Pharmacodynamic Drug Interaction of Metformin with Statins in Rats

N. Anitha, J.V. Rao, S. Kavimani and V. Himabindu,
1Department of Pharmacology, Sultan-ul-Uloom College of Pharmacy, Hyderabad, Andra Pradesh, India
2Sultan-ul-Uloom College of Pharmacy, Hyderabad, Andra Pradesh, India
3Department of Pharmacology, Mother Theresa Institute of Health Sciences, Pondicherry, Tamil Nadu, India
4Department of Environmental Science, Jawaharlal Nehru Technological University, Hyderabad, Andra Pradesh, India

Abstract: The present study is aimed to explore the pharmacodynamic interaction of metformin with statins like atorvastatin and rosuvastatin in rats. Wistar albino rats of either sex (150-200 g) were induced diabetes by administering alloxan and they were divided into six groups, each consisting of six rats. Normal control group (1) is treated with 1% w/v carboxy methyl cellulose (CMC) suspension. Group 2 served as diabetic control. To the diabetic 3rd, 4th and 5th group metformin, atorvastatin and rosuvastatin were administered orally respectively for 7 days. The combination of metformin + atorvastatin and metformin + rosuvastatin were administered to the 6th and 7th group of diabetic rats for 7 days. On the last day blood samples were collected, serum was isolated and subjected to glucose, triglycerides (TG), total cholesterol (TC), low density lipoprotein (LDL) and high density lipoprotein (HDL) estimation. Body weight was also calculated. Metformin significantly reduced the serum glucose level in diabetic rats. Atorvastatin and rosuvastatin produced mild hypoglycemia. On the other hand the combination of metformin + atorvastatin and metformin + rosuvastatin significantly reduced the serum glucose level when compared to metformin alone. Atorvastatin and rosuvastatin significantly reduced the serum TG, TC and LDL and increased HDL level. Metformin also altered the lipid profile of diabetic rats. Whereas the combination of metformin + atorvastatin and metformin + rosuvastatin significantly reduced the lipid profile when compared to atorvastatin and rosuvastatin alone. The combination of drugs also increased the body weight of diabetic animals. The antidiabetic drug metformin enhanced the hypolipidemic activity of atorvastatin and rosuvastatin. Similarly atorvastatin and rosuvastatin enhanced the hypoglycemic activity of metformin due to pharmacodynamic interactions.

Key words: Diabetes, hyperlipidaemia, pharmacodynamic, drug-drug interactions, hypoglycemic activity, lipid profile

INTRODUCTION

Diabetes is a group of syndromes characterized by hyperglycemia, altered metabolism of lipids, carbohydrates and proteins and an increased risk of complications from vascular diseases. Among diabetics, approximately 95% of patients have type 2 diabetes mellitus (DM), whereas about 5% of patients have type 1 diabetes mellitus (DM). Patients with DM are at risk for microvascular complications like retinopathy, nephropathy and neuropathy and macrovascular complications like myocardial infarction that increase morbidity and mortality (Cerveny et al., 1998).
Polypharmacy and multiple drug therapy assume importance in present day clinical practice, since newer molecules are invented everyday and newer challenges face clinicians in managing either a single diseases or simultaneously occurring different diseases. According to one report, the drug interactions may be fourth to sixth leading cause of death in United States (Yuan et al., 1999). Hence the metabolic drug interaction between drugs is a major concern for the health care professionals and their patients. As per one survey, the incidence of drug–drug interaction range from 3 to 5% in patients taking a few drugs to 20% in patients receiving 10 to 20 drugs (Alan and Stephen, 1996). Hence it is necessary to understand and establish such interactions in clinical practice. The clinical observations are very vital in noting the interactions of drugs, but to study the mechanisms of such interactions clinical studies cannot be carried out using human models. Hence animal model studies help in understanding the underlying mechanisms in drug interactions (Satyanarayana et al., 2007). The present study was intended for studying pharmacodynamic interactions between metformin and statins in rats since cardiovascular problems are more common in diabetics and the possibility for the simultaneous use of such combination is more.

