STUDY OF PHARMACODYNAMIC DRUG-DRUG INTERACTION BETWEEN TOPIRAMATE AND ROSUVASTATIN

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Summary

The present study is planned to explore the pharmacodynamic drug-drug interaction between antiobesity drug Topiramate and hypolipidemic drug Rosuvastatin in rats. Wistar albino rats of either sex were induced obesity by administering cafeteria diet [CD] for 40 days and divided into 5 groups – normal control group, CD treated, CD + topiramate, CD + rosuvastatin and CD + topiramate + rosuvastatin. The animals were treated with drugs for 7 days. On 7th day 2 hours later drug administration the following parameters were recorded – body weight, organ weights, rectal temperature, locomotor activity and various biochemical parameters like serum glucose, total cholesterol (TC), triglycerides (TG), low-density lipoprotein (LDL) and high-density lipoprotein (HDL) levels. There was a significant reduction in body weight, organ weights, serum glucose, serum TC, TG, LDL and increase in body temperature, locomotor activity and HDL levels in cafeteria diet fed rats treated with the combination of topiramate + rosuvastatin than topiramate and rosuvastatin *per se* treatment. The result clearly shows that there may be pharmacodynamic interaction are possible between topiramate and rosuvastatin.

Keywords: Pharmacodynamic, polypharmacy, Drug-Drug Interaction, antiobesity, Hypolipidemic.

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Introduction

Obesity is nowadays a common and challenging health problem. It is not only a problem in itself but also a predisposing factor for many other adverse health outcomes likes non insulin dependent diabetes mellitus, insulin resistance, arteriosclerosis, dyslipidemia, cardiovascular and all cause mortality (1). Among the multiple factors contributing to etiology, the sedentary life styles, white-collar jobs, lack of exercise, psychological factors and the energy rich diets are the major ones (2,3).

To ameliorate the co-morbidities of obesity such as diabetes mellitus, hyperlipidemia and hypertension, polypharmacy and multiple drugs assume importance in present day clinical practice, since newer molecules are invented every day and newer challenges face clinicians in managing either a single disease or simultaneously occurring different disease. Due to polypharmacy drug interactions may be possible. According to one report, the drug interactions may be fourth to sixth leading cause of death in United States (4). 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 (5). 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 mechanism of such interactions, clinical studies cannot be carried out using human models. Hence animal model studies help in understanding the underlying mechanism in drug interactions (6). The present study was intended for studying pharmacodynamic interactions between topiramate and rosuvastatin in rats since cardiovascular problems are more common in obese patients and the possibility for the simultaneous use of such combination is more.

Materials and methods

Animal

Wistar albino rats of either sex weighing 150 –200 gm were used for the studies. They were fed with a standard pellet and water *ad libitum* and maintained under standard laboratory conditions. The rats were procured from Sainath animal agency, Hyderabad. Prior approval by institutional ethics committee was obtained for conduction of experiment (Ref: IAEC/SUCP/02/2007).

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 was procured from Qualigens fine chemicals Mumbai.

Rosuvastatin and Topiramate were procured as gift samples from Dr.Reddy's Laboratories, Hyderabad and Torrent Pharmaceuticals, Ahmedabad respectively.

Carboxy methylcellulose was purchased from S.D. fine chemicals.

Cafeteria diet (CD) induced obesity in rats

Obesity was induced in rats by administering Cafeteria Diet (7) (CD). The CD consisted of three diets (condensed milk 40 gm + bread 40 gm), (chocolate 15 gm +biscuit 30 gm+ dried coconut 30 gm), (cheese 40 gm + boiled potatoes 50 gm). The three diets presented to 4 groups of rats on

day 1, 2, and 3 respectively and then repeated in same succession for 40 days. These diets were provided in addition to normal pellet chow.
These obese animals were divided into 4 groups and each consisting of six rats as follows. One group of 6 identical rats was kept under normal diet as normal control group. CD group (obese control) was given vehicle (1%w/v CMC); CD fed obese rats given topiramate (0.45 mg/kg, ip in 1%w/v CMC); CD fed obese rats was given rosuvastatin (0.36 mg/kg, ip in 1%w/v CMC). This treatment was given for 7 days. To the 4^{th} group of CD fed obese animal topiramate was administered, 30 minutes later rosuvastatin was administered for 7 days. On 7^{th} day, 2 hours after drug treatment blood samples and organs were collected. Serum was isolated and subjected to glucose (8), TG (9), TC (10), LDL and HDL (11) estimation.

Parameters tested and procedures

Body weight
The body weight (gm) was recorded on day 1 and then on day 7 in each group.

Body temperature
Body temperature was recorded on day 1 and on day 7 using rectal thermometer before and after drug administration at 30, 60, 90 and 120, minutes with a contact time of 1 minute.

