Interaction of the effects of domperidone and sub-anaesthetic concentrations of isoflurane on the immediate and sustained hypoxic ventilatory response in humans†

I. T. Foo, S. E. Martin, R. J. Lee, G. B. Drummond and P. M. Warren

Summary
Twenty normal male subjects with brisk hypoxic ventilatory responses were recruited and ventilatory responses to sustained isocapnic hypoxia (Sao₂, 80.4 (± 1.3)% for 20 min) were studied on separate days under four conditions: hypoxia alone, with or without domperidone, and 0.1 MAC of end-tidal isoflurane, with or without domperidone. Ventilatory variables were subjected to analysis of variance with estimation of the effects of isoflurane and domperidone, and their interaction. Isoflurane reduced the initial increase in ventilation significantly by 3.12 (95% confidence limits 1.69, 4.55) litre min⁻¹ (P < 0.05) and domperidone increased the initial increase in ventilation by 1.78 (0.35, 3.21) litre min⁻¹ (P < 0.05). Neither isoflurane nor domperidone affected the subsequent ventilatory decline. No interaction was found between these agents. These results confirm that 0.1 MAC of isoflurane suppressed the initial hypoxic ventilatory response but not the subsequent ventilatory decline when hypoxia was sustained. Domperidone offset the suppressive effect of isoflurane on the hypoxic ventilatory response but no interaction was detected. (Br. J. Anaesth. 1995; 74: 134-140)

Key words
Anaesthetics; volatile, isoflurane, Hypoxia, Ventilation, hypoxic response. Pharmacology, domperidone.

Sub-anaesthetic concentrations (0.1 MAC) of volatile anaesthetic agents suppress the ventilatory response to hypoxia [1–3] and, as a consequence, patients may not respond fully to hypoxia in the early postoperative period. However, the effect of low doses of isoflurane on the hypoxic ventilatory response remains unclear; Temp, Henson and Ward [4] found no effect with 0.1 MAC of isoflurane on the initial ventilatory response to hypoxia. This is in direct contrast with suppression of the hypoxic ventilatory response noted by Knill and co-workers with 0.1 MAC of isoflurane [3]. Potential factors resulting in the discrepancy of the results have been discussed recently [5, 6]; small numbers of subjects, different experimental techniques and laboratory conditions may have contributed to the conflicting data.

Little is known about the site and mechanism of the suppressive effect of volatile agents. Indirect evidence suggests that the most likely sites of action are the carotid body chemoreceptors [7]. Dopamine D₂ receptors are present in carotid bodies [8] and dopamine may be involved in mediating the hypoxic ventilatory response [9]. In humans, infusion of low-dose dopamine depresses the response [10] and domperidone, a selective dopamine D₂ receptor antagonist which does not readily cross the blood–brain barrier [11], augments it [12]. Dopamine antagonists may act by reversing an inhibitory effect of dopamine and revealing dopamine excitatory receptors [13].

We considered if domperidone might reverse depression of carotid chemoreceptors by isoflurane, and perhaps indicate the mechanism of action of isoflurane. We therefore studied the effect of 0.1 MAC of isoflurane on the ventilatory response to sustained hypoxia with and without domperidone to determine if sub-anaesthetic levels of this volatile agent do suppress the hypoxic ventilatory response and to determine if domperidone influenced this effect.

Subjects and methods
We studied 20 healthy male volunteers with no history of cardiopulmonary disease. None was taking medication at the time of study and all were asked to refrain from taking substances known to affect respiration for a minimum of 6 h before the study. Local Ethics Committee approval was obtained and all subjects gave written informed consent.

