VENTILATORY EFFECTS OF MEPTAZINOL AND PETHIDINE IN ANAESTHETIZED PATIENTS

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Meptazinol is a relatively new analgesic agent that has been found to have few ventilatory side effects (Jordan et al., 1979; Cohen et al., 1983). However, it was noted by one of the present authors that the administration of meptazinol i.v. during anaesthesia resulted in profound ventilatory depression. This study was designed to investigate the ventilatory effects of meptazinol in anaesthetized patients.

PATIENTS AND METHODS

Twenty-four fit female patients undergoing minor gynaecological surgery were studied after giving written consent. The study was approved by the local hospital Ethics Committee. The patients were randomly allocated to four groups of six as indicated in table I. No patient was taking medication likely to influence ventilatory control. All patients received temazepam 10 mg orally as premedication 1 h before the commencement of anaesthesia.

Anaesthesia was induced with etomidate 20 mg i.v. and maintained with halothane in oxygen, initially at a 4% inspired concentration, stepping down at 5-min intervals to 3% and then 1.5%. The patients continued to breathe 1.5% halothane in oxygen for 5-min before the start of the study. By this time they were in a stable anaesthetized state as indicated by regular ventilation and stable minute volume. The study was completed before the commencement of surgery. All patients breathed halothane from the same vaporizer (Fluotec Mark 2), the output of which was verified by interferometry before the study. The halothane-oxygen mixture was inspired through a breathing system which led from a standard Boyle anaesthetic machine via a reservoir bag and low resistance spill valve, through a dry gas meter (Parkinson Cowan) and screen pneumotachograph (Mercury Fl) to a close fitting face mask (Portex), incorporating a low resistance, non-rebreathing valve (Ambu Hesse) (fig. 1). The spill valve opened at very low pressures (< 10 Pa at 10 litre min⁻¹), so that gas only passed through the dry gas meter when the patient breathed in. The

<table>
<thead>
<tr>
<th>Group</th>
<th>Age (yr)</th>
<th>Height (m)</th>
<th>Weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P20</td>
<td>37.8 (5.3)</td>
<td>1.62 (0.07)</td>
<td>61 (7.1)</td>
</tr>
<tr>
<td>M20</td>
<td>30.7 (8.8)</td>
<td>1.64 (0.10)</td>
<td>60 (16.8)</td>
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<tr>
<td>M30</td>
<td>38.2 (9.6)</td>
<td>1.58 (0.07)</td>
<td>56.7 (8.5)</td>
</tr>
<tr>
<td>M48</td>
<td>34.3 (8.3)</td>
<td>1.66 (0.08)</td>
<td>65.2 (14.2)</td>
</tr>
</tbody>
</table>

SUMMARY

The ventilatory effects of three doses of meptazinol (20 mg, 30 mg and 48 mg) were studied in anaesthetized patients and compared with those of pethidine 20 mg. Minute volume, tidal volume, ventilatory frequency, inspiratory and expiratory times were measured and mean inspiratory flow rates calculated. Each patient received a first dose of drug which was followed after 5 min by a second identical dose. After the first injection the ventilatory effects of meptazinol were dose-dependent and meptazinol 20 mg had an effect similar to pethidine 20 mg. Following repeated injection the effects on ventilation were markedly different between the drugs. Carbon dioxide retention and other compensatory mechanisms attenuate the ventilatory depression of meptazinol, but these may be inadequate in the anaesthetized patient.
meter dial had been modified to give an electrical signal that was recorded using a potentiometric recorder (Servoscribe). The differential pressure from the pneumotachograph was measured with a Furness transducer and the flow signal recorded with a heated pen recorder (Devices M2) to allow measurement of inspiratory and expiratory times.

Baseline 5-min recordings of ventilation and flow were obtained once stable anaesthesia was attained. The first dose of the relevant drug (see below) was administered, and a further 5-min recording obtained. This was repeated after the second dose of the drug to assess the possibility of an alteration in response to a second dose as is seen for agonist–antagonist agents such as pentazocine. The drugs (and doses) studied were pethidine 20 mg + 20 mg, meptazinol 20 mg + 20 mg, meptazinol 30 mg + 30 mg and meptazinol 48 mg + 48 mg (groups I–IV, respectively).

