A DOUBLE-BLIND CONTROLLED STUDY OF THE EFFECTS ON RESPIRATION OF PENTAZOCINE, PHENOPERIDINE AND MORPHINE IN NORMAL MAN

BY

SHEILA JENNETT, J. G. BARKER AND J. B. FORREST

SUMMARY

Three drugs and saline were given intravenously, on separate occasions, to eight normal subjects. The doses used were pentazocine 20 mg, phenoperidine 1.5 mg and morphine sulphate 10 mg, each per 70 kg body weight. End-tidal PCO₂ and ventilatory pattern were followed continuously; expired volume and oxygen consumption were measured before and at intervals after injection; a rebreathing carbon dioxide-response test was also applied. The three drugs produced similar, and significant increases, of the order of 5 torr in PCO₂ and dissimilar, significant, reductions in ventilation which could be related to dissimilar effects on oxygen consumption: injection of morphine or of phenoperidine was followed within 10 minutes by an average reduction in oxygen consumption by 20-30 per cent whereas after pentazocine the reduction was only about 10 per cent. The rises in PCO₂ provided a guide to respiratory depression which was as consistent and as statistically significant as most quoted changes in parameters of carbon dioxide-response tests. The results of the carbon dioxide-response test used in this trial were very variable.

Respiratory depression is known to follow the administration of narcotic analgesic drugs, even in small therapeutic doses. The term respiratory depression is taken here to mean a disturbance of the respiratory control mechanisms such as to allow a rise above normal in the level of arterial PCO₂ whilst breathing air; this implies a reduction in alveolar ventilation. A reduction in ventilation does not, however, necessarily indicate respiratory depression, since ventilation could be expected to decrease if resting metabolic rate were to decrease; depressant drugs might have this effect. With these considerations in mind, three drugs have been assessed for their effects on respiration and on oxygen consumption.

Pentazocine is an analgesic of the narcotic-antagonist group of drugs, derived from the benzomorphans; it is of particular interest because there is no evidence of addiction and the drug is free of all narcotic and DDA restrictions. There is some doubt concerning the amount which is equi-analgesic with a standard dose of morphine; at the most commonly quoted value (20 mg pentazocine = 10 mg morphine) it has been reported to be of similar respiratory depressant effect to morphine in normal subjects (Keats and Telford, 1964; Bellville and Green, 1965).

Phenoperidine is a narcotic analgesic related to pethidine; it is usually paired with a neuroleptic drug for neuroleptanalgesia and there are very few reports of its effects when given alone. Prys-Roberts and Kelman (1967) have studied its respiratory effects in anaesthetized man but there appear to be no previous reports of studies with conscious normal volunteers, nor any which quantitatively relate any depressant effect in man to that of other drugs. There is some evidence that this drug may reduce oxygen consumption (see Discussion).

Morphine is frequently used as a standard for comparison in trials of new analgesic drugs but there are only a few studies in which its effects on breathing have been followed continuously (Dripps and Comroe, 1945) or in which such effects have been related to metabolic rate (Smith et al., 1967; Orkin, Egge and Rovenstine, 1955).

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This paper reports the changes found in normal men after small intravenous doses of these drugs, and in respect to these changes compares the drugs with each other and with saline. Data for ventilation, end-tidal Pco₂ and oxygen consumption are presented, and also the results of a rebreathing method for measuring the ventilatory response to increasing carbon dioxide (carbon dioxide-response test).

There are two further aims: first, to demonstrate that there may be a metabolic component contributing to any reduction of ventilation after such drugs, making this reduction a misleading guide to respiratory depression as defined; secondly, to question the contention that air-breathing measurements are of little value in drug assessment, and the corollary that one kind of index or another derived from one of the various types of carbon dioxide-response test is the only precise and quantitative method of describing respiratory depression.

METHODS

The methods which were used in this study have been described in detail (Jennett, 1968) and will be outlined only briefly.

The subjects were eight normal men aged 18 to 35. Drugs were given in doses standardized to body weight: none of the subjects was obese. Each attended for the four different injections on four separate days, not less than five days apart.

The drugs were given intravenously in the following doses:
- pentazocine 20 mg per 70 kg;
- phenoperidine 1.5 mg per 70 kg;
- morphine sulphate 10 mg per 70 kg.

The three drugs and saline were allocated randomly to the letters A–D by J.B. who thereafter held the key to the code. He or J.F. was aware on each occasion of which drug the subject was given, but S.J. remained “blind” and was responsible for all measurements, extraction of data and submission of results for statistical analysis, before breaking the code. The subject was also kept in ignorance throughout, having been told that four drugs were to be tested. The order of administration of drugs to subjects was randomized on the basis of two Latin squares of four.

Each session was conducted as follows. The subject arrived at least 3 hours after the previous meal. He rested for 5–10 minutes before he was required to start breathing into the apparatus. A further period of at least 10 minutes was required for instrumental adjustments and stabilization of breathing pattern.

“Unit-runs” of respiratory and metabolic measurements.

