The Respiratory Effects of Meperidine and Propiomazine in Man

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The authors studied the respiratory effects of meperidine, propiomazine, and their combination in man. Static lung volumes were not changed and the ventilations after the three regimens were not significantly different from each other, although in the case of meperidine alone, there had been significant reductions from control minute and tidal volumes. However, the ventilatory responses to carbon dioxide were shifted rightward and clearly differentiated the three treatments. Twenty milligrams of propiomazine displaced the curve 2.6 torr to the right (depression) and 100 mg meperidine displaced it 5.0 torr. Given together, they caused an 8.2 torr displacement. The slopes were not altered. Thus, carbon dioxide challenge clearly showed respiratory depression after propiomazine alone, and at least an additive effect when propiomazine and meperidine were combined. (Key words: Respiratory effects; Meperidine; Propiomazine.)

ATARACTIC DRUGS are widely used for preoperative sedation. They are reputedly free from harmful side-effects such as respiratory depression.[1-5] When given alone, however, they may cause restlessness,[1,5] and an opioid ‡ is customarily added to produce tranquility.[1,2,4] From a clinical standpoint we suspected that opioid–ataractic mixtures caused considerably more respiratory depression than opioids alone. This standpoint is supported by the work of Lambertsen *et al.*, who used a sensitive and quantitative method to study chlorpromazine–meperidine.[9]

Of the many possible mixtures we decided to study propiomazine (Largon) and meperidine (Demerol) because of their widespread use as preanesthetic medication. Dundee and his colleagues [1] examined many phenothiazines and found that 20 mg propiomazine had the best overall effect as a sedative, antiemetic, and analgesic, producing no dyskinesia or hypotension. They characterized the mixture of 100 mg meperidine with 20 mg propiomazine as a mild nontoxic hypnotic with a moderate antiemetic action.[2] We found, and now report, that the combination of meperidine and propriomazine is more depressing to respiration than either drug alone.

Methods

Six healthy, male volunteers from 21 to 23 years of age participated in a complete, double-blind, crossover study. At least four days separated the three studies in any one individual. Treatments consisted of propiomazine, 20 mg per 70 kg body weight, or meperidine, 70 mg per 70 kg body weight, or their combination. All drugs were administered intramuscularly in 4-ml volumes. A trace of yellow vitamin B and C solution (Berocca-C) in all syringes disguised the presence of propiomazine. The order of administration was assigned randomly to include all six possible sequences.

Subjects were put at ease on a comfortable operating-room table. After resting half an hour they breathed an oxygen–air mixture through a mouthpiece connected to a one-way breathing circuit modified from previous experiments to reduce resistance and facilitate data retrieval (fig. 1). They inhaled from one limb of the circuit via a Sadd valve and ex-

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‡ "Opioid" designates those analgesics whose pattern of agonistic effects is typified by morphine. Opioid antagonists are those drugs of the family typified by nalorphine. These terms avoid the historical and legal confusion of the term "narcotic" and the implication of origin contained in "opiate."

haled via a second Sadd valve and mixing chamber[10] into the expiratory limb, which led to a Wedge § spirometer with an automatic recycler. A large bore three-way stopcock connected the inspiratory limb with either room air, providing a nonrebreathing circuit, or the spirometer via a carbon-dioxide-absorption canister, for closed-system measurements.

Minute ventilation (V_E), tidal volume (V_T) corrected to B.T.P.S., and respiratory frequency (f) were determined from the spirometer record during nonrebreathing. Spirometric lung volumes at B.T.P.S. were measured during rebreathing. For CO_2 challenge the circuit was returned to the nonrebreathing mode.

