Influence of dose of domperidone on the acute ventilatory response to hypoxia in humans

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Summary

We have studied the ventilatory responses to acute isocapnic hypoxia (\(\text{SpO}_2\) 78.8 (SD 1.4)\% for 10 min) in 10 male volunteers given three different doses of oral domperidone: placebo, domperidone tablets 10 mg, 20 mg or 30 mg every 8 h for 48 h on separate days. Neither baseline ventilation nor the acute hypoxic ventilatory response was significantly different from placebo for any of the domperidone doses. However, hypoxic responses were either increased with increments of domperidone or subjects were not sensitive. We arbitrarily divided subjects into two groups according to their hypoxic response-plasma domperidone concentration relationship. Analysis of subjects (\(n=5\)) who demonstrated at least a 2-litre min\(^{-1}\) increase in ventilation per 10 ng ml\(^{-1}\) increase in plasma domperidone concentration showed the greatest augmentation of hypoxic responses with the 20-mg dose (median 19.45 (range 13.37, 22.30) litre min\(^{-1}\)) compared with placebo (median 8.21 (3.74, 9.47)) (\(P=0.003\)). We were unable to predict which subjects would be sensitive to the effects of domperidone. (Br. J. Anaesth. 1998; 81: 322–326).

Keywords: hypoxia; pharmacology, domperidone; ventilation, hypoxic response

The carotid bodies mediate the ventilatory response to hypoxia in humans. Dopamine, the predominant catecholamine found in human carotid bodies,\(^1\) appears to be involved in the chemotransduction of this effect.\(^2\) In animals, administration of dopamine decreases ventilation and peripheral chemoreceptor activity.\(^3\)\(^4\) Infusions of low-dose dopamine in humans also depress the ventilatory response to hypoxia\(^6\) and this effect may be prevented by droperidol, a non-specific dopamine antagonist.\(^7\) However, as droperidol is able to cross the blood-brain barrier, a central effect cannot be excluded.

Dopamine receptors in the carotid bodies are of the D2 subtype\(^8\) and domperidone is a specific D2 receptor antagonist which does not readily cross the blood–brain barrier.\(^9\) Although it has a variable effect on baseline normoxic ventilation, it increases the ventilatory response to hypoxia.\(^2\)\(^10\)\(^11\) In a previous study,\(^12\) we confirmed that oral domperidone increased the hypoxic ventilatory response and offset depression of the initial phase of the hypoxic response caused by 0.1 MAC of isoflurane. In that study, we used a fixed dose of domperidone and found wide variations in plasma concentrations of domperidone. There was no clear relationship between plasma domperidone concentration and the degree of augmentation of the hypoxic response, perhaps because the hypoxic response varied between subjects.

In this study, we determined, within individual subjects, the effect of domperidone dose on the potentiation of the hypoxic ventilatory response, and the optimum dose of domperidone required to reduce the suppressive effects of subanaesthetic doses of volatile agents on this response.

Subjects and methods

We studied 12 healthy male volunteers. The nature and purpose of the study were explained and written consent was obtained. The study was approved by the Local Ethics Committee. None of the subjects was receiving any medication throughout the study and all were asked to refrain from substances known to affect respiration (e.g. alcohol, tobacco, etc.) for at least 6 h before study.

Each subject attended the laboratory on five occasions. The first visit was a familiarization period where the ventilatory response to isocapnic hypoxia (oxygen saturation was reduced to 80\% for 10 min) was measured. In the remaining four visits to the laboratory, subjects were allocated randomly to receive placebo or domperidone tablets 10 mg, 20 mg or 30 mg every 8 h for 48 h before and on the day of their visit to the laboratory. As this was a double-blind study, the number of tablets taken was standardized to three 8-hourly, regardless of dose of domperidone. To avoid any drug carryover effect, a washout period of at least 3 days separated treatment regimens for the same subject as the elimination half-life of domperidone is 12–16 h.\(^13\) To minimize the effect of diurnal variation on the hypoxic ventilatory response,\(^14\) subjects were scheduled to visit the laboratory at the same time of day for all four visits.

At each visit, subjects were asked about side effects while taking the tablets and were withdrawn from the study if they reported unpleasant adverse effects. We did not enquire about specific side effects. At the end of each visit, a venous sample was obtained for
measurement of plasma concentrations of domperidone. The sample was separated by centrifugation and the resultant serum stored at \(-20^\circ\text{C}\). Samples were batched and sent to the Janssen Research Foundation in Belgium at completion of the study for measurement of plasma concentrations of domperidone.