The subjects attended the laboratory on five occasions. The first visit was a familiarization and screening study. A medical history was taken and FEV₁ and FVC were measured to confirm normal lung function. The ventilatory response to sustained
Domperidone, isoflurane and ventilation in hypoxia

hypoxia was then measured. Subjects were studied further only if their initial increase in ventilation in response to a reduction in ear oxygen saturation ($S_{aO_2}$) to 80% was 20% or more above their baseline level. The remaining four visits were organized as a 2 x 2 factorial experiment using a four-period crossover design. All subjects received four treatment combinations: control gas mixture and placebo, control gas mixture and domperidone, isoflurane gas mixture and placebo, and isoflurane gas mixture and domperidone. Twenty of the possible 24 sequences of four treatments were selected. One of these sequences was allocated randomly to each of the 20 subjects to determine the order in which each subject was given the four treatment combinations. Each visit was on a separate day and treatment visits were separated by 2 days to ensure elimination of domperidone. To minimize the effects of diurnal variation on the hypoxic ventilatory response, visits were scheduled at the same time of day for any given subject.

The methods used for recording ventilatory variables have been described previously [14]. Briefly, the subjects were seated upright in a comfortable armchair in a well-lit room and breathed through a mouthpiece and low resistance two-way valve. The inspiratory port of the valve was connected to a five-way valve (Hans-Rudolf 5-way Gatlin Valve series 2430) which allowed inspired gases to be changed 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 ($P_{iO_2}$, $P_{eO_2}$) and carbon dioxide ($P_{iCO_2}$, $P_{eCO_2}$) partial pressures were measured at the lips with a mass spectrometer (VG Spectralab M). Ear arterial oxygen saturation ($S_{aO_2}$) was recorded continuously using a Hewlett-Packard 47201A ear oximeter adapted to give a fast response time of 1.6 s [15]. The electrocardiogram (Hewlett-Packard 78351A) was monitored throughout. Breath-by-breath values of inspiratory time ($T_i$), expiratory time ($T_e$), total breath time ($T_{bm} = T_i + T_e$), ventilatory frequency ($f = 60/T_{bm}$), tidal volume ($V_T$, btps), instantaneous minute ventilation ($V_{Ebm} = f x V_T$, btps), mean inspiratory flow ($V_{I}: T_i$), inspiratory time:total breath time ratio ($T_i/T_{bm}$), $S_{aO_2}$ inspired and end-tidal partial pressures were digitized using a DEC PDP 11/23 computer and stored on disk for offline analysis. Oxygen consumption ($V_{O_2}$, STPD) and carbon dioxide output ($V_{CO_2}$, STPD) were measured from collections of mixed expired gas made over 2-min periods and the gas exchange ratio calculated ($R$). During the measurement periods subjects listened to music through headphones. In addition, to avoid any depression of the hypoxic ventilatory response by sleep [16], they were asked to remain awake and were aroused if they appeared to be asleep.

In seven of the 20 subjects, sleep state was monitored using electroencephalography (EEG). Two electrooculograms, two EEG signals (CZ–PZ), two mixed channels (CZ–right outer canthus, CZ–left outer canthus) and submental electromyogram were recorded on a paper polygraph and subsequently scored in 20-s epochs for sleep according to conventional criteria [17].

Measurements were made with the subjects seated at rest. Initially, room air was breathed for 15 min and duplicate measurements of $V_{O_2}$ and $V_{CO_2}$ were made between 5 and 10 min. $S_{aO_2}$ was then reduced to 80–81% for 20 min. To achieve a square wave response, subjects were initially given two breaths of 100% nitrogen followed by an inspired oxygen concentration of approximately 10%. At the end of hypoxia, subjects were given one breath of 100% oxygen before returning to room air. All changes in gas concentrations were made during expiration. During hypoxia, carbon dioxide was added to the inspired gas to maintain $P_{eCO_2}$ as close as possible to the baseline normoxic value.

Isoflurane was given using a Cyprane Isotec Mark 3 vaporizer. The inspired concentration was adjusted as necessary to maintain an inspired concentration of 0.19% throughout. Concentrations were measured at the lips with a Brüel and Kjær gas analyser (model 1304) and values recorded at 6-s intervals using a custom-written program on a BBC microcomputer.

Subjects received oral domperidone 20 mg or placebo the night before the measurement visit and then domperidone 10 mg or placebo every 4 h after waking on the day of the visit. Venous blood samples were obtained for measurement of plasma concentrations of domperidone at the end of each measurement period.

