EFFECTS OF ALAPROCLATE AND MORPHINE ON THE VENTILATORY RESPONSE TO CARBON DIOXIDE IN NORMAL MAN

P. M. A. CALVERLEY, G. L. M. CARMICHAEL AND D. B. SCOTT

SUMMARY

The ventilatory response to carbon dioxide was determined in six healthy volunteers given alaprodate alone and combined with morphine. A rebreathing technique was used and the slope of the ventilatory response to carbon dioxide was plotted. A comparison of these responses after alaprodate or a placebo showed no significant difference. Following the administration of morphine i.v., respiration was depressed, but there was no enhancement of the depression of the ventilatory response to carbon dioxide in subjects pretreated with alaprodate.

Although morphine is still one of the most widely used analgesics its effectiveness is limited in many patients by respiratory depression, and this is particularly so in patients with pulmonary or thoracic disease. Although other agents such as chlorpromazine potentiate opiate analgesia, they also further depress ventilation (Moore and Dundee, 1961). Alaproclate (fig. 1) is a new antidepressant agent with a specific action in blocking serotonin re-uptake and little or no effect upon noradrenaline (Lindberg, Thorberg and Bengtsson, 1978). It has been shown to enhance opiate-induced analgesia in animal studies (Ogren and Holm, 1980). However, before investigating the clinical usefulness of this interaction in man, it appeared necessary to determine whether alaproclate potentiated the respiratory depression of morphine. Moreover, it is important to know whether patients receiving alaproclate for the treatment of depression would react adversely to opiates given for intercurrent disease. Therefore, we have investigated the effect of alaproclate on ventilation in man before and after the administration of morphine.

Fig. 1. Alaproclate.

SUBJECTS AND METHODS

Six healthy male subjects were each studied on two afternoons in a double-blind crossover study. All subjects gave their informed consent, the studies being approved by the Hospital Ethics Committee. The subjects abstained from tea, coffee and alcohol for 12 h and fasted for 4 h before the study. A cannula was inserted to a large forearm vein before each study for ease of blood sampling. The ventilatory response to carbon dioxide in hyperoxia was measured using the rebreathing method with a "bag-in-a-box" technique (Clark, Clarke and Hughes, 1966). With the subject seated comfortably, room air was breathed through a mouthpiece. After 2 min a three-way tap was switched so that the subject rebreathed from a 6-litre bag filled with 7% carbon dioxide and 40% oxygen (balance gas, nitrogen). End-tidal oxygen (PeO₂) and carbon dioxide (PeCO₂) tensions were sampled at the lips by a mass spectrometer previously calibrated against four gases analysed in a Lloyd Haldane apparatus. The bag was enclosed in a Perspex box and the gas displaced by respiration flowed through a pneumotachograph (Fleish No. 3) which generated signals for tidal volume (VT) and frequency (f) of respiration. These signals, together with those for PeO₂, PeCO₂ and heart rate (which was derived from the ECG) were recorded on-line by a PDP 11/40 computer with a visual digital output every five breaths.

Ventilation was recorded for 4 min after the start of each test or until the subject reached a minute ventilation of 50 litre min⁻¹. After a 10-min rest period, the study was repeated and the results of these two tests were pooled for further analysis. Ventilation was expressed as instantaneous minute
ventilation ($V_{	ext{Etot}} = V_T \times f$) and ventilatory response to carbon dioxide as the slope of $V_E/PE'_{CO_2}$ in litre min$^{-1}$kPa$^{-1}$. During the off-line analysis of these data, points where ventilation exceeded 50 litre min$^{-1}$ or $PE'_{CO_2}$ was less than 15 kPa were discarded. The apnoeic threshold for carbon dioxide was calculated as the point where the extrapolated carbon dioxide response curve crossed the intercept with zero ventilation.

Each subject attended on two days not less than 7 days apart. The ventilatory response to hypercapnia ($S$) was measured on each day before and 60 min after the administration of either placebo or alaproclate 200 mg. The study was double-blind. Immediately after the second set of measurements morphine sulphate 5 mg was given i.v. and 10 min later, the ventilatory response to hypercapnia was repeated. Blood was sampled for estimations of plasma alaproclate before the second and third measurements and 2 h after the administration of either drug or placebo. Alaproclate concentrations were determined by gas chromatography/mass spectrography. Statistical analysis was performed using Student’s paired $t$ test.

**RESULTS**

The height, weight and age of the six subjects are given in table I.

