SHORT COMMUNICATION

NEUROPHARMACOLOGICAL ACTIONS OF LABETALOL

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Summary: Labetalol, an alpha- and beta- adrenoceptor antagonist, was investigated for its central nervous system effects in rats and mice. A marked reduction in the spontaneous motor activity with no concommitant muscle weakness was produced. The drug caused closure of eyelids in rats. Labetalol caused hypothermia and prolonged the pentobarbitone-induced hypnosis. In animals trained for conditioned avoidance response the drug blocked the SCR in all the animals and CAR in a few number of animals. The drug did not protect the animals against electroshock convulsions. From the results it appears that labetalol is a central nervous system depressant.

Key words: labetalol spontaneous motor activity rectal temperature conditioned avoidance response pentobarbitone induced hypnosis

INTRODUCTION

Labetalol (2-hydroxy-5-[(1-hydroxy-2-[(1-methyl-3-phenylpropyl) amino]-ethyl-1-t] benzamide hydrochloride) is a competitive antagonist at both alpha- and beta- adrenoceptors in the experimental animals (7) and in man (4, 16). Martin et al. (14) have reported that little labetalol enters the central nervous system. On the other hand it has been observed that the drug may cause such central nervous system side effects as dreams, nightmares, dizziness, depression, lethargy, drowsiness etc. in man (8, 10, 15). Further, it is suggested that an action within the central nervous system may contribute to the hypotensive effect of labetalol (5). The drug also modifies morphine-induced analgesia (11). Hence it was thought worth-while to investigate some of the central nervous system effects of the drug. Further, a dose of 30 mg/kg ip has been used in most of the experiments because both α- and β-receptors are significantly blocked at the level of high doses (6).

MATERIALS AND METHODS

Spontaneous motor activity (SMA) and ptosis:

Twelve albino rats of either sex (120-150 g) were divided into two equal groups. The animals of the first group served as control and received saline ip. The animals of the second group were treated with labetalol in doses of 30 mg/kg ip. The animals were observed carefully and changes in their SMA and eyelids were scored 30 min after drug treatment and thereafter at hourly intervals for 3 hr.
**Rotarod performance:**

A group of twenty mice of either sex (20-30 g) were employed. The animals were so selected that they could remain for five min without falling from a cylinder (15 cm diameter) rotating at the rate of 3 revolutions per min. The test was performed before drug treatment and then the drug, labetalol (30 mg/kg ip), was administered to ten mice. The other animals, treated with saline ip, served as control. The test was repeated 30 min later and thereafter at hourly interval for 3 hr.

**Rectal temperature:**

The experiment was performed at room temperature (21 ± 1°C). Eighteen rats (130-175 g) were divided into three equal groups. They were kept in individual cages and the rectal temperature of each animal was measured by inserting the bulb of a clinical thermometer 1 cm into the rectum and keeping it there for a period of 1 min. Group I (controls) rats received saline. Labetalol was given in doses of 30 mg/kg ip to the rats of second group. The animals of the third group were given chlorpromazine (5 mg/kg ip). The temperature was again measured 30 min after drug treatment and thereafter at hourly intervals for 4 hr.

**Pentobarbitone-induced hypnosis:**

Twelve albino rats (120-160 g) of either sex were divided into two equal groups. The animals of the first group were treated with saline ip and that of the second group with labetalol in doses of 30 mg/kg ip. Fifteen min later all the animals received pentobarbitone sodium in doses of 20 mg/kg ip. When the animals lost their righting reflex they were kept on their backs. The time when these animals regained their righting reflex and started moving about was noted.

**Conditioned avoidance response (CAR) and secondary conditioned response (SCR) of trained rats:**

Twelve albino rats (120-160 g) of either sex were so trained in jumping box (Techno Electronics, Lal Bagh, Lucknow) that they jumped from one chamber to the adjacent chamber on hearing a bell sound in order to avoid an electric shock passed through the floor grid ten sec later. Further training led to the development of secondary conditioned response (SCR) in these animals, as shown by Maffi (13), where the animals passed from one chamber to the other immediately after being placed in the cage and before hearing the bell sound. The trained rats were tested before drug treatment and only those which show SCR were selected. After administering the drug (30 mg/kg ip) the animals were again tested 15 min and 30 min later and thereafter at hourly intervals for 2 hr. Chlorpromazine hydrochloride (5 mg/kg ip) was given to another group of trained rats and they were tested 15 and 30 min later and thereafter at hourly intervals for 2 hr.
Maximum electroshock seizures

Seizures were produced in albino rats of either sex weighting between 125 and 170 g according to the method of Hendley et al. (9). The shocks (150 mA, 0.2 sec and 50 cycles A.C.) were applied through ear electrodes. The prevention of the extensor tonic spasm and death were accepted as the criteria for protection. Five groups of 6 animals each were employed. One group served as control (saline ip) and labetalol in doses of 0.1, 1, 10 and 30 mg/kg was given ip to the second, third, fourth and fifth groups respectively followed 30 min later by the shock.