Mean values of the ventilatory variables were calculated for each subject for every minute and also during the following four phases of each measurement period: baseline normoxia (A1: 4 min immediately before the onset of hypoxia); early hypoxia (H1: minutes 3–6 inclusive of hypoxia); late hypoxia (H2: minutes 17–20 inclusive of hypoxia); and normoxic recovery (A2: minutes 2–5 inclusive after return to breathing room air).

Group means ($SD$) for imposed ventilatory variables and group means and confidence limits (CL) for studied ventilatory variables in the four phases were calculated for each treatment combination. The ventilatory variables in each phase were subjected to analysis of variance allowing for the differences between subjects, visits, treatment combinations, first-order carry-over effects of the treatment combinations, and using A1 and H1 as covariates where appropriate. The effects of isoflurane and domperidone and the interaction between the treatments were estimated and significance tests performed to examine if these effects were different from zero. All tests of significance were two-tailed and unadjusted $P$ values are presented.

The EEG data were used to calculate the percentage of the measurement period spent in any stage of sleep for each individual and the median (range) given for each treatment combination.

Results

Twenty-six subjects were screened. Two were rejected because their initial response to hypoxia was less than 20%. Four others were not studied for...
other reasons. The 20 subjects recruited into the study had a mean age of 32 (range 25–49) yr, mean height 1.80 (1.64–1.93) m and weight 76.5 (63.5–96.2) kg. All had normal values for ventilatory capacity (FEV, 84–117 % predicted; FVC 89–124 % predicted). All completed the study without any adverse effects. Mean inspired isoflurane concentration was 0.19 (SD 0.02)% and end-tidal isoflurane was 0.13 (0.01)%. For technical reasons these results were based on 37 instead of 40 isoflurane periods. The mean plasma concentration of domperidone for the subjects was 8.14 (SD 2.86) ng ml⁻¹.

The pattern of the ventilatory response to hypoxia was the same for the four treatment combinations with an initial brisk increase in ventilation followed by a slower decrease (fig. 1). During hypoxia, PeCO₂ was maintained within 0.12 kPa of the baseline normoxic value and SaO₂ was reduced to approximately 80 % (fig. 1). There was no significant difference in either variable between the four treatment combinations at any of the four phases (table 1). PeCO₂ was reduced to approximately 6.3 kPa during hypoxia and was similar during the four phases of measurement for the four treatment conditions, except during late hypoxia in the presence of isoflurane alone when PeCO₂ was increased significantly (table 1).

Isoflurane had no significant effect on V̇O₂ but caused a small but significant decrease in V̇CO₂ (P = 0.002) during baseline normoxia (table 2). Isoflurane had no significant effect during this phase on any ventilatory variable (tables 3, 4). In contrast, during early hypoxia, isoflurane decreased Ve, V̇̇T, Ṫ and Ṫ:Ṫ:Ṫ significantly and increased Ṫ significantly but had no significant effect on f and V̇:Ṫ:Ṫ (fig. 2, tables 3, 4). The time taken for ventilation to increase to a maximum value was prolonged also (fig. 3). During late hypoxia, isoflurane had no effect on any ventilatory variable except Ṫ:Ṫ, which was increased significantly (tables 3, 4). No significant isoflurane effects were detected during normoxic recovery.

Domperidone had no significant effect on V̇O₂ but caused a small but significant decrease in V̇CO₂ (P = 0.01) compared with control.

### Table 1
Mean (SD) imposed ventilatory variables in the four phases during treatment with control and placebo (Control), isoflurane and placebo (Isoflurane), control and domperidone (Domperidone), and isoflurane and domperidone (I + D). **Significant difference (P = 0.01) compared with control.