MATERIALS AND METHODS

Wistar albino rats of either sex were procured from Sainath animal agency, Hyderabad. Prior approval by institutional ethics committee was obtained for conduct of experiments. The experiment was conducted in the Department of Pharmacology, Sultan-ul-Uloom College of Pharmacy, Hyderabad during the period of January-2008.

Glucose kit (GOD/POD method), total cholesterol (Enzymatic method), HDL cholesterol (Precipitation and Enzymatic method) and triglycerides (Enzymatic method) kits manufactured by Sigma Diagnostics (India) Pvt. Ltd. Baroda were procured from Qualigens Fine Chemicals, Mumbai.

Metformin, atorvastatin and rosuvastatin were procured as gift sample from Dr. Reddy’s Laboratories, Hyderabad.

Alloxan and CMC were purchased from S.D. Fine Chemicals.

Animal

Wistar albino rats of either sex weighing 150-200 g were used for the studies. They were fed a standard rat pellet and water ad libitum and maintained under standard laboratory conditions. Animals described as fasted were deprived of food for 18 h but had free access to water.

Alloxan Induced Diabetic Rats

The fasted rats were injected with alloxan (150 mg kg⁻¹, ip) (Dhawan et al., 1996). One group of six identical rats were kept without alloxan treatment as normal control, group 1. Five days later blood was collected from tail vein under mild ether anesthesia and blood glucose levels were determined. Rats with blood sugar level of 200-350 mg dL⁻¹ were considered as diabetic and were employed in the study (Dhanabal et al., 2004).

The diabetic rats were subdivided into five groups as follows; group 2 (diabetic control) given vehicle (1% W/V CMC); group 3 diabetic rats given metformin (100 mg kg⁻¹, orally in 1% W/V CMC); group 4 diabetic rats given atorvastatin (10 mg kg⁻¹, orally in 1% W/V CMC); group 5 diabetic rats were given rosuvastatin (20 mg kg⁻¹, orally in 1% W/V CMC). The treatment was given for seven days. To the 6th and 7th group of diabetic rats atorvastatin and rosuvastatin were administered respectively and 30 min later metformin was administered. Later from second day onwards they were treated daily with atorvastatin and rosuvastatin for six days. During this period the animals had free access to food and water. After 18 h fast on seventh day they were again given the combined treatment with atorvastatin and rosuvastatin and 30 min later Metformin. In all the groups, the blood sample was
collected after 1 h drug treatment. The serum was isolated by centrifugation of blood for 20 min at 2000 rpm and subjected to glucose (Trinder, 1969), TG (Fossati and Lorenzo, 1982), TC (Allain et al., 1974), LDL and HDL (Lopes virella et al., 1977) estimation.

Statistical Analysis

Statistical analysis was done using One Way ANOVA. The combination of metformin + atorvastatin and metformin+rosuvastatin was compared with diabetic control. A p-value <0.05 was considered significant.

RESULTS AND DISCUSSION

The body weight was slightly increased in the normal control rats, whereas in the diabetic rats there was a significant reduction in body weight is due to poor glycemir control and impaired carbohydrate metabolism. Metformin, atorvastatin, rosuvastatin* per se and in combination of metformin + atorvastatin and metformin + rosuvastatin treatment significantly prevented this reduction in the body weight of animals in these groups. Although there is a marginal reduction in the body weight of animals in these groups compared to initial body weights it fell short of statistical significance. However the reduction in the body weight was significant when compared to the final weight of normal control rats (Table 1).

Diabetic rats showed increase in serum glucose levels than control. Serum glucose levels showed a reversal near to control values by treatment with metformin. On the other hand the treatment with atorvastatin and rosuvastatin slightly decreased the serum glucose level but it lacks statistical significance. Whereas treatment with combination of metformin + atorvastatin and metformin+rosuvastatin decreased the serum glucose concentration lower than metformin treatment per se which is statistically significant (Table 1).