The methods used for recording ventilatory variables have been described previously.\(^{15}\) Briefly, subjects were seated upright in a comfortable armchair in a well-lit room and breathed via a mouthpiece and noseclip arrangement through a low resistance two-way valve. A five-way valve (Hans-Rudolf Gatlin Valve series 2430) was connected to the inspiratory port of the two-way valve to allow changes in inspired gases without the subject’s knowledge. Expiratory gas passed via a heated pneumotachograph (Fleisch No. 2) and the signal was integrated to give breath-by-breath tidal volume. Inspiratory and end-tidal oxygen (\(P_{\text{ItO}_2}, P_{\text{EtO}_2}\)) and carbon dioxide (\(P_{\text{ItCO}_2}, P_{\text{EtCO}_2}\)) partial pressures were measured at the lips via a mass spectrometer (VG Spectralab M). Pulse oximetry (\(Sp_{\text{O}_2}\)) (Ohmeda Biox 3700, set to fast averaging time of 2 s) and electrocardiogram (Hewlett-Packard 78351A) were measured continuously throughout the study.

Breath-by-breath values of inspiratory time (\(T_i\), s), expiratory time (\(T_e\), s), total breath time (\(T_{\text{TOT}} = T_i + T_e\), s), ventilatory frequency (\(f = 60/T_{\text{TOT}}\), bpm), tidal volume (\(V_T\), litre \(\text{BTPS}\)), instantaneous minute ventilation (\(\dot{V}_E^\text{inst} = f \cdot V_T\), litre \(\text{BTPS}\)), mean inspiratory flow (\(\dot{V}_I = T_i \cdot V_T\), litre s\(^{-1}\)), inspiratory time:total breath time ratio (\(T_i/T_{\text{TOT}}\)), \(Sp_{\text{O}_2}\) (%), inspired and end-tidal partial pressures were digitized using a DEC PDP 11/23 computer and stored on disk for off-line analysis. During each study, subjects listened to music through headsets to mask any laboratory noise and were requested to remain awake. The laboratory was well-lit to help prevent subjects falling asleep.

Subjects breathed room air for 15 min before two breaths of 100% nitrogen were given followed by an inspired oxygen concentration of 10% to reduce oxygen saturation abruptly to 80–82%. This was maintained for 10 min after which one breath of 100% oxygen was given before returning to room air and the study terminated. Isocapnia was maintained for 10 min after which one breath of 100% oxygen was given before returning to room air and the study terminated.

\textbf{Results}

All 12 subjects completed the study visits without any complications and none reported significant side effects. Two of the 12 subjects had markedly irregular breathing which made analysis of ventilatory variables extremely difficult and they were excluded from analysis. The 10 subjects analysed had a mean age of 33 (range 26–49) yr, mean height 1.80 (1.64–1.88) m and mean weight 76.8 (60.0–94.5) kg.

With domperidone 10 mg, plasma concentrations were median 9.7 (interquartile range 7.5–14.4) ng ml\(^{-1}\), which increased to 25.1 (22.6–28.9) ng ml\(^{-1}\) with 20 mg. Concentrations after 30 mg (30.3 (20.1–33.2) ng ml\(^{-1}\)) were not significantly different from those after 20 mg.

In all subjects, the abrupt reduction in oxygen saturation to 80% (±2%) caused a sharp increase in ventilation, with peak ventilation occurring within

\textbf{DATA ANALYSIS AND STATISTICS}

The relationship between domperidone dose and plasma domperidone concentrations for the group was determined and subjected to the Friedman test and Dunn’s multiple comparison test for significant differences.

Mean values of the measured ventilatory variables were calculated for each subject for every minute of each study. Two specific 1-min periods were used for analysis based on minute ventilation. They were: baseline ventilation during normoxia (B), defined as minute ventilation during the last minute before the onset of hypoxia, and peak minute ventilation during the hypoxic period (H) (fig. 1). The acute hypoxic ventilatory response was defined as the difference between the two periods H and B. The Friedman test was used to examine the effect of increasing domperidone dose on baseline ventilation (B) and the hypoxic response (H–B). In cases of statistical significance, multiple pairwise comparisons were made post hoc with Dunn’s multiple comparison test.

As the bioavailability of oral domperidone is low (approximately 13–17\(^{\text{\%}}\)) because of hepatic and gut wall metabolism, plasma domperidone concentrations for any of the dose regimens may vary substantially. To allow for this possibility, individual results of hypoxic responses were plotted against plasma domperidone concentrations and the best linear relationship fitted (using the least squares linear regression method) for every subject. Further analyses were undertaken using parametric or non-parametric tests as appropriate.

