RESPIRATORY DEPRESSION FOLLOWING SINGLE AND REPEATED DOSES OF PENTAZOCINE AND PETHIDINE

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SUMMARY

Pentazocine and pethidine have been compared in the dose ratio 45:75 for their depression of respiration in normal subjects. The respective additive actions of the two drugs were investigated by comparing the effects of a single dose with those of two repeated half-doses. Some degree of ventilatory depression was found consistently. A first half-dose of pentazocine 22.5 mg had a greater effect than a first half-dose of pethidine 37.5 mg, but a second half-dose of pentazocine had a smaller additive effect. The results support existing evidence that a "ceiling" for respiratory depression is attained at a relatively low dosage of pentazocine.

There is evidence that repeated doses of pentazocine may have diminishing respiratory depressant effects, as compared with the additive effects of repeated dosage of the narcotic analgesics.

Davie, Scott and Stephen (1970) have shown that in anaesthetized subjects, for the same dose by weight of pentazocine and pethidine, pentazocine gave a relatively small additional effect when injection was repeated.

In conscious volunteers, Dyrberg and Kolliker (1971), have shown a less steep, but nevertheless progressive, respiratory depression with three repeated injections of pentazocine than with three repeated injections of pethidine in doses considered to be equianalgesic. Ominsky, Kallos and Smith (1969) report a "ceiling" for depression by pentazocine at about 60 mg/70 kg, and no such ceiling for morphine over a full clinical dose range.

In the present study, pentazocine and pethidine, in dose ratio 45:75, have been given to normal conscious subjects. Two forms of administration have been compared: a full dose given singly, and the same dose halved and repeated. Comparisons could thus be made (1) between the two drugs in the full dose given, (2) between the two drugs in half that dosage, (3) for each separate drug, between the two modes of administration and (4) between the two drugs, in respect to the different forms of administration—whether or not the effect of the second dose was similarly additive.

Subjects and plan of trial.

Sixteen subjects were included in the trial. All were healthy male volunteers in the age range 18–27. Each subject attended twice, at an interval of not less than a week.

The subjects were divided into two groups of 8, with respect to the method of administration of the drugs: half received the drugs in two half-doses, and half received the drugs in single whole doses; each subject was given pethidine on one occasion, and pentazocine on the other; half the subjects had pethidine on the first occasion, and half had pentazocine on the first occasion. Allocation to these groups was random (table I).

<table>
<thead>
<tr>
<th>Occasion of administration</th>
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<tr>
<td>Form of administration</td>
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<tr>
<td>Whole dose</td>
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<td>Pethidine first, pentazocine second</td>
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<td>Pentazocine first, pethidine second</td>
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The doses used were 45 mg pentazocine and 75 mg pethidine, each per 70 kg body weight, given intravenously. In any one experiment, two injections were given, at an interval of 20 min. Subjects who were given the whole dose of drug in the first injection were given a second injection of saline. Volume and duration of injection were the same whether whole dose, half dose or saline was given.

The methods for assessing respiratory depression were similar to those previously described in a com-
Comparative study of three analgesic drugs (Jennett, Barker and Forrest, 1968). In that study, complete saline control experiments were included on each subject; the criteria applied showed a consistent distinction between any drug and saline injection. We therefore felt justified in omitting placebo experiments in the present study, and making direct double-blind comparisons between the two drugs.

The particular drug and method of administration used on any particular occasion was known to S.J. but not to S.E., who extracted data from the records whilst still "blind".

Procedure.

Each subject was studied at least four hours after his last meal. He rested, semi-recumbent, for 10–15 min and was then attached to the apparatus. When the ventilation was reasonably steady, base-line measurements were started.

Air breathing ventilation (V) and end-tidal CO₂ (PₐO₂) were recorded and measurements of oxygen consumption (Vₒ₂) and carbon dioxide output (VₐCO₂) were made. A rebreathing CO₂ response test was then applied. This whole sequence took 15 min. A second sequence was then carried out, giving two sets of baseline observations.

Without interruption of recording of V and PₐO₂, the first injection was given. Five min later, gas exchange measurements were made and followed at 12 min by a CO₂-response test; 20 min after the first injection the second injection was given, and the same sequence of measurements made. V and PₐO₂ recording were continued, and final measurements of gas exchange made at one hour after the first injection. At the end of the experiment the subject was asked to describe his subjective sensations.

Methods of Measurement.

Ventilation and gas exchange.

