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Original Research Article

Study of Interaction Between Antiobesity and Hypolipidemic Drugs

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Abstract

PURPOSE: *To explore the interaction between antiobesity drug, topiramate, and hypolipidemic drug, atorvastatin, in rats.*

METHODS: *Obesity was induced in Wistar albino rats by administering cafeteria diet (CD) for 40 days and divided into 5 groups. While one group served as control, each other group received either alone or in combination with either topiramate, atorvastatin or topiramate plus atorvastatin. The animals were treated with the drugs for 7 days. On 7th day, 2 hr after drug administration, the 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 were determined. The data were analysed statistically.*

RESULTS: *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 and atorvastatin when compared with those treated with topiramate and atorvastatin alone.*

CONCLUSION: *There is interaction between topiramate and atorvastatin when administered together.*

Keywords: *Antiobesity drugs; Atorvastatin; Drug interaction; Hypolipidemic; Topiramate.*

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Introduction

Obesity is nowadays a common and challenging health problem. It is a predisposing factor for many other adverse health outcomes including non-insulin dependent diabetes mellitus, insulin resistance, arteriosclerosis, dyslipidemia, and cardiovascular diseases[1]. Among the multiple factors contributing to the 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. In a 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]. It is therefore necessary to understand and establish such interactions in clinical practice. Although clinical observations are very vital in noting the interactions of drugs, clinical studies cannot be carried out using human models to study the mechanism of such interactions, Hence animal model studies help in understanding the underlying mechanism in drug interactions[6].

The present study was intended to study the pharmacodynamic interactions between topiramate and atorvastatin in rats.

Experimental

Animal

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

Chemical and reagents

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, India. Atorvastatin and topiramate were obtained as gift samples from Dr.Reddy's Laboratories, Hyderabad and Torrent Pharmaceuticals, Ahmedabad respectively. Alloxan monohydrate and Carboxymethylcellulose were purchased from S.D. Fine Chemicals, India.

Study design

Obesity was induced in rats by administering Cafeteria Diet (CD)[7]. The CD consisted of three diets, namely 40 g of condensed milk plus 40 g of bread, (15 g of chocolate plus 30 g of biscuit plus 30g of dried coconut, and 40 g of cheese plus 50 g of boiled potatoes. Four groups of rats were fed on day 1, 2, and 3, respectively, with the three diets and then repeated in succession for 40 days. These diets were provided in addition to normal pellet chow.

The obese animals were divided into 4 groups and each consisting of 6 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 was given topiramate (0.45 mg/kg, ip in 1%w/v CMC); CD fed obese rats was given atorvastatin (0.36 mg/kg, ip in 1%w/v CMC). This treatment was given for 7 days. To the 4th group of CD fed obese animal, topiramate was administered and 30 min later, atorvastatin was administered for 7 days. On 7th day, 2 hr after drug treatment, blood samples were collected. Serum was isolated and subjected to glucose[8], *triglycerides (TG)*[9], *total cholesterol (TC)*[10], *low-density lipoprotein (LDL) and high-density lipoprotein (HDL)*[11] estimation.

The body weight (gm) was recorded on day 1 and then on day 7 in each group. 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 min with a contact time of 1 min. Locomotor activity was recorded on day 7, 30 min after drug treatment. The ambulatory, rearing and grooming activity of animals were recorded for a period of 5 min.

The animals were sacrificed on day 7 by cervical dislocation and the different organs like kidney, liver, heart and spleen were removed and weighed.

Statistical methods

Estimates were made in duplicates and all results are expressed as mean±SEM. Comparison between treatment groups and CD fed animals were performed using ANOVA. At 95% confidence interval, 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 atorvastatin *per se* and the combination of topiramate+atorvastatin caused significant reduction in body weight when compared to CD fed animals (Table 1).

Effect on organ weights

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

Effect on Body Temperature

CD caused defective thermogenesis. Treatment with topiramate, atorvastatin *per se* and the combination of topiramate + atorvastatin on cafeteria diet (CD) fed animals significantly increased the body temperature. The rise in temperature was maximum at 60 and 90 min (Table 3).

Table 1: Effect of topiramate, atorvastatin *per se* and the combination of Topiramate+atorvastatin treatment on body weight of cafeteria diet (CD) fed rats

Treatment	Body Weight	
	Initial (0 Day)	Final (7th Day)
Control	182.4 ± 2.1	193.6 ± 2.8
CD	223.2 ± 3.4	231.4 ± 5.3
CD + Topiramate	224.6 ± 3.7	201.8 ± 3.2*
CD + Atorvastatin	221.2 ± 4.8	198.6 ± 5.6*
CD + Topiramate + Atorvastatin	224.8 ± 5.3	197.4 ± 4.1*

**p<0.05 compared to CD fed group*

Table 2: Effect of topiramate, atorvastatin *per se* and the combination of topiramate+atorvastatin treatment on organ weights of cafeteria diet (CD) fed rats

Treatment	Left kidney	Right kidney	Heart	Spleen	Liver
Control	0.65 ± 0.03	0.68 ± 0.03	0.71 ± 0.12	0.82 ± 0.04	6.29 ± 0.14
CD	1.61 ± 0.04	1.69 ± 0.04	1.03 ± 0.13	1.31 ± 0.05	10.31 ± 0.08
CD + Topiramate	0.82 ± 0.05*	0.91 ± 0.01*	0.85 ± 0.16*	0.91 ± 0.07*	7.12 ± 0.07*
CD + Atorvastatin	0.81 ± 0.01*	0.92 ± 0.12*	0.86 ± 0.19*	0.90 ± 0.07*	7.03 ± 0.03*
CD + Topiramate + atorvastatin	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*

