A COMPARISON OF THE RESPIRATORY EFFECTS OF MEPTAZINOL, PENTAZOCINE AND MORPHINE

C. JORDAN, J. R. LEHANE, P. J. ROBSON AND J. G. JONES

SUMMARY

The respiratory effects of a new strong analgesic, meptazinol, were compared with a placebo and with equianalgesic doses of morphine and pentazocine in a double-blind crossover trial in seven healthy volunteers. No significant change in the ventilatory response to rebreathing carbon dioxide was observed after meptazinol 100 mg/70 kg or placebo. However, both morphine 10 mg/70 kg and pentazocine 60 mg/70 kg depressed the slope of the ventilatory response (—30.0% and —31.6% respectively, P < 0.02, averaged over the first 3.5-h period). End-tidal carbon dioxide tension (P^2) while breathing room air increased significantly following all three drugs. However, the increase in P^2 after meptazinol (0.22 kPa averaged over 3.5 h) was significantly less than that following morphine (0.40 kPa, P < 0.05) and pentazocine (0.59 kPa, P < 0.01). While breathing room air with a resistive inspiratory load of 8 kPa litre⁻¹ s⁻¹, P^2 again increased significantly (P < 0.05) following all three drugs. The increase in P^2 after meptazinol was then the same as that after morphine (0.51 kPa averaged over 3.5 h). The increase following pentazocine (0.80 kPa) was significantly greater than that after both morphine and meptazinol (P < 0.02).

Doses of analgesics adequate for complete pain relief are often withheld because of the danger of inducing respiratory depression and physical or psychological dependence. A potent analgesic with negligible depressant effects on respiration would be particularly useful when pain relief is required in patients with poor pulmonary function, in women at term and during the period after operation. If such a drug were also free of abuse potential it would offer considerable advantages over the established opiate drugs.

Meptazinol (m (3-ethyl-l-methyl hexahydro 1-H-azepin-3-yl)phenol hydrochloride, Wyeth Laboratories) is an opioid antagonist drug with analgesic properties. It has been shown to produce significant pain relief in doses of 60–150 mg/70 kg i.m. in patients recovering from abdominal surgery (Paymaster, 1976, 1977). There was no evidence of physical dependence in experiments in rats (Goode and White, 1971) and in the monkey (Swain, Villalcal and Seavers, 1973). Observations in animals (K. Rhodes, personal communication) and man (Verschraegen et al., 1976) have shown that meptazinol is relatively free of respiratory side-effects, although this has not been investigated formally in man. We have studied the respiratory effects of meptazinol in human subjects and compared these effects with those of morphine, pentazocine and placebo.

METHODS

Seven healthy male volunteers aged 25–33 yr gave informed consent for this study, which was carried out with the approval of the Hospital Ethics Committee. Each subject was studied on four non-consecutive days on each of which he was given meptazinol 100 mg/70 kg, morphine 10 mg/70 kg, pentazocine 60 mg/70 kg or 2 ml of 0.9% saline by i.m. injection. The injections were administered in a double-blind manner and in a random order which was different for each subject.

Three tests of the respiratory effects of these drugs were used:

(1) The ventilatory response to hypercapnia (Ve/P^2CO) was determined by a modified Read rebreathing method similar to that developed by Milledge, Minty and Duncalf (1974). Ventilation was measured using an Ohio spirometer and carbon dioxide concentration was measured using a Godart infra-red analyser. The rebreathing test was performed in duplicate on each occasion.

(2) The end-tidal P^2CO (P^2CO) was measured with the subjects breathing room air via a non-rebreathing valve (Hook and Tucker, London) over a period of 7 min. The mean P^2CO during each 1-min interval was derived electronically.


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(3) The effect of an inspiratory load of 8 kPa litre$^{-1}$ s on the regulation of ventilation was determined from measurements of $P_{E}CO_{2}$ over 7 min. The resistive load was connected to the inspiratory limb of the non-rebreathing valve.

Following a light breakfast, subjects arrived at the laboratory at 9.00 a.m. and rested for 30 min. A series of control measurements followed. At 10.00 a.m. the injection was given and the tests were repeated after 15 min, 1 h, 2 h, 3 h and 4 h. The subjects then ate a light lunch and a final series of measurements was made at 4.00 p.m. (6 h).

During the tests great care was taken to ensure that the subjects were comfortable and undisturbed. They remained supine throughout and listened to music via headphones.