Alloxan treatment not only increases blood glucose levels but also increases the levels of TG, TC and LDL in diabetic rats (Babu et al., 2002; Triveni et al., 2004). Diabetic rats showed increase in the serum levels of TG, TC and LDL and decrease HDL level when compared to control (Table 1). Atorvastatin and rosuvastatin decreased the lipid profile near to normal control, which is statistically significant. Metformin also slightly altered the lipid profile. On the other hand the treatment with combination of metformin + atorvastatin and metformin + rosuvastatin on diabetic rats decreased serum TG ,TC and LDL levels and increased HDL levels than atorvastatin and rosuvastatin per se treatment, which is statistically significant.

In the present study all the drugs increased the body weight of diabetic rats, which was checked on 7th day of treatment. Alloxan treatment decreased the body weight, which is associated with decreased rate of glucose utilization and impaired carbohydrate metabolism. It induces diabetes by

<table>
<thead>
<tr>
<th>Body weight (g)</th>
<th>Serum glucose (mg dL⁻¹)</th>
<th>Serum lipid profile (mg dL⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Groups</td>
<td>Initial (0 day)</td>
<td>Final (7th day)</td>
</tr>
<tr>
<td>Normal control (1)</td>
<td>183.5±11.4</td>
<td>195.0±7.60</td>
</tr>
<tr>
<td>Diabetic control (2)</td>
<td>182.1±10.2</td>
<td>135.5±8.10</td>
</tr>
<tr>
<td>Metformin (3)</td>
<td>185.6±8.6</td>
<td>170.5±9.40</td>
</tr>
<tr>
<td>Atorvastatin (4)</td>
<td>188.6±10.2</td>
<td>172.5±10.3*</td>
</tr>
<tr>
<td>Rosuvastatin (5)</td>
<td>186.7±9.2</td>
<td>171.0±9.8*</td>
</tr>
<tr>
<td>Metformin+</td>
<td>187.2±10.5</td>
<td>174.0±9.2*</td>
</tr>
<tr>
<td>Metformin+</td>
<td>182.4±11.6</td>
<td>175.5±9.5*</td>
</tr>
</tbody>
</table>

*p<0.05 compared to diabetic control; **p<0.05 compared to diabetic + metformin; ***p<0.05 compared to Atorvastatin and Rosuvastatin in diabetic rats.
destroying β-cells of pancreas and the destruction is almost complete. Alloxan in addition to hyperglycemia also induces hyperlipidemia (Khan and Schechter, 1991; Khorala et al., 1995). This is one of the common complications of NIDDM.

Currently Metformin is a top selling OHA in USA (Chakrabarti and Rajagopalan, 2002). In this study metformin decreased serum glucose level near to control in diabetic rats after 7 days treatment. Treatment with atorvastatin and rosuvastatin in diabetic rats produced minor hypoglycemia which lacks statistical significant. On the other hand treatment with combination of drugs such as metformin + atorvastatin and metformin + rosuvastatin on diabetic rats reduced the serum glucose levels much lower than metformin per se treatment. It shows the pharmacodynamic interaction between metformin and statins. This interaction may increase the bioavailability of metformin and exhibit marked decrease in serum glucose level when compared to metformin alone. Hence atorvastatin and rosuvastatin enhanced the antidiabetic activity of metformin.

A marked increase in serum TG, TC and LDL levels were observed in diabetic rats. This is in agreement with findings of Nikichila and Kekki (1973). Elevation of plasma lipid concentration in diabetic rats is well documented. The lipid profile was estimated on the 7th day of treatment. Atorvastatin and rosuvastatin decreased the serum TG, TC and LDL and increased HDL levels in diabetic rats. Metformin, which is an antidiabetic drug, also reduced the serum lipids, which is in accordance with Babu et al. (2003). Whereas treatment with combination of metformin + atorvastatin and metformin + rosuvastatin significantly reduced serum TG, TC and LDL levels much lower than atorvastatin and rosuvastatin per se treatment and increased serum HDL level. It clearly indicates the pharmacodynamic interaction between metformin and statins. Hence it has been concluded that metformin significantly enhanced the hypolipidaemic activity of atorvastatin and rosuvastatin.

ACKNOWLEDGMENT

The authors are grateful to Sultan-ul-Uloom Educational Society for providing the necessary facilities to carry out the research.

REFERENCES


