

# Effects of Rosiglitazone and Acarbose (with and without Cornstarch Diet) on Serum Electrolytes in Diabetic Rats

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## ABSTRACT

The purpose of this study is to highlight potential risks associated with the use of oral hypoglycemics as monotherapy in treatment of type 2 diabetes mellitus. For this study 40 Wistar albino rats were equally divided into four groups. Group I served as diabetic control and II, III and IV were treated with acarbose with regular diet, acarbose with cooked cornstarch diet and rosiglitazone respectively. Diabetes was induced with a single dose of alloxan monohydrate IP at a dose of 150 mg/kg body weight. Drug samples were administered orally for a period of 4 weeks and effects of the drugs were studied on day 7, 15 and 30 for serum level of sodium and potassium. Results showed decrease in sodium and potassium level in all treated groups on day 7. On day 30 levels were increased in group II and IV but decreased significantly in group III. It has been concluded that chronic doses of rosiglitazone and acarbose with regular diet may cause abnormal levels of electrolytes which may cause irregular cardiac contractility. Administration of acarbose with cornstarch diet may be beneficial in regulating cardiac contractility.

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## INTRODUCTION

Metabolic disturbances in diabetes mellitus are frequently accompanied with electrolyte imbalances and thought to be responsible for the development of neuropathy, nephropathy and vascular diseases. Saito *et al.* (1999) reported that impaired insulin function in diabetes mellitus results in an inverse relationship between serum sodium and potassium levels which may be based on the movement of electrolytes between intra and extra cellular space. Previous studies showed that chronic use of oral hypoglycemics caused hepatic, renal and cardiovascular effects which prompted us to further investigate the effects of

acarbose and rosiglitazone on serum electrolytes. This study was aimed to evaluate the electrolyte homeostasis during the progression of diabetes mellitus and to highlight potential risks associated with prolonged use of acarbose and rosiglitazone as monotherapy in treatment of type 2 diabetes mellitus. In 1986, Glick *et al* reported that cooked cornstarch diet is very helpful in minimizing GI adverse effects associated with acarbose therapy. In our present study we have evaluated the effects of resistant starch diet in electrolyte homeostasis when administered along with acarbose and compared with rosiglitazone. Acarbose is metabolized within the gastrointestinal tract and is completely excreted by the kidneys. The recommended initial acarbose dose is 25 mg orally t.i.d. with the first bite of each meal. The most common side effects with acarbose therapy are abdominal pain, diarrhea and flatulence and increase in liver enzymes (Hoffmann and Spengler, 1997).

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Rosiglitazone is extensively metabolized in the liver and excreted through kidneys. It may be administered at a starting dose of 4 mg daily. Plasma rosiglitazone concentrations may be significantly increased in patients with pre-existing hepatic impairment (Avandia package insert, 2000).

## MATERIALS AND METHODS

### Selection of animal & treatment

The present study was carried out on 40 adult albino rats (either sex) of Wistar strain weighing 200-300 gram. Animals bred locally in animal house of Department of Pharmacology, University of Karachi, were used in this study. The animals were housed in iron cages as groups of 3 animals per cage. Before induction of diabetes and administration of drugs the animals were fed on regular rat pellet diet and water ad libitum. One of the groups was fed with cooked cornstarch diet.

Animals were handled as per specifications provided in Helsinki Resolution 1964 and study is approved by our Board of Advanced Studies and Research vide Resol. No. 12(30) dated: 14-04-2010.

### Induction of diabetes

To induce diabetes, animals were injected with a single dose of freshly prepared aqueous solution of alloxan monohydrate (intraperitoneally at a dose of 150mg/kg body weight ( Rao *et al.*, 2001). Since alloxan is capable of producing total hypoglycemia as a result of massive pancreatic insulin release, the rats were kept for the next 24 hours on 5% glucose solution orally (Gupta *et al.*, 1984). Controlled rats treated identically and served as diabetic control. After 48 hours, the blood samples were drawn in order to ensure that hyperglycemia has been induced. Blood glucose levels were determined by using a portable glucose analyzer (Abbott Medisense Optium Blood Glucose analyser). The levels of blood glucose considered to be normal ranges from 50-135mg /dl. Animals with glucose levels >200mg/dl were considered as diabetic and selected for experimental study (Pari and Maheswari, 1999).