The arrangement of apparatus is shown in figure 1. The flow head (F1) of a pneumotachograph (Computing Spirometer CS1, Mercury Electronics (Scotland) Ltd.) was placed in the path of inspired air; tidal pattern and cumulative volume were recorded. From the record, minute volume, frequency and

![Diagram of apparatus](image-url)

FIG. 1. Arrangement of apparatus. With the different outlets of the sliding valve opposite the mouthpiece, the subject (1) breathes room air; (2) breathes in through the flow head (F1) and out through the mixing chamber; (3) rebreathes from bag through flow head (F2).
tidal volume could be calculated over any required period.

Expired air passed into a mixing chamber and was continuously sampled during \( V_O^2 \) and \( V_{CO_2} \) estimations. The sample passed through an infrared CO\(_2\) analyser (URAS, Hartmann & Braun) and a paramagnetic oxygen analyser (Servomex 101). \( V_O^2 \) and \( V_{CO_2} \) were calculated from ventilatory volume and expired gas analysis.

**End-tidal CO\(_2\).**

Continuous sampling from the mouthpiece to the infrared analyser allowed breath-by-breath recording of CO\(_2\) per cent during the whole study, except for the periods of gas exchange measurement, when sampling was switched to the expired air chamber.

**Recording.**

Ventilation and CO\(_2\) were recorded on a U-V recorder (S.E.L.).

**CO\(_2\) response test.**

The method was similar to that used previously in this laboratory (Jennett, Barker and Forrest, 1968) and to that described by Read (1967). Rebreathing is from a small volume of gas at an initial CO\(_2\) concentration which is near to mixed venous tension. In these circumstances the concentration of CO\(_2\) in bag, lungs and blood rises linearly after about the first half-minute (Fowle and Campbell, 1964).

Without interruption of CO\(_2\) recording at the mouth, the subject was switched to breathing in and out of a bag containing 6–8 litres of 7% CO\(_2\) in oxygen. A second flow head (F2, fig. 1) was brought into use to record ventilation. Rebreathing was continued for 3–4 min, and the subject then switched back to room air.

From the records ventilation and Pco\(_2\) were calculated for each successive 20-sec period after the initial equilibration; thus 9–12 points were available for calculation of the regression equation of \( V \) against Pco\(_2\). This gave the slope (S) of the response line. Two other parameters were derived: the ventilation of 57 mm Hg Pco\(_2\) ("\( V_{57} \)") and the Pco\(_2\) at a ventilation of 20 l./min ("Pco\(_2_{20} \)"); these were chosen as indices of shift, comparable to those sometimes used by other workers, and within the observed range in all tests (fig. 2).

**Processing of data.**

The investigation was designed as a series of 3-factor experiments so that significance of the results could be assessed by analysis of variance. The three factors were (1) drug (pethidine, pentazocine) (2) time during study at which measurements were made (A, B, C, D, fig. 3) and (3) method of administration (whole dose, 2 x half dose). Significance was tested at the 5 per cent level. There were a few gaps in the data which were filled with values estimated by the missing data technique.

**RESULTS**

Alteration in breathing pattern and increase in end-tidal CO\(_2\) was virtually always discernible within 5 min of the first injection of either drug. Irregularity developed in some cases, most commonly, but not exclusively, after the whole dose of pethidine. In a few instances this was very marked, and persisted until the end of the study.

The values for all variables were coded as follows (fig. 3):

- **A**: average of two base-line measurements.
- **B**: measurements starting 5 min after the first injection. (Ventilation, Pco\(_2\) and gas exchange values apply to the period 5–10 min after injection; CO\(_2\) response parameters apply to 12–16 min after injection.)
- **C**: measurements starting 5 min after second injection (timing as in B).
- **D**: measurements made one hour after the first injection (ventilation, Pco\(_2\), and gas exchange, over a 10 min period).
Plan of Experiment

- Ventilation
- End-tidal CO₂
- Gas exchange
- CO₂ response

FIG. 3. The timing of the several measurements. Ventilation is recorded throughout; end-tidal CO₂ recording is interrupted only during expired air analysis (gas exchange).

Baseline measurements—A.

Baseline values (A) were appropriate for normal resting subjects (table II), and there were no statistically significant differences in the average of the two initial readings, between the two "administration" groups, or between the pentazocine and pethidine experiments.

Changes after injection—B-C-D.

Mean values for periods B, C and D are shown in table II. For presentation in figures 4 and 5 these values have been calculated as percentage changes from baseline and scales have been inverted where necessary so that the direction of depression is downwards throughout.

