A STUDY ON WITHDRAWAL RELATED HAEMODYNAMIC RESPONSE IN CHRONIC PROPRANOLOL TREATED CONSCIOUS RATS

A. CHAKRABARTI AND P. L. SHARMA*

Department of Pharmacology, Postgraduate Institute of Medical Education & Research, Chandigarh - 160 012

(Received on June 20, 1992)

Abstract: Single dose of propranolol hydrochloride (5 mg/kg, i.p) caused significant fall in heart rate (HR) but not in systolic blood pressure (SBP) in normotensive conscious rats. Multiple doses of propranolol (5 mg/kg, i.p., twice-a-day for 5 wk) caused significant fall in both HR and SBP at 2 wk and 4 wk in normotensive conscious rats. Sudden withdrawal of propranolol at 5 wk caused a significant blood pressure upswing and tachycardia between 12-24 h followed by normalization of both blood pressure and heart rate. The study documents a possible model of rebound hypertension in normotensive conscious rats.

Key words: conscious rats propranolol blood pressure drug withdrawal

INTRODUCTION

Propranolol is a non-selective β-adrenoceptor antagonist used widely in the treatment of hypertension, angina pectoris, cardiac arrhythmia etc. It causes a decrease in the heart rate (HR), cardiac output (CO) and systolic blood pressure (SBP) is resting normotensive human subjects (1, 2). However, its effects on the haemodynamic response in normotensive animals is equivocal (3, 4). Since no report pertaining to propranolol withdrawal in either the normotensive or the hypertensive animals is available in the literature, the present study was therefore, designed to investigate the effect of chronic treatment followed by sudden withdrawal of propranolol on the HR and SBP of normotensive conscious rats.

METHODS

The study was conducted in 20 random bred, Wistar strain of male, normotensive healthy rats weighing between 150-200 g from September to November.

SBP and HR of the conscious rats were measured by the 'UGO-basile' BP recorder instrument. It is an indirect recording of SBP and HR with the help of a tail cuff and a pulse sensing transducer, the method of which was standardized in our laboratory with the modification of that described by Gerold and Tschirky (5).

Each rat was trained over a period of one week for acclimatization and those which showing inconsistent reading of SBP and HR during the last 2 days were discarded from the study.

An open, crossover design of study was planned. Baseline SBP and HR were recorded at three different times of the day i.e. 8 A.M., 2 P.M. and 8 P.M. to look for any time related changes in the aforementioned haemodynamic parameters. Haemodynamic responses to both the single dose and the multiple doses of propranolol was then studied. In the single dose study, propranolol hydrochloride (dissolved in sterile, normal saline to give a final concentration of 2 mg/ml) was injected i.p. at doses of 1 mg/kg, 3 mg/kg and 5 mg/kg on three alternate days to each rat. The volume of fluid injected did not exceed 0.5 ml. The drug was given at 12 noon and a single reading of SBP and HR was recorded 2 h post dose i.e. at 2 PM.

*Corresponding Author
A washout period of 5 days was given between the single dose and the multiple dose study. At the end of the washout period the control SBP and HR were recorded for two consecutive days (day 1 and day 2) at 0, 6, 12, 24, 30 and 36 h (0, 6 and 12 h corresponded to 8 A.M. 2 P.M. and 8 P.M. recordings on day 1 while 24, 30 and 36 h corresponded to readings at 8 A.M., 2 P.M and 8 P.M on day 2).

In the multiple dose study, the same drug was injected (5 mg/kg, i.p.), twice a day at 8 A.M. and 8 P.M. for 35 consecutive days. SBP and HR were recorded at 0, 6, 12, 24, 30 and 36 h on 14th and 15th, on 28th and 29th, and 36th and 37th day of drug therapy in order to observe the haemodynamic response to the steady-state level post-withdrawal and of propranolol.

Paired ‘t’ test was applied for statistical purposes and P < 0.05 was considered statistically significant.

RESULTS

There was no significant time related variation in SBP. These were 120±5 mm Hg at 8 A.M., 120±3 mmHg at 2 P.M. and 114±3 mm Hg at 8 P.M. The HR was significantly less at 8 P.M. than at 8 A.M. (326±8 beats/min and 344±10 beats/min respectively; (P<0.05). At 8 P.M., the HR was also less as compared to 2 P.M. (326±8 beats/min and 339±10 beats/min respectively). After single doses of propranolol at 1 mg/kg and 3 mg/kg, i.p. there was no significant difference in SBP and HR as compared to the baseline values. After 5 mg/kg, i.p., administration, there was no significant difference in SBP as compared to the baseline value (121±6 mmHg and 120±3 mmHg respectively), although the HR was significantly less than the baseline value (304±7 beats/min and 339±10 beats/min respectively; P < 0.05).