### Preparation of Diet

The animals were kept on regular rat pallet diet .Since flatulence, diarrhea and GI distention are major adverse effects associated with acarbose therapy, one of the groups was fed on cooked cornstarch diet to minimize these effects (Glick *et al.*, 1986). Cooked cornstarch diet was prepared by the method described by Miller (1978) in her study using corn starch as a source of carbohydrate and no sugars.

### Experimental protocol

The animals were divided into 4 groups of 10 animals each:

- Group I was alloxan treated (served as diabetic control).
- Group II was acarbose with regular diet treated at a dose of 1.66 mg/kg/three times a day.

- Group III was acarbose with cooked cornstarch diet treated at a dose of 1.66 mg/kg/three times a day.
- Group IV was rosiglitazone treated at a dose of 0.034 mg/kg/ twice a day.

The doses of acarbose and rosiglitazone were prepared in distilled water in concentration of 50 mg/5 ml and 2mg/2ml respectively by serial dilution method. The control group animals were given distilled water only. Diabetic rats were subjected to drug treatment on the 2<sup>nd</sup> day after induction. Drug samples were administered orally for a period of total four weeks. Blood samples were collected from caudal vein of each animal and plasma/serum was separated out by centrifuging the blood samples in Humax 14 K (Germany) at 3000 RPM for 15 minutes. Effects of drugs on serum electrolytes were monitored on day 7, 15 and 30.

### Estimation of serum sodium and potassium

For estimation of serum sodium and potassium samples were sent to *Dr. Punjwani Center for Molecular Medicine and Drug Research (PCMD) diagnostic laboratory* located in H.E.J Research Institute, University of Karachi within 1 hour after collection.

## STATISTICAL ANALYSIS

Results were expressed as mean  $\pm$  SEM. Differences were statistically analyzed by one-way ANOVA, followed by Students–Newman–Keuls *post hoc* analysis. P- values < 0.005 were considered statistically significant.

## RESULTS AND DISCUSSION

It has been reported that impaired insulin action as well as hyperosmolality results in abnormalities in the movement of electrolytes between intra and extra cellular space (Saito *et al.*, 1999). Intra and extra cellular cationic homeostasis is regulated by the red cell Na<sup>+</sup>-K<sup>+</sup>-ATPase. Alterations of this transport enzyme are thought to be linked to several complications of diabetes mellitus. Totan and Greaby (2002) reported decreased Na<sup>+</sup>-K<sup>+</sup>-ATPase activity in diabetic animals in various tissues including erythrocytes. A decrease in this enzyme activity has been implicated in the pathogenesis of diabetes neuropathy, nephropathy and vascular diseases in humans. Recently, Shahid *et al.* (2005) reported that Na<sup>+</sup>-K<sup>+</sup>-ATPase dysfunction results in significant increase in serum potassium and calcium levels whereas serum sodium were significantly decreased in diabetic patients.

Results of our present study showed a non significant decrease in serum sodium levels in group IV on day 7 and 15 (table #1). Potassium levels were also decreased on day 7 then increased (p<0.001) after 15 days in the same group (table #2). However, there was a significant rise in sodium (p<0.005) and potassium levels (p<0.001) after prolonged administration of rosiglitazone (table # 1, 2).

**Table. 1:** Effect of drugs on serum sodium level.

Groups	Serum sodium mEq/L					
	Day 7		Day 15		Day 30	
	Mean ± S.E	P	Mean ± S.E	P	Mean ± S.E	P
I	145.40±3.98	-	148.09±2.84	-	140.90±3.48	-
II	136.80±3.85	0.0001	146.42±4.24	0.32	146.30±3.33	0.0025
III	139.00±4.00	0.0023	137.09±4.29	0.0000	135.80±3.43	0.0042
IV	141.80±4.53	0.062	147.42±4.48	0.7	145.90±3.48	0.0048

Values are mean ± S.E. (n=10). Significant differences by Newman-Keuls test \*p<0.005, \*\*p<0.0025 and \*\*\* p<0.001 as compared to control rats, following one-way ANOVA df(3,39).