The data from each of the tests were analysed in the following manner.

The ventilatory response to hypercapnia

The slopes of $V_{E}/P_{E}CO_{2}$ response curves were determined by drawing a line of best fit through the linear portion of each curve. The intercepts were determined by extrapolating these lines of best fit to zero ventilation. The control data were the means of duplicate measurements made at the start of the day since the within-day variability of $V_{E}/P_{E}CO_{2}$ curves is much less than between-day variability (Jennett, 1968; Sahn et al., 1977).

Slopes obtained following injection were compared with control data from the same day by calculating:

$$\Delta \text{slope} = \log_{10} \left( \text{test slope} \right) - \log_{10} \left( \text{mean control slope} \right)$$

Logarithms of the slopes were used to permit the application of standard $t$ tests to the data because the distribution of $V_{E}/P_{E}CO_{2}$ slopes in the population is skewed (log normal) (Irshigler, 1976; Mustchin, 1977).

The above equation can be re-written:

$$\Delta \text{slope} = \log_{10} \left( \text{test slope/mean control slope} \right)$$

By taking antilog$_{10}$ ($\Delta$ slope), changes in slope may be expressed as ratios. Mean changes in slope calculated by this method are geometric means.

Intercepts were compared with control data from the same day by calculating (test intercept—mean control intercept).

$P_{E}CO_{2}$ while breathing with the inspiratory load

Our previous observations had shown that the between-day variability of $P_{E}CO_{2}$ is similar to that within a day and also that there was a small increase during the course of the day. The control used, therefore, was mean $P_{E}CO_{2}$ obtained over the first 4 h after injection of saline. Test data were compared with this mean by calculating (test $P_{E}CO_{2}$—mean control $P_{E}CO_{2}$).

$P_{E}CO_{2}$ while breathing with the inspiratory load

Test $P_{E}CO_{2}$ was compared with control $P_{E}CO_{2}$ whilst breathing with the load in a similar way:

test $P_{E}CO_{2}$ (loaded) — mean control $P_{E}CO_{2}$ (loaded)

Statistical analysis

In order to compare data obtained after each injection with control values the means of $V_{E}/P_{E}CO_{2}$ slopes and intercepts, and $P_{E}CO_{2}$ measurements were calculated at each time interval. Differences between these values and control values were obtained as described above and tested using the unpaired (two-sample) $t$ test.

In order to perform a useful comparison between the drugs, the average of the results of the first four measurements after injection (over the first 3.5-h period) was obtained. Differences in $V_{E}/P_{E}CO_{2}$ slopes were expressed as geometric mean percentage changes, and tested by applying the paired $t$ test to the log data. Changes in $P_{E}CO_{2}$ were expressed as mean differences with the variability expressed as the standard error of the difference (SED) and tested by means of paired $t$ tests.

RESULTS

The ventilatory response to hypercapnia

Morphine and pentazocine produced significant depression of the $V_{E}/P_{E}CO_{2}$ slope whereas meptazinol and saline did not (fig. 1).

![Fig. 1. Mean changes in $V_{E}/P_{E}CO_{2}$ slopes (±1 SEM). *P<0.05; **P<0.01 (unpaired $t$ test). O = saline; • = meptazinol; □ = morphine; ■ = pentazocine.](https://academic.oup.com/bja/article-abstract/51/6/497/243867/fig1)
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Table I. Slope and $P_{E'CO_2}$ changes during the first 3.5 h after drug. Mean (SED).

$*P<0.05; **P<0.005$

<table>
<thead>
<tr>
<th></th>
<th>Meptazinol</th>
<th>Morphine</th>
<th>Pentazocine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ slope (± SE)</td>
<td>$-0.03 (0.02)$</td>
<td>$-0.16** (0.04)$</td>
<td>$-0.17* (0.05)$</td>
</tr>
<tr>
<td>(% slope change)</td>
<td>$-6.7$</td>
<td>$-30.0**$</td>
<td>$-31.8*$</td>
</tr>
<tr>
<td>Change in resting $P_{E'CO_2}$ (kPa)</td>
<td>$0.22* (0.08)$</td>
<td>$0.41** (0.05)$</td>
<td>$0.59** (0.08)$</td>
</tr>
<tr>
<td>Change in loaded $P_{E'CO_2}$ (kPa)</td>
<td>$0.51* (0.13)$</td>
<td>$0.51** (0.10)$</td>
<td>$0.80** (0.11)$</td>
</tr>
</tbody>
</table>

Changes in slope from control values for the 3.5-h period following injection are shown in table I. The change following both morphine and pentazocine was greater than that after meptazinol, the difference being 25.4% ($P<0.02$) and 26.8% ($P<0.05$) respectively. It should be noted that these values are not the arithmetic differences of the results shown in table I as they are derived from the logarithmic data.