The first control run (C₁) was next carried out as follows: ventilatory pattern and end-tidal Pco₂ were charted continuously on a U-V recorder (S.E.L.) by means of an integrated tidal pneumotachograph (Greer, 1966) and infra-red carbon dioxide analyzer (URAS4, Godart CPI Ltd.); expired volume was measured by dry gas meter (Parkinson Cowan Type D4) and expired air collected for analysis over a period of 5 minutes; a carbon dioxide-response test, by a method of rebreathing from a bag containing 7 per cent carbon dioxide in oxygen, occupied the final 5 minutes. (This and succeeding unit-runs are summarized diagrammatically in figure 1.) A rest of 5–10 minutes was allowed before the second run (C₂). After the second rest period, recording was begun again, breathing allowed to stabilize and the injection then given over 2–2½ minutes. The end of injection was taken as the zero time reference for later measurements. Three sets of observations were obtained from three unit-runs after injection: D₁, D₂, and D₃.

![Diagram of an experiment

Plan of an experiment. The five “unit-runs”, two before and three after injection, are indicated by the letters C₁, C₂ (control) and D₁, D₂, D₃ (drug or saline). V and Pₐco₂ indicate continuously recorded pneumotachography and analysis of expired air for carbon dioxide; Vₒ and V/Pₐco₂ indicate the timing of the intermittent measurements of oxygen consumption and the carbon dioxide-response test respectively.
The first (D1) set of data after injection for expired minute volume (VE), oxygen consumption (VO₂) and carbon dioxide output (VCO₂) refer to the period from the 5th to the 10th minute after the end of injection; mean levels for end-tidal Pco₂ (PAO₂) and for respiratory frequency (f) were taken from the continuous records for that same 5 minutes; parameters of the carbon dioxide-response test refer to about 5 minutes later. The timing of this D1 run did not vary between different experiments. For reasons such as instrumental adjustments, and differing rest periods according to degrees of discomfort, the timing of the D2 and D3 runs was less precise; D2 started 30-40, and D3 60-80 minutes after injection.

Simultaneous values were thus obtained for VE, VO₂, VCO₂, respiratory exchange ratio (R), PAO₂ and f, for two pre-injection and three postinjection occasions; and from the records of V and of Pco₂ which continued during the rebreathing test, two parameters were derived: “V₁₇”, the ventilation at PAO₂ of 57 torr, and “S”, the rate of change of ventilation with rising carbon dioxide, both during a linear rise in Pco₂ of 7 torr or more. In addition to this set of measurements, the time-course of ventilatory changes was on record, in terms of both the tidal volume:frequency pattern and of breath-by-breath PAO₂, during and immediately after injection and for the whole period of observation apart from rest periods and the 5-minute rebreathing periods.

Other observations.

Heart rate and sphygmonanometric readings of arterial blood pressure were taken at 10-15 minute intervals.

During the rest intervals following runs C1, D1 and D3, pH and Pco₂ of arterialized capillary blood were estimated by the micro-Astrup technique (Radiometer, Copenhagen). Samples were collected from thumb stabs, as freely flowing as possible; measurements were made within a few minutes of mixing in heparinized capillary tubes. In nearly all instances a sufficient sample was collected for double estimations so that the reproducibility of individual values could be checked. The range and stability of the pH meter were checked before each experiment and calibrated where necessary against fixed resistances. The gas mixtures used in the equilibration chambers of the tonometer were analyzed for carbon dioxide using the Lloyd-Haldane apparatus, and Pco₂ calculated for the ambient pressure at 38°C. Before each measurement the calomel electrode reservoir was cleaned and filled with fresh saturated KCl solution and the pH meter calibrated against precision buffer solution. After each measurement the glass electrode was cleaned and filled with fresh buffer solution. Calculation of the actual Pco₂ was made from the pH of the equilibrated tonometer samples and the actual pH, using the Siggaard-Andersen nomogram.

Statistical treatment of results.

Subjects 2 and 7 were stimulated by morphine and were excluded from the analysis (see Results). Where information was lacking, and missing values could not be readily estimated for a subject, he in addition was excluded.

For all parameters. The differences between the mean pre-injection value and the first post-injection value D1, the second D2, and the third D3, respectively, were calculated for each subject, for each drug. A two-factor analysis of variance was performed for all postinjection occasions and separately for each of the occasions D1, D2 and D3; tests of significance were applied to the differences between drug and saline means.

Mean control values were also compared with the mean of all drug values, for each subject.

For VE, PAO₂ and VO₂. These factors showed the most consistently significant changes in the initial analysis and proved to be of the most interest in distinguishing between drugs. A further analysis was carried out in order to give a more complete comparison between the three drugs and the time-course of their effects.

A three-factor analysis of variance was performed: pre- and postinjection values were compared between subjects, between injections and between occasions of measurement. To assess the drug x occasion interaction, tests of significance were applied to all possible comparisons between any two injections for each occasion.

In all instances significance was tested at the 5 per cent and 1 per cent levels.

