VENTILATORY RESPONSE TO CARBON DIOXIDE DURING EXTRADURAL ANAESTHESIA WITH LIGNOCAINE AND FENTANYL

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Postoperative analgesia may be achieved by the use of extradural opioids [1–6] which enhance both the intensity and duration of analgesia produced by extradural local anaesthetics [7–10]. The most serious adverse effect associated with extradural injection of opioids is ventilatory depression [2,11–21]. As with other side effects, this is dose dependent and more likely to occur with lipid-insoluble opioids [12]. Fentanyl is highly lipid-soluble, and has a rapid onset of action (5–10 min) [22], producing good analgesia with a dose as small as 50 mg extradurally [18,22–24]. The respiratory depressant action of extradural fentanyl has been investigated previously in higher doses, usually in postoperative analgesia [4,5,24] by measurement of ventilatory response to carbon dioxide [25,26].

This study was designed to see if extradural anaesthesia (extending to T4) with a mixture of 2% lignocaine (with adrenaline 1 in 200000) and fentanyl 50 mg causes respiratory depression and to compare this with that, if any, caused by extradural lignocaine alone or with fentanyl 50 mg i.v.

PATIENTS AND METHODS

We studied 27 patients (ASA status I–II) requiring extradural anaesthesia for extracorporeal shock-wave lithotripsy (ESWL) (n = 18) or knee arthroscopy (n = 9). These procedures were chosen because of their brief duration (less than 60 min) and because they do not affect the mechanical properties of the lungs or chest wall. There were 19 males and eight females, age range 24-59 yr, weights 49-103 kg and heights 155-193 cm. No patient had clinical or radiological signs of chest disease. All patients gave informed consent for the study, which was approved by the local Ethics Committee. The ventilatory response to carbon dioxide was assessed by Read’s method [27] the day before the procedure and, after operation, 1 and 2 h after the extradural injection.

The first part of the study was carried out in
nine subjects undergoing ESWL under extradural lignocaine–fentanyl combination. The decrease in sensitivity to carbon dioxide documented previously with higher doses of fentanyl [25,26] was found also with the dose of 50 μg.

In the second part of the study, 18 other patients were allocated randomly to three groups of six each:

Group X-0 received only extradural 2% ligno-
caine with adrenaline 1 in 200000, without i.v. sedation.

Group X-F received the same dose of extradural lignocaine with adrenaline and an i.v. injection of fentanyl 50 μg administered when the extradural injection was completed.

The third group received extradurally a mixture of 2% lignocaine with adrenaline 1 in 200000 and fentanyl 50 μg.

Thus a total of 15 patients received the extradural mixture of lignocaine and fentanyl: nine in the first part and six in the second part of the study. After the absence of significant differences between these two subgroups at rest and on carbon dioxide rebreathing was verified, they were pooled together and are termed X-Fext.

Three overweight patients were graded ASA II (two in group X-Fext, the third in group X-0).

The three groups were comparable in age, weight and height (table I).

Extradural anaesthesia

Patients were not premedicated and they fasted overnight. Arterial pressure and heart rate were recorded with an automatic monitor (Dinamap) and ECG was displayed continuously. An i.v. infusion was started and Ringer Lactate solution 1 litre was infused during the first 20 min. The total volume of i.v. infusion for the 2 h was 1500–2000 ml.

With the patient in the lateral position, extradural puncture was performed at either the T12 space for ESWL or the L2 space for knee arthroscopy. After a test dose of 2% lignocaine 3 ml with adrenaline 1 in 200000, 9 ml (T12) or 17 ml (L2) of the same anaesthetic solution with or without fentanyl 50 μg was injected slowly through the Tuohy needle. The spread of sensory block was assessed by altered sensation to pinprick at the time of the first postoperative carbon dioxide rebreathing test (i.e. 1 h after extradural injection). Three patients developed hypotension at the onset of anaesthesia and were treated with ephedrine 3 mg i.v. No side effects (pruritus, nausea or vomiting, urinary retention) were noted in the patients receiving fentanyl.

Carbon dioxide rebreathing test

The ventilatory response to carbon dioxide was measured by Read's method [27] with a bag-in-the-box system. A 7-litre rebreathing bag was enclosed in a rigid, air-tight box with a side port connected to a Fleisch type 3 pneumotachograph and a Godart 17 212 differential pressure transducer. Wearing a tight fitting nasal mask and with the mouth closed, the patients breathed either room air or from the bag via a wide-bore respiratory circuit including a low resistance inspiratory/expiratory valve and a large three-way stopcock (Rudolph M 2 100). Carbon dioxide concentration in the expired gas was measured continuously by drawing gas from the mask at a flow rate of 500 ml min⁻¹ through a Beckman LB-2 capnograph. During carbon dioxide rebreathing, the sampled gas was returned to the rebreathing bag. A two-channel recorder Allco ED 242-B was used to record ventilation and expired carbon dioxide concentration at a paper speed of 1 mm s⁻¹.