Overall pattern of changes. There were significant changes in all the variables shown during the course of the experiments; in terms of the analysis of variance, the factor "time of measurement" was always significant at the 5 per cent level at least. Taking each variable separately, the analysis showed only two differences between the two drugs or between the two methods of administration, which reached significance. These two were (1) a difference between pentazocine and pethidine in the pattern of change in carbon dioxide output (VCO₂) and (2) for pentazocine, a difference between the modes of administration in the pattern of change of the slope of the CO₂ response line (S). This lack of attainment of significant differences, on the part of single separate criteria of depression need not however invalidate trends shown by the behaviour of all criteria considered together: such consideration indicates differences between the drugs and between their effects when administered repeatedly. These can be seen in figures 4 and 5.

Effect of first injection—B. The change A-B represents the effect of either a half dose or a whole dose.

Table II, and the profile of changes in figures 4

| Table II. Mean values for 8 subjects receiving “divided” and 8 receiving “whole” doses. |
|---|---|---|---|---|
| | Mean V (l/min) | Mean P_{A_{CO₂}} (mm Hg) |
| | A | B | C | D | A | B | C | D |
| **Ventilation and P_{CO₂}** | **Divided** | Pentazocine | 7.9 | 6.4 | 7.4 | 7.2 | 39.6 | 43.4 | 43.8 | 43.6 |
| | | Pethidine | 8.0 | 7.3 | 6.6 | 6.4 | 39.5 | 42.0 | 44.4 | 43.6 |
| | **Whole** | Pentazocine | 6.8 | 5.6 | 6.2 | 6.6 | 40.8 | 45.2 | 44.7 | 43.2 |
| | | Pethidine | 7.2 | 5.7 | 6.1 | 6.2 | 40.8 | 45.2 | 45.1 | 45.3 |
| | **Gas exchange** | **Divided** | Pentazocine | 271 | 238 | 251 | 265 | 216 | 174 | 199 | 231 |
| | | Pethidine | 258 | 227 | 233 | 221 | 217 | 199 | 185 | 176 |
| | | **Whole** | Pentazocine | 275 | 264 | 260 | 259 | 206 | 168 | 189 | 198 |
| | | Pethidine | 250 | 235 | 230 | 225 | 203 | 170 | 181 | 178 |
| | **CO₂ response** | **Divided** | Pentazocine | 4.24 | 3.24 | 1.87 | 2.24 | 1.87 | 2.24 | 1.87 | 2.24 |
| | | Pethidine | 3.62 | 3.38 | 2.39 | 2.50 | 3.06 | 2.50 | 2.50 | 2.50 |
| | | **Whole** | Pentazocine | 4.17 | 3.31 | 3.79 | 52.0 | 27.3 | 43.3 | 51.1 | 56.3 | 33.4 |
| | | Pethidine | 4.86 | 2.27 | 3.12 | 48.9 | 19.2 | 22.6 | 51.7 | 58.7 | 56.2 |

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and 5 show that the half dose of pentazocine 22.5 mg had on average a greater depressant effect than the half dose of pethidine 37.5 mg (left side, fig. 4 and 5) whereas the whole dose of pentazocine 45 mg had a similar or smaller effect than the whole dose of pethidine 75 mg (right side, fig. 4 and 5).

Effect of second injection—C. The condition at C represents in divided dose experiments (left side) the additional effect of the second dose, and in whole dose experiments (right side) the effect of the one dose at 25–30 min after injection.

The graphs referring to divided dose experiments show that in general the second dose of pentazocine caused little or no further depression, whereas the second dose of pethidine increased depression for all parameters. Those referring to whole dose experiments show that in general pethidine had a greater effect persisting at C than had pentazocine.

One hour after first injection—D. In divided dose experiments the condition at D compares the duration of the effects of the drugs. Whether given singly or divided, there is in general a greater effect persisting at D after pethidine than there is after pentazocine.

The several variables will now be considered.

Ventilation and PAO₂.

Each drug, with either form of administration, caused a significant reduction in ventilation and increase in PAO₂ (fig. 4:1, 2 and table II). There was a tendency to further depression after the second half-dose of pethidine, but not after the second half-dose of pentazocine. In terms of analysis of variance, there was for ventilation a significant “Drug x time of measurement” interaction—that is, the pattern of change varied according to the drug given. On average, V and PAO₂ had returned nearer to baseline an hour after pentazocine than an hour after pethidine, however administered.