Table 3: Effect of topiramate, atorvastatin *per se* and the combination of topiramate+atorvastatin treatment on body temperature of cafeteria diet (CD) fed rats

Treatment	Body temperature at different times (min)				
	0	30	60	90	180
Control	36.3 ± 1.2	36.1 ± 1.3	35.7 ± 0.5	36.0 ± 0.8	36.2 ± 1.0
CD	34.1 ± 2.1	34.3 ± 1.2	34.2 ± 1.6	34.8 ± 1.5	34.6 ± 1.1
CD + Topiramate	34.5 ± 0.9	34.9 ± 0.8	36.2 ± 1.1*	36.8 ± 0.7*	36.3 ± 0.8
CD + Atorvastatin	34.3 ± 0.4	34.8 ± 0.8	36.8 ± 1.4*	36.7 ± 1.3*	36.1 ± 0.7
CD + Topiramate + atorvastatin	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, atorvastatin *per se* and the combination of topiramate+atorvastatin combination of topiramate+atorvastatin treatment in CD fed animals when compared to CD group (Table 4).

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 atorvastatin *per se* decreased TC, TG, and LDL significantly and increased HDL levels. Moreover the combinations of topiramate+atorvastatin decreased serum lipid profile lower than topiramate and atorvastatin *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 . Atorvastatin also decreased the serum glucose level but it is not significant. Whereas treatment with combination of topiramate+atorvastatin on CD fed rats decreased the serum glucose concentration near to control, which is statistically more significant (Table 5).

Discussion

Drug-interaction studies are usually conducted in animal models to assess the

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

Treatment	Locomotor Activity		
	Ambulation	Rearing	Grooming
Control	65.3 ± 5.43	20.5 ± 3.65	6.8 ± 1.18
CD	50.8 ± 4.89	14.1 ± 2.61	4.2 ± 2.30
CD + Topiramate	68.3 ± 3.72*	26.3 ± 4.62*	7.3 ± 2.16*
CD + Atorvastatin	69.5 ± 4.31*	25.4 ± 5.36*	7.9 ± 3.42*
CD + Topiramate + Atorvastatin	69.7 ± 7.30*	27.3 ± 5.12*	7.6 ± 1.76*

**p<0.05 compared to CD fed group*

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

Treatment	Biochemical Parameters				
	TC	TG	LDL	HDL	Glucose
Control	139 ± 5.6	105 ± 6.2	82 ± 5.2	51 ± 6.1	106 ± 4.3
CD	191 ± 5.8	173 ± 5.8	138 ± 5.3	28 ± 5.8	240 ± 6.1
CD + Topiramate	165 ± 4.9	144 ± 4.8	108 ± 5.6	40 ± 5.3	212 ± 5.3
CD + Atorvastatin	163 ± 4.4	138 ± 3.6	102 ± 4.4	44 ± 4.3	214 ± 4.7
CD + Topiramate + Atorvastatin	140 ± 5.5*	109 ± 4.4*	80 ± 3.3*	55 ± 3.8*	202± 5.3*

**p<0.05 compared to topiramate and atorvastatin per se treatment*

safety before they are conducted in humans. conducted in humans. The CD induced obesity in animal model closely resembles that of humans[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 our study topiramate, which is an antiepileptic drug, reduced the body weight and decreased the blood glucose levels and lipid profile. It decreased food intake acutely and increased metabolic rate. These findings are in accordance with Liang *et al*[19] and York *et al*[20]. Wilkes *et al* [21]stated that the antihyperglycemic activity of topiramate may be due to topiramate induced glucose stimulated insulin release. 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. The leptin level was also reduced significantly by topiramate treatment. It also inhibits fat deposition by reducing the activity of lipoprotein lipase in various white adipose tissues depots.

Atorvastatin which is a hypolipidemic drug also decreases the body weight and lipid profile. It improves glucose metabolism by improving insulin resistance[22]. Hence the combination of topiramate+atorvastatin

exhibit additive type of pharmacodynamic interaction which is beneficial one. Pharmacokinetic interaction may also be possible at absorption level because both the drugs are rapidly absorbed orally but study has to be done to confirm it. Topiramate is 15-41% bound to plasma proteins[23] and atorvastatin is highly protein bound drug approximately 98%[24]. Hence interaction might be possible at distribution phase which need further confirmation. Hepatic CYP 3A4 isoenzyme is mainly involved in the metabolism of atorvastatin[24]. Whereas topiramate is not extensively metabolized and is primarily eliminated in urine[23]. This indicates that interaction does not occur at metabolic level. Further atorvastatin is mainly eliminated through fecal route[24] and topiramate through renal route[23]. Hence there might not be interaction at elimination level. However the results are yet to be confirmed by understanding pharmacokinetic parameters like AUC, C_{max} and t_{max} of topiramate after treatment with atorvastatin.

Conclusion

The present study suggests that Obesity and Hyperlipidemia can be treated simultaneously with the combination of topiramate and atorvastatin with additional advantage due to their additive type of interaction.

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