SHORT COMMUNICATION

Effect of propranolol on the ventilatory response to hypercapnia in man

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Summary

1. The effect of a single oral dose of propranolol on the ventilatory response to hypercapnia has been studied in five healthy subjects.

2. Propranolol produced a small but significant reduction in the slope of the ventilation/end-tidal $PCO_2$ regression line.

3. Propranolol did not significantly change vital capacity or forced expiratory volume in 1 s.

Key words: hypercapnia, propranolol, ventilatory response.

Introduction

The measurement of ventilatory response to hypercapnia is employed as a method of assessing the action of drugs on ventilatory drive. A number of drugs have now been studied, including aminophylline and pethidine (Stroud, Lambertsen, Ewing, Kough, Gold & Schmidt, 1955), lorazepam and morphine (Cormack, Milledge & Hanning, 1977), and propranolol (Mustchin, Gribbin, Tattersfield & George, 1976; Patrick, Tutty & Pearson, 1978). However, in some cases, conflicting results have been reported. Mustchin et al. (1976) found that propranolol reduced the ventilatory response to hypercapnia in the presence of hypoxia, and suggested that this may be a centrally mediated effect of the drug. These results could not be confirmed in a similar study by Patrick et al. (1978). There is considerable within- and between-subject variation in repeated measurement of the ventilatory response to hypercapnia, which may contribute to the difficulty of obtaining consistent results by different workers.

We have also studied the effect of propranolol on the ventilatory response to hypercapnia, but with a larger number of test runs for each subject, in order to minimize the risk of failing to detect significant changes due to within-subject variability.

Methods

Five non-smoking healthy subjects (three male, two female) aged between 23 and 34 years gave their informed consent to participate. Preliminary spirometry confirmed the absence of obstructive airways disease, and all subjects were given 'trial runs' with the re-breathing procedure on a number of occasions before the test days, in order to familiarize them with the apparatus and test method.

The ventilatory response to hypercapnia was measured with a modification of the re-breathing method of Read (1967). The re-breathing circuit consisted of a Godart Expirograph spirometer connected by flexible tubing to a low-resistance one-way valve (P. K. Morgan 75122) at the mouth. The expired $PCO_2$ was measured by sampling at low flow rate immediately distal to the expiratory valve passing this sample through a Godart Capnograph infrared analyser connected to a chart recorder. The sampled gas was then returned to the expiratory line of the re-breathing circuit. A gas mixture of $CO_2 + O_2$ (5:95, v/v) was used to flush the circuit initially, and at the commencement of each re-breathing run the total

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volume of the re-breathing circuit was made up to 7.5 litres with this gas mixture.

After a 10 min rest, the subject commenced the re-breathing procedure, starting at functional residual capacity. The test run was terminated when the end-tidal $PCO_2$ reached 8.25 kPa, or earlier if the subject felt too uncomfortable to continue. Ventilation ($VE$, l/min) was estimated at 30 s intervals by averaging the tidal volume of three consecutive breaths and measuring the time taken for these breaths from the spirometer tracing, and corrected to $V_e$ at body temperature and pressure, saturated (BTPS). The end-tidal $PCO_2$ values were obtained at corresponding times and all values above 6.2 kPa were used to plot $V_e$ and $PCO_2$. The slope, $S$ (l/min·kPa$^{-1}$), and $X$ axis intercept, $B$ (kPa), of the line of best fit were determined by linear regression analysis, by the method of least squares.

Each subject was studied on 2 days at least 1 week apart. After the subject had fasted overnight, oral DL-propranolol (80 mg; I.C.I. Ltd) or a matched placebo tablet was taken according to a randomized double-blind protocol. A light breakfast was taken 1-5 h later, and caffeine-containing beverages were excluded from the diet on the day of the study. The ventilatory response to hypercapnia was measured 2, 5 and 8 h after taking the test tablet. Duplicate runs were performed at each of these times, with a 10 min rest between the runs, and venous blood was collected for subsequent plasma propranolol determination with a fluorimetric method (Shand, Nuckolls & Oates, 1970).

**Results**

Sixty re-breathing runs were performed, and data from four runs were excluded from further analysis owing to technically unsatisfactory recordings. Linear regression analysis of the remaining data revealed significant correlation coefficients ($P < 0.05$) in all but two re-breathing runs. Consequently, data from 25 pairs of re-breathing runs (five from each subject) were available for statistical analysis.

There was no significant change in vital capacity or 1 s forced expiratory volume ($FEV_{1.0}$) between the two treatment days, the average fall in $FEV_{1.0}$ with propranolol being 3.6%. The between-subject coefficient of variance (100 × sd/mean) for the slope, $S$, in the control runs was 40%. The standard deviation of replicate regression lines was calculated using the formula

$$SD = \sqrt{\frac{\sum (x_1 - x_2)^2}{2 \times \text{no. of pairs}}}$$

where $x_1$ and $x_2$ are replicate values for $S$. The average within-subject coefficient of variance was 24% (range 16–35%).