Mean changes in the intercept of the $V_{E'}/P_{E'CO_2}$ curve were less than 0.23 kPa (SEM 0.14 kPa) and there were no significant differences between drugs and placebo.

$P_{E'CO_2}$ while breathing at rest

The $P_{E'CO_2}$ was increased significantly for the whole 6-h period following morphine and pentazocine and for 3 of the 6 h following meptazinol (fig. 2).

Mean changes in $P_{E'CO_2}$ over the first 3.5 h after injection were analysed (table I). Meptazinol produced a small but significant increase compared with saline, the mean difference being 0.25 kPa (SED 0.08 kPa) ($P<0.05$), saline values being 0.03 kPa less than control. Morphine produced a greater increase in $P_{E'CO_2}$ and the difference between morphone and meptazinol, 0.19 kPa (SED 0.05 kPa) was significant ($P<0.02$). Pentazocine produced the greatest increase in $P_{E'CO_2}$ being greater than morphine by 0.19 kPa (SED 0.07 kPa) ($P<0.05$). The mean $P_{E'CO_2}$ values observed during this 3.5-h period are shown in figure 3.

$P_{E'CO_2}$ while breathing with the inspiratory load

Following all three active drugs there was again a significant increase in $P_{E'CO_2}$ compared with that after placebo while breathing with the load ($P<0.05$).

The average $P_{E'CO_2}$ values during these tests over 3.5 h are shown in figure 3. Under these conditions the increase in $P_{E'CO_2}$ after meptazinol was such that there was no longer any significant difference between it and morphine, the mean difference being 0.003 kPa (SED 0.09 kPa). The mean difference between pentazocine and meptazinol was 0.29 kPa (SED 0.05 kPa) ($P<0.02$) and between pentazocine and morphine was 0.30 kPa (SED 0.09 kPa) ($P<0.02$).

Side-effects

All three active drugs produced noticeable side-effects during the course of the study, while no side-effects were observed following the placebo (table II).
TABLE II. Side-effects reported among seven volunteers

<table>
<thead>
<tr>
<th>Side-effect</th>
<th>Morphine</th>
<th>Pentazocine</th>
<th>Meptazinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild euphoria</td>
<td>2</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Dysphoria</td>
<td>—</td>
<td>4</td>
<td>—</td>
</tr>
<tr>
<td>Nausea alone</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>1</td>
<td>—</td>
<td>4</td>
</tr>
</tbody>
</table>

DISCUSSION

The results of this study demonstrated that meptazinol 100 mg/70 kg body weight had a negligible effect on the slope and intercept of the ventilatory response to hypercapnia whereas morphine 10 mg/70 kg and pentazocine 60 mg/70 kg both produced large changes in slope. The changes observed following morphine and pentazocine were similar to those reported by other workers when their data were analysed by the same methods (table III).

TABLE III. Reported results of the effects of morphine and pentazocine on ventilation

<table>
<thead>
<tr>
<th>Drug (source)</th>
<th>Change in $P\dot{E}'CO_2$ (kPa)</th>
<th>Change in slope of $\dot{V}_E/P\dot{E}'CO_2$ curve (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine 7.5 mg (Weil et al., 1975)</td>
<td>+0.33</td>
<td>-42</td>
</tr>
<tr>
<td>Morphine 10 mg (Jennett, Barker and Forrest, 1968)</td>
<td>+0.41</td>
<td>-31</td>
</tr>
<tr>
<td>Morphine 10 mg (Present study)</td>
<td>+0.44</td>
<td>-34</td>
</tr>
<tr>
<td>Pentazocine 20 mg (Jennett, Barker and Forrest, 1968)</td>
<td>+0.59</td>
<td>-25</td>
</tr>
<tr>
<td>Pentazocine 45 mg (Engineer and Jennett, 1972)</td>
<td>+0.54</td>
<td>-33</td>
</tr>
<tr>
<td>Pentazocine 60 mg (Present study)</td>
<td>+0.64</td>
<td>-36</td>
</tr>
</tbody>
</table>