Minute volume, tidal volume and ventilatory frequency were measured from the Servoscribe recording. Inspiratory and expiratory times were measured from the pneumotachograph record and mean inspiratory flow rate calculated from the above data. Statistical comparison between and within groups was by Student's t test, paired or unpaired, as appropriate.

RESULTS

There were no significant differences between the groups in respect of age, height and weight (table I).

The mean minute volume was not significantly different between the groups throughout the control period and remained steady (fig. 2).

Following the administration of the first dose of drug there was a significant decrease in minute volume in all groups. The time course of effect on minute volume was maximal at 2 min with meptazinol and 3 min with pethidine. Accordingly, statistical comparison was made between the final control measurement and the mean value of minute ventilation 2 min later in the meptazinol groups and 3 min later in the pethidine group. Following the second dose of drug there was a further significant decrease in minute ventilation after 3 min in the pethidine group, but no effect in any of the meptazinol groups.

Mean ventilatory frequency remained steady throughout the control period and was comparable between groups. After the first dose of drug there was a significant decrease in ventilatory frequency in all groups which plateaued at the end of the 5-min period (fig. 3). The extent of this effect was dose-dependent with meptazinol. After the second dose of drug there were further significant decreases in ventilatory frequency in the pethi-
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Pethidine, and meptazinol 20 mg, groups. Ventilatory frequency decreased following the second dose of drug in the meptazinol 30 mg and 48 mg groups, but this failed to achieve significance.

Pethidine had no effect on tidal volume (fig. 4). In all three meptazinol groups there was an initial (non-significant) decrease in tidal volume 2 min after the first dose of drug. This was followed by a steady increase in tidal volume, which was significant after the first dose in the meptazinol 48 mg group, and after the second dose in the meptazinol 30 mg and 48 mg groups. Comparison was between the beginning and end of each 5-min period in all cases.

The log dose–response curve of meptazinol against ventilation following a single dose was approximately linear and demonstrated meptazinol 20 mg to be equipotent with pethidine 20 mg (fig. 5). These two groups were therefore considered capable of statistical comparison after the second dose of drug. Before the administration of the second dose there were no significant differences between these two groups in respect of minute ventilation, frequency or tidal volume. After the second dose there was a significant difference in ventilation, although no statistical differences could be demonstrated for tidal volume and frequency between the two groups (fig. 6).

Mean inspiratory time was unaffected by any dose of either drug (fig. 7).

Mean expiratory time was steady in each group throughout the control period. After the injection
of the first dose of drug there was a significant increase in mean expiratory time in all groups which plateaued by the end of the 5-min period (fig. 8). After injection of the second dose of drug there was a further significant increase in
expiratory time in all groups except the meptazinol 30 mg group, in which there was a wider scatter of results. The log dose–response curve of meptazinol against expiratory time after a single dose was linear and again demonstrated meptazinol 20 mg to be equipotent with pethidine 20 mg (fig. 9).

Mean inspiratory flow rate remained unchanged after both doses of pethidine. In all three meptazinol groups there was an initial non-significant decrease in mean inspiratory flow rate 2 min after the first dose of drug. This was followed by a steady increase which was significant after the second dose in the 30-mg and 48-mg groups (fig. 10).

**DISCUSSION**

This study has clearly shown meptazinol to have potent effects on ventilation in anaesthetized subjects.

Three doses of meptazinol were studied, encompassing the range of doses reported as equianalgesic to pethidine by other authors (Paymaster, 1977; Slattery et al., 1981). We constructed log dose–response curves of the effects of meptazinol on ventilation and found that the potency ratio, at the 20-mg dose, relative to pethidine, was 1:1. Both drugs have marked effects on ventilation, but there are striking differences in their behaviour after repeated injections. Consequently, it was only possible to compare potency after a single injection. In this respect the actions of meptazinol are very similar to those of another agonist–antagonist drug, namely pentazocine (Davie, Scott and Stephen, 1970). However, meptazinol and pentazocine have been shown to differ in their effects on ventilation in conscious volunteers (Jordan et al., 1979) and the "ceiling effect" seen with pentazocine is probably not the effect that is being seen with meptazinol, as will be discussed later.

In this study the basic indices of breathing, namely ventilatory drive and timing (Clark and von Euler, 1972; Gautier, 1980) were assessed by calculating $\frac{VT}{Ti}$ and measuring inspiratory and expiratory timing intervals.