Gas Analysis

A Godart N.V. infrared analyzer was calibrated against six tanks of carbon dioxide–oxygen mixtures previously analyzed by the micro-Scholander technique.[11] Gases sampled from both the mouthpiece (for end-tidal tension, $P_{ET_{CO_2}}$) and beyond the mixing chamber (for mixed expired tension, $P_{E_{CO_2}}$) were returned to the circuit to avoid volume loss during closed-system studies. Appropriate corrections were made for nitrogen collision broadening and water-vapor dilution and collision broadening. Rebreathing (oxygenated) mixed venous carbon dioxide tension ($P_{v_{CO_2}}$) was determined by the method of Collier.[12] Inspired oxygen tensions were monitored with a Beckman C2 oxygen analyzer and controlled between 30 and 50 per cent by adding oxygen to the inspired gas.

Ventilatory Response to Carbon Dioxide

Carbon dioxide (approximately 300, 600 and 900 ml/min) was added to the oxygen in the inspiratory line to provide four-point ventilatory response curves before and 60 to 80 minutes after treatment, the time of peak ef-

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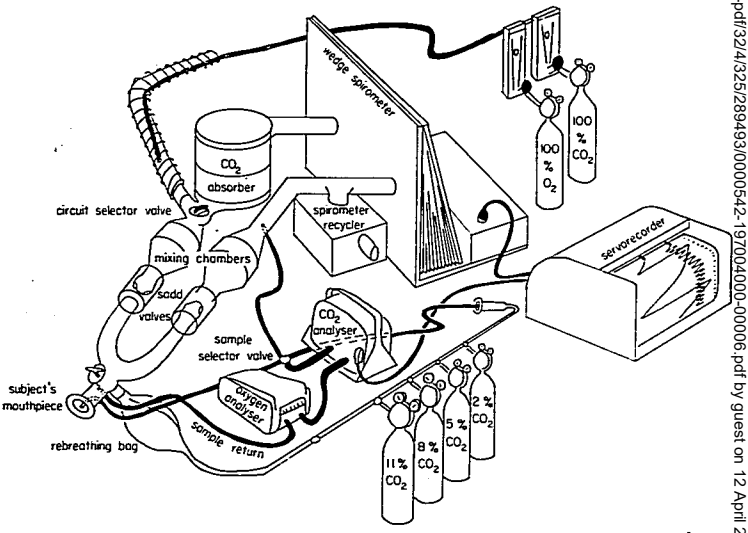

Fig. 1. Apparatus used in ventilatory studies of drug effects. The circuit-selector valve permits the choice of either a nonrebreathing system or a closed-circle system. A valve at the mouthpiece may connect the subject to a rebreathing bag for measurements of mixed venous carbon dioxide.

TABLE 1. Static Lung Volumes in Six Subjects before and after Meperidine, Propiomazine and Their Combination*

	Pre-drug			Post-drug		
	Meperidine	Propiomazine	Combination	Meperidine	Propiomazine	Combination
Vital capacity (l)						
Mean	5.23	5.01	5.18	5.43	5.19	5.30
SE	0.10	0.23	0.14	0.12	0.17	0.08
P	—	—	—	NS	NS	NS
Inspiratory capacity (l)						
Mean	4.15	4.00	4.03	4.16	4.04	3.92
SE	0.16	0.13	0.18	0.15	0.14	0.13
P	—	—	—	NS	NS	NS
Expiratory reserve volume (l)						
Mean	1.29	1.21	1.31	1.20	1.23	1.30
SE	0.09	0.08	0.06	0.09	0.10	0.10
P	—	—	—	NS	NS	NS
Forced expiratory volume 1 (per cent)						
Mean	76.4	77.4	77.1	74.3	76.7	77.7
SE	3.9	2.9	4.7	3.5	3.2	3.3
P	—	—	—	NS	NS	NS
Forced expiratory volume 3 (per cent)						
Mean	94.9	95.6	95.4	93.0	96.1	95.9
SE	1.9	1.5	2.1	2.2	1.7	1.5
P	—	—	—	NS	NS	NS

* *P* = probability that the difference (drug–control) arose by chance.
NS = probability that the difference (drug–control) arose by chance is greater than 5 per cent.

