it is hard to make a definitive course of treatment[7] [12]. Drugs that have been used in the management of diabetic neuropathy include tricyclic antidepressants (TCA), SSRI and AED lines of medications[8]. The TCA drugs include imipramine, amitriptyline, desipramine and which help to decrease the associated pain but the side effects do not often make the patients feel any better at first. The and serotonin reuptake inhibitors (SSRI) line of medications includes fluxetine, paroxetine, sertraline and citalopram which are generally less effective than the TCA drugs and have minimal or no side effects in some patients but can cause weight gain or may make glycemic control more difficult. Antiepileptic drugs (AED) are the first lines of treatment for diabetic neuropathy and includes gabapentin and pregabalin. When administered with gabapentin, the effectiveness of amitriptyline is enhanced even though sedation and weight gain are main side effects. Nevertheless, TCA, SSRI and AED are only mainly useful in relieving the pain of neuropathy[9, 10]. Sertaline, amitriptyline and anticonvulsant drugs are used in the treatment of diabetic neuropathy but they all have side effects.

Therefore this present investigation was undertaken to investigate a possible better drug for the treatment of diabetic neuropathy.

Material and Methods

Animals

Thirty-six adult albino wistar rats weighing 150-200g were used. All animals were housed at 21±2˚C with a 12 h light/dark cycle. They were kept on amrut rat feed (Pune, India). The guidelines for the care and use of experimental animals were strictly followed and adhered to while performing all the procedures. Ethical approval was

obtained from Integral University, Lucknow, Uttar Pradesh, India Animal Ethics Committee (Reg. No. 157/1999/CPCSEA).

Drugs and reagents

Amitriptyline (Ami) and sertraline (Sert) were purchased from Intas Pharmaceutical Ltd., Ahmedabad, India. STZ was purchased from Sigma Aldrich, USA. Stock solution of STZ was freshly prepared in 0.1 M citrate buffer. Tween 80 (1%) and 0.9% normal saline were used to dissolve amitriptyline and sertraline.

Study design

The rats were divided into 6 groups (each group containing 6 rats): Group 1 received saline (0.5ml/gm body weight) and served as a control; group 2 received streptozotocin (STZ, 55 mg/kg, i.p.); group 3 received amiyriptyline (Ami, 15 mg/kg, p.o.); group 4 received sertraline (Sert, 30 mg/kg, p.o.); group 5 received STZ (55 mg/kg, i.p.) + Ami (15 mg/kg, p.o.) and group 6 received STZ (55 mg/kg, i.p) + Sert (30 mg/kg, p.o.).

Induction of diabetes IDDM

Insulin dependent diabetes mellitus (IDDM) was induced in the rats by administering streptozotocin (STZ, 55mg/kg, i.p.) prepared in 0.1 M citrate buffer, pH 4.5 for seven days. Blood glucose and glycosylated hemoglobin (GHb) of pre-diabetic and post- diabetic rats were measured using glucose kit[11].

Measurement of diabetic neuropathy by behavioral studies

A grip strength meter was used for evaluating neuromuscular strength[12]. The rats were held by the tail above the grid of a grip strength meter, moved down until its front legs grasped the grid and it was brought to an almost horizontal position. Base of the tail was then pulled following the axle of the sensor until it released the grid. The force achieved by the animal was then displayed on the screen and was recorded.

Evaluation of the effect of diabetic neuropathy on pain sensitivity and pain threshold were done by Hot Plate method[13]. The rats were placed on the hot plate (55-56 ℃) and the time until either licking or jumping occurs was recorded by a stop watch. A cut off time of 10 sec was kept to avoid damage to the paw of the animal.