At 2 wk and 4 wk, both SBP and HR were significantly less compared to the baseline values at each point of time (0, 6, 12, 24, 30 and 36 h; P < 0.05), though no significant difference could be observed between the 2 wk and 4 wk values. In the drug withdrawal group, the 0 and 6 h values for SBP and HR were significantly less compared to the baseline values and did not differ significantly from the 2 wk and 4 wk of propranolol treatment values at similar time points. The 12 h and 24 h values for SBP and HR in the drug withdrawal group showed a significant rise compared to the baseline and propranolol (at 2 wk and 4 wk) treated values at the same time points (P < 0.05 and P < 0.05 respectively). The 30 h and 36 h values for SBP and HR in the drug withdrawal group were comparable to the baseline values but significantly higher than the propranolol (at 2 and 4 wk) treated values at the same time points. The rebound rise in SBP and HR at 12 h and 24 h after propranolol withdrawal was observed in seventeen out of the twenty rats studied.

DISCUSSION

In the present study, the lack of any effect of propranolol 5 mg/kg, i.p., single dose on SBP could be due to the fact that propranolol blocks cardiac β-adrenoceptor causing decrease in cardiac output and also blocks vascular β-adrenoceptor thereby accentuating peripheral resistance (6). Bradycardia was obviously the result of cardiac β-adrenoceptor blockade thereby minimising the resting sympathetic drive on heart. Lower doses of propranolol (i.e. 1 mg/kg and 3 mg/kg, i.p) had no significant influence on either the heart rate or the systolic blood pressure. Similarly, in the present study it was observed that multiple doses of propranolol (5 mg/kg i.p. twice-a-day) given intermittently to conscious rats, resulted in a significant drop in both SBP and HR at 2 weeks and 4 weeks.

Human hypertensive patients might experience rebound hypertension within hours to 1 to 2 days after sudden withdrawal of chronically given propranolol (7). In the present study it was observed that, propranolol given intermittently over a long period (5 wk), on sudden withdrawal resulted in a rebound rise of BP and HR which peaked at 24 h after the drug withdrawal. The precise reason for the lack of such rebound response in three rats, as seen in the present study, was not clear. It could be because of biological variation in response to therapy or due to inherent lacuna in the method of BP measurement which was intermittent (every 6 h) rather than being a continuous monitoring.
The present study provides an animal model for studying the rebound hypertension on sudden withdrawal of chronically given propranolol in normotensive conscious rats. The tachycardia and BP upswing after propranolol withdrawal observed in the present study could be the result of exaggerated response to the resting sympathetic drive because of cardiac β-adrenoceptor supersensitivity. Further studies on this hypertensive model are in progress.

**TABLE I**: Effect of chronic propranolol treatment (5 mg/kg, i.p. twice-a-day) followed by sudden withdrawal in normotensive conscious rats.

<table>
<thead>
<tr>
<th>Time**</th>
<th>Parameters</th>
<th>C</th>
<th>Prop. (2 wk)</th>
<th>Prop. (4 wk)</th>
<th>Drug withdrawal (5 wk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>BP (mmHg)</td>
<td>121±4</td>
<td>104±4*</td>
<td>104±4*</td>
<td>109±7*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>343±8</td>
<td>291±10*</td>
<td>290±7*</td>
<td>294±10*</td>
</tr>
<tr>
<td>6</td>
<td>BP (mmHg)</td>
<td>118±5</td>
<td>109±7*</td>
<td>103±8*</td>
<td>100±6*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>330±11</td>
<td>288±10*</td>
<td>286±12*</td>
<td>292±8*</td>
</tr>
<tr>
<td>12</td>
<td>BP (mmHg)</td>
<td>116±5</td>
<td>102±6*</td>
<td>98±8*</td>
<td>128±6*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>324±9</td>
<td>278±12*</td>
<td>285±6*</td>
<td>355±13*</td>
</tr>
<tr>
<td>24</td>
<td>BP (mmHg)</td>
<td>120±4</td>
<td>103±5*</td>
<td>101±7*</td>
<td>153±8*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>326±7</td>
<td>293±11*</td>
<td>298±11*</td>
<td>375±9*</td>
</tr>
<tr>
<td>30</td>
<td>BP (mmHg)</td>
<td>122±6</td>
<td>108±7*</td>
<td>104±4*</td>
<td>123±10*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>328±10</td>
<td>291±9*</td>
<td>296±7*</td>
<td>331±7*</td>
</tr>
<tr>
<td>36</td>
<td>BP (mmHg)</td>
<td>118±4</td>
<td>102±5*</td>
<td>98±6*</td>
<td>122±7*</td>
</tr>
<tr>
<td></td>
<td>HR (beats/min)</td>
<td>320±7</td>
<td>295±11*</td>
<td>292±8*</td>
<td>330±11*</td>
</tr>
</tbody>
</table>

C: Control (baseline values)
Prop.: Propranolol treated.
* : P < 0.05 vs control
+ : P < 0.05 vs control
† : P < 0.05 vs Propranolol treated groups (2 wk and 4 wk)
** : 0, 6 and 12 h correspond to 8 AM, 2 PM and 8 PM readings on day 1.
24, 30 and 35 h correspond to 8 AM, 2 PM and 8 PM readings on day 2.

**REFERENCES**