fect of meperidine as determined in previous experiments of the same type.[9, 13] Calculations of the slopes of these curves and their displacement from control utilized only measurements during CO_2 challenge when ventilation exceeded 8 l/min, thus minimizing psychologic and other influences which profoundly affect resting ventilation.[14] The displacement of a curve from the control was measured at $V_E = 15$ l/min. The values for ventilation stimulated by 900 ml/min of added CO_2 in individual studies tended to distribute between 15 and 20 l/min, so that 15 l/min was selected in preference to the more-frequently-used ventilation of 20 l/min to avoid the necessity of extrapolating curves beyond measured limits.

PULMONARY FUNCTION TESTS

Inspiratory capacity, expiratory reserve volume, vital capacity and forced expiratory volume were measured before and about 80 to 90 minutes after treatment. Physiologic dead space and alveolar ventilation were calculated from the carbon dioxide tensions by:

$$V_D = \frac{P_{ET} - P_E}{P_V - 7 - P_I} \times V_T,$$

and

$$\dot{V}_A = \frac{\dot{V}_E \times P_E}{P_V - 7 - P_I}$$

Control measurements, subjected to an analysis of variance, demonstrated no significant differences among groups before treatment. Effects of the three regimens were similarly analyzed. If an F ratio denoted a probability of 5 per cent or less, differences before and after each treatment were further examined with a paired *t* test. Subjects reported the presence and duration of symptoms on a standard written form.

TABLE 2. Respiratory Values before and after Meperidine, Propiomazine and the Combination*

	Pre-drug			Post-drug		
	100 mg Meperidine	20 mg Propiomazine	Combination	100 mg Meperidine	20 mg Propiomazine	Combination
Frequency						
Mean	15.4	16.0	15.7	15.5	16.6	14.3
SE	1.19	1.39	1.10	1.01	1.18	1.80
P	—	—	—	NS	NS	NS
Tidal volume (l)						
Mean	.494	.452	.450	.378	.443	.364
SE	.050	.051	.058	.035	.038	.042
P	—	—	—	<0.01	NS	NS
Minute volume (l/min)						
Mean	7.24	6.90	6.81	5.73	7.14	5.01
SE	0.75	0.40	0.46	0.33	0.22	0.48
P	—	—	—	<0.02	NS	NS
Alveolar ventilation (l/min)						
Mean	4.75	4.30	4.37	3.53	4.11	2.87
SE	0.32	0.45	0.57	0.17	0.27	0.22
P	—	—	—	<0.01	NS	NS
Alveolar deadspace (ml)						
Mean	18	6	−10	−4	10	0
SE	6	6	21	7	5	6
P	—	—	—	NS	NS	NS
Anatomic deadspace (ml)						
Mean	157	156	150	142	146	147
SE	25	13	10	14	9	17
P	—	—	—	NS	NS	NS
Deadspace-to-tidal volume ratio (per cent)						
Mean	30	35	33	34	36	38
SE	5	3	5	3	3	3
P	—	—	—	NS	NS	NS
P_{ETCO_2} (torr)						
Mean	40.4	41.7	40.8	45.2	42.3	45.6
SE	0.8	1.3	0.6	0.6	1.0	1.3
P	—	—	—	<0.01	NS	<0.01
P_{ECO_2} (torr)						
Mean	28.3	27.6	27.2	28.9	28.0	28.1
SE	1.2	1.0	0.8	0.4	1.0	0.9
P	—	—	—	NS	NS	NS
P_{VCO_2} (torr)						
Mean	47.9	49.7	47.5	51.6	51.2	52.6
SE	1.6	1.3	1.6	1.0	1.2	1.4
P	—	—	—	<0.01	NS	<0.01
Slope of CO_2 response curve $\dot{V}_E/P_{ETCO_2}$						
Mean	1.88	1.74	1.90	1.88	1.85	1.65
SE	0.25	0.12	0.17	0.27	0.39	0.19
P	—	—	—	NS	NS	NS
Displacement of response curve after drug (torr)						
Mean	—	—	—	5.00	2.58	8.22
SE	—	—	—	0.73	1.22	1.26
P	—	—	—	<0.01	NS	<0.01

* P = probability that the difference (drug–control) arose by chance.
NS = probability that the difference (drug–control) arose by chance is greater than 5 per cent.