<table>
<thead>
<tr>
<th></th>
<th>Normoxia baseline</th>
<th>Early hypoxia</th>
<th>Late hypoxia</th>
<th>Normoxia recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>PeCO₂ (kPa)</td>
<td>5.37 (0.40)</td>
<td>5.34 (0.40)</td>
<td>5.36 (0.40)</td>
<td>5.44 (0.36)</td>
</tr>
<tr>
<td>Control</td>
<td>5.40 (0.45)</td>
<td>5.40 (0.40)</td>
<td>5.46 (0.40)</td>
<td>5.41 (0.36)</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>5.36 (0.40)</td>
<td>5.36 (0.40)</td>
<td>5.37 (0.36)</td>
<td>5.40 (0.40)</td>
</tr>
<tr>
<td>Domperidone</td>
<td>5.35 (0.31)</td>
<td>5.37 (0.31)</td>
<td>5.37 (0.36)</td>
<td>5.41 (0.45)</td>
</tr>
<tr>
<td>I + D</td>
<td>13.52 (0.49)</td>
<td>6.22 (0.27)</td>
<td>6.39 (0.27)</td>
<td>12.42 (0.67)</td>
</tr>
<tr>
<td>PeO₂ (kPa)</td>
<td>13.43 (0.49)</td>
<td>6.29 (0.31)</td>
<td>6.56 (0.31)**</td>
<td>12.77 (0.98)</td>
</tr>
<tr>
<td>Control</td>
<td>13.52 (0.72)</td>
<td>6.18 (0.36)</td>
<td>6.33 (0.22)</td>
<td>12.54 (0.80)</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>13.35 (0.49)</td>
<td>6.19 (0.22)</td>
<td>6.51 (0.45)</td>
<td>12.39 (1.03)</td>
</tr>
<tr>
<td>Domperidone</td>
<td>96.0 (0.9)</td>
<td>80.2 (1.3)</td>
<td>80.7 (0.9)</td>
<td>95.3 (0.9)</td>
</tr>
<tr>
<td>Control</td>
<td>95.9 (0.5)</td>
<td>80.0 (1.3)</td>
<td>80.8 (1.8)</td>
<td>95.4 (1.3)</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>96.2 (0.9)</td>
<td>80.2 (1.3)</td>
<td>80.3 (1.8)</td>
<td>95.2 (0.9)</td>
</tr>
<tr>
<td>Domperidone</td>
<td>96.2 (0.9)</td>
<td>80.2 (1.3)</td>
<td>80.3 (1.8)</td>
<td>95.2 (0.9)</td>
</tr>
</tbody>
</table>
affected by domperidone during late hypoxia. During normoxic recovery, domperidone increased $f$ significantly, but had no effect on any other variable (tables 3, 4).

No significant interaction was found between domperidone and isoflurane with regard to the hypoxic ventilatory response (tables 3, 4). There was no evidence of any first-order carry-over effects of treatment or any visit/period effect.

In the seven subjects in which the EEG was monitored, there was wide variation between subjects in the percentage of sleep during the measurement periods. Median (range) percent values for the four measurement periods were: control and placebo 0 (0–18.5)%, isoflurane and placebo 8 (0–25.6)%, control and domperidone 0 (0–12.5)%, and isoflurane and domperidone 6.1 (2.1–11)%. The episodes of sleep occurred throughout the measurements and were not concentrated in any one phase.

**Discussion**

We have shown that a sub-anaesthetic dose (0.1 MAC) of isoflurane reduced the early increase in ventilation in response to hypoxia, but did not affect the late response when hypoxia was sustained for 20 min. The effect on ventilation during early hypoxia was caused by a reduction in $\nu_T$ which, in turn, was a result of a shortening of $T_1$. Domperidone increased significantly the early response of ventilation to hypoxia but had no significant effect on the late response. The influence of domperidone on ventilation was caused by an increase in $\nu_T: T_1$ with no apparent changes in respiratory timing. Thus
Isoflurane and domperidone appear to affect different aspects of ventilatory control. This is supported by the observation that although domperidone offset the suppressive effect of isoflurane on the hypoxic ventilatory response, there was no interaction between the two agents.

As we were investigating both inhibition and potentiation of the hypoxic ventilatory response, we studied subjects who had a brisk response to hypoxia in order to minimize the number required to provide significant results. However, only two potential subjects were rejected because their initial ventilatory response to hypoxia was less than 20%. There was wide variation in our subjects' ventilatory response, for example to 30.25 and 35.91 litre min⁻¹. The variation in hypoxic response found was similar to that of Temp, Henson and Ward [4], and our results resemble those reported in the male population by Suzuki and co-workers [18].