**Plasma alaproclate concentrations (table II)**

The plasma alaproclate concentration achieved 60 min after administration of the active tablet varied from 300 to 727 ng ml$^{-1}$ (mean 535 ng ml$^{-1}$). Very small values (less than 55 ng ml$^{-1}$) were recorded in all subjects on the placebo days and before taking the drug on active days. These probably represent the lower limits of detection of the assay. There was no significant difference between the plasma alaproclate concentrations before or after opiate administration and substantial concentrations were still present 60 min after the end of the study.

**The ventilatory response to carbon dioxide in hyperoxia**

The ventilatory response to carbon dioxide ($S$) varied considerably among the group—from 15 to 22.9 litre min$^{-1}$kPa$^{-1}$ when measured before drug or placebo administration—but was highly reproducible in the same subject on the two days of the study (table III). There were, additionally, no significant differences between the mean of $S$ before and 60 min after the oral administration of either placebo or alaproclate.

Following the administration of morphine the mean of $S$ decreased from 20.4 to 13.5 litre min$^{-1}$kPa$^{-1}$ on the days when the placebo was given. This compared with a reduction from 20.0 to 14.5 litre min$^{-1}$kPa$^{-1}$ on the days when alaproclate was administered. Thus $S$ decreased by a similar amount regardless of whether morphine was given after placebo or after alaproclate.

The apnoeic threshold for carbon dioxide was more variable than $S$ when the same subjects were compared on the two days of the study. Within a single day however, the variation was much less. The threshold decreased slightly in most subjects after morphine, but this was not universal (table IV). Alaproclate did not have a consistent or sig-
TABLE III. Ventilatory response to carbon dioxide (S) (litre min⁻¹ kPa⁻¹) before and after drug or placebo, and after opiate i.v.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Before drug</th>
<th></th>
<th>After drug</th>
<th></th>
<th>After opiate</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
<td>Placebo</td>
<td>Active</td>
</tr>
<tr>
<td>1</td>
<td>15.6</td>
<td>15.0</td>
<td>14.4</td>
<td>14.3</td>
<td>12.1</td>
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<tr>
<td>2</td>
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<td>16.0</td>
<td>16.4</td>
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<td>12.2</td>
</tr>
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<td>22.0</td>
<td>21.7</td>
<td>20.4</td>
<td>16.8</td>
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<td>4</td>
<td>20.3</td>
<td>19.2</td>
<td>22.9</td>
<td>22.9</td>
<td>9.6</td>
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<td>5</td>
<td>22.7</td>
<td>22.9</td>
<td>21.8</td>
<td>23.2</td>
<td>19.1</td>
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<td>21.4</td>
<td>20.2</td>
<td>22.7</td>
<td>23.9</td>
<td>17.3</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>19.3 ± 3.0</td>
<td>19.3 ± 3.2</td>
<td>20.0 ± 3.6</td>
<td>20.4 ± 3.7</td>
<td>14.5 ± 3.7</td>
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</table>

TABLE IV. Carbon dioxide intercept (apnoeic threshold) (kPa) of the ventilatory response to carbon dioxide before and after drug or placebo and after opiate

<table>
<thead>
<tr>
<th>Subject</th>
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<th></th>
<th>After drug</th>
<th></th>
<th>After opiate</th>
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<td>Active</td>
<td>Placebo</td>
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<td>4</td>
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<td>5.47</td>
<td>4.75</td>
<td>5.60</td>
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<td>5</td>
<td>5.18</td>
<td>5.31</td>
<td>5.46</td>
<td>5.28</td>
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<tr>
<td>6</td>
<td>5.90</td>
<td>5.43</td>
<td>5.88</td>
<td>5.51</td>
<td>5.68</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.26 ± 0.37</td>
<td>5.33 ± 0.28</td>
<td>5.31 ± 0.39</td>
<td>5.19 ± 0.39</td>
<td>5.21 ± 0.5</td>
</tr>
</tbody>
</table>

Significant effect on the apnoeic threshold for carbon dioxide.

Side-effects

Subjective side-effects were reported in four subjects during alaproclate treatment (usually slight light headedness) and in one subject receiving the placebo tablet (slight drowsiness). After administration of morphine, all subjects except one reported different degrees of drowsiness. Two subjects were given naloxone 0.4 mg i.v. at the end of the study because of excessive drowsiness. One recovered rapidly, but the other required observation for a further 2 h. This occurred only after alaproclate—morphine treatment.

DISCUSSION

Brain and spinal serotoninergic neurones are involved in the inhibition of nociceptive responses as well as the analgesic effects of opiates (Yaksh and Tyce, 1979). Since alaproclate is a specific inhibitor of serotonin (5-HT) uptake in animal preparations, it was not surprising to find that the drug potentiated the effects of morphine analgesia, at least in rats (Ogren and Holm, 1980). Preliminary studies using this species have failed to demonstrate any synergism between alaproclate and the ventilatory depressant effects of opiates (A. C. Holm; personal communication).