Baseline values were obtained the day before the procedure. The subject had no tea or coffee for 3 h and was at rest and seated comfortably for 10 min before the test. Postoperative tests were performed at 1 and 2 h following extradural anaesthesia (H₁ and H₂ values, respectively) while subjects reclined in bed at a 45° head-up position in the recovery-room.

The bag was filled with 5 litre of 7% carbon dioxide in oxygen at the start of each test and the subject breathed room air for approximately 5 min, during which time ventilation and end-tidal PCO₂ (P\textit{CO}_2) were monitored. When stable ventilatory frequency and P\textit{CO}_2 had been achieved, resting values were recorded for 1 min, which allowed determination of minute ventilation (\(\text{Ve}\)), respiratory rate (RR) and P\textit{CO}_2. The stopcock was turned to the rebreathing bag and the subject asked to take three large breaths. Rebreathing then continued for 4.5 min.

\(P\text{\textit{CO}}_2\) and \(\text{Ve}\) were determined at 30-s intervals.

| Table I. Physical characteristics of the subjects (mean (SD)) |
|-----------------|-----------------|-----------------|-----------------|
| n               | Age (yr) (SD)   | Height (cm) (SD)| Weight (kg) (SD)|
| Group X-0       | 6               | 41 (9)          | 172 (13)        | 72 (18)         |
| Group X-F       | 6               | 41 (12)         | 168 (10)        | 70 (15)         |
| Group X-Fext    | 15              | 37 (9)          | 169 (7)         | 69 (10)         |
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\( \dot{V}_E \) was calculated as the product of the mean of tidal volume and frequency of the three ventilatory cycles bracketing the moment of \( P'_{\text{CO}_2} \), readings. The line of best fit of \( \dot{V}_E \) as a function of \( P'_{\text{CO}_2} \) was calculated using a linear least square regression (as a non-linear description offers no advantage [28]). In addition, the goodness of fit shown by correlation coefficients (r) ranging between 0.91 and 0.98 \((P < 0.01)\) allowed the determination of the slope \( \dot{V}_E/P'_{\text{CO}_2} \) and the intra- or extrapolated value of \( \dot{V}_E \) for \( P'_{\text{CO}_2} = 7.3 \) kPa \((\dot{V}_E 7.3) \) [27,29].

**Statistical analysis**

As distribution of data was log-normally skewed, logarithmic transformation was performed [30]. Statistical comparisons were made using two-way analysis of variance for repeated measures followed by paired-sampled \( t \) tests to compare values at \( H_1 \) and \( H_2 \) with baseline values when the analysis of variance had disclosed significant intra-group differences. The chosen level of statistical significance was \( P < 0.05 \).

**RESULTS**

The height of analgesia attained T4–T5 in 18 of 27 patients with a range from T3 to T8 and no difference between groups. The range of the baseline slope \( \dot{V}_E/P'_{\text{CO}_2} \) was 0.08–0.8 litre min\(^{-1}\) kPa\(^{-1}\); that is, the ventilatory response to carbon dioxide was within the limits of normal responses in young adults [31]. Maximal values of \( P'_{\text{CO}_2} \) at the end of the three tests were close in each patient, but between patients the variations were large, ranging from 6.7 to 9.3 kPa. In general, the greater the \( P'_{\text{CO}_2} \) at onset, the greater it was at the end of the test. All values are given as mean (SD) in table II.

There was no difference between the observed variables for the three groups at the time of baseline measurements.

In group X-0 at 2 h lignocaine with adrenaline caused an increase in \( \dot{V}_E \), a decrease in \( P'_{\text{CO}_2} \) and an increase in ventilatory response to carbon dioxide. However, these variations were not significant. In contrast, in the two groups receiving fentanyl there was evidence of slight ventilatory depression. In group X-F\(_{\text{iv}}\), resting ventilatory frequency was slower and resting \( \dot{V}_E \) lower at 1 h but it returned to normal at 2 h, and the ventilatory response to carbon dioxide was not changed. In group X-F\(_{\text{ext}}\) at rest, ventilatory frequency was slower both at 1 and 2 h and \( \dot{V}_E \) was decreased with \( \dot{V}_E \) being lower at both time points than at baseline in 11 of 15 subjects. It is

