

A STUDY ON THE HAEMODYNAMIC INTERACTIONS BETWEEN ACTIVATED CHARCOAL AND PROPRANOLOL/ATENOLOL IN NORMAL HUMAN SUBJECTS

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(Received on July 29, 1998)

Abstract : A random, observer blind, crossover design of study was undertaken in twelve normal male volunteers. Both propranolol (40 mg) and atenolol (50 mg) in single dose oral administration had significantly reduced the heart rate, systolic blood pressure and the value for double product under resting and postexercise conditions compared to the corresponding pretreatment values. Orally administered activated charcoal (15 g) had abolished the haemodynamic effects of propranolol but failed to do so against atenolol under both resting and postexercise periods. The results suggest the possibility of successful antidotal intervention with activated charcoal in the case of propranolol overdosage only.

Key words : activated charcoal
atenolol

propranolol
human-volunteers

INTRODUCTION

Activated charcoal is a powerful adsorbent of many drugs and other poisons, including gases (1). It is of therapeutic value in the poisoning due to several drugs like carbamazepine, dapsone, phenobarbitone, theophylline and salicylate while it is not useful in poisoning due to ethanol, iron, lithium or tolbutamide (2). No such published document is available on the interaction between activated charcoal and beta-blockers. Beta-blockers are widely prescribed drugs for various ailments of human beings including hypertension (3), angina pectoris (4, 5, 6), cardiac arrhythmia (7, 8, 9), myocardial infarction (9, 10), portal hypertension (11) and others. Further,

overdose toxicity with beta-blockers resulting in ventricular asystole and death are also reported in the literature (12, 13). Keeping in view of the fact that activated charcoal is an useful antidote in several drug related toxicities, it was thought prudent to undertake a comparative interactional study between activated charcoal and two beta blockers namely propranolol, the prototypical non-selective beta blocker and atenolol, the widely prescribed cardioselective beta blocker.

METHODS

The study was performed according to the revised declaration of Helsinki. Ethical approval of the study protocol was obtained

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from the Institutional Ethical Committee. Twelve preselected normal male volunteers aged 19–28 years (Median 20 years) took part in the study after their written, informed consent. Three volunteers were invited to take part on each day of the study. A random, observer blind, within-volunteer crossover design of study was adopted with a washout period of seven days after each drug treatment. A standardized breakfast comprising of four bread slices, 25 g butter, one boiled egg and a cup of tea was given at 8.00 h on each of the study days to each volunteer. The volunteers reported to the laboratory at 9.30 h and participated in the study according to the following protocol:

Study day 1 : After a resting period of 30 min, the baseline blood pressure (BP) and heart rate (HR) were measured in sitting posture between 10.00–10.30 h followed by standardized exercise between 12.00–12.30 h and recording of sitting BP and HR within 30 s of completion of exercise schedule.

Study day 2 : After a resting period of 30 min, an assured administration of a single oral dose of 40 mg of propranolol hydrochloride tablet (Inderal, ICI India Ltd., batch number 0676) was undertaken between 10.00–10.30 h. Propranolol was administered with 150 ml of water in sitting posture. Postdrug sitting BP and HR was recorded after 2 h, followed immediately by subjecting the volunteers to standardized exercise and recording of postexercise BP and HR as stated above.

Study day 3 : Administration of a propranolol tablet (40 mg) as stated above followed 10 min later by oral administration of activated charcoal LR (source: S. D. Fine-

Chem Ltd., India, batch number s/0694/1291/140911) amounting to 15 g of fine, black-powder suspended in 150 ml of sweetened lemon water. Sitting BP and HR were measured 2 h later, followed immediately by subjecting the volunteers to standardized exercise and the recording of postexercise BP and HR.

Study days 4 and 5 : Similar programme of studies as mentioned above (i.e. study days 2 and 3) were adopted except that instead of propranolol, a single oral dose of 50 mg of atenolol tablet (Tenolol, IPCA Laboratories India Ltd., batch number 5042) was administered. Baseline BP and HR were recorded on all the study days and pooled for the purpose of comparison with the drug-treated values.

Measurement of BP, HR and double product (DP) : Sitting systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured by the same observer throughout the study using the same mercury sphygmomanometer. The first and the fifth korotkoff sounds were considered for documenting SBP and DBP respectively. HR was measured from the lead I of a direct writing electrocardiograph (BPL, model Cardiart 408). DP was calculated according to the formula $SBP \times HR / 100$.

Standardized exercise : A semiquantitative bicycle ergometer of (Hero Company allegro model) was used. Preselection of volunteers was undertaken based on the average postexercise HR between 140–160 beats/min of three trial runs of standardized exercise (pedal rate 60–70/min; speed 20–25 km/h; distance travelled 0.9–1.1 km and duration of exercise 3 min) performed against an arbitrary but constant load. Similar

conditions for exercise were maintained throughout the study.

