COMPARISON OF EFFECTS OF PHENAZOCINE AND MEPERIDINE ON RESPIRATION

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The purpose of this study was to observe and compare the effects of phenazocine and meperidine on alveolar ventilation and carbon dioxide tension of alveolar air. Observations were made before and after the administration of the drugs, during normal respiration and during rebreathing, when endogenous carbon dioxide was allowed to build up to about 7 per cent. Recordings were made on an 8-channel Electronics for Medicine research recorder.

Sixteen healthy, intelligent and cooperative adults served as subjects. The group comprised seven women and nine men, with an age range of 21 to 32 years, and a weight range of 115 to 171 pounds. All subjects received all three study drugs (sodium chloride, phenazocine and meperidine) and the drug assignments were randomized. Each subject served as his own control on each experimental day. These subjects were instructed about the procedure of the experiment, and were told to eat a light breakfast, and nothing afterward, on the days of the tests. The tests were done between 12 and 2:30 p.m. The interval between two successive tests on any one subject varied from 24 hours (in one individual) to two weeks.

The subject was in the supine position. An intravenous drip of 5 per cent dextrose in water was given throughout the observation period. A blood-pressure cuff was applied and the pressure recorded at intervals. One observer remained with the subject continuously and another did the recording and injecting, hidden by a curtain from the subject. With the above preparation of the subject completed, the carbon dioxide analyzer (Liston-Becker) was set and calibrated, using tanks of known carbon dioxide concentration in oxygen. The composition of the tanks was determined by analysis on the Scholander micro gas analyzer. The carbon dioxide analyzer was remarkably steady throughout the observations each day.

After completing the calibration of the analyzer, a mouthpiece, which had been shortened to reduce dead space, was introduced and a nose clip applied. The subject was then attached to the carbon dioxide analyzer incorporated with a breathe-through cell. The analyzer was attached to a pneumotachograph, which in turn was attached to a carbon dioxide absorber through an expiratory valve. The absorber could be bypassed when desired. The remaining expired gas entered a rebreathing bag where it was mixed with oxygen at the required flow rate to meet the subject's metabolic requirements. The mixture passed through an inspiratory valve to the mouthpiece. The method is essentially that used by Eckenhoff and co-workers.[1, 2] A diagram of the setup is shown in figure 1.

The pneumotachograph enabled us to record individual respirations, and by means of an integrator, to record the integral of flow rate or minute volume. The carbon dioxide tension was recorded during each expiration when desired and was monitored continuously.

As soon as the subject was attached to the apparatus, the integrator was balanced, and time allowed for accommodating to the nose clip and mouthpiece (9 minutes). A four-minute record was then made of normal or nonrebreathing respiration. At the end of the four-minute period, a noiseless signal was given by the person recording to the person with the subject to bypass the absorber without the subject's knowledge. The indicator meter on the control box of the carbon dioxide analyzer was closely watched, and as soon as the endogenous carbon dioxide accumulated to about 6.7 per cent a rebreathing record was begun and continued to about 7.5 per cent.[3, 4] At this point the signal was given to turn the carbon dioxide absorber back into the circuit,

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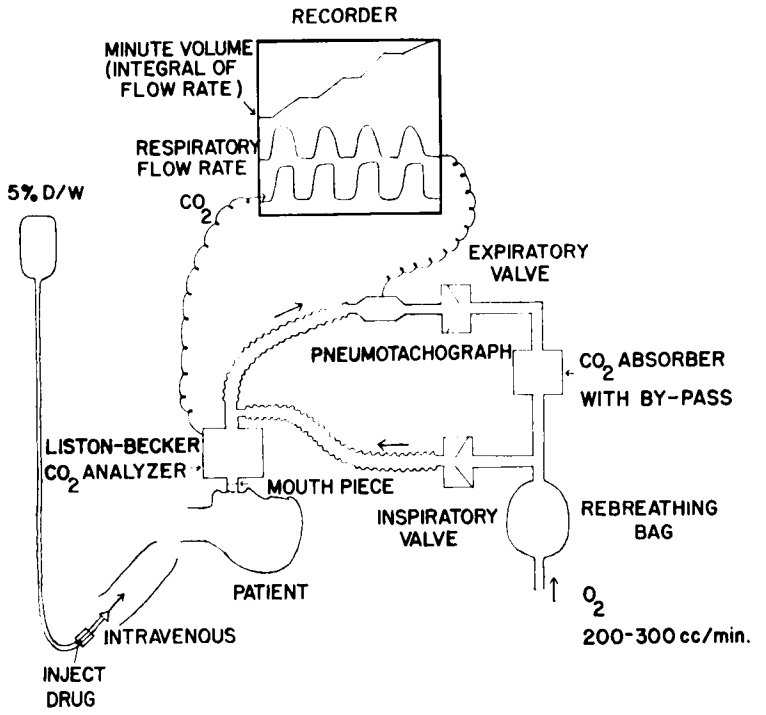