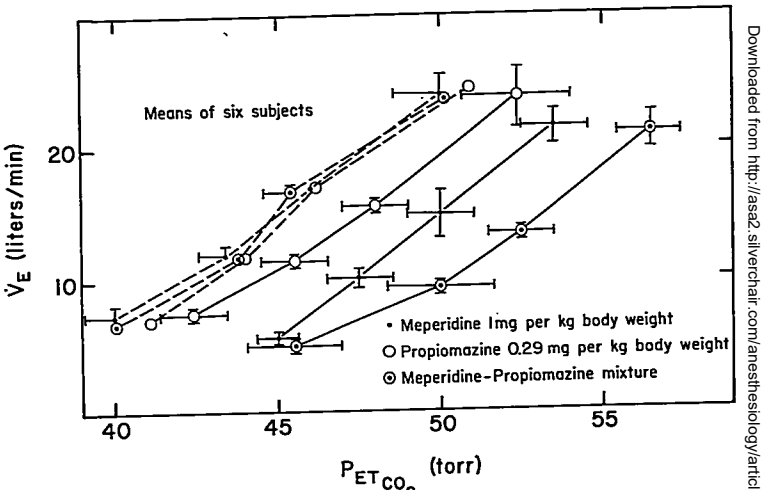

FIG. 2. Ventilatory responses to carbon dioxide before (interrupted line) and after meperidine and propiomazine, alone or in combination.

Results and Interpretation

Static lung volumes and forced expiratory volume were not reduced by the drugs, suggesting that the effects noted below were not due to alteration in the mechanics of breathing (table 1). After meperidine, resting ventilation fell 1.5 l/min (table 2), mostly due to an average decrease in tidal volume of 116 ml. Alveolar ventilation decreased 1.22 l/min. There was no significant change in resting ventilation after propiomazine. Although the average ventilation after the mixture fell more than after meperidine alone, resting ventilation actually increased in two subjects after the mixture.

$P_{ET_{CO_2}}$ increased by 4.8 torr after meperidine, and by the same amount after the meperidine–propiomazine mixture. The increase was small after propiomazine alone (0.6 torr). The deadspace-to-tidal volume ratio, the anatomic deadspace, and the alveolar deadspace were unchanged by any treatment. The measurements of resting ventilation and resting P_{CO_2}, if considered alone, might suggest that meperidine and the combination were equally depressing to respiration. However, the more sensitive test of ventilatory response to carbon dioxide clearly showed that the combination was more depressing.

Carbon dioxide response curves before and after each treatment are shown in figure 2. The displacements produced by the drugs were 5.0 torr for meperidine alone and 2.6 torr for propiomazine alone. Following the meperidine–propiomazine combination, the shift was 8.2 torr, slightly more than the sum of the displacements caused by the two separate treatments. All three displacements are significantly different from zero and from one another. The displacement seen after the combined drugs was greater than that produced by 15 mg of morphine in our laboratory. The slopes of the CO_2 response curves after treatment were not significantly different from control. The mean slope of the curve in 18 control measurements was 1.84 l/min/torr.