Statistical analysis

Data were expressed as the mean ± SEM. For the statistical analysis of the data, group means were compared by one-way analysis of variance (ANOVA). Dunnett's T-test, was used to identify differences between groups. At 95% confidence interval, 2-tailed p value < 0.05 were considered to be statistically significant**.**

Results

Effect of Sert, Ami and STZ on blood glucose levels in normal and diabetic rats

The blood glucose levels of the rats are given in the table. The levels were stable throughout the experimental period in normal control (group I) animals whereas group 2 (STZ, 55mg/kg, i.p.) showed significant increase ($p < 0.01$). Sert (30mg/kg, p.o.) produced significant hypoglycaemia in diabetic rats and normal rat while Ami (15mg/kg, p.o.) produced severe hyperglycemia in diabetic and normal rats ($p< 0.01$).

Effect of Sert, Ami and STZ on blood glycosylated haemoglobin levels in normal and diabetic rats

The glycosylated haemoglobin percentage (GHb%) in normal and diabetic rats are shown in the table. STZ and Ami *per se* significantly increased the GHb% level when compared with normal control group. Sert per se has no significant effect, whereas Sert and Ami reduced the same in diabetic rats (although non-significant, when compared with STZ control group).

Table: Effect of Sert, Ami and STZ on blood glucose level, glycosylated haemoglobin percent, grip strength and pain sensitivity

Group	Treatment	Glucose level (mg/dl.)	Gly. hemoglobin Percent (GHb %)	Grip-Strength (Kg/Unit)	Pain-Sensitivity (Sec.)
I	Normal saline (0.5 ml/gm, B.W.)	62.6 ± 1.89**	3.7 ± 0.263**	0.571± 0.0457**	5.75 ± 0.0963
II	STZ (55 mg/kg, i.p.)	175.3 ± 2.62##	9.83 ± 0.597##	0.362 ± 0.01##	4.04 ± 0.472
III	Ami (15 mg/kg, p.o.)	139.26 ± 23.34*, # #	6.50 ± 0.355**, # #	0.699 ± 0.029**, #	5.837 ± 0.996
IV	Sert (30 mg/kg, p.o.)	65.85 ± 3.35**	5.85 ± 0.104**	0.710 ± 0.0362 **, #	7.421 ± 0.260**
V	STZ (55 mg/kg, i.p.) + Ami (15 mg/kg, p.o.)	185.87 ± 0.593# #	6.507 ± 0.203**, # #	0.690 ± 0.0367**	5.260 ± 0.348
VI	STZ (55 mg/kg, i.p.) + Sert (30 mg/kg, p.o.)	90.19 ± 6.06**	5.67 ± 0.499**, # #	0.657 ± 0.012**	6.053 ± 0.288*

n=6; values are mean ± SEM; **p < 0.01, * p< 0.05 Vs STZ control group; # # p< 0.01, # p< 0.05 Vs Normal control group.

Effect of Ami, Sert and STZ on grip strength measurement test in rats

The effects of STZ, Ami and Sert on grip strength in the rats are presented in the table. STZ significantly reduced the grip strength in rats, whereas both Ami and Sert per se raised it. When administered for 3 weeks, Ami and Sert increased the STZ induced reduction of the grip strength in diabetic rats (p< 0.01).

Effect of STZ, Ami and Sert on pain sensitivity using hot plate in rats

STZ increased the pain sensitivity and thus the pain threshold was reduced. Ami per se reduces the same marginally compared to normal control group. However in diabetic group, Ami showed greater reduction in pain sensitivity. Compared to Ami, Sert had significant reduction in the pain sensitivity in diabetic as well as normal rats (p<0.01) (Table).

Discussion

The present study characterizes the effect of amitriptyline and sertraline on blood glucose, glycosylated haemoglobin (HbA_{1C}), grip strength and pain sensitivity in diabetic and normal rats. When administered to normal and diabetic rat, amitriptyline (Ami) produced severe hyperglycemia. These results are in agreement with other reports confirming the worsening of glycaemia with Ami in diabetes[14, 15]. Such effects with Ami are due to the blockade of the uptake of monoaminergic transmitters across axoplasmic membrane[14]. On the other hand, sertraline (Sert) produced hypoglycaemic effects in non-diabetic and diabetic rats most likely related to increased insulin output, decreased gluconeogenesis and increased insulin receptor sensitivity[16]. The role of K^+ channel has also been described for the hypoglycaemic effects of sertraline[19].