FIG. 1. Schematic diagram of equipment.

and immediately thereafter the nose clip and mouthpiece were removed and the subject permitted to rest for ten minutes.

At the end of the rest period the drug injection was begun without the subject's knowledge. The syringe contained 6 ml. which was administered at a rate of 1 ml. per minute. Neither the investigators nor the subjects knew which drug was given. The dose of phenazocine was 0.1 mg. per 7 pounds of body weight, with a maximum dosage of 2.1 mg. The dose of meperidine was 4 mg. per 7 pounds of body weight, with a maximum dosage of 84 mg. The ratio was 1 mg. of phenazocine to 40 mg. of meperidine. On the "control" day, 6 ml. of 0.9 per cent sodium chloride were administered. At the end of the injection each day, the mouthpiece was reinserted, the nose clip reapplied, and respiratory data were obtained as described for the control period. At the termination of this, the mouthpiece and nose clip were removed and the subject instructed to lie quietly while the calibration of the carbon dioxide analyzer was repeated and the integrator (flow volume) calibration completed. The subject was then questioned as to subjective impressions, and taken to the recovery room, by litter, if necessary.

The entire record of the four-minute runs was measured and averaged for results on control respiration. In the rebreathing records, a midpoint as near 7 per cent carbon dioxide as possible was chosen, and measurements made for about the preceding and ensuing 30 seconds. In this way, measurements were made at comparable carbon dioxide tension before and after drug administratoin. In every instance the minute volume during rebreathing was measured about the same midpoint.

To translate the values found for minute volume into alveolar ventilation, it was necessary to calculate the dead space for normal respiration and during hypercapnia. The dead space during normal respiration was taken as 35 per cent of the tidal volume.[5] The dead space during hyperventilation was calculated by the formula:

$$V_D = 0.35\ V_T + 0.35\ V_T/8$$

times the liter increase in tidal volume.[6]

The calculated dead space was subtracted from the tidal volume and an additional 70 ml.

TABLE 1

ALVEOLAR VENTILATION AND PER CENT CHANGE PRODUCED BY DRUGS ON NORMAL RESPIRATION

Drug	Alveolar Ventilation Average (ml.)	% Change after Drug Administration*
Sodium chloride	3,446	−0.16
Phenazocine	3,339	−35.78
Meperidine	3,261	−28.39

* Standard deviation is 15.6 per cent.

TABLE 2

ALVEOLAR VENTILATION AND PER CENT CHANGE PRODUCED BY DRUGS ON REBREATHING

Drug	Alveolar Ventilation Average (ml.)	% Change after Drug Administration*
Sodium chloride	15,469	+2.18
Phenazocine	13,708	−55.59
Meperidine	11,937	−42.05

* Standard deviation is 18.1 per cent.

was deducted for dead space of the mouthpiece and carbon dioxide analyzer. The remainder was multiplied by the rate of respiration to give alveolar ventilation per minute.

RESULTS

Alveolar Ventilation. The average alveolar ventilation and the percentage change produced by the drugs and placebo on normal respiration are shown in table 1. Phenazocine and meperidine depress alveolar ventilation to almost the same extent. The difference between them is not statistically significant. The standard deviation for the percentage change derived from the Analysis of Variance [7] is 15.6 per cent.*

The average alveolar ventilation and the percentage change produced by the drugs and placebo on rebreathing are shown in table 2. It is evident that the sensitivity of the respiratory center to accumulating endogenous carbon dioxide is depressed by both phenazocine and meperidine. The standard deviation is 18.1 per cent and the difference between the two drugs is statistically significant to the 5 per cent level.

