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ANOREXIC EFFECT OF (R)-SIBUTRAMINE : COMPARISON WITH (R)-SIBUTRAMINE AND (S)-SIBUTRAMINE

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Abstract : Sibutramine is one of the very few drugs that are approved for long-term treatment of obesity. Sibutramine is a racemic mixture (RS) containing two equal forms of the R(+) and S(–) enantiomers. In this paper, we have investigated comparative anorexic effect of sibutramine enantiomers and their recemate form in rats. After obtaining two days of baseline results, rats were administered orally either with (RS)-sibutramine or its enantiomers (R)- or (S)-sibutramine at dose levels of 5, 10, 20 mg/kg each for 4 days and body weight, food intake and water intake were measured daily. Locomotor activity score of each rat was also recorded on each day. R-Sibutramine and (RS)-sibutramine produced dose dependant decrease in the body weight and food intake. On the other hand, (S)-sibutramine was shown to increase in these parameters. Neither sibutramine nor it's enantiomers showed any consistent effects on spontaneous motor activity (SMA) scores. In conclusion, (R)-sibutramine is better anorexic than or (RS)-sibutramine or it's (S)-enantiomers.

Key words : sibutramine stereoisomerism anorexia motor activity

INTRODUCTION

Long-term if not life-long therapy is usually required when drugs are used to treat obesity. Once treatment is stopped, obese persons usually regain the weight that was lost due to drug treatment (1). Sibutramine (1-(4-chlorophenyl)-N,N- dimethyl -a-(2-methylpropyl)-cyclobutanemethanamine) is one of the very few drugs that are approved (November 1997) for long-term treatment of obesity. Clinical trials have shown that sibutramine can induce and maintain weight loss, even in patients with co-morbid conditions such as hypertension or type II diabetes (1). Sibutramine is a derivative of the amphetamine precursor, β-phenethylamine, and blocks presynaptic nerve terminal reuptake of norepinephrine, serotonin, and dopamine (1, 2). The weight reducing effect of sibutramine in humans is caused by a dual mechanism: 1) reduction of energy intake by increasing satiety thereby decreasing hunger (3) and 2) by increasing glucose utilization in brown adipose tissue (4) and resulted into combination of reduced appetite, feelings of satiety and possibly the induction of thermogenesis (5). The assessment of the benefit-risk profile of sibutramine necessitates it to be kept under regular review due to its most common nervous system adverse effects like headache, constipation and nausea, dizziness, dry mouth and insomnia (5).

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Sibutramine is a racemic mixture containing two equal forms of the R(+) and S(–) enantiomers (6). Furthermore, (RS)-sibutramine has two active metabolites, desmethylsibutramine and didesmethyl-sibutramine that are optically active and may be safer than racemate (7). R(+) and S(–) enantiomers of sibutramine were also differs in their pharmacokinetic standpoint and R-sibutramine might represent the more advantageous sibutramine enantiomer from the pharmacokinetic standpoint (6). However, anorexic effects of these two enantiomers viz (R)- and (S)- sibutramine are not reported. The objective of this study was to compare the anorexic effect of sibutramine with that of its enantiomers forms in rats.

METHODS

Material

Wistar albino rats (300–400 g) of either sex were purchased from National Toxicological Centre, Pune and were housed in polypropelene cages at a temperature of 25±1°C and relative humidity of 45 to 55% in clean environment under 12 h : 12 h light: dark cycle. They had free access to food pellets (Chakan Oil Mills, Pune) and filtered water was made available ad libitum. Sibutramine (RS) and its enantiomers (R)- and (S)-Sibutramine were supplied by Emcure Pharmaceuticals Ltd., Pune as gift sample. The experimental protocol was approved by Institutional Animal Ethics Committee (IAEC) of Poona College of Pharmacy constituted under Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Government of India.

Measurement of body weight, food intake and water intake

To measure food intake, rats were housed individually in the metabolic cages (Technoplast, Italy) and were allowed to consume food pellets ad libitum. The rats were divided into 5 groups of 6 animals per group (on day 0) and body weight of each rat, and its food and water consumption were recorded at interval of 24 hours for next 2 days (day 0 to day 2). After obtaining two days of baseline results, rats were administered orally (immediately following the recording at 10:00 AM) either with (RS)-sibutramine, (R)-sibutramine or (S)-sibutramine at dose levels of 5, 10, 20 mg/kg each in the suspension made with 1% w/v Tween 80. Body weights food intake and water intake were measured daily up to 6th day (i.e. 4 days of treatment). Mean change in body weight, food intake and water intake between day 2 and day 6 for each group of rats was calculated and presented as Fig. 1.

Measurement of spontaneous motor activity (SMA)

Each day, before drug administration, spontaneous motor activity score of each rat was recorded by the help of actophotometer (INCO, Ambala, India). Each rat was scored for the period of 5 minutes period at various time points (at 0, 30, 60, 120, 180 and 240 min) on day-2 (treatment day) and day 6 of the study. Total of SMA scores on day-2 and day-6 for each group was calculated and expressed as mean change in SMA scores± SEM (Fig. 1 D).

Data analysis

The mean change in each of the parameter (body weight, food intake, water intake and spontaneous motor score) after 4 days of treatment is presented as mean change ± SEM as Fig. 1. The data was analyzed by two-way repeated measure ANOVA followed by *post hoc* Bonferroni test. P values < 0.05 were considered stastically significant.

RESULTS

The three test drugs did not alter body weight at 5 mg/kg, p.o. dose (Fig. 1-A). However, higher doses (10 and 20 mg/kg) of (R)-sibutramine decreased body weight of rats significantly ($P<0.01$) after 4 days of treatment whereas (S)-sibutramine increased the weights of the rats ($P<0.05$). (RS)-sibutramine did not change the weight of the animals in any of the tested doses. (R)- and (RS)- sibutramine did not show any significant change in food intake at any of the tested doses (Fig. 1-B) after 4 days of treatment. However, (S)-sibutramine at 10 mg/kg, p.o. showed significant ($P<0.05$) increase in food intake. None of the drugs in the tested doses showed any significant change in food intake (Fig. 1-B).