To assess the quality of the imposed ventilatory variables (i.e. \(P_{\text{EtCO}_2}, Sp_{\text{O}_2}\) and \(P_{\text{ItCO}_2}\)), two-way analysis of variance for repeated measures (balanced design) was performed. In cases of statistical significance, multiple pairwise comparisons were made post hoc with the Tukey test. Statistical significance was set at \(P < 0.05\) for all analyses. All computations were carried out using GraphPad Prism 2.01 statistical package, running within MS DOS 6.2.

\textbf{Figure 1} Oxygen saturation (\(Sp_{\text{O}_2}\)), instantaneous minute ventilation (\(\dot{V}_E^\text{inst}\)) and end-tidal carbon dioxide (\(P_{\text{EtCO}_2}\)) plotted against time, for a typical subject. Mean values for each 1-min period are presented, with periods B (baseline ventilation) and H (peak ventilation during hypoxic period) shown for this subject.

\textbf{Results}
the first 5 min followed by a decline in ventilation by the end of the 10-min hypoxic period. Ventilation returned to baseline on returning to normoxia. There were no significant differences in $P_CO_2$ during the measurement periods for all domperidone treatment regimens in all subjects. $Sp_O_2$, during the hypoxic measurement period (H) was not significantly different for all domperidone doses for any of the subjects. This was also the case for $E_P/H$. Table 1 shows the results for imposed ventilatory variables.

Increasing doses of domperidone did not significantly affect either baseline minute ventilation or mean inspiratory flow rate. The hypoxic responses for each subject for all four treatment regimens are shown in table 2. There was no significant difference in the hypoxic response between the four treatment regimens (Friedman test) but there was a trend for the 20-mg dose of domperidone to be greater than placebo. However, when individual subject hypoxic responses were plotted against plasma domperidone concentrations and linear relationships constructed, they appeared to fall into two groups: five subjects (subject Nos 2, 3, 6, 11 and 12) showed a good hypoxic response to increasing concentrations of domperidone (increase of at least 2 litre min$^{-1}$ per 10 ng ml$^{-1}$ increase in plasma domperidone concentration) and the other five only minimally (fig. 2). When the slopes of these two groups were compared using the Mann–Whitney U test, they differed significantly ($P=0.008$). No correlation was found between the magnitude of placebo hypoxic response and the responsiveness to increasing concentrations of domperidone (correlation coefficient $=0.31$).

In the group of subjects whose hypoxic responses were augmented by at least 2 litre min$^{-1}$ per 10 ng ml$^{-1}$ increase in plasma domperidone concentration (table 3), there were differences between treatment regimens (Friedman analysis, $P=0.003$). The hypoxic responses of domperidone 20 mg and 30 mg were

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**Table 1** Mean (sd) imposed variables in the two measurement periods for the four treatment regimens. B = Baseline; H = hypoxia

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_CO_2$</td>
<td>5.29 (0.24)</td>
<td>5.30 (0.31)</td>
<td>5.33 (0.44)</td>
<td>5.28 (0.34)</td>
</tr>
<tr>
<td>$P_CO_2$</td>
<td>13.37 (0.36)</td>
<td>13.29 (0.24)</td>
<td>13.28 (0.60)</td>
<td>13.45 (0.47)</td>
</tr>
<tr>
<td>$Sp_O_2$</td>
<td>95.8 (1.8)</td>
<td>95.3 (1.6)</td>
<td>96.3 (1.2)</td>
<td>95.6 (1.3)</td>
</tr>
</tbody>
</table>

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**Table 2** Acute hypoxic ventilatory response for the four treatment regimens for all subjects

<table>
<thead>
<tr>
<th>Subject No.</th>
<th>Placebo (litre min$^{-1}$)</th>
<th>10 mg (litre min$^{-1}$)</th>
<th>20 mg (litre min$^{-1}$)</th>
<th>30 mg (litre min$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3.57</td>
<td>4.18</td>
<td>2.50</td>
<td>4.69</td>
</tr>
<tr>
<td>2</td>
<td>9.46</td>
<td>8.56</td>
<td>19.45</td>
<td>15.60</td>
</tr>
<tr>
<td>3</td>
<td>7.65</td>
<td>7.94</td>
<td>13.36</td>
<td>27.04</td>
</tr>
<tr>
<td>5</td>
<td>8.72</td>
<td>5.93</td>
<td>10.76</td>
<td>4.23</td>
</tr>
<tr>
<td>6</td>
<td>8.21</td>
<td>15.56</td>
<td>22.30</td>
<td>25.85</td>
</tr>
<tr>
<td>7</td>
<td>4.48</td>
<td>9.31</td>
<td>6.27</td>
<td>4.25</td>
</tr>
<tr>
<td>8</td>
<td>8.83</td>
<td>6.61</td>
<td>10.21</td>
<td>6.74</td>
</tr>
<tr>
<td>9</td>
<td>7.64</td>
<td>3.53</td>
<td>4.73</td>
<td>5.77</td>
</tr>
<tr>
<td>11</td>
<td>8.27</td>
<td>19.40</td>
<td>20.82</td>
<td>11.22</td>
</tr>
<tr>
<td>12</td>
<td>3.74</td>
<td>4.79</td>
<td>15.78</td>
<td>15.69</td>
</tr>
<tr>
<td>Median</td>
<td>7.93 (6.06, 8.05)</td>
<td>7.28 (5.36, 8.94)</td>
<td>12.06 (8.24, 17.61)</td>
<td>8.98 (5.23, 15.65)</td>
</tr>
</tbody>
</table>