Symptoms

All subjects were drowsy after every treatment. This symptom was most prolonged (eight hours in two subjects) after propiomazine. After the meperidine–propiomazine combination all subjects reported impaired performance of manual tasks and inability to

concentrate, typically: difficulties in turning book pages and shortened attention span when reading. Four of the subjects were moderately affected by these symptoms after propiomazine, and three to a mild degree after meperidine. Two subjects reported odd dreams (fantasies) as they dozed in the hour between injection and testing. One had meperidine and one the meperidine–propriomazine combination. Dreams were not experienced after propiomazine alone. Dry mouth, anorexia, and nausea were not reported, contrasting with previous comparable studies of morphine and of fentanyl.[15, 16]

Discussion

Since ataractics alone are mild respiratory depressants at this dose level,[1-9] one might ask if the respiratory effects of the combination are almost entirely due to the narcotic. This question has been examined,[3, 5, 6, 7, 9, 16] but not in sufficient detail to resolve conflicting data. Egbert *et al.*[7] interpreted their results as showing that promethazine has little significant effect on respiration either alone or in combination with meperidine in man; they did not measure alveolar or arterial P_{CO_2}. Davis and Janicek[6] found an increase in resting ventilation after a propiomazine–meperidine combination. Pearson and DeKornfeld were the first to employ CO_2 challenge.[5] They saw no change after a methotrimeprazine–meperidine combination. However, in the absence of either several levels of inspired carbon dioxide or alveolar carbon dioxide analyses, their results are difficult to interpret. Using a CO_2-rebreathing method, Steen *et al.*[3] studied meperidine and propiomazine; their results are variable and inconclusive, largely because of small sample size and the small doses of drugs used. After a meperidine–promethazine combination, Keats *et al.*[17] saw no change in displacement compared with that caused by meperidine alone, measured at $\dot{V}_A = 8.5$ l/min.

Lambertsen[9] demonstrated the respiratory effects of drugs by measuring changes in ventilation while maintaining the end-tidal carbon dioxide constant (usually 46 torr) by adding carbon dioxide. He found that chlorpromazine, when combined with meperidine, produced depression that was greater in degree and duration than that caused by meperidine alone. The depression of ventilation measured by Lambertsen *et al.* after the chlorpromazine–meperidine combination was nearly equal to the sum of the depressions caused by the two drugs separately, compared with the placebo response. However, they chose to compare post-drug ventilation with the pre-drug control value, rather than with ventilation at equivalent times after placebo, and drew a different conclusion, that there was insignificant interaction.

A further difficulty in Lambertsen's work has been pointed out by Keats[18]—the lack of data on the slope of the CO_2 response near the controlled alveolar carbon dioxide tension. Figure 2 shows that, in our study, the effect of the combined drugs appears to be additive when viewed as a measured displacement of parallel segments of the curves at an elevated ventilation. Had we examined differences in ventilation at a constant P_{CO_2} of 46 torr, as Lambertsen's experiment does, the effect of the mixture would have appeared less than additive due to the decrease in slope near the resting point. Comparisons of ventilation at 50 torr show the same relative depression as that assessed from lateral displacement, since the lines are parallel at that point. Thus, failure to determine the slope of the CO_2 response curve is an important drawback in Lambertsen's valuable technique.

Our comparison of CO_2 response curves shows that while the respiratory "threshold" for carbon dioxide (measured by displacement) is elevated, the "sensitivity" of the respiratory center (measured by slope) is unchanged even after combining these doses. Where there is no change in sensitivity one might be willing to accept the minor degree of respiratory acidosis if other advantages accrue. Commonly an opioid dose is reduced by a third to half when an ataractic is added to preanesthetic medication. While the doses of drugs used in the present study produced no change in the slope of the ventilatory response, higher doses or addition of other drugs might. Neither fentanyl (Sublimaze) alone[16] nor the opioid-ataractic mixture of fentanyl with droperidol (Innovar) causes a reduction in slope of the ventilatory response in doses appropriate for

premedication.[17] However, there is a clear dose-related decrease in slope during Innovar-supplemented anesthesia,[19] as well as with other agents.[20, 21] Therefore, the assumption of a satisfactory, normal responsiveness to added carbon dioxide after opioid–ataractic premedication should not be extended to the intra-anesthetic period.

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