**Table II. Ventilation at rest and ventilatory response to carbon dioxide rebreathing (mean (SD)).** \( P'_{\text{CO}_2} \) = end-tidal partial pressure of carbon dioxide; \( RR = \) respiratory rate; \( \dot{V}_E = \) expiratory minute ventilation; \( \dot{V}_E/P'_{\text{CO}_2} \) and \( \dot{V}_E 7.3 \) = slope of the line of best fit of \( \dot{V}_E \) as a function of \( P'_{\text{CO}_2} \) and \( \dot{V}_E \) at \( P'_{\text{CO}_2} = 7.3 \) kPa during carbon dioxide rebreathing. Group X-0 = lignocaine; X-F\(_{\text{iv}}\) = lignocaine + i.v. fentanyl; X-F\(_{\text{ext}}\) = lignocaine + extradural fentanyl. *Significant difference \((P < 0.05)\) from baseline

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 h</th>
<th>2 h</th>
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<tbody>
<tr>
<td><strong>Resting ( P'_{\text{CO}_2} ) (kPa)</strong></td>
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<tr>
<td>Group X-0</td>
<td>5.1 (0.68)</td>
<td>4.8 (0.72)</td>
<td>4.9 (0.62)</td>
</tr>
<tr>
<td>Group X-F(_{\text{iv}})</td>
<td>4.73 (0.78)</td>
<td>4.7 (0.69)</td>
<td>4.8 (0.48)</td>
</tr>
<tr>
<td>Group X-F(_{\text{ext}})</td>
<td>5.2 (1.00)</td>
<td>5.1 (0.73)</td>
<td>5.3 (0.53)</td>
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<tr>
<td><strong>Resting RR (b.p.m.)</strong></td>
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<td></td>
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<tr>
<td>Group X-0</td>
<td>13.2 (4.6)</td>
<td>11.8 (2.6)</td>
<td>13.6 (2.0)</td>
</tr>
<tr>
<td>Group X-F(_{\text{iv}})</td>
<td>14.2 (3.7)</td>
<td>11.0 (2.8)*</td>
<td>12.9 (2.4)</td>
</tr>
<tr>
<td>Group X-F(_{\text{ext}})</td>
<td>15.6 (4.4)</td>
<td>14.2 (3.9)*</td>
<td>13.4 (3.6)*</td>
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<tr>
<td><strong>Resting ( \dot{V}_E ) (litre min(^{-1}))</strong></td>
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<tr>
<td>Group X-0</td>
<td>6.4 (0.8)</td>
<td>7.0 (1.3)</td>
<td>7.8 (3.6)</td>
</tr>
<tr>
<td>Group X-F(_{\text{iv}})</td>
<td>7.6 (1.5)</td>
<td>6.1 (4.1)*</td>
<td>6.8 (1.7)</td>
</tr>
<tr>
<td>Group X-F(_{\text{ext}})</td>
<td>8.1 (2.5)</td>
<td>5.9 (1.8)*</td>
<td>5.9 (1.4)*</td>
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<tr>
<td><strong>Slope ( \dot{V}<em>E/P'</em>{\text{CO}_2} )</strong></td>
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<tr>
<td>Group X-0</td>
<td>0.23 (0.08)</td>
<td>0.23 (0.09)</td>
<td>0.27 (0.11)</td>
</tr>
<tr>
<td>Group X-F(_{\text{iv}})</td>
<td>0.21 (0.05)</td>
<td>0.21 (0.11)</td>
<td>0.25 (0.08)</td>
</tr>
<tr>
<td>Group X-F(_{\text{ext}})</td>
<td>0.24 (0.17)</td>
<td>0.20 (0.21)*</td>
<td>0.21 (0.17)</td>
</tr>
<tr>
<td><strong>( \dot{V}_E 7.3 ) (litre min(^{-1}) kPa(^{-1}))</strong></td>
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<tr>
<td>Group X-0</td>
<td>20.2 (7.5)</td>
<td>26.1 (12.8)</td>
<td>24.8 (12.5)</td>
</tr>
<tr>
<td>Group X-F(_{\text{iv}})</td>
<td>20.4 (6.0)</td>
<td>19.1 (10.3)</td>
<td>19.7 (9.0)</td>
</tr>
<tr>
<td>Group X-F(_{\text{ext}})</td>
<td>19.9 (16.0)</td>
<td>18.8 (23.2)*</td>
<td>16.2 (12.7)*</td>
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</table>
noteworthy that the slope of the ventilatory response to carbon dioxide decreased by more than 20% from baseline in eight of 15 patients receiving extradural fentanyl and increased by more than 10% in only one. In addition, there was a decrease in ventilatory response to carbon dioxide in group X-F<sub>ext</sub>. The slope $\dot{V}E/\dot{P}e_{\text{CO}_2}$ at 1 h but not at 2 h was less steep than at baseline, and $\dot{V}E$ 7.3 was reduced at 1 and 2 h. However, there was no significant increase in $P\dot{e}_{\text{CO}_2}$ at rest.