We chose to maintain the inspired concentration of isoflurane at 0.19% throughout the study rather than attempt to adjust the concentration to achieve a constant end-tidal concentration. This was because the resolution of the digital output from the gas analyser was limited at this concentration. Furthermore, fluctuations in end-tidal isoflurane concentrations over short periods do not necessarily reflect cerebral concentrations. After about 15 min of 0.19% inspired isoflurane, end-tidal concentration is 0.12-0.14%, giving the desired level of approximately 0.1 MAC [19].

Multiple tests of significance were performed. We specified a priori that we would test the effects of both isoflurane and domperidone alone, and also the interaction of the two agents. As the ventilatory variables measured are not independent, and the measurements from the four phases during each measurement period cannot be regarded as independent, formal correction for multiple testing is difficult. We have therefore presented unadjusted $P$ values which should be interpreted with caution because of multiple comparisons.

There is debate on the sensitivity of the hypoxic ventilatory response to sub-anaesthetic levels of volatile agents. Early work by Knill and co-workers showed that 0.1 MAC of halothane, enflurane and isoflurane all reduced the ventilatory response to

<table>
<thead>
<tr>
<th>$V_{T}$</th>
<th>Normoxia baseline</th>
<th>Early hypoxia</th>
<th>Late hypoxia</th>
<th>Normoxia recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{litre min}^{-1}$</td>
<td>$-0.07 (-0.53, 0.39)$</td>
<td>$-3.12 (-4.55, -1.69)$</td>
<td>$0.97 (-0.38, 2.32)$</td>
<td>$0.30 (-0.40, 1.00)$</td>
</tr>
<tr>
<td>Domperidone</td>
<td>$0.05 (-0.41, 0.51)$</td>
<td>$1.78 (0.35, 3.21)$</td>
<td>$0.64 (-0.59, 1.87)$</td>
<td>$0.41 (-0.23, 1.05)$</td>
</tr>
<tr>
<td>Interaction</td>
<td>$-0.10 (-0.56, 0.36)$</td>
<td>$0.02 (-1.41, 1.45)$</td>
<td>$0.29 (-0.88, 1.46)$</td>
<td>$-0.15 (-0.75, 0.45)$</td>
</tr>
<tr>
<td>$f$ (b.p.m.)</td>
<td>$0.01 (-0.03, 0.05)$</td>
<td>$-0.15 (-0.21, -0.09)$</td>
<td>$0.10 (0.00, 0.02)$</td>
<td>$0.06 (0.00, 0.12)$</td>
</tr>
<tr>
<td>Domperidone</td>
<td>$0.00 (-0.04, 0.04)$</td>
<td>$0.10 (0.04, 0.16)$</td>
<td>$0.06 (-0.04, 0.16)$</td>
<td>$-0.01 (-0.07, 0.05)$</td>
</tr>
<tr>
<td>Interaction</td>
<td>$0.00 (-0.04, 0.04)$</td>
<td>$0.00 (-0.06, 0.06)$</td>
<td>$0.03 (-0.05, 0.11)$</td>
<td>$0.02 (-0.04, 0.08)$</td>
</tr>
<tr>
<td>$\text{litre}$</td>
<td>$0.02 (-0.74, 0.70)$</td>
<td>$-0.56 (-1.16, 0.04)$</td>
<td>$-0.02 (-0.74, 0.70)$</td>
<td>$0.33 (-0.23, 0.89)$</td>
</tr>
<tr>
<td>Domperidone</td>
<td>$0.02 (-0.70, 0.74)$</td>
<td>$0.10 (-0.50, 0.70)$</td>
<td>$-0.04 (-0.76, 0.68)$</td>
<td>$0.64 (0.10, 1.18)$</td>
</tr>
<tr>
<td>Interaction</td>
<td>$-0.43 (-1.15, 0.29)$</td>
<td>$0.22 (-0.40, 0.84)$</td>
<td>$-0.04 (-0.76, 0.68)$</td>
<td>$0.09 (-0.45, 0.63)$</td>
</tr>
<tr>
<td>$\text{litre}^{*}$</td>
<td>$0.13 (-0.07, 0.33)$</td>
<td>$0.36 (0.18, 0.54)$</td>
<td>$0.32 (-0.06, 0.70)$</td>
<td>$0.02 (-0.26, 0.30)$</td>
</tr>
<tr>
<td>Domperidone</td>
<td>$0.07 (-0.13, 0.27)$</td>
<td>$0.01 (-0.17, 0.19)$</td>
<td>$0.10 (-0.24, 0.44)$</td>
<td>$-0.20 (-0.44, 0.04)$</td>
</tr>
<tr>
<td>Interaction</td>
<td>$0.07 (-0.13, 0.27)$</td>
<td>$0.02 (-0.16, 0.20)$</td>
<td>$0.05 (-0.29, 0.39)$</td>
<td>$-0.21 (-0.45, 0.03)$</td>
</tr>
</tbody>
</table>