The measurement of changes in $P\dot{E}'CO_2$ during quiet breathing of room air is another direct test of respiratory depression which has proved to be repeatable and sensitive (Jennett, 1968). The consistency of the measurements in this study was such that the small increase in $P\dot{E}'CO_2$ after meptazinol could be shown to be significant. Moreover, using paired $t$ tests, the effects of the three drugs were shown to differ significantly so that the increase in $P\dot{E}'CO_2$ after drug increased in the order meptazinol $\rightarrow$ morphine $\rightarrow$ pentazocine. The observed increases in $P\dot{E}'CO_2$ following morphine and pentazocine were similar to those reported by other workers (table III).

These two tests are used in the laboratory to determine the effects of drugs on the control of ventilation in man. It is possible, however, that a drug which does not produce gross changes in these tests may impair the ability of a patient with an abnormal respiratory load to maintain adequate ventilation. To investigate this possibility we studied the effects of a severe inspiratory load of 8 kPa litre$^{-1}$s which was the minimum necessary to produce appreciable changes in $P\dot{E}'CO_2$ in healthy volunteers. Under these conditions, after meptazinol, $P\dot{E}'CO_2$ did not differ significantly from that after morphine but both were significantly greater than after placebo. This result suggests a difference between the effects of meptazinol on non-loaded and loaded breathing. However, the clinical relevance of the effects of drugs on loaded breathing in healthy volunteers remains to be established.

In studies of the respiratory effects of drugs it is essential to compare equipotent doses of each drug. Paymaster has shown that, for pain relief after operation, meptazinol 100 mg was equianalgesic with pentazocine 60 mg and pethidine 100 mg (Paymaster, 1977). It is concluded that, for equivalent pain relief, meptazinol causes substantially less respiratory depression than morphine 10 mg and pentazocine 60 mg. Further, in a pilot study on two subjects both of whom received meptazinol 60 mg/70 kg and 150 mg/70 kg, no dose-related respiratory effects were observed. These doses cover the range used so far in pain relief after operation (Paymaster, 1976, 1977) and in obstetric analgesia (M. B. A. Jackson, personal communication).

The only side-effects of meptazinol observed in this trial were nausea and vomiting, the frequencies of which were greater than following the other drugs. However, it is known that side-effects of analgesics differ both in type and severity in patients in pain and in normal pain-free subjects (Dundee, 1977). In patients recovering from abdominal and orthopaedic surgery (Paymaster, 1976, 1977) the frequency of nausea and vomiting after meptazinol was not significantly different from that following pethidine or pentazocine. No psychotomimetic effects were observed after meptazinol, and the absence of euphoric or dysphoric effects is encouraging, particularly in view of the low physical dependence potential shown in animals (Goode and White, 1971; Swain, Villancal and Seevers, 1973).

The results of this study, and observations made
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in clinical studies, suggest that meptazinol has significant advantages over the currently available opiate analgesics.

ACKNOWLEDGEMENTS

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REFERENCES


COMPARAISON DES EFFETS RESPIRATOIRES DU MEPTAZINOL, DE LA PENTAZOCINE ET DE LA MORPHINE

RESUME

Les effets respiratoires d'un nouvel analgésique puissant: le meptazinol, ont été comparés à un placebo et à des doses équianalgésiques de morphine et de pentazocine au cours d'une étude à double inconnue avec inversion des séries à la fin de la première période, effectuée sur six volontaires en bonne santé. On n'a observé aucune variation importante dans la réaction ventilatoire à la re-respiration de gaz carbonique après le meptazinol (100 mg 70 kg⁻¹) ou le placebo. Cependant, aussi bien la morphine (10 mg 70 kg⁻¹), que la pentazocine (60 mg 70 kg⁻¹) ont fait baisser la pente de la réaction ventilatoire (-30,0% et -31,6% respectivement, P<0,02, moyenne sur la première période de 3,5 h). La tension du gaz carbonique en fin d'expiration (Pe'CO₂) a augmenté d'une manière significative après les trois médicaments, pendant que les volontaires respiraient l'air ambiant. L'augmentation de la Pe'CO₂ après l'administration de meptazinol (0,22 kPa, moyenne sur 3,5 h) a été nettement inférieure à celle qui a suivi la morphine (0,40 kPa, P<0,05) et la pentazocine (0,59 kPa, P<0,01). Alors que les volontaires respiraient l'air ambiant avec une charge inspiratoire résistive de 8 kPa litre⁻¹ s, la Pe'CO₂ a à nouveau augmenté d'une manière significative (P<0,05) après les trois médicaments. L'augmentation de la Pe'CO₂ après le meptazinol a alors été la même que celle qui a suivi la morphine (0,51 kPa, moyenne sur 3,5 h). L'augmentation qui a suivi la pentazocine (0,80 kPa) a été nettement plus grande que celle qui a suivi la morphine et le meptazinol (P<0,02).