There was no significant reduction in respiratory frequency (from an overall mean baseline value of 12.7 b.p.m.). Tidal volume changes paralleled the changes in ventilation.

Slope of response line, S. On average this decreased significantly during each type of experiment, despite considerable variation in baseline values, and despite the fact that there were 12 individual instances in the 32 experiments in which S was not diminished following drug injection. The difference between the two drugs did not reach significance, although the mean depression was greater after the whole dose of pethidine than after any other first injection (at B, fig. 4:3). Second drug injections produced greater effects than saline: there was a significant difference in S at time C related to “mode of administration”.

"Shift" parameters.

When S is decreased, the two parameters Pco₂,20 and V₅₇₇, are inevitably also altered in the direction
of depression, unless the intercept of the response line on the CO₂ axis is shifted to the left. In this study there were only 5 instances of a change in these without a change in slope: mean changes can therefore be taken only as supportive, not additional, evidence of depression.

The mean "shift to the right" at a ventilation of 20 l/min ranged from 5-9 mm Hg PCO₂ (value at B or C minus value at A) in the different types of experiment; this provides a comparison with other studies which quote such an index, (e.g., Bellville and Green, 1965).

Gas exchange.
Oxygen consumption was significantly diminished over the period of the experiments, but the changes were not statistically different between drugs, or between modes of administration; the profile of mean changes (fig. 5:1) shows a tendency which parallels those described for ventilation.

Carbon dioxide output also diminished significantly, and for this there was a significant difference between the two drugs after an hour (at D). After pethidine, VCO₂ remained low, whereas it tended to return to normal after pentazocine, even when a second half-dose was given (fig. 5:2).

Side-effects.
The one subject who had to be omitted from the trial suffered no ill effects on the first occasion when he received the split dose of pethidine. On the second occasion, nausea developed after the first half-dose of pentazocine; the second half-dose caused vomiting and the study was abandoned. He and one other subject suffered nausea for at least 6 hours after pentazocine. All other side effects were minor, but followed a fairly constant pattern: the main components have been scored in table III. In general, sensations immediately following pentazocine were described as distinctly pleasurable.

**DISCUSSION**

**Methods: Criteria of Depression.**

*Air-breathing changes in ventilation and PCO₂.*
As in the study of Jennett, Barker and Forrest (1968) we have found significant changes in the values for air-breathing ventilation and PCO₂; we have thus confirmed the impression that these are valuable in the assessment of drug-induced respiratory depression, even in the conscious subject. It is of interest to compare similar measurements, following administration of these same drugs, albeit in different dosage, to the anaesthetized subjects of Davie, Scott and Stephen (1970). Table IV shows the percentage maximal reduction in ventilation in the two series. The much greater depression in anaesthetized subjects presumably reflects their reduced responsiveness to CO₂.

**Table IV. Comparison of ventilatory depression in conscious and anaesthetized subjects.**

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<tr>
<th></th>
<th>Conscious subjects (this series)</th>
<th>Anaesthetized subjects (Davie, Scott and Stephen, 1970)</th>
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<tbody>
<tr>
<td><strong>Dose (mg)</strong></td>
<td><strong>Mean maximal reduction in V (%)</strong></td>
<td><strong>Dose (mg)</strong></td>
</tr>
<tr>
<td>Pentazocine 22.5</td>
<td>19</td>
<td>30</td>
</tr>
<tr>
<td>Pentazocine 45</td>
<td>18</td>
<td></td>
</tr>
<tr>
<td>Pentazocine 37.5</td>
<td>9</td>
<td>30</td>
</tr>
<tr>
<td>Pentazocine 75</td>
<td>21</td>
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</table>

**CO₂ response tests.**
The results were more consistent and therefore more significant than in the 1968 series. Nevertheless in any one subject there was always a reduction in ventilation and increase in PAO₂ following a first drug injection: there was not always a depression of the CO₂ response relative to the two base-line measurements.

There was a more consistent change in slope than found by many authors (e.g., Bellville and Green, 1965) who applied steady-state CO₂ response tests in studies of drug depression. A shift to the right of the response curve is the most frequently quoted index of depression; however such a shift, unless it...
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refers to the intercept on the CO₂ axis, inevitably accompanies a reduction in slope, so that the two criteria are confounded (Jennett, 1968). Slope should most appropriately reflect the sensitivity of the respiratory control system to increasing CO₂.