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**Figure 2** Individual subject hypoxic responses (acute hypoxic ventilatory response (AHVR)) plotted against plasma domperidone concentration with regression lines. Subject Nos 2, 3, 6, 11 and 12 on the left responded briskly to increasing concentrations of domperidone.
Domperidone dose and hypoxic ventilation

Table 3 Acute hypoxic ventilatory response for the subjects \( n = 5 \) who showed a good response to increasing doses of domperidone (litre min\(^{-1}\)). *Significant difference \( (P < 0.05) \) compared with placebo

<table>
<thead>
<tr>
<th>Placebo</th>
<th>10 mg</th>
<th>20 mg</th>
<th>30 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>8.21</td>
<td>8.56</td>
<td>19.45*</td>
</tr>
<tr>
<td>(range)</td>
<td>(3.74, 9.47)</td>
<td>(4.79, 19.40)</td>
<td>(13.37, 22.30)</td>
</tr>
</tbody>
</table>

significantly greater than those for placebo (post hoc Dunn’s multiple comparison test) but no difference in hypoxic responses were found between placebo and the 10-mg dose or between domperidone 20 mg and 30 mg.

Discussion

In this study, we wished to determine the relationship between incremental doses of domperidone and the potentiation of the acute hypoxic ventilatory response in male subjects. We found that increasing the dose of domperidone beyond 20 mg 8 hourly did not reliably increase plasma domperidone concentrations further and plasma domperidone concentrations in different subjects given the same dose were quite variable. Domperidone did not affect baseline ventilation and increasing doses appeared not to augment hypoxic responses in our subjects but there was marked individual variation in hypoxic responsiveness to domperidone. In subjects who were sensitive to increasing doses of domperidone, hypoxic responses appeared to be greatest with the 20-mg dose but this must be interpreted with caution because only five subjects were analysed. It was not possible to predict which subjects were likely to respond to domperidone.

As we encountered wide plasma variations in a previous study\(^2\) and the bioavailability of oral domperidone is 13–17%\(^{16}\) because of substantial hepatic and gut metabolism, we opted for a 2-day treatment regimen for the different doses to achieve steady-state plasma concentrations. The variability in plasma domperidone concentrations found at each dose in this study was likely to be caused by individual differences in “first-pass” metabolism. However, pharmacogenetic differences in domperidone metabolism could not be excluded although we could find no evidence to support this hypothesis. Drug carry-over effects were also unlikely to be responsible for the variability in plasma concentrations at each dose level as we had a minimum 3-day washout period (the majority had 5 days) between finishing and starting the next treatment regimen.

We were surprised that increasing doses of domperidone did not augment the mean hypoxic response in our subjects. Our previous study\(^2\) and other investigators\(^\text{2, 10, 11}\) have demonstrated an increase in the hypoxic response in humans after pretreatment with domperidone. When the hypoxic responses were plotted against plasma domperidone concentrations in each of our subjects, we found that they either responded well to increasing doses or were only minimally responsive to the effects of domperidone. The effect of domperidone on the hypoxic response appears to be variable in humans, and in our study we probably encountered an exaggerated division in responses thus resulting in our inability to demonstrate any augmentation of the hypoxic response with domperidone pretreatment. Nevertheless, using our arbitrary division based on subjects’ hypoxic response–plasma domperidone concentration relationship, we decided to perform subgroup analysis in subjects sensitive to the effects of domperidone as there was sufficient evidence from other investigators\(^\text{2, 10, 11}\) that domperidone augmented the hypoxic response.