RESULTS

During injection there were minor variations in
ventilation and in $P_{ACO_2}$ due to transient breath-holding or slight overbreathing. Maximal changes usually occurred within the first 5 minutes of injection, and within 2–3 minutes it was possible, with few exceptions, to see on the continuous record a change in breathing pattern (reduction in $V_T$ or $f$ or both) and a rise in $P_{ACO_2}$, when any of the three drugs had been given. The exceptions to this were some pentazocine runs, runs on subject 5 who was less affected in any way by any drug than the other subjects, and the morphine experiments on subjects 2 and 7. These two subjects both showed an initial dramatic stimulation of breathing after morphine injections; this apparently unusual reaction is reported and discussed separately elsewhere (Jennett, Barker and Forrest, in preparation). When all results were analyzed and the code broken, the inclusion of the results for these subjects made all indices of respiratory depression appear non-significant for morphine. Since the depressant action of morphine was the one to which the other drugs were to be compared, and since the other six subjects showed a consistent pattern of depression of similar degree to that reported by others, it seemed reasonable to re-analyze the results for the six subjects only, excluding subjects 2 and 7 from all analyses of variance. The mean changes shown in table I (b) and the values in table II therefore refer to six subjects, unless otherwise stated.

Ventilation (tables I and II; fig. 2).

The expired minute volume was reduced below control level in almost all instances, after all drugs, and for the entire period of observation. For the D1 period, mean reductions for the six subjects were of the order of 20–35 per cent. There was a very slight tendency for ventilation to fall during the saline runs, and a trend towards recovery in the drug runs (fig. 2).

Statistical analysis showed that, in their effect on ventilation, all drugs differed significantly from saline at the 1 per cent level on all postinjection occasions (“occasion” here means the period of measurement D1, D2 or D3). In addition, in the D1 period, phenoperidine caused significantly more reduction than pentazocine; no other difference between drugs was significant. This means that the initial ventilatory reduction after phenoperidine was large by comparison with that after pentazocine; the effect of morphine was intermediate.

Respiratory frequency.

Despite the quite considerable changes in ventilation, alterations in respiratory frequency were not important (table I).

$P_{CO_2}$.

End-tidal measurements (tables I and II; fig. 2). After injection of all three drugs there were individually significant rises above control level in nearly all instances; statistical analysis showed that, in their effect on $P_{ACO_2}$, all drugs differed from saline at the 1 per cent level on all postinjection occasions. In the D1 period there was no significant difference between any two drugs, but in the D2 period phenoperidine maintained a significantly higher $P_{CO_2}$ than either morphine or pentazocine, meaning that the persistence of respiratory depressant effect was greatest following phenoperidine.

Astrup measurements (table I). The pooled mean control measurements and the pooled mean post-drug measurements show values which are 4–5 torr higher than the comparable means for $P_{ACO_2}$, and they also show larger standard deviations than the $P_{ACO_2}$ measurements. The difference between control and drug means, overall, is significant. However, for individual drugs and subjects there were much wider variations in the values than in those for $P_{ACO_2}$. Mean rises after phenoperidine and morphine appeared to parallel the rises in $P_{ACO_2}$ but were not statistically significant, on account of wide variations; the small mean rise after pentazocine was largely due to some apparent falls of $P_{ACO_2}$, or no change from control level, at times when the $P_{ACO_2}$ had clearly risen. Such values, erratically lower than the end-tidal measurements, led us to discount the Astrup results in these instances, and accordingly conclusions are based on $P_{ACO_2}$ values.

Oxygen consumption (tables I and II; fig. 2).

In the period 5–10 minutes after injection, all subjects on all drugs, with the exception of subject 7 after morphine and subjects 4 and 5 after pentazocine, showed a fall in oxygen consumption. Statistical analysis showed that with respect to oxygen consumption all drugs differed from
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**TABLE I**

Measurements during air-breathing.

(a) Mean and standard deviation of control and drug values for all eight subjects for all measurements during air-breathing.

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control values</th>
<th>Drug values</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>f (b.p.m.)</td>
<td>11.9</td>
<td>3.4</td>
</tr>
<tr>
<td>V E (l./min BTPS)</td>
<td>7.31</td>
<td>0.95</td>
</tr>
<tr>
<td>P A02 (torr)</td>
<td>37.5</td>
<td>2.4</td>
</tr>
<tr>
<td>P Aco2 (torr)</td>
<td>42.1</td>
<td>3.3</td>
</tr>
<tr>
<td>V O2 (ml/min)</td>
<td>249.1</td>
<td>34.9</td>
</tr>
<tr>
<td>V CO2 (ml/min)</td>
<td>210.0</td>
<td>30.1</td>
</tr>
<tr>
<td>R</td>
<td>0.86</td>
<td>0.07</td>
</tr>
<tr>
<td>Mean BP</td>
<td>104.9</td>
<td>9.2</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68.4</td>
<td>6.8</td>
</tr>
</tbody>
</table>

* Significant at 1 per cent level.
† Significant at 5 per cent level.
‡ Control values consist of pre-injection values of all three active drugs, and pre- and postinjection values of saline.
§ Drug values consist of postinjection values of all three active drugs.