DISCUSSION AND CONCLUSION

Catecholamine, dopamine, serotonine (5HT) and neuronal histamine are anorectic monoamines. Anorectic agents acting as modulators of these monoamines inhibit appetite by activating release together with suppressing reuptake of these monoamines (8). The anorectic agents are classified in clinical use as either alpha 1, β-adrenergic receptor agonists or 5HT-receptor agonist. Sibutramine has been reported to have

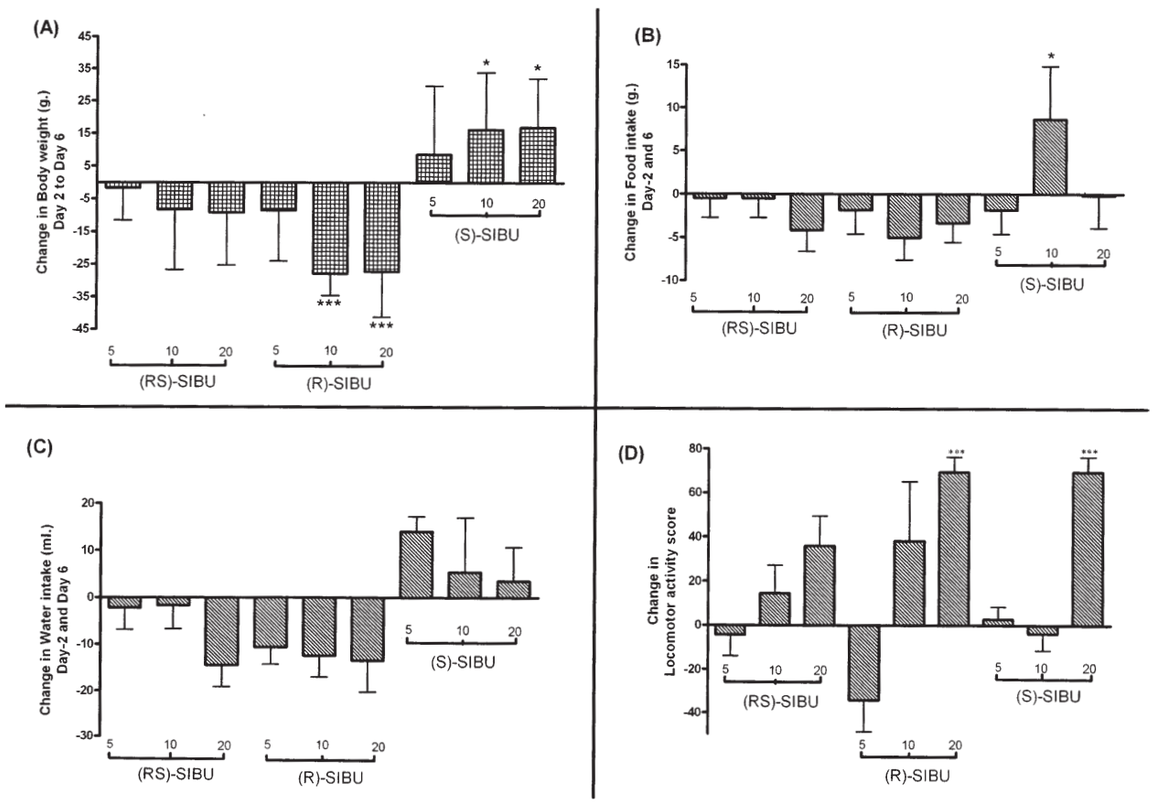

Fig. 1: Effect of sibutramine (SIBU) and it's enantiomers on change in A) body weight B) food intake C) water intake D) spontaneous motor activity (SMA) score during day-2 and day 6 of the study. Each group contains 6 rats each. Data was analyzed by two-way repeated measure ANOVA followed by Bonferroni posttests. *P<0.05, **P<0.01, ***P<0.001 as compared with day-2 readings of corresponding groups. Other values are non-significant.

agonistic effects on both β-adrenergic and serotonergic receptor agonist (9, 10). Sibutramine induces not only appetite suppression but also accelerates peripheral energy expenditure (8). In the present study, R-Sibutramine and (RS)-sibutramine produced dose dependant decrease in the body weight and food intake. On the other hand, (S)-sibutramine was shown to increase body weight, and food intake (although not significantly) as opposed to (R)-sibutramine. In the recent *in vitro* metabolism study, (R)-sibutramine was shown to be metabolized into 2 metabolites whereas S-sibutramine or (RS)-sibutramine metabolized to four major metabolites along with 2 or 3 minor metabolites (6, 7). The difference in anorexic effects among these enantiomers can be attributed to different pharmacokinetic profiles (6).

Spontaneous motor activity was also measured in view of some uncertainty regarding "dopaminergic effects of sibutramine (7). Sibutramine was reported to cause a dose-dependent increase in locomotor activity of rats, which may be parallel with increase in energy expenditure (11). In the present study, neither sibutramine nor it's enantiomers showed consistent effect (Fig. 1-D) on SMA scores in lower dose. At higher dose (20 mg/kg, p.o.), sibutramine enantiomers but not (RS)-sibutramine, increased SMA scores. These results are in line with prior report that (R)-enantiomer of sibutramine metabolites have more potent effects than recemic sibutramine in locomotor activity (7). In conclusion, (R)-sibutramine showed better anorexic effect than (RS)-sibutramine or it's (S)-enantiomers.

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