Locomotor activity
It was recorded on day 7, 30 min after drug treatment. The ambulatory, rearing and grooming activity of animals were recorded for a period of 5min.

Organ weights
The animals were sacrificed by cervical dislocation and then different organs like kidney, liver, heart and spleen were removed and weighed.

Statistical methods
The results are expressed as mean±SEM. Comparison between treatment groups and CD fed animals were performed by ANOVA. In all tests the criterion for statistical significance was $p<0.05$.

Results

Effect on body weight

There was a significant increase in body weight of CD fed animals when compared to control group. Treatment with topiramate and rosuvastatin *per se* and the combination of topiramate+rosuvastatin caused significant reduction in body weight when compared to CD fed animals (Table-1).

Table 1: Effect of topiramate, rosuvastatin *per se* and the combination of Topiramate+rosuvastatin treatment on body weight of CD fed rats.

S.No	Treatment	Body Weight	
		Initial (0 Day)	Final (7^{th} Day)
1.	Control	182.4 ± 2.1	193.6 ± 2.8
2.	CD	223.2 ± 3.4	231.4 ± 5.3
3.	CD + Topiramate	224.6 ± 3.7	201.8 ± 3.2*
4.	CD + Rosuvastatin	221.2 ± 4.8	198.6 ± 5.6*
5.	CD + Topiramate + Rosuvastatin	224.8 ± 5.3	197.4 ± 4.1*

*p<0.05 compared to CD fed group

Effect on organ weights

Treatment with topiramate, rosuvastatin per *se* and the combination of topiramate+rosuvastatin in CD fed animals significantly decreased the weight of kidney, liver, spleen and heart (Table-2).

Table 2: Effect of topiramate, rosuvastatin *per se* and the combination of topiramate+rosuvastatin treatment on organ weights of CD fed rats

S.No	Treatment	Kidney		Different organ weights		
		Left	Right	Heart	Spleen	Liver
1.	Control	0.65 ± 0.03	0.68 ± 0.03	0.71 ± 0.12	0.82 ± 0.04	6.29 ± 0.14
2.	CD	1.61 ± 0.04	1.69 ± 0.04	1.03 ± 0.13	1.31 ± 0.05	10.31 ± 0.08
3.	CD + Topiramate	0.82 ± 0.05*	0.91 ± 0.01*	0.85 ± 0.16*	0.91 ± 0.07*	7.12 ± 0.07*
4.	CD + Rosuvastatin	0.81 ± 0.01*	0.92 ± 0.12*	0.86 ± 0.19*	0.90 ± 0.07*	7.03 ± 0.03*
5.	CD + Topiramate + Rosuvastatin	0.82 ± 0.01*	0.83 ± 0.16*	0.80 ± 0.14*	0.84 ±0.06*	6.93 ± 0.11*

*p<0.05 compared to CD fed group

Effect on Body Temperature

CD caused defective thermogenesis. Treatment with topiramate, rosuvastatin *per se* and the combination of topiramate+rosuvastatin on CD fed animals significantly increased the body temperature. The rise in temperature was maximum at 60 and 90 min.

Table 3: Effect of topiramate, rosuvastatin *per se* and the combination of topiramate+rosuvastatin treatment on body temperature of CD fed rats

S.No	Treatment	Body Temperature at time (min)				
		0	30	60	90	180
1.	Control	36.3 ± 1.2	36.1 ± 1.3	35.7 ± 0.5	36.0 ± 0.8	36.2 ± 1.0
2.	CD	34.1 ± 2.1	34.3 ± 1.2	34.2 ± 1.6	34.8 ± 1.5	34.6 ± 1.1
3.	CD + Topiramate	34.5 ± 0.9	34.9 ± 0.8	36.2 ± 1.1*	36.8 ± 0.7*	36.3 ± 0.8
4.	CD + Rosuvastatin	34.3 ± 0.4	34.8 ± 0.8	36.8 ± 1.4*	36.7 ± 1.3*	36.1 ± 0.7
5.	CD + Topiramate + Rosuvastatin	34.4 ± 0.8	34.8 ± 0.6	36.8 ± 1.2*	36.5 ± 2.1*	36.0 ± 1.3

*p<0.05 compared to CD fed group

Effect on Locomotor activity

There was a significant increase in ambulatory, rearing and grooming activity in topiramate, rosuvastatin *per se* and the combination of topiramate+rosuvastatin treatment in CD fed animals When compared to CD group (Table 4)

Table 4: Effect of topiramate, rosuvastatin *per se* and the combination of Topiramate+rosuvastatin treatment on locomotor activity of CD fed rats.