VERGLEICH DER AUSWIRKUNGEN AUF DIE ATMUNG VON MEPTAZINOL, PENTAZOCIN UND MORPHIUM

ZUSAMMENFASSUNG

Die Auswirkungen eines starken neuen Analgetikums Meptazinol, auf die Atmung wurden mit einem Plazebo und mit gleichwirk samen Dosen von Morphium und Pentazocin in einem Doppelblind-Kreuzversuch an 7 gesunden Versuchspersonen verglichen. Nach 100 mg/70 kg Meptazinol wurde keine wesentliche Änderung der Atmungsreaktion auf die Wiedereinatmung von Kohlendioxyd beobachtet, auch nicht nach Plazebo. Aber sowohl 10 mg/70 kg Morphium und 60 mg/70 kg Pentazocin unterdrückten die Belüftungsreaktion (−30,0% und −31,6%, P<0,02. Durchschnittlich über den ersten Abschnitt von 3,5 Stunden). Die Endausatmungs-Kohlendioxyddspannung (Pe'CO₂) stieg nach allen drei Drogen deutlich an, während Zimmerluft geatmet wurde. Aber der Anstieg dieses Wertes nach Meptazinol (0,22 kPa Durchschnitt über 3,5 Stunden) war wesentlich geringer als nach Morphium (0,40 kPa, P<0,05) und nach Pentazocin (0,59 kPa, P<0,01). Bei normaler Luftatmung bei Einatmungsbelastung von 8 kPa litre⁻¹ s stieg dieser Wert wieder stark an (P<0,05), nach allen drei Drogen. Der Anstieg nach Meptazinol war derselbe wie nach Morphium (0,51 kPa Durchschnitt über 3,5 Stunden). Der Anstieg nach Pentazocin (0,80 kPa) war deutlich größer als nach Morphium oder Meptazinol (P<0,02).
Se procedió a la comparación de los efectos respiratorios de un nuevo analgésico fuerte, el meptazinol, con los de un placebo y con unas dosis equianalgesicas de morfina y de pentazocina en una prueba de traspaso ciega doble en siete voluntarios sanos. No se observó ningún cambio significativo en la respuesta ventilatoria al respirar de nuevo el dióxido de carbono, después de la administración de 100 mg 70 kg$^{-1}$ de meptazinol o de placebo. Sin embargo, después de la administración de 100 mg 70 kg$^{-1}$ de morfina y de 60 mg 70 kg$^{-1}$ de pentazocina, el declive de la respuesta ventilatoria se deprimió (–30,0% y –31,6%, respectivamente, $P < 0,02$, promediado sobre el primer período de 3,5 h). La tensión respiratoria terminal del dióxido de carbono ($P_{E'CO_2}$), al respirar el aire del cuarto, subió de manera significativa después de las tres drogas. Sin embargo, el aumento del $P_{E'CO_2}$ después del meptazinol (0,22 kPa, promediado sobre 3,5 h) era mucho menor que después de la morfina (0,40 kPa, $P < 0,05$) y de la pentazocina (0,59 kPa, $P < 0,01$). Mientras respiraban el aire del cuarto con una carga inspiratoria resistiva de 8 kPa litre$^{-1}$ s, el $P_{E'CO_2}$ aumentó de nuevo significativamente ($P < 0,05$) después de la tres drogas. El incremento del $P_{E'CO_2}$ después del meptazinol era entonces el mismo que después de la morfina (0,51 kPa promediado sobre 3,5 h). El aumento que siguió a la pentazocina (0,80 kPa) era mucho mayor que después de ambos productos: morfina y meptazinol ($P < 0,02$).