Previous studies have shown that alaproclate is well tolerated in man, with few side-effects (G. R. Arthur and colleagues; unpublished observations). Using the pharmacokinetic data from that study, we were able to produce stable plasma concentrations of alaproclate during the measurement of the ventilatory response to carbon dioxide. The doses used were similar to those likely to be used clinically. The effect of alaproclate on respiration in man has not been studied previously and it was important to know if this was any additive or synergistic effect with the depressant action of opiates.

The assessment of the ventilatory response to carbon dioxide in hyperoxia is a technique commonly used in the assessment of many therapeutic agents. However, there is surprisingly little information about its immediate and day-to-day reproducibility, the best data being those of Clark (1968), who found that carbon dioxide rebreathing was repeat-
able in the subjects with low ventilatory responses. Our data support this earlier evidence, since our subjects had very reproducible values for S both 60 min and 7–14 days after its initial estimation. The intercept or apnoeic threshold was less reproducible day by day, but had a good immediate reproducibility. The values for S reported in the literature vary considerably. Our results lie well within the ranges recorded in the larger studies of normal subjects (Clark, Clarke and Hughes, 1966; Rebuck, Jones and Campbell, 1972; Matthews and Howell, 1975), but are rather higher than those reported by Weil and colleagues (1975), who used a different technique when they demonstrated that opiates depressed hypoxic and hypercapnic drives to breathing. Well and colleagues found that morphine 7.5 mg s.c. depressed S by an average of 5.3 litre min⁻¹ kPa⁻¹, a value closely resembling the results we observed with a smaller dose i.v.

In the current study, carbon dioxide rebreathing, as described above, proved to be an accurate and reproducible method of testing the hypercapnic ventilatory drive. The ventilatory response to carbon dioxide was not affected by alaproclate and, although in some subjects the changes were small, there was no evidence of potentiation of opiate-induced hyperventilation with this drug.

In general, the side-effects were few and short-lived. However, more pronounced drowsiness was observed after morphine and alaproclate compared with morphine plus placebo. Patients receiving alaproclate therapy for endogenous depression should not present a problem if intercurrent disease necessitates the administration of opiates.

ACKNOWLEDGEMENTS
The authors would like to thank Professor David Flenley, Department of Respiratory Medicine, City Hospital, Edinburgh, for his advice and the use of his research laboratory for this study. We also thank Astra Lakemedel AB Södertalje, Sweden for supplying alaproclate and placebo tablets and undertaking the estimations of the blood concentration of this drug.

REFERENCES

LES EFFETS DE L'ALAPROCLATE ET DE LA MORPHINE SUR LA REPONSE VENTILATOIRE AU DIOXYDE DE CARBONE CHEZ L'HOMME NORMAL

RESUME
La réponse ventilatoire au dioxyde de carbone a été déterminée chez six volontaires bien portants recevant de l'alaproclate seul ou associé à la morphine. Une technique de rebreathing a été utilisée et la pente de la réponse ventilatoire au dioxyde de carbone calculée. Une comparaison de ces réponses après alaproclate ou placebo n'a pas montré de différence significative. Après l'administration de morphine i.v., la respiration était déprimée mais il n'y avait aucune aggravation de la dépression de la réponse ventilatoire au dioxyde de carbone chez les sujets pré-traités à l'alaproclate.

DIE WIRKUNG VON ALAPROCLAT UND MORPHIUM AUF DIE VENTILATORISCHE CO₂-Antwort BEIM GESUNDEN MENSCHEN

ZUSAMMENFASSUNG
VENTILATORY RESPONSE TO CARBON DIOXIDE: ALAPROCLATE

EFFECTOS DEL ALAPROCLATO Y DE LA MORFINA EN LA RESPUESTA RESPIRATORIA DEL ANTE EL DIOXIDO DE CARBONO EN EL HOMBRE SANO

SUMARIO
Se determinó la respuesta respiratoria al dióxido de carbono en seis voluntarios sanos a los que se les administró alaproclato, sólo y en combinación con morfina. Se utilizó una técnica de segunda respiración y se trazó la pendiente de la respuesta respiratoria ante el dióxido de carbono. La comparación de estas respuestas después del alaproclato o de placebo no mostró diferencia significativa alguna. A raíz de la administración intravenosa de morfina la respiración sufrió depresión, pero tal depresión no apareció ante el dióxido de carbono en los pacientes tratados previamente con alaproclato.