**DISCUSSION**

Our results confirm that a low dose of fentanyl 50 $\mu$g injected extradurally (irrespective of the presence of lignocaine and adrenaline), caused slight ventilatory depression. The small decrease in frequency, minute ventilation and ventilatory response to carbon dioxide is consistent with the effects of other extradural opioids [2-4, 10, 19, 22].

We used only single estimates of the carbon dioxide response at each stage of our study, and this may be insensitive. Indeed, it has been shown by Goodman and Curnow that the coefficient of variation of the slope of the ventilatory response to carbon dioxide was about 20% with Read's method in four normal subjects studied on 3 days and 10 occasions over 1 month [28]. In our subjects there was a mean reduction of 16.6% from baseline at 1 h after extradural fentanyl (table II). There are four reasons why we believe that this change is real. First, it confirms established results: diamorphine depresses the carbon dioxide response slope after 30 min [13, 19]; a single extradural injection of fentanyl 200 $\mu$g depresses ventilation also at 30 min, maximally at 1 h and decreasing slowly at 2 and 3 h [25]; a priming dose of fentanyl 1 $\mu$g kg<sup>-1</sup> followed by a continuous extradural infusion of 1 $\mu$g kg<sup>-1</sup> depresses the carbon dioxide response slope at 1 h by 47.9% [26]. Second, the slope of the ventilatory response to carbon dioxide measured at 15-min intervals in 111 young normal subjects was highly reproducible [31]. Third, not only was the slope of the ventilatory response depressed, but $\dot{V}E$ 7.3 was reduced also with extradural fentanyl (table II). Fourth, because of the high correlation coefficient ($\geq 0.91$, $P < 0.01$) of the linear regression of $\dot{V}E$ as a function of $P\dot{e}_{\text{CO}_2}$, the 95% confidence interval was at most 20% of the group average slope [29].

However, the magnitude of the response was small and less than that occurring with higher doses of fentanyl [25, 26], and it is probably of little, if any clinical relevance.

The ventilatory depression produced by extradural opioids has been attributed to diffusion of the drug either within the CSF [32] or through the venous spinal blood flow towards cerebral vessels [2]. The blood concentration of fentanyl attained after extradural injection of 200 $\mu$g was too low to produce respiratory depression [4, 25]. Ventilatory depression probably lasts a little longer than the period used in this study, as elimination of the drug either within the CSF [32] or through the venous spinal blood flow towards cerebral vessels [2]. The blood concentration of fentanyl attained after extradural injection of 200 $\mu$g was too low to produce respiratory depression [4, 25]. Ventilatory depression probably lasts a little longer than the period used in this study, as elimination of fentanyl takes more than 2 h [33].

That fentanyl was responsible for the slower rate of ventilation is suggested by the lack of change in group X-0. However, a slower rate of ventilation was not found by Gaffud and colleagues with fentanyl 100 $\mu$g [9], by Negre and co-workers with 200 $\mu$g [25] or by Torda and Pybus with 60 $\mu$g [24].

It is unlikely that the lignocaine and adrenaline used in this study were responsible for the slight depression of ventilation. Adrenaline alone (50 $\mu$g in 10 ml of saline) was injected extradurally in a young volunteer by Bromage and colleagues, who reported that “objective signs of limited segmental (T10-L2) hypoaesthesia developed 20 min after injection, and lasted about 6 hours”, but the carbon dioxide response curve did not change from control [34]. Klepper and colleagues compared the effects of extradural sufentanil alone or with adrenaline and observed that the extent of respiratory depression was similar [35].

Extradural analgesia with lignocaine does not modify the ventilatory response to acute carbon dioxide challenge. In patients who had undergone prosthetic replacement of the lower aorta, no significant decrease in ventilatory response to carbon dioxide was found on the first day after operation [13], and others found no change with extradural chloroprocaine 500-800 mg [14]. In healthy patients, functional residual capacity and vital capacity do not change after extradural anaesthesia with sensory block to T3 [36].

Toxic effects of local anaesthetics on the central nervous system (CNS) are well documented and occur at blood concentration much higher than those likely to be present in our patients. “During the phase of CNS excitation prior to development of frank convulsions, an increased respiratory rate may be observed in patients. Animal studies in dogs and sheepes have shown that these animals tend to hyperventilate during convulsive activity such that little changes in $p_{O_2}$ and $p_{CO_2}$ is seen”
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[37]. Our data accord with this hypothesis that hyperventilation preceeds convulsions, as slight, although not significant, variations in ventilation at rest and in response to carbon dioxide were observed, consistent with a stimulating effect of extradural lignocaine.

REFERENCES