Domperidone, regardless of the dose used, did not affect baseline ventilation. Similar results were found in our previous study\(^\text{12}\) and also by other investigators.\(^\text{2, 10}\) However, Bascom and co-workers\(^\text{11}\) found that domperidone significantly increased baseline ventilation (mean increase of 2 litre min\(^{-1}\) or 14% of control baseline). This difference may have resulted from different study conditions. In the study of Bascom and colleagues, subjects were studied under conditions of mild hypercapnia while our study was conducted at isocapnia with subjects remaining at their resting \( P_t CO_2 \) level throughout the hypoxic period. Both Javaheri and Guerra\(^2\) and Delpierre and co-workers\(^\text{10}\) used a rebreathing isocapnic hypoxic ventilatory response technique (maintaining end-tidal carbon dioxide concentration at 7%). Therefore, it was likely that different experimental conditions determined whether or not domperidone increased baseline ventilation.

Previous studies examining the influence of domperidone on the hypoxic response also showed wide variability in individual sensitivities. Delpierre and co-workers\(^\text{10}\) gave domperidone 0.1 mg kg\(^{-1}\) i.v. and measured the ventilatory response to hypoxia 30 min after injection. They found a mean increase in the relationship of ventilation to \(\Delta H_\text{O_2} \) (slope A) of 50 (sd 64)% with progressive hypoxia (\(\Delta H_\text{O_2} \), 70–80%) after domperidone. The slope increased by more than 20% in only six of 10 subjects (their fig. 1). It is possible that they had also studied subjects who were minimally sensitive to the effects of domperidone, as found in our study. As their study used an i.v. preparation of domperidone, it was unlikely that the lack of effect seen in four of their subjects was a result of inadequate plasma concentrations. Unfortunately, plasma venous domperidone concentrations were not measured in their study. Similarly, Javaheri and Guerra\(^2\) studied eight male subjects and found that domperidone 20 mg orally 8 hourly, significantly augmented the hypoxic response by a mean of 52%. However, by examining individual responses to domperidone (their fig. 2) it can be seen that at least three of their subjects responded only minimally to domperidone.

In contrast, Bascom and colleagues\(^\text{11}\) examined six subjects and all had augmented hypoxic responses after domperidone pretreatment. As their subjects were studied under conditions of mild hypercapnia, this may well have influenced their overall results. Furthermore, Javaheri and Guerra\(^2\) found that domperidone caused a small (but insignificant) augmentation of the hypercapnic ventilatory response. This small degree of potentiation of the hypercapnic ventilatory response coupled with the hypoxic/hypercapnic interaction at the peripheral chemoreceptors may
well have resulted in all of Bascom’s subjects increasing their hypoxic responses significantly after domperidone. Therefore, the available evidence suggests that subjects differ in their hypoxic sensitivity to domperidone and up to 50% of the population may not increase their hypoxic response when pretreated with domperidone. However, this may not be the case if hypercapnia was also present, as in Bascom’s study. Further investigation would be required to assess the magnitude of the hypercapnic/hypoxic interaction after pretreatment with domperidone.

Our study attempted to examine the dose–response relationship between domperidone and the acute hypoxic ventilatory response. Only 50% of our subjects responded to increasing doses of domperidone and in this group we found the greatest increase with the 20-mg dose, with no additional effect from the 30-mg dose. However, as the number of subjects analysed was small, we were unable to assess if a plateau had been reached with the 20-mg dose without risking a type II statistical error. Nevertheless, 60 mg per day appears to be the maximal acceptable amount for most investigators using domperidone to treat gastrointestinal disorders. Therefore, 20 mg 8 hourly would seem to be the most appropriate regimen for augmentation of the hypoxic response, although some variation in plasma domperidone concentrations achieved would be expected. Unfortunately, in our study, it was not possible to predict from baseline ventilatory variables which subject would be sensitive to domperidone.

Animal studies have suggested that there may be two sets of dopamine receptors (inhibitory and excitatory) located in the carotid body with different affinities for dopamine. In a recent review of carotid body chemoreceptors, Gonzalez and co-workers proposed that the more accessible dopamine receptors with higher affinity for dopamine were responsible for the inhibitory action of dopamine. Domperidone would be more likely to bind onto these high affinity inhibitory receptors rather than the low affinity dopamine excitatory receptors thus resulting in augmentation of the hypoxic response. The degree of accessibility of these high affinity inhibitory dopamine receptors to domperidone may account for the variation in hypoxic responses seen in humans or alternatively, differences in the expression of active transporters (e.g. P-glycoprotein) controlling the removal of domperidone from the carotid bodies may be responsible.

In summary, we have demonstrated that domperidone increased the ventilatory response to hypoxia in only 50% of subjects. In those that were sensitive to the effects of domperidone, the 20-mg dose regimen appeared to be adequate in augmenting the hypoxic response. However, we were unable to predict which subjects would respond to increasing doses of domperidone.

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References