(b) Differences between pre-injection and “D1” values for measurements during air-breathing.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>f (b.p.m.)</td>
<td>0.0</td>
<td>-0.9</td>
<td>-2.4</td>
<td>-1.25</td>
</tr>
<tr>
<td>V E (l./min BTPS)</td>
<td>-0.01</td>
<td>-1.57*</td>
<td>-2.14*</td>
<td>-2.80*</td>
</tr>
<tr>
<td>P Aco2 (torr)</td>
<td>-1.4</td>
<td>2.5*</td>
<td>3.6*</td>
<td>5.2*</td>
</tr>
<tr>
<td>P Aco2 (torr)</td>
<td>1.3</td>
<td>1.1</td>
<td>6.4</td>
<td>7.5</td>
</tr>
<tr>
<td>V O2 (ml/min)</td>
<td>4.7</td>
<td>-27.9†</td>
<td>-53.1*</td>
<td>-100.7*</td>
</tr>
<tr>
<td>V CO2 (ml/min)</td>
<td>-5.8</td>
<td>-48.4*</td>
<td>-68.4*</td>
<td>-86.2*</td>
</tr>
<tr>
<td>R</td>
<td>-0.02</td>
<td>-0.11</td>
<td>-0.125</td>
<td>-0.14</td>
</tr>
<tr>
<td>Mean BP</td>
<td>1.4</td>
<td>1.5</td>
<td>-2.6</td>
<td>-3.4</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>-1.6</td>
<td>0.3</td>
<td>2.2</td>
<td>-5.8</td>
</tr>
</tbody>
</table>

* Significant at 1 per cent level.
† Significant at 5 per cent level.

**TABLE II**

Ventilation, alveolar Pco2 and oxygen consumption: mean values before the different injections and in the different periods of measurement after injection ( "injection x occasion").

<table>
<thead>
<tr>
<th>Injection</th>
<th>C</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE (l./min BTPS)</td>
<td>Saline</td>
<td>7.5</td>
<td>7.5</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>Pentazocine</td>
<td>7.4</td>
<td>5.9*</td>
<td>5.8*</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>7.5</td>
<td>5.3*</td>
<td>5.9*</td>
</tr>
<tr>
<td></td>
<td>Phenoperidine</td>
<td>7.5</td>
<td>4.7*</td>
<td>5.4*</td>
</tr>
<tr>
<td>PAco2 (torr)</td>
<td>Saline</td>
<td>37.9</td>
<td>36.5</td>
<td>37.6</td>
</tr>
<tr>
<td></td>
<td>Pentazocine</td>
<td>36.8</td>
<td>41.9*</td>
<td>41.2*</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>38.2</td>
<td>41.8*</td>
<td>41.3*</td>
</tr>
<tr>
<td></td>
<td>Phenoperidine</td>
<td>38.4</td>
<td>43.7*</td>
<td>44.1*</td>
</tr>
<tr>
<td>VO2 (ml/min STPD)</td>
<td>Saline</td>
<td>249.0</td>
<td>253.2</td>
<td>242.6</td>
</tr>
<tr>
<td></td>
<td>Pentazocine</td>
<td>249.0</td>
<td>219.6†</td>
<td>231.8</td>
</tr>
<tr>
<td></td>
<td>Morphine</td>
<td>233.2</td>
<td>178.4*</td>
<td>211.2</td>
</tr>
<tr>
<td></td>
<td>Phenoperidine</td>
<td>239.8</td>
<td>152.8*</td>
<td>199.6</td>
</tr>
</tbody>
</table>

* Indicates significant difference from saline at 1 per cent level.
† Indicates significant difference from saline at 5 per cent level.
Similar underlining (--- or .........) indicates significant difference between the two values underlined.
Analysis refers to 6 subjects for VE and PAco2; 5 subjects for VO2.
The extent and pattern of changes in ventilation, $P_{A\text{CO}_2}$, and oxygen consumption, to show the differences between the effects of the four injections related to the different occasions of measurement (cf. table II where significance of differences is indicated).

At C: mean pre-injection values.
At D1, D2, D3: mean values on the three occasions of measurement after injection.
(Actual timing as described in text.)

Data from six subjects.

saline in the D1 period: phenoperidine and morphine at the 1 per cent level (with reductions of the order of 20–30 per cent), but pentazocine only at the 5 per cent level. Also in the D1 period, both morphine and phenoperidine differed significantly from pentazocine. There were still mean reductions in the D2 and D3 periods, but these were non-significant. These results imply that initially morphine and phenoperidine reduced oxygen consumption markedly, and much more than pentazocine, but that this reduction tended, after any drug, to recover sooner than the ventilatory changes.

### Rebreathing carbon dioxide-response test (table III).

"S". The mean differences between control and all postinjection values appear to show, for all drugs combined, and for each drug separately, a reduction in this parameter. However, variations were large and the changes after drugs were not significantly different from those after saline (table III). Two individual missing values were estimated in order to perform an analysis of variance for six subjects.

When each subject was considered separately, only four showed a significant mean reduction in S for all drug periods compared with control periods. When each experiment was considered separately, there were only three instances of reduction in S in the D1 period which was significant at the 5 per cent level: two after phenoperidine, one after morphine.

"$\dot{V}_{S}$". For each subject the mean of all measurements after all drugs was compared with his own mean control value: two subjects showed a reduction which was significant at the 5 per cent level. Comparison of each individual change after each drug with that after saline, showed two instances of significant change, both after phenoperidine.