We also observed the percentage of glycosylated haemoglobin on normal and diabetic rats treated with Ami and Sert for 3 weeks. STZ, Ami and Sert per se increased

the GHb %; the STZ effects were more prominent. The observed increase in the level of HbA_{1C} in diabetic control group rats might be due to the presence of excessive amounts of blood glucose. During diabetes, the excess of glucose present in blood reacts with the haemoglobin to form HbA_{1c} which has been found to be increased over a long period of time in diabetes mellitus. There is an evidence that glycation may itself induce the generation of oxygen derived free radicals in diabetic condition[15].

The diabetic rats showed significant reduction in grip strength as compared to normal rat indicating muscle weakness in diabetes. However, the treatment with Ami and Sert improved the same significantly in diabetic and normal rats.

When Ami and Sert were studied for pain sensitivity measurement, their results indicate that both the drugs produced almost complete reversal of thermal hyper-analgesia in diabetic ratsl Sert effects being more prominent[19]. Recent studies have indicated that the neurons in the spinal cord that release the neurotransmitter, 5-HT and NE from nerve endings inhibit pain transmission .[24] Accordingly, Ami and Sert might modulate the effects of NE and 5-HT which are expected to inhibit pain transmission causing a reduction in the intensity of pain. It has also been shown that hyperalgesia may be spinally mediated through NMDA receptors on the same neuron and allodynia may be spinally mediated through AMPA receptors[20]. In addition to its effect on monoamine reuptake, Ami also exert its effect by consequent changes in central amine receptor system, as well as antagonism at muscarinic, histamine, α-adrenergic, NMDA and substance P receptors[15, 21]. Ami antagonistic actions at NMDA receptors could be one of the other possible responsible factors for antihyperalgesic action.

Painful diabetic neuropathy significantly affects the quality of life; so far no ideal drug has been available for its management. In the absence of curative therapy, the main aim of the management is to provide symptomatic pain control along with good glycemic control. The mechanism of therapeutic action of Sert for pain management is also thought to be via potentiation of 5-HT and NE nervous system pathways. It is well known that promotion of central noradrenergic tone lead to activation of descending adrenergic inhibitory circuits that alleviates neuropathic pain from chronic nerve constriction injury[22]. It is also known that 5-HT causes NE release from noradrenergic nerve terminals by a receptor mechanism. In addition, 5-HT has weak sympathomimetic action, which results from its ability to interact with noradrenergic removal process[23, 24].

Our results have indicated better efficacy of Sert on pain management both in diabetic and normal rats. It would therefore be possible that Sert being selective in nature, causes the indirect release of NE and delays the release of pain producing substance. Harris et al[21] have suggested that 5-HT antagonists cause a concentration dependent inhibition on the NE release and prejunctional 5-HT heteroreceptors also regulate the release of NE. Conversely, drugs improving serotonergic neurotransmission (SSRIs, 5-HT agonist) can initiate NE release that stimulate sympathetic activity, hence decrease in pain.

A perusal of our study indicates that Sert has better effects as compared to Ami. While Ami has been found to be hyperglycaemic, Sert produces hypoglycaemic actions making it more useful in diabetic conditions. It has also been found better on pain sensitivity as compared to Ami. Literature supports that Ami treatment is associated with sedation, urinary retention and other anticholinergic effects, hence the use of Sert for pain management in diabetic neuropathy could be more beneficial.

Conclusion

From the present study it can be concluded that sertraline could offer a better choice in the treatment of diabetic neuropathy

particularly in patients with depression on amitriptyline

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