| $T_{i}$ (s) | $-0.08 (-1.57, 1.40)$ | $-0.98 (-4.60, 2.64)$ | $8.68 (4.80, 12.56)$ | $1.55 (-0.36, 3.46)$ |
| Domperidone | $0.67 (-0.82, 2.16)$ | $4.62 (0.98, 8.26)$ | $1.75 (-2.37, 5.87)$ | $0.72 (-1.31, 2.75)$ |
| Interaction | $-0.27 (-1.76, 1.22)$ | $1.35 (-2.27, 4.97)$ | $0.61 (-3.27, 4.49)$ | $-1.10 (-3.01, 0.81)$ |
| $T_{i}$: $\text{litre}^{*}$ (%) | $-0.3 (-1.3, 0.7)$ | $-5.9 (-7.1, -4.7)$ | $-1.9 (-3.7, 0.1)$ | $0.2 (-1.6, 2.0)$ |
| Domperidone | $-1.1 (-2.1, -0.1)$ | $0.4 (-1.0, 1.8)$ | $-0.1 (-1.3, 1.1)$ | $0.1 (-1.1, 1.3)$ |
| Interaction | $0.4 (-0.6, 1.4)$ | $-0.7 (-1.9, 0.5)$ | $0.6 (-0.6, 1.8)$ | $0.6 (-0.6, 1.8)$ |
Domperidone, isoflurane and ventilation in hypoxia

1. Isoflurane and placebo

2. Control and domperidone

3. Isoflurane and domperidone

Figure 2 \( V_T \) vs the subdivisions of \( T_{	ext{awake}} \) in the early hypoxia phase, comparing the values during the control gas mixture and placebo treatment (---) with those obtained during the three other treatment combinations (---).

Figure 3 Histogram of the time to reach maximum ventilation after the onset of hypoxia in the presence (---) and absence (---) of isoflurane.

Downloaded from https://academic.oup.com/bja/article-abstract/74/2/134/452221 by guest on 03 February 2019

F
hypothesis to less than half the awake value [1-3]. However, subsequent studies have given conflicting results. Temp, Henson and Ward [4] could not demonstrate an effect of 0.1 MAC of isoflurane on the ventilatory response to acute or sustained hypoxia, while the study by Nagyova, Dorrington and Robbins [20] using sub-anaesthetic doses of enflurane agreed with the findings of Knill's group. This controversy has been reviewed recently [5, 6] and several differences suggested to account for discrepancies between studies such as the rate of onset of hypoxic stimulus, the state of wakefulness during the studies and the number of subjects studied.

Temp, Henson and Ward examined whether or not the rate of onset of hypoxic stimulus, that is step stimulus (Temp's approach) and ramp stimulus (Knill's approach), explained the differences in results. They found that isoflurane did not affect the response to these stimuli [21]. We have used a similar method to Temp, Henson and Ward and found a significant effect of 0.1 MAC of isoflurane on the early ventilatory response. Both Nagyova's and Dahan's groups also used a step hypoxic stimulus and were able to demonstrate suppressive effects by both enflurane and halothane, respectively [20, 22]. The rate of onset of the hypoxic stimulus therefore appears to be an unlikely explanation of the conflicting isoflurane results.