### Heart rate and blood pressure (table I).

Analysis which included all subjects showed a significant mean fall of about 6 beats/min for postinjection periods after phenoperidine. A similar mean change is also shown in the analysis excluding subjects 2 and 7, but variations made this non-significant. There were no other significant changes in heart rate.

There were no significant changes in mean blood pressure.

### Changes in breathing pattern.

Irregularity of both frequency and tidal volume were seen consistently after phenoperidine, in most cases after morphine, and occasionally after pentazocine. It was a striking feature of the phenoperidine experiments that a clear change of
pattern (fig. 3) persisted often throughout the period of observation, even on occasions when the mean PAO₂ was not more than 2-3 torr above control value, and when the response to inspired carbon dioxide was virtually normal. This same dissociation between respiratory depression and interference with regularity was also seen in some of the morphine experiments. There was no instance of regular periodic breathing after morphine.

### TABLE III

<table>
<thead>
<tr>
<th>Subject</th>
<th>Control values</th>
<th>Drug values</th>
<th>Change from pre-injection values to first value after injection (D1-C)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>“S” (l./min/mm Hg Pco₂)</td>
<td>Saline</td>
<td>Pent.</td>
</tr>
<tr>
<td>1</td>
<td>2.20 0.40</td>
<td>Mean 0.20</td>
<td>-1.00</td>
</tr>
<tr>
<td>2</td>
<td>2.69 1.09</td>
<td>Mean 1.35</td>
<td>-1.20</td>
</tr>
<tr>
<td>3</td>
<td>0.74 0.23</td>
<td>Mean 0.87</td>
<td>0.15</td>
</tr>
<tr>
<td>4</td>
<td>4.03 0.78</td>
<td>Mean 2.97</td>
<td>0.80</td>
</tr>
<tr>
<td>5</td>
<td>1.31 0.66</td>
<td>Mean 1.94</td>
<td>0.35</td>
</tr>
<tr>
<td>6</td>
<td>1.28 0.55</td>
<td>Mean 1.39</td>
<td>-0.05</td>
</tr>
<tr>
<td>7</td>
<td>4.60 1.48</td>
<td>Mean 3.24</td>
<td>0.70</td>
</tr>
<tr>
<td>8</td>
<td>2.24 0.83</td>
<td>Mean 1.40</td>
<td>-0.05</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subject</th>
<th>Values for all 8 subjects</th>
<th>Saline</th>
<th>Pent.</th>
<th>Morph.</th>
<th>Phen.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>22.4 1.48</td>
<td>Mean 2.15</td>
<td>3.4</td>
<td>8.5</td>
<td>-14.5</td>
</tr>
<tr>
<td>2</td>
<td>27.1 5.1</td>
<td>Mean 13.25</td>
<td>6.3</td>
<td>-14.0</td>
<td>-16.0</td>
</tr>
<tr>
<td>3</td>
<td>16.6 4.6</td>
<td>Mean 15.1</td>
<td>4.7</td>
<td>-1.0</td>
<td>-1.0</td>
</tr>
<tr>
<td>4</td>
<td>50.8 8.7</td>
<td>Mean 14.2</td>
<td>0.6</td>
<td>3.0</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>26.0 9.2</td>
<td>Mean 33.0</td>
<td>6.2</td>
<td>1.5</td>
<td>-3.58</td>
</tr>
<tr>
<td>6</td>
<td>24.3 6.9</td>
<td>Mean 19.9</td>
<td>4.8</td>
<td>-1.0</td>
<td>-10.5</td>
</tr>
<tr>
<td>7</td>
<td>76.6 24.4</td>
<td>Mean 49.1</td>
<td>20.8</td>
<td>-22.5</td>
<td>—</td>
</tr>
<tr>
<td>8</td>
<td>28.1 7.7</td>
<td>Mean 17.9</td>
<td>3.6</td>
<td>-2.0</td>
<td>-15.5</td>
</tr>
</tbody>
</table>

† Difference significant at 5 per cent level.
‡ Subject 1: difference appears non-significant but t-test not performed as no information on morphine.
§ Subject 2: difference appears significant but t-test not performed as no information on morphine.
Subject 4: difference appears significant but t-test not performed as information on phenoperidine only.

### FIG. 3

Examples of the breathing patterns observed after each of the three drugs. Upper trace, carbon dioxide; lower trace, inspired tidal volume. The end-tidal carbon dioxide level is similar in each case. (Calibrations not the same for tidal volume.)
DISCUSSION

Reliability of measurements.