**Table. 2:** Effect of drugs on serum potassium level.

Groups	Serum potassium mEq/L					
	Day 7		Day 15		Day 30	
	Mean ± S.E	P	Mean ± S.E	P	Mean ± S.E	P
I	7.06±0.45	-	7.06±0.27	-	6.85±0.30	-
II	5.94±0.64	0.0004	7.19±0.58	0.52	8.99±0.38	0.0000
III	6.01±0.43	0.0001	5.67±0.46	0.0000	5.86±0.32	0.0000
IV	6.95±0.42	0.58	7.80±0.29	0.0000	7.94±0.39	0.0000

Values are mean ± S.E. (n=10). Significant differences by Newman-Keuls test \*p<0.005, \*\*p<0.0025 and \*\*\* p<0.001 as compared to control rats, following one-way ANOVA df(3,39).

Mechanism which may be involved is explained by Guan et al. (2005) and Zhang et al. (2005) that PPAR- $\gamma$  agonists upregulate the collecting duct sodium channel (ENaC) and stimulate active sodium transport in this nephron segment. The above findings also complemented by the study of Chen et al. (2005) that in the renal medulla PPAR- $\gamma$  agonists increase the expression of the ENaC as well as transcellular sodium transport such as Na,K-ATPase. Results of our present study are in accordance to pioneer studies. A consensus statement was published simultaneously in *Circulation* and *Diabetes Care* from the American Heart Association and the American Diabetes Association that thiazolidinediones use is associated with fluid retention and thus increases the risk of congestive heart failure in diabetic patients (Nesto *et al.*, 2003) and is characterised by raised cytosolic levels of Na<sup>+</sup>, Na<sup>+</sup>-K<sup>+</sup> pump inhibition and diastolic dysfunction. Raised cytosolic levels of Na<sup>+</sup> may contribute to removal of cytosolic Ca<sup>2+</sup> via Na<sup>+</sup>-Ca<sup>2+</sup> exchange and hence to diastolic relaxation (Weber and Piacentino, 2003).

In the present study when acarbose was administered with regular diet (Group II) it showed a significantly decreased sodium level (p<0.001) on day 7 (table #1). The level was found to be decreased on day 15 but not significantly and then maintained on the same level (p≤ 0.0025) on 30<sup>th</sup> day (table #1). Significant decrease in the potassium level (p<0.001) was observed on day 7 in the same group and then increased significantly (p<0.001) on long run (table #2). The probable mechanism involved being the restored Na<sup>+</sup>-K<sup>+</sup>-ATPase and insulin function.

However, results of acarbose when administered with cornstarch diet (Group III) showed a significant reduction in serum sodium as well as potassium levels. Decrease in sodium level is thought to be due to Na<sup>+</sup>-K<sup>+</sup>-ATPase dysfunction, impaired insulin action as well as hyperosmolality (Shahid *et al.*, 2005) as discussed above. Decrease in serum potassium level may be through transport of potassium inside due to better insulin release and glycemic control. This effect need to be further investigated.

## CONCLUSION

The above results suggest that there may be progression in electrolyte abnormalities in diabetes mellitus leading to end stage renal disease along with the abnormality of their chief transport mechanism. It also shows the potentiality of electrolytes disturbances as indicators for the progression of diabetic nephropathy and also beneficial in prognosis and treatment of the disease.

Based on our current findings it has been concluded that treatment of type 2 diabetes mellitus with acarbose is more beneficial when it is administered with cooked cornstarch diet as indicated by significant reduction in serum sodium and potassium levels in group III. Chronic doses of rosiglitazone (group IV) and acarbose (group II) may cause abnormal levels of electrolytes. Increased serum level of potassium with rosiglitazone and acarbose when administered with regular diet may depresses cardiac contractility, automaticity, conductivity and excitability leading to ECG changes, which may not be the beneficial effect of acarbose therapy in type 2 diabetes mellitus. Administration of acarbose with cornstarch diet may be beneficial in regulating cardiac contractility and therefore suggested that other serum electrolytes e.g. magnesium and calcium should also be monitored in diabetic patients when treated with acarbose.

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