* For the experimental design used here, the analysis of variance considers subjects, drugs, and residual error as the appropriate sources of variation. The standard deviation is derived from the last source named.

CARBON DIOXIDE TENSION. The average alveolar carbon dioxide tension and the percentage change produced by the drugs and placebo on normal respiration are shown in table 3. The depression of respiration by both phenazocine and meperidine is indicated by the rise in carbon dioxide tension. The standard deviaiton is 9.6, and the difference between the effect of the two drugs is not statistically significant.

The average alveolar carbon dioxide tension and the percentage change produced by the drugs and placebo on rebreathing are shown in table 4. We wish to point out again that we attempted to record the respiratory functions from the time the carbon dioxide concentration rose from about 6.7 to 7.5 per cent, and that the measurements were made about a midpoint of 50 mm. Hg tension, using approximately the preceding and ensuing 30 seconds. By this means it was possible to compare the results of rebreathing before and after the administration of the various drugs under similar conditions of carbon dioxide accumulation. The majority of subjects experienced discomfort during rebreathing before drug administration, but none were uncomfortable, after either phenazocine or meperidine was administered.

TABLE 3

ALVEOLAR CARBON DIOXIDE TENSION AND PER CENT CHANGE PRODUCED BY DRUGS ON NORMAL RESPIRATION

Drug	Carbon Dioxide Tension Average (mm. Hg)	% Change after Drug Administration*
Sodium chloride	37.1	−0.14
Phenazocine	38.0	+17.92
Meperidine	36.5	+19.84

* Standard deviation to 9.6 per cent.

TABLE 4

ALVEOLAR CARBON DIOXIDE TENSION AND PER CENT CHANGE PRODUCED BY DRUGS ON REBREATHING

Drug	Carbon Dioxide Tension Average (mm. Hg)	% Change after Drug Administration*
Sodium chloride	50.4	−0.228
Phenazocine	50.2	+0.086
Meperidine	50.3	+0.067

* Standard deviation is 0.57 per cent.

Discussion

This study was so designed that each subject served as his own control for each drug. There is considerable variation between individuals, but that is of no importance in this study, since we are not comparing individuals but rather the effect of drugs in a given individual.

Our subjects were conscious and had not had previous sedation. The tests were performed in a small room separated by a curtain from a corridor of the operating theater. Disturbing noises could not be excluded. This is undoubtedly a factor to be considered in the alveolar carbon dioxide tensions recorded in normal respiration; these are in the low normal range.

Although phenazocine and meperidine both decrease the sensitivity of the respiratory center to carbon dioxide, it does not signify that the reception of other types of stimuli is equally depressed by the two drugs. Clinically, the individual is less sedated by phenazocine than by meperidine, and more excitatory afferent impulses from various receptors may reach the respiratory center. Consequently, respiration may be less depressed. We have tested only one of the many factors involved in the control of respiration. Perhaps the situation is comparable to that during ether anesthesia, in which, although there is depression of the sensitivity of the respiratory center to carbon dioxide, it is overcome in part by excitatory afferent impulses, especially from the respiratory passages. The end result is actually a stimulation of respiration.[8] We call attention to this because it may be a possible explanation of the difference between these results and our clinical impression that phenazocine does not depress respiration as much as does meperidine.

Summary

The effects of phenazocine, meperidine and 0.9 per cent sodium chloride (placebo) on alveolar ventilation and carbon dioxide tension during normal respiration and rebreathing were observed on 16 healthy young adults. The carbon dioxide in alveolar air was permitted to rise to about 7.5 per cent during rebreathing.

The alveolar ventilation during rebreathing, as well as during normal breathing, was decreased by both phenazocine and meperidine.

The alveolar carbon dioxide tension during normal breathing was elevated after the administration of both drugs.

Dr. Rusy is a Postdoctoral fellow of the National Institute of Neurological Diseases and Blindness, National Institutes of Health.

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