The continuous recording of ventilatory pattern and end-tidal carbon dioxide enabled a cross-check to be made of any change in one or the other; instrumental faults could be suspected and corrected, for example, if there were a bizarre change in carbon dioxide level without a corresponding inverse change in ventilation. Preliminary calibration as already described (Jennett, 1968) indicated linearity of the integrated pneumotachograph deflection over the appropriate range of tidal volumes; continued reliability of this was checked by comparing estimated minute volume from the trace with gas-metered minute volume for different periods of the same experiment. Repeated calibration and zero-check of the carbon dioxide analyzer during each experiment, together with the repeatability of any one individual’s resting end-tidal carbon dioxide level, gave confidence in the validity of the measured increases in this level following drugs. The Astrup Pco₂ measurements did not, as described above, agree well with the end-tidal levels, but they were not taken simultaneously; it was more notable that they were so much more widely variable than the end-tidal levels; the precautions taken in the instrumental technique suggested that the unreliability was probably due to the collection of the samples and attendant variables—transient breath-holding or overbreathing, venous congestion, changes of temperature. It seems reasonable to place more confidence in a mean level derived from a continuous recording. End-tidal levels may sometimes underestimate arterial Pco₂: where small breaths occurred during drug-induced irregularity, alveolar plateaus were not reached. However, there were sufficient larger breaths to give valid readings, although admittedly the mean of such plateaus might still underestimate the mean Pao₂. Nevertheless a value for Pao₂ derived from a 5-minute continuous trace would appear likely to be a better estimate of the mean Pao₂ for that period than a single capillary blood sample; indeed this argument is all the stronger when the pattern is irregular.

Measurements of expired volume, oxygen consumption and carbon dioxide output, based on a background of repeated calibration of instruments and of known control variability for each subject, as already described, could be further checked for consistency with the concurrent findings on the continuous trace; for example, when alveolar Pco₂ was rising, carbon dioxide output should be lower and R smaller; any values showing discrepancies were examined for the source of inaccuracy and any non-valid findings rejected. The calculation of Vo₂ involved multiplication by the value for ventilation, and this was reduced after drugs: the results were critically assessed to determine whether any consistent underestimate of ventilation could account for the apparent fall in oxygen consumption, and it could not.

Interpretation of results.

On the basis of rise in Pao₂ it could be concluded that 20 mg pentazocine, 10 mg morphine sulphate and 1.5 mg phenoperidine showed similar respiratory depressant action, except that the effect of phenoperidine persisted or tended to continue increasing for longer than the effects of the other drugs (fig. 2).

It is of interest that these changes in Pao₂ were significant, not only by comparison of means, but also for most individual experiments, for all drugs, and throughout the 1½ hours or more of observation.

It could be argued that our pre-injection levels were below normal, representing hyperventilation, and that the drug-induced change was simply to a more normal—sedated rather than depressed—condition. The normal pre-injection values for respiratory exchange ratio (R) and for Vco₂ are against this; also R fell to below normal values after drug injection, but not during saline experiments. A further possibility would be that the measured changes were simply due to sleep; the changes are of an appropriate order for this. We cannot guarantee that no subject fell asleep within a minute or two of any injection (i.e. at the time of greatest rise of Paco₂) but certainly most were awake throughout.

The reduction in ventilation, taken alone, would suggest that pentazocine is a considerably less potent respiratory depressant than the other drugs (fig. 2). However, this apparent discrepancy between the rise of Pao₂ and the fall in ventilation is readily explained by reference to the third graph in figure 2: considering the D1 period, the
greatest reduction in oxygen consumption after phenoperidine, and the greater reduction of oxygen consumption after morphine, could be expected to be associated with appropriately different falls in ventilation, even though the rises in PAO2 were similar for the three drugs. In other words, the reduction of ventilation had in each case both a respiratory and a metabolic depressant component and the two were additive. This finding could go some way towards explaining differences between clinical and laboratory findings for so-called respiratory depression: when only ventilation (whether total or alveolar) is measured, misleading comparisons could be made between two drugs if one of the drugs were more of a metabolic depressant than the other; measurements of air-breathing Pco2, or of shift of a carbon dioxide-response curve could show these same two drugs to be of equal respiratory depressant potency. For this reason we suggest that a reduction in ventilation, still more in respiratory frequency, should not be referred to as respiratory depression, this term being reserved for those cases in which a rise in Pco2, or a change in responsiveness to inspired carbon dioxide, is demonstrable.

This paper quotes values for VE and not for alveolar ventilation VA. Admittedly VA is more significant in relation to both rises of PAO2 and changes in oxygen consumption. There were two reasons for using VE: changes in f were minimal, so if a constant deadspace were assumed, changes in VA would in any case parallel changes in VE; secondly, if either deadspace were not assumed constant, but calculated from PAO2, expired carbon dioxide and VE, and deadspace V subtracted, or if VA were calculated directly from VeO2 and alveolar carbon dioxide per cent, the answer would be affected by any errors in carbon dioxide analysis, VE measurement, and in estimation of mean value for PAO2 during the period of collection. It was considered better to analyze the values as measured rather than compound several possible sources of error. The use of VA rather than VE would not alter the findings on the relative metabolic and respiratory components of fall in ventilation, and PAO2 increases were in themselves an index of reduced alveolar ventilation.

The lack of significance in changes in respiratory frequency is notable, in view of the fact that this is often taken as an index of depression. Thus Prys-Roberts and Kelman (1967), studying subjects under nitrous oxide and oxygen anaesthesia, describe the extent and the time-course of respiratory depression following analgesic drugs in terms of f, although end-tidal carbon dioxide was also measured: our findings would suggest that the two changes might not follow a similar pattern, nor indicate similar degrees of depression.