The effect of propranolol on the slope $S$ and $X$-intercept $B$ was assessed statistically by using the Wilcoxon test for pair differences. The individual values for $S$ are shown in Table 1. Propranolol

### Table 1: Individual and mean $S$ and mean $B$ values for the linear regression of ventilation and end-tidal $PCO_2$ at the specified times after taking either placebo or propranolol tablets

<table>
<thead>
<tr>
<th>Subject</th>
<th>$S$ (l/min·kPa$^{-1}$)</th>
<th>Mean $B$ (kPa)</th>
<th>Mean plasma propranolol (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 h after</td>
<td>5 h after</td>
<td>8 h after</td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>Propranolol</td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>24.1</td>
<td>17.4</td>
<td>21.0</td>
</tr>
<tr>
<td>2</td>
<td>34.9</td>
<td>18.5</td>
<td>30.8</td>
</tr>
<tr>
<td>3</td>
<td>30.7</td>
<td>16.7</td>
<td>23.1</td>
</tr>
<tr>
<td>4</td>
<td>26.5</td>
<td>21.7</td>
<td>20.1</td>
</tr>
<tr>
<td>5</td>
<td>16.6</td>
<td>19.8</td>
<td>31.4</td>
</tr>
<tr>
<td>Mean $S$</td>
<td></td>
<td></td>
<td>22.8</td>
</tr>
<tr>
<td>Mean $B$</td>
<td>5.2</td>
<td>5.2</td>
<td>5.2</td>
</tr>
<tr>
<td>Mean plasma propranolol</td>
<td>74.6(17-0)</td>
<td>44.2(17-2)</td>
<td>22-4(8-9)</td>
</tr>
</tbody>
</table>


significantly reduced $S$ at 2 h ($P < 0.05$), but the changes at 5 and 8 h were not statistically significant. The overall mean value for $S$ with propranolol was 17.82 l min$^{-1}$ kPa$^{-1}$, which was significantly less than the corresponding placebo value of 21.51 l min$^{-1}$ kPa$^{-1}$ ($P < 0.02$). The mean values for $B$ did not differ significantly between treatments (Table 1).

The mean plasma propranolol concentrations are also shown in Table 1. These values ranged from 114 to 23 ng/ml at 2 h. There were no side-effects reported, apart from a transient headache after completing a re-breathing run, with either treatment.

**Discussion**

In the present study, propranolol produced a small but significant reduction in the slope of the $V_e/P_{co_2}$ regression line at 2 h, although the differences in the slope at 5 and 8 h were not statistically significant. Mustchin et al. (1976) had reported a greater reduction in slope at 2 h, but no such change could be found in a more recent study by Patrick et al. (1978), who used 100 mg of propranolol and measured the ventilatory response to hypercapnia between 2 and 4 h later. These varying results are unlikely to be due to differences in tissue concentrations of propranolol. The mean plasma propranolol concentration in our study (74.6 ng/ml) is comparable with the mean value (80.5 ng/ml) obtained in the open series by Patrick et al. (1978), who also confirmed the presence of $\beta$-adrenoreceptor blockade by using the heart-rate response to exercise. Mustchin et al. (1976) did not report the plasma propranolol concentrations in their subjects, although the dose and testing time at 2 h was the same as in our study.

One of the major difficulties in assessing the ventilatory response to hypercapnia in clinical studies is the very large between-subject variability. The inter-subject coefficient of variance for $S$ was 40% in our subjects; other workers have found similar values, such as 47% (Patrick et al., 1978), 46% (Read, 1967), 45% (Hirshman, McCullough & Weil, 1975) and 39% (Mustchin et al., 1976). Attempts to isolate factors contributing to this source of inter-subject variation have shown that the slope of the response is dependent on age (Kronenberg & Drage, 1973), height and body weight (Hirshman et al., 1975) and familial factors (Mountain, Zwillich & Weil, 1978).

The within-subject variability of the test adds to the difficulty of obtaining consistent results. Our subjects had been given at least five trial runs before the study days, and two re-breathing runs were performed by each subject at each test time. The regression lines were calculated from measurements taken every 30 s during the re-breathing runs, and the regression equations accepted only if $P$ was less than 0.05 for the correlation coefficient. Patrick et al. (1978) carried out a more sophisticated breath-by-breath analysis of $V_e$ and $P_{co_2}$, with an on-line computer. It is quite likely that the more frequent measurements used in their method would add to the precision of the linear regression analysis. It is possible that more consistent results would have been achieved if subjects were selected only if they had a highly reproducible response to hypercapnia on repeated testing. However, extrapolation of the findings from such a group to the population in question would require further validation, owing to the biased method of selection.

We believe that the changes produced by propranolol on the ventilatory response to hypercapnia are small, and unlikely to have a profound effect on ventilatory drive. However, propranolol should still be used with caution in patients with obstructive airways disease associated with chronic bronchitis, because of the additional possibility of an exacerbation of the airways obstruction (Sinclair, 1979).

**Acknowledgments**

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**References**