In common with other opioids (Rigg and Rondi, 1981; Drummond, 1983) the predominant effect of meptazinol and pethidine was on timing, resulting in a decrease in ventilatory frequency entirely as a result of a prolongation of expiration. These effects are much more evident in patients during anaesthesia than in the conscious state. Although other changes would be occurring after administration of the drug, it would be unlikely for these changes to contribute to the effects on timing. The alveolar concentration of halothane would be decreasing and alveolar $PCO_2$ increasing because of the depression of ventilation and these changes would be occurring at different rates. However, changes in the depth of anaesthesia with
vola ble agents do not appear to have a marked effect on timing (Drummond, 1983; Murat et al., 1985) and neither does an increasing $P_{aCO_2}$ in the early stages (Drummond, 1984).

Ventilatory drive, as measured by $VT/TI$, underwent an initial non-significant decrease 2 min after all first doses of meptazinol. This contributed to the early depression of minute ventilation and is similar to fentanyl, which has effects on timing and drive (Drummond, 1983). With fentanyl the effect on timing is more marked and takes longer to develop than the effect on drive, which occurs within 1–2 min. Following the initial depression of $VT/TI$ after meptazinol there was a steady increase. This achieved significance after the second doses in the 30-mg and 48-mg groups and also accounts for the increases in tidal volume. This increase in ventilatory drive is presumably the result of increasing values of $P_{aCO_2}$. In the presence of meptazinol, in contrast to pethidine, an increase in ventilation can occur after minute ventilation has been reduced by changes in ventilatory frequency caused by altered timing intervals. This is substantiated by the work of Jordan and colleagues (1979) and is consistent with their findings that the slope of the ventilatory response to rebreathing carbon dioxide is largely unaffected by meptazinol. This is in contrast to their finding that pentazocine has marked effects on the slope of the ventilatory response to rebreathing carbon dioxide. A ceiling effect with pentazocine can be seen after successive doses in the same patient (Davie, Scott and Stephen, 1970). In conjunction with this lack of effect on frequency and tidal volume following a second dose of pentazocine, Jordan and colleagues’ findings would suggest that the ceiling effect seen with pentazocine is not a result of the compensatory mechanisms that come into play following repeated doses of meptazinol.

The depressant effect of drugs may be caused by a predominant effect on only one of the basic indices of breathing. For example, volatile anaesthetics predominantly influence inspiratory flow (Drummond, 1983; Murat et al., 1985), whereas opioids and ketamine predominantly influence timing (Drummond, 1983; Jaspar et al., 1983). Compensation may occur, through the effects of carbon dioxide retention, but this may lag behind the rate of onset of action of the depressant. In addition, the mechanism of compensation may be different from the manifest depressant effects. In this study the initial effect was a reduction in minute ventilation which was attributable partly to a reduction in tidal volume, but this was followed by an increase in $VT/TI$ and tidal volume as $TI/T10^t$ continued to decrease. After oral administration the relatively slow absorption of a drug may allow adequate compensation for its effects, but after i.v. administration compensation may not be achieved rapidly enough for safety. Concurrent administration of other ventilatory depressants such as volatile anaesthetics is a common clinical situation and may influence the margin of safety. Investigations commonly used to assess ventilatory depression may not be relevant for all circumstances in which a drug is used clinically.

Ventilatory depression by meptazinol is predominantly the result of its effects on timing. It may also have a direct depressant effect on the neural mechanisms responsible for “drive”, but compensation after ventilatory depression can occur by an increase in inspiratory flow. Although this compensation for ventilatory depression by meptazinol may be greater than with other opioids, it takes some time to develop and patients could possibly become hypoxic in the period immediately following i.v. administration. It should be remembered that the hypoxic drive to ventilation is abolished by volatile agents (Knill and Gelb, 1978) and depressed by opioids (Weil et al., 1975). It has not been ascertained what effect meptazinol has on the ventilatory response to hypoxia, but even with low concentrations of volatile agents the response to hypoxia is markedly reduced.

There is no doubt that i.v. administration of meptazinol during anaesthesia has to be viewed with as much caution as administration of any other opioid.

REFERENCES

Ventilatory Effects of Meptazinol