It is, of course, well known that in severe respiratory depression there is slowing of breathing; the present argument is only against the use of change in f as a quantitative assessment of the degree of such depression. Several publications on this subject appear to imply the assumption that a respiratory depressant drug primarily affects the frequency of breathing, and that tidal volume may or may not "compensate" for any such change—presumably by some intact mechanism other than the "depressed" respiratory centre. Normally, however, it seems that the respiratory control mechanism selects an appropriate ventilation, at an optimal combination of f and tidal volume; if the effect of a drug were an alteration in this f/tidal-volume relationship, yet alveolar ventilation remained unchanged, the condition could hardly be described as a depression of the respiratory centre, but only as what it is: a derangement of the normal pattern.

The changes in oxygen consumption, apart from explaining the differences in ventilatory reduction, are of some interest in themselves. The extent of the reductions in VeO2, following pheno- peridine and morphine was considerably greater than any which could be accounted for by a change from "resting" to a properly "basal" state, or from wakefulness to sleep. There appears to be no methodological artefact which could lead to a falsely low result after drug injection: if ventilation values were underestimated or expired oxygen percentages overestimated, then VeO2 values would be low: low expired volumes could be confirmed by comparison with the pneumotachograph trace; normality and repeatability of oxygen consumption measurements in saline and other control studies gave confidence in the method of gas analysis. No significant fall in oxygen uptake (which would lead to an underestimation of tissue consumption) is calculable from the small rise in Pco2, in its effect of either
reducing alveolar $P_{O_2}$, or of modifying the oxygenhaemoglobin dissociation curve, thereby reducing arterial oxygen content—such an effect would in any case be transient if tissue consumption were maintained as mixed venous oxygen would become lower also. Similarly there would be no significant reduction from any disturbance of $V/Q$ distribution.

It would appear that the measured fall in oxygen uptake is likely to be a reflection of a reduced tissue consumption occurring particularly during the initial period of maximal drug activity.

Following morphine there have been two reports of the effects on oxygen consumption of intravenous administration of a 10-mg dose, and in neither was a significant fall in $V_O$ found. Orkin, Egge and Rovenstine (1955) measured $V_O$ spirometrically, with the subjects breathing 100 per cent oxygen. Measurements were taken continuously for consecutive periods starting at 1 minute after injection. There is no indication of even a small initial fall on their published graphs. Smith and associates (1967) also measured $V_O$ spirometrically, using 50 per cent oxygen. In this series values were found half an hour after injection: at a time when, according to our findings, the maximal reduction would perhaps be over; they showed a small reduction after morphine and also after a placebo, so concluding that both were due to a change towards the basal state.

Earlier studies following intramuscular injection indicated a 5–10 per cent reduction in metabolic rate or $V_O$ (Bornstein and Holm, 1926; David, 1934).

The present results therefore appear to be the only positive evidence that morphine causes a reduction in metabolic rate in man.

There is, however, a precedent for the demonstration of a reduction in $V_O$ following phenoperidine. The present results confirm those of Macdonald and associates (1966) who measured $V_O$ from cardiac output and A-V difference during cardiac catheterization of patients with mitral valve disease; two of their subjects had phenoperidine 1.5 mg only, and showed about a 20 per cent fall in $V_O$.

Gemperli (1965) has reported greater reductions following various neuroleptanalgesic drug combinations in dogs anaesthetized with nitrous oxide and oxygen. On the other hand, Forbes and associates (1967) showed no such fall in man after fentanyl and droperidol, in doses sufficient to produce anaesthesia and apnoea.

The results of the tests of ventilatory response to carbon dioxide were far less consistent and conclusive, largely on account of wide variability in both control and experimental values.

The application of this particular method to the study of drug effects has not previously been reported but a similar method has been shown to distinguish clearly between normal subjects and those with chronic obstructive airways disease (Read, 1967). Since other methods for evaluating carbon dioxide-responsiveness, or carbon dioxide-tolerance, have shown statistically significant differences after drugs in similar dosage to those used in this trial, it could be argued that this rebreathing method is therefore unsuitable as a sensitive index of respiratory depression. The fact remains that there were some significant changes revealed by this method but that there was frequently no significant depression shown by this index at a time when there was clearly a significant rise in the $P_{ACO_2}$ breathing air. Conversely, there was no instance in which the carbon dioxide-response test demonstrated depression which was not already evident from the rise in $P_{CO_2}$.

**Differences between the drugs.**

It seemed surprising that in terms of $P_{ACO_2}$ the final analysis showed 20 mg pentazocine to be of similar respiratory depressant potency to the other two drugs: surprising by comparison with clinical observation of the subjects, who seemed to be in general less affected by this drug than by the others. (There was less detachment, less nausea, no pallor, no eye symptoms, no noticeable after-effects; we did not, however, attempt rigorous assessment of these factors, and would accept the data of Keats and Telford (1964) who scored the side-effects on a larger series, and showed no difference between pentazocine and morphine in these same doses, except that nausea was significantly less after pentazocine.) It was also surprising in view of all objective measurements other than $P_{CO_2}$, which showed in general less effect after pentazocine than after the narcotic analgesics. Conversely, in general, 1.5 mg phenoperidine appeared to have a more profound effect than 10 mg morphine, although the only clear
indication of this in terms of $\text{Pco}_2$ was the longer-lasting effect.