S.No	Treatment	Locomotor Activity		
		Ambulation	Rearing	Grooming
1.	Control	65.3 ± 5.43	20.5 ± 3.65	6.8 ± 1.18
2.	CD	50.8 ± 4.89	14.1 ± 2.61	4.2 ± 2.30
3.	CD + Topiramate	68.3 ± 3.72*	26.3 ± 4.62*	7.3 ± 2.16*
4.	CD + Rosuvastatin	69.5 ± 4.31*	25.4 ± 5.36*	7.9 ± 3.42*
5.	CD + Topiramate + Rosuvastatin	69.7 ± 7.30*	27.3 ± 5.12*	7.6 ± 1.76*

*p<0.05 compared to CD fed group

Effect on biochemical parameters

Administration of CD significantly increased TC, TG, and LDL and decreased HDL levels as compared to control group. Treatment with topiramate and rosuvastatin *per se* decreased TC, TG, and LDL significantly and increased HDL levels. Moreover the combinations of topiramate+rosuvastatin decreased serum lipid profile lower than topiramate and rosuvastatin *per se* treatment, which is statistically more significant.

CD also increased serum glucose level than control. Serum glucose level showed a reversal near to control value by treatment with topiramate when compared to control. Rosuvastatin also decreased the serum glucose level but it is not significant. Whereas treatment with combination of topiramate+rosuvastatin on CD fed rats decreased the serum glucose concentration near to control, which is statistically more significant (Table 5).

Table 5: Effect of topiramate, rosuvastatin *per se* and the combination of topiramate + rosuvastatin treatment on biochemical parameters of CD fed rats.

S.No	Treatment	Biochemical Parameters				
		TC	TG	LDL	HDL	Glucose
1.	Control	139 ± 5.6	105 ± 6.2	82 ± 5.2	51 ± 6.1	106 ± 4.3
2.	CD	191 ± 5.8	173 ± 5.8	138 ± 5.3	28 ± 5.8	240 ± 6.1
3.	CD + Topiramate	165 ± 4.9	144 ± 4.8	108 ± 5.6	40 ± 5.3	212 ± 5.3
4.	CD + Rosuvastatin	163 ± 4.4	138 ± 3.6	102 ± 4.4	44 ± 4.3	214 ± 4.7
5.	CD + Topiramate + Rosuvastatin	140 ± 5.5*	109 ± 4.4*	80 ± 3.3*	55 ± 3.8*	202± 5.3*

*$p<0.05$ compared to Topiramate and rosuvastatin per se treatment.

Discussion

The CD induced obesity animal model closely resembles to human obesity (12).The results of our study showed that rats fed with variety of highly palatable, energy rich, high carbohydrate cafeteria foods elicited significant increase in body weight. CD has been previously reported to increase energy intake and cause obesity in humans (13) as well as animals (14). Further the composition (15), (16) and variety (17), (18) of cafeteria food also exerts synergistic effects on the development of obesity.

In the present study topiramate and rosuvastatin decreased the body weight, organ weight and increased the body temperature and locomotor activity on CD induced obesity rats, which was checked on 7^{th} day of treatment.

Topiramate, which is an antiepileptic drug, reduced the body weight and decreased the blood glucose levels. These findings are in accordance with Liang *et al* (19). The antihyperglycemic activity of topiramate may be due to topiramate induced glucose stimulated insulin release (20). They also observed a 1.4 fold increase of pancreatic insulin content and heightened insulin immunoassaying in pancreatic β cells in db/db mice treated with topiramate.

Some of the studies reported that topiramate reduced body weight gain and fat deposition (21). It decreased food intake acutely and increased metabolic rate. There was significant reduction in leptin. Topiramate inhibits fat deposition while reducing the activity of lipoprotein lipase in various white adipose tissues depots. In our study treatment with topiramate decreased the serum glucose level near to control after 7 days of treatment. Rosuvastatin slightly decreased the serum glucose level, which fell short of significance.

On the other hand treatment with combination of topiramate and rosuvastatin on CD induced obesity rats reduced the glucose levels near to control, which is similar to that of topiramate per se, treatment. The fall in serum glucose was due to topiramate and this effect of topiramate was not altered by rosuvastatin.
Topiramate and rosuvastatin per se treatment decreased the lipid profile. Moreover the combination of topiramate+rosuvastatin also decreased the lipid profile, which is more significant than rosuvastatin *per se*, treatment. It clearly shows there may be an additive type of interaction between the drugs.

Conclusion

The results of the above study shows that the combination of topiamate+rosuvastatin more significantly reduced the serum lipid profile and glucose concentration in CD fed animals than topiramate and rosuvastatin *per se* treatment. This clearly indicates that there may be pharmacodynamic interaction is possible between topiramate and rosuvastatin.

Acknowledgement

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

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