Data presentation and analysis : Data pertaining to BP, HR and DP were expressed in terms of $\bar{X} \pm \text{SEM}$. Statistical analysis of the data for each parameter was performed using analysis of variance (ANOVA). When the overall ANOVA was

significant, paired 't' test was applied to study the differences amongst the means (14). P values less than 0.05 were considered statistically significant.

RESULTS

Propranolol, atenolol and atenolol + activated charcoal significantly reduced the

TABLE I : Effect of single oral dose of propranolol only, atenolol only and in combination with activated charcoal on resting haemodynamic parameters.

Parameter	Control (Resting)	Propranolol (40 mg)	Propranolol+ activated Charcoal (40 mg+15 g)	Atenolol (50 mg)	Atenolol+activated charcoal (50 mg+15 g)
Heart rate (beats/min)	78.00±4.60	57.50±3.30*	76.70±9.10 [§]	63.10±3.20*	65.30±6.10*
Systolic blood pressure (mm Hg)	118.20±4.30	102.10±3.60*	118.30±2.30 [§]	106.00±2.80*	105.20±3.20*
Diastolic blood pressure (mm Hg)	77.30±2.80	81.30±3.50	79.00±1.90	73.00±3.05	74.30±3.20
Double product (mm Hg. beats/min/100)	9192.50±580.20	6593.70±449.50*	8813.00±346.90 [§]	6985.67±359.20*	7207.30±850.60*

*Statistically significant at P<0.05 compared to the control (resting) value.

[§]Statistically significant at P<0.05 compared to propranolol (40 mg) treated group.

TABLE II : Effect of single oral dose of propranolol only, atenolol only and in combination with activated charcoal on post exercise haemodynamic parameters.

Parameter	Control (Postexercise)	Propranolol (40 mg)	Propranolol+ activated charcoal (40 mg+15 g)	Atenolol (50 mg)	Atenolol+activated charcoal (50 mg+15 g)
Heart rate (beats/min)	155.17±8.37	103.80±5.60*	150.80±8.30 [§]	120.00±5.80*	134.30±3.50*
Systolic blood pressure (mm Hg)	150.83±6.23	135.30±6.30*	149.70±4.50 [§]	122.00±6.70*	130.20±6.80*
Diastolic blood pressure (mm Hg)	70.00±3.50	80.20±3.10*	68.50±2.60 [§]	67.00±0.90	67.20±2.50
Double product (mm Hg. beats/min/100)	23367.70±1464.90	14193.70±1373.80*	22369.30±1648.90 [§]	14689.20±1173.90*	17911.30±1427.40*

*Statistically significant at P<0.05 compared to the pretreatment control (Postexercise) value

[§]Significantly different at P<0.05 compared to propranolol (40 mg) treated group.

HR, SBP and DP compared to the corresponding values in the pretreatment control group. HR, SBP, DBP and DP in the propranolol+activated charcoal treated group were not significantly different compared to that of the pretreatment control group but, other than DBP, the values were significantly more compared to the corresponding data in the propranolol (40 mg) alone treated group (Table I). The postexercise control values for HR, SBP and DP were significantly higher as compared to the corresponding values for HR, SBP and DP under resting condition. However, propranolol, atenolol and atenolol+activated charcoal significantly attenuated the exercise induced rise in the HR, SBP and DP. The value for DBP was significantly more in propranolol (40 mg) treated group compared to the corresponding data in the postexercise control group. The values for HR, SBP, DBP and DP in the **propranolol+activated charcoal treated group** were comparable to that of the postexercise control values but the values for HR, SBP and DP were significantly more while that of DBP was significantly less as compared to the corresponding values in propranolol (40 mg) treated group (Table II).

DISCUSSION

Kinetics and dynamics of propranolol, a non-selective beta-blocker have been studied extensively (15, 16). Both atenolol, a cardio-

selective beta blocker and propranolol are being used for various cardiac (3, 4, 5, 6) and non-cardiac ailments (17, 18). However, there is no such published document on the interaction between activated charcoal and propranolol or atenolol. The results of the present study clearly established that activated charcoal had virtually abolished the haemodynamic responses to propranolol both under resting and postexercise conditions. This could be due to physical adsorption of propranolol by activated charcoal resulting in its poor bioavailability. However, activated charcoal had no significant effect on the haemodynamic influences of atenolol either in the resting or postexercise conditions.

Adsorption of drugs or toxin by activated charcoal is dependent on physical and electrical forces rather than on chemical interaction (1). Propranolol and atenolol have different physicochemical properties (16), hence, it might be surmised that differential adsorptive forces in terms of both nature and magnitude are in operation between activated charcoal on one hand and propranolol or atenolol on the other hand. The results of the present study had suggested that activated charcoal might justifiably be used orally and early in the management of propranolol overdose toxicity. However, further studies are required to evaluate the pharmacokinetic interaction between activated charcoal and beta blockers.

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