The relative absence of disturbance of breathing pattern by pentazocine was also a most striking feature; on the other hand, the consistency of early development of an irregular pattern following phenoperidine was equally striking.

The equivalence of 10 mg morphine and 20 mg pentazocine is in line with the findings of the other authors quoted but like that of Dyrberg, Henningsen and Johansen (1967) the present study does not confirm the findings of Bellville and Green (1965) that pentazocine has a greater initial but more rapidly recovering effect than morphine. If the equi-analgesic dose ratio for pentazocine:morphine is greater than 2:1, as apparently it may be (Cass, Frederik and Teodoro, 1964), then knowledge of the relative dose-effect curves for respiratory depression is important: there is no evidence that this is less steep for pentazocine than for morphine in the range of 10–40 mg but it may be that with repeated doses of pentazocine a ceiling level of only moderately severe respiratory depression may be reached whereas equivalent increase in narcotic analgesics would lead to apnoea (Bellville and Green, 1965).

It is reported, however, from clinical studies that the increase in end-tidal carbon dioxide is linearly related to the dosage from 40–180 mg (Brown, A., 1967, personal communication).

CONCLUSIONS

When evaluated by the initial, maximal rise in $\text{PAO}_2$, 20 mg pentazocine, 10 mg morphine sulphate and 1.5 mg phenoperidine had comparable respiratory depressant effects; the effect of phenoperidine was more persistent than that of either of the other two drugs; there was no difference between the patterns of recovery from morphine and pentazocine. However, pentazocine was generally less disturbing, both subjectively and as reflected in whole body oxygen consumption.

This similarity of respiratory depression in terms of $\text{PAO}_2$, agrees with the findings of others in terms of ventilatory response to increased carbon dioxide; but this similarity should perhaps be considered in conjunction with differences in respiratory derangement: it could well be that the greater interference with regularity of breathing by the narcotic analgesics, observed even when homeostasis for carbon dioxide is only slightly and similarly altered, presages their potentially greater effect at higher doses.

Experience with repeated and continuous air-breathing measurements has led to the conclusion that they can give useful information, and that rise in $\text{PAO}_2$ is defensible as an index of respiratory depression against the claims of the many methods of testing carbon dioxide responsiveness; the normal value for $\text{PAO}_2$ is more clearly defined and less variable, and small changes are accurately measurable and comparable, without recourse to complex calculations, from one laboratory to another.

It is already widely agreed that a full picture of the respiratory effect of a drug cannot be drawn from observations of ventilation alone; it is further suggested that an incomplete picture may result from using only an index of "respiratory depression" whether it be an actual rise of $\text{Pco}_2$ breathing air, or a change in a parameter of the relationship between ventilation and increased $\text{Pco}_2$; similar changes in such criteria may be associated with dissimilar effects on metabolism, and on the pattern of breathing, which may indicate differences in potential toxic effect on the medullary centres.

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REFERENCES


STUDY OF PENTAZOCINE, PHENOPERIDINE AND MORPHINE


EINE KONTROLLIERTE DOPPELBLIND-UNTERSUCHUNG DER EINFLUSES VON PENTAZOCINE, PHENOPERIDINE UND MORPHIN AUF DIE ATMUNG BEIM GESUNDEN MENSCHEN

ZUSAMMENFASSUNG


UNE ETUDE CONTROLEE, DOUBLEMENT AVEUGLE DES EFFETS SUR LA RESPIRATION DE PENTAZOCINE, PHENOPERIDINE ET MORPHINE CHEZ L'HOMME NORMAL

SOMMAIRE

Trois médicaments et une solution saline ont été administrés séparément par voie intraveineuse à huit sujets normaux. Les doses administrées étaient pentazocine 20 mg, phenoperidine 1,5 mg et sulphate de morphine 10 mg, chaque fois pour un poids corporel de 70 kg. Le Pco₂ terminal et la ventilation ont été contrôlés sans interruption; le volume expiré et la consommation d'oxygène ont été mesurés avant et à intervalles après l'injection; un test de réaction à la réinspiration de CO₂ a également été appliqué. Les trois médicaments causaient une augmentation similaire et significative de l'ordre de 5 torr du Pco₂ et une réduction dissimilaire et significative de la ventilation, qui pouvait être mise en rapport avec l'influence dissimilaire sur la consommation d'oxygène: l'injection de morphine ou de phenoperidine était suivie dans les 10 minutes d'une réduction moyenne de 20–30 pour cent de la consommation d'oxygène, tandis que la réduction n'était que d'environ 10 pour cent après pentazocine. L'augmentation du Pco₂ servait d'indicateur de la dépression respiratoire, qui était aussi constante et significative statistiquement que la majorité des modifications citées des paramètres du test de réaction au CO₂. Les résultats du test de réaction au CO₂, appliqué dans cet essai, étaient très variables.