The low-volume high-CO₂ rebreathing method is a suitable one for assessing drug-induced depression. It is brief enough to allow time for air-breathing measurements also; theoretical considerations suggest that it is a suitable approximation to a stimulus-response test for cerebral extracellular pH and respiratory centre activity, because CO₂ concentration measured at the mouth is rapidly reflected in pH at the central chemoreceptors (Read and Leigh, 1968).

Comparison between drugs.

Dosage. The question of equianalgesic dosage is still open to considerable discussion. Dyrberg and Kolliker (1971) collected from different sources a range of 11–50 mg pentazocine, quoted as equivalent to 50 mg pethidine; they themselves used 15 mg pentazocine: 50 mg pethidine. In this study we have deliberately erred on the side of a relatively high pentazocine:pethidine ratio.

“Ceiling” effect. Our results support the suggestion that a second (or subsequent) dose of pentazocine does not have a simply additive respiratory depressant effect. This is in agreement with Davie, Scott and Stephen (1970) who measured changes in minute volume after repeated doses of 30 mg of each drug and found a relatively small decrease after the second dose of pentazocine; also with Ominsky, Kallos and Smith (1969) who found that the log-dose/response curve for pentazocine (where the response was a decrease in ventilation at high controlled Pco₂) showed that successively higher doses produced successively less additional depression, with a maximum at about 60 mg/70 kg. Our results might suggest an even lower “ceiling”.

The findings of Dyrberg and Kolliker (1971) appear to be a little different: they report a steeper increase in depression with repeated 50 mg doses of pethidine than with repeated 15 mg doses of pentazocine. However, their dose ratio was 15:50 compared to our 45:50, pentazocine:pethidine; also their graphs of log Ve against repeated doses of pentazocine, although fitted to regression lines, show for 4 of the 5 subjects a possible levelling off of the effect on ventilation between the second and third injections: after the first 30 mg of pentazocine, the effect of the next 15 mg appears to be smaller.

CONCLUSIONS

From these results it appears that for pentazocine the respiratory depressant effect of 45 mg is similar to that of 22.5 mg; for pethidine, by contrast, the effect of 75 mg is clearly greater than that of 37.5 mg. A dose of pentazocine which is small by any standards (22.5 mg) has a similar immediate depressant effect to 75 mg pethidine. However, doubling the dose of pentazocine even in this low range, whether by repetition or by giving twice the dose initially, tends to give no greater depression. Taken in conjunction with the results of other authors, it appears that depressant effects may increase with dose up to 30–60 mg per 70 kg, but that the increase will not be proportionate even at this low dosage.

ACKNOWLEDGEMENTS

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REFERENCES


DEPRESSION RESPIRATOIRE APRES DOSE UNIQUES ET DOSES REPETEE DE PENTAZOCINE ET PETHIDINE

SOMMAIRE

Pentazocine et pethidine ont été comparés en proportion posologique 45:75 du point de vue de leur effet déprimant sur la respiration chez des sujets normaux. Les effets additifs respectifs des deux médicaments ont été étudiés en comparant l'action d'une dose unique complète avec celle de deux demi-doses successives. On observa de manière constante un certain degré de dépression de la ventilation. Une première demi-dose de pentazocine 22.5 mg exerça un effet plus prononcé qu'une première demi-dose de pethidine 37.5 mg, mais l'effet additif d'une seconde demi-dose de pentazocine était moins grand. Les résultats confirment les preuves existantes qu'un "plafond" de dépression respiratoire est atteint à une dose relativement petite de pentazocine.

ATEMDEPRESSION NACH EINMALIGER UND WEIDERHOLTER DOSIS VON PENTAZOCINE UND PETHIDIN

ZUSAMMENFASSUNG


DEPRESION RESPIRATORIA DESPUES DE DOSIS UNICAS Y REPETIDAS DE PENTAZOCINA Y PETHIDINA

RESUMEN

Ha sido comparada la depresión de la respiración producida en sujetos normales por pentazocina y pethidina en la proporción de dosis de 45:75. La acción aditiva de cada una de las drogas fue investigada comparando los efectos de una dosis única con los de dos medias dosis repetidas. Hubo constantemente cierto grado de depresión ventilatoria. Una primera media dosis de 22,5 mg de pentazocina tuvo un efecto mayor que una primera media dosis de 37,5 mg de pethidina, pero una segunda media dosis de pentazocina tuvo un efecto aditivo menor. Los resultados apoyan las pruebas ya conocidas de que se alcanzado un límite superior para la depresión respiratoria con una dosis relativamente baja de pentazocina.

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