RESULTS

Sedative effect of the drug:

Marked reduction in the SMA was observed in all six animals treated with labetalol. This effect lasted for more than 1 hr in 4 animals; more than 2 hr in 2 animals; and more than 3 hr in one animal. Five of the six rats were seen lying on their sides during the first hr. When they moved about in the cages, their gait was normal. All the drug-treated animals showed closure of the eyelids: three animals showed complete closure and the other three 3/4 closure of eye lids. Maximum effect was observed at 1 hr.

Rotarod performance:

Before drug treatment no mice fell down from the rotating cylinder during five min test period. Labetalol had no statistically significant effect on this response.

Effect on the rectal temperature of rats:

Labetalol produced hypothermic effect in rats and maximum fall of 2.5±0.1°C occurred at 15 min. The hypothermic effect lasted less than 3 hr. Chlorpromazine also induced hypothermic effect and a maximum decrease of 3.0±0.5°C occurred at 15 min. The hypothermic effect persisted more than 4 hr.

Pentobarbitone-induced hypnosis:

In the saline treated control animals, the mean sleeping time was 118±16.3 min. Pretreatment of the animals with 30 mg/kg of labetalol caused an increase in sleeping time (232±33.8 min, P<0.05).

Effect on the CAR and SCR of trained rats:

The results given in Table I show that the labetalol was very effective in blocking SCR of trained rats but blocked the CAR only in less number of animals. On the other hand chlorpromazine hydrochloride (5 mg/kg) blocked the SCR of all the animals and CAR of majority of the animals.

Anticonvulsant effect:

Labetalol did not protect the animals against electroshock convulsions.
TABLE I: Effect of labetalol and chlorpromazine on the conditioned avoidance response (CAR) and secondary conditioned response (SCR) in rats.

<table>
<thead>
<tr>
<th>Drug</th>
<th>ip dose mg/kg</th>
<th>No. of rats</th>
<th>15 min.</th>
<th>30 min.</th>
<th>1 hr.</th>
<th>2 hr.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorpromazine</td>
<td>5</td>
<td>6</td>
<td>6</td>
<td>6</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Labetalol</td>
<td>30</td>
<td>6</td>
<td>6</td>
<td>3</td>
<td>6</td>
<td>2</td>
</tr>
</tbody>
</table>

DISCUSSION

One of the most obvious signs of sedation in animals is the reduction of spontaneous movement (SMA). Spontaneous activity of rats and mice is depressed by most of the tranquilizers, e.g. chlorpromazine, meprobamate (1,2,18), reserpine (17) etc., a property which is shared by labetalol too. Labetalol, in doses of 30 mg/kg, caused a significant reduction in SMA and closure of eye lids.

Labetalol did not possess any hypnotic action of its own though like chlorpromazine it significantly potentiated the hypnotic action of pentobarbitone. As studied for its effect on conditioned behaviour of rats, labetalol in doses of 30 mg/kg was slightly different from chlorpromazine. Chlorpromazine has been shown to cause a blockade of both the CAR (3) and SCR (13) but in the present study labetalol was very effective in blocking the SCR whereas it blocked the CAR in a few animals.

The sedative effects of tranquilizers like chlorpromazine and reserpine as measured by potentiation of barbiturate sleep or reduction of activity have been found to be proportional to the accompanying fall of body temperature and it has consequently been suggested that sedation is caused by interference with the mechanism of temperature regulation (12). Labetalol and chlorpromazine reduced the body temperature of rats in the present study. The only difference was shorter duration of hypothermic action of labetalol than of chlorpromazine.

Like chlorpromazine labetalol did not antagonize the convulsions induced by electric shocks.

ACKNOWLEDGEMENTS

The authors are grateful to M/s Allen & Hanburys Research Ltd., Ware, Herts., SG12 ODJ, England for the generous supply of labetalol. They are also thankful to Shri Fulsi Das for the technical assistance.
is the reduction of so-called SCR in rats. This is a property which is shared by most of the tranquilizers, e.g., a significant reduction in SMA though like chlorpromazine one. As studied for its effect in blocking the SCR and reserpine as measured by hypothermia and sedation in the mouse. J. Pharm. Pharmac., 9: 657-662, 1957.


REFERENCES