Sleep depresses the hypoxic ventilatory response by 30% to 60% [16] and it has been suggested that Knill's experimental conditions (subjects semi-recumbent in a quiet darkened room) predisposed his subjects to sleep, especially during administration of isoflurane. This would overestimate the effect of isoflurane. Temp's subjects were essentially "awake" (visual stimulation, manual arousal by observer [4]). We attempted to ensure our subjects remained awake (well-lit room, seated upright, auditory stimulation, manual arousal by observer) but monitoring showed a tendency for subjects to fall asleep during the measurement period, especially in the presence of isoflurane. Sleep may therefore have contributed to the larger effect reported by Knill's group. Sleep probably did not affect our results to any great extent as the amount of time spent asleep by monitored subjects was less than 5 min, spread over the measurement period.

Variation of the hypoxic ventilatory response between days [23] may have resulted in Temp's inability to demonstrate an effect since their control and isoflurane experiments were performed on separate days. By combining the results in 16 subjects from two separate studies [4, 21] they concluded that although they were unable to demonstrate an isoflurane effect, a 20–30% reduction could not be excluded. Similar to Temp, we also measured the control and isoflurane responses on separate days. However, using 20 subjects with our study design (factorial design) allowed the effects of isoflurane to be based on 80 observations as there was no interaction with domperidone. We found a mean reduction of 17% (95% confidence interval 9–25%). The smaller confidence limits indicate a more precise estimate of the true effect of isoflurane. We conclude that isoflurane causes a moderate reduction of the initial hypoxic ventilatory response which Temp and co-workers could not detect because of the variability of the effect.

Unlike halothane [14], isoflurane appeared to
reduce the hypoxic ventilatory response by altering respiratory timing rather than drive. The decrease in ventilation during hypoxia appeared to be caused by reductions in $VT$ and $Ti$ with no significant change in $VT:Ti$. If isoflurane alters respiratory timing whereas halothane affects inspiratory flow rate, then isoflurane may be acting at a different site from halothane. This is in accord with other suggestions [21, 22] that isoflurane behaves differently from halothane. The effect on timing suggests that isoflurane is acting centrally either by a direct action on the medullary rhythm generating centre or by altering integration at that level of signals from the peripheral chemoreceptors, higher centres or feedback from the respiratory muscles. Isoflurane increased the time taken for ventilation to increase to a maximum value, which also suggests an influence on complex integrative systems such as at central sites. The exact mechanism of isoflurane cannot be resolved by this study.

The second aim of this study was to determine if domperidone could counteract the suppressive effects of isoflurane on the hypoxic ventilatory response. Domperidone was chosen as it is a specific dopamine $D2$ receptor antagonist which does not readily cross the blood–brain barrier [11] and therefore its effect on ventilation would be peripheral rather than central. We found that although domperidone augmented the hypoxic ventilatory response, there was no statistical evidence of interaction between isoflurane and domperidone. Domperidone merely offset the suppressive effect of isoflurane during early hypoxia and did not prevent the subsequent decline in ventilation during sustained hypoxia. This effect of domperidone was not proportional to the subject’s response to hypoxia but plasma concentrations of domperidone varied widely between subjects. The inability to show any interaction between isoflurane and domperidone suggests that isoflurane either did not act via mechanisms involving dopamine in the carotid bodies or exerted its suppressive effects centrally through a change in respiratory timing.

Acknowledgements

We thank Dr N. J. Douglas for loan of EEG equipment, the Sir Stanley and Lady Davidson bequest of the University of Edinburgh for funds for consumables, Sanofi Winthrop for supplies of domperidone and the Janssen Research Foundation for funds for consumables, Sanofi Winthrop for supplies of domperidone and the Janssen Research Foundation Edinburgh for funds for consumables, Sanofi Winthrop for

References


