Effect of Methotrimeprazine on Respiration

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THERE have been a number of reports to the effect that methotrimeprazine, a phenothiazine derivative, is a potent analgesic in both mice and men.[1-4] Lasagna and DeKornfeld [1] evaluated methotrimeprazine in 66 patients with postoperative pain. The drug was administered intramuscularly in a double-blind fashion, morphine being the control drug. They found that 10 mg. methotrimeprazine was equipotent to 10 mg. morphine in its analgesic activity. With such an apparently effective analgesic drug, it is important to determine if there are serious side effects which might contraindicate its use. Both excessive sedation and postural hypotension have been reported after large oral doses of methotrimeprazine.[3, 4, 5] Paradis [3] stated that respiratory depression did not occur, but no measurements to substantiate this claim were published. The investigations described in this paper are an attempt to answer this problem.

Methods

Six young, healthy, adult men volunteered for the study. Each volunteer was given three treatments: (1) methotrimeprazine, 15 mg., intramuscularly (MTM); (2) morphine sulfate, 10 mg., intramuscularly (MS); and both drugs given simultaneously (MTM + MS). Neither the investigators nor the subjects knew the identity of the drugs until all of the experiments were completed. Each treatment consisted of the injection of 1 ml. of each of two solutions, a methotrimeprazine solution, morphine, or isotonic sodium chloride. At least five days separated each study in any one subject, and the sequence of treatments was different in all cases. Investigations were undertaken during the afternoon on subjects who had had only a light breakfast and no lunch. Subjects rested supine for twenty minutes before control measurements. Subsequent measurements were made thirty and sixty minutes after injection of the drugs.

Measurements were made of end-expiratory carbon dioxide concentration, respiratory rate, and minute volume. Carbon dioxide was measured with a Liston-Becker Model 16 CO_2 analyzer. Minute volume was measured (over two-minute periods) with a Wright Ventilation Meter.

After the twenty minute rest period, minute volume and respiratory rate were measured over two periods of two minutes each, and three determinations of end-expiratory CO_2 concentration were made. The subject was then made to breathe a mixture of 6 per cent CO_2 and 94 per cent air from a reservoir bag using a nonrebreathing system. At the end of four minutes, minute volume and respiratory rate were measured again during two periods of two minutes each and determinations of end-expiratory CO_2 were made.

One milliliter of each of the two medications tested, *i.e.*, methotrimeprazine and placebo, morphine and placebo, or methotrimeprazine and morphine, was injected into the subject (one injection in each deltoid region).

Thirty and sixty minutes later the measurements described above were repeated, with the subject breathing both room air and the CO_2 mixture.

The values for end-tidal CO_2 concentration, for alveolar ventilation, and for tidal volume were compared. In these experiments we expressed the physiological dead space as 1 ml. per pound body weight. The values for alveolar ventilation in each case were obtained by subtracting the product of respiratory rate and dead space from the minute volume. Average values for tidal volumes were determined by dividing total ventilation during a two-minute period by the number of respirations.

The data for alveolar ventilation of the lungs were analyzed by the technique of the analysis of variance. Where applicable, differences

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in mean values were tested by a multiple range technique.[6]

Results

Alveolar Ventilation—Room Air. The average values for alveolar ventilation for six subjects according to treatment and time of observation are given in table 1. From an analysis of these average values the following conclusions were drawn:

(1) There was a significant difference between the treatment mean values, with MTM giving a value of 4.11 liters/minute, which was significantly greater than with either MS (2.98 liters/minute) or MTM + MS (3.21 liters/minute). The difference between MS and MTM + MS was not significant statistically at the $P \leq 0.05$ level.

(2) There was a significant difference between the values obtained at times 0, 30, and 60 minutes. The control value, 4.60 liters/minute, was significantly greater than either the 30 or 60-minutes average at the $P \leq 0.05$ level. The 30 and 60-minutes values were not significantly different from each other.

(3) The three treatments gave similar response with respect to time of observations, *i.e.*, a decrease of ventilation with time.

Alveolar Ventilation—6 Per Cent Carbon Dioxide in Room Air: The average values for alveolar ventilation for six subjects according to treatment and time of observations are given in table 2. An interesting finding during the CO_2 test that was not seen when the subjects breathed room air was that alveolar ventilation values after the treatment with MTM failed to show a decrease with time. On the other hand, the MS and MTM + MS values did show a decrease with time. This differential response between treatments and the three observation times appears as a significant interaction term in the analysis of variance. A comparison of the three treatments at each stage of observation assists in the interpretation of these results (table 3).

The mean values in table 3 underscored by a common line are not significantly different ($P \leq 0.05$). Thus, at time 0 minutes, the three treatments gave essentially the same result. After 30 minutes, the mean value for alveolar ventilation in subjects given MTM + MS was significantly lower than MTM alone. After 60 minutes, subjects given both MS and MTM + MS showed values significantly lower than those given MTM alone.

Tidal Volume. Analysis of the values for tidal volume with both room air and with the carbon dioxide mixture followed the same pattern as with alveolar ventilation. The differences between these values were not tested by the analysis of variance.

TABLE 1. Alveolar Ventilation (Liters/Minute)—Room Air

(Average of Six Subjects)

Treatment	Time of Observation—Minutes			
	0	30	60	Average for all Observation Times
MTM	5.41	3.55	3.36	4.11
MS	3.98	2.53	2.44	2.98
MTM + MS	4.42	2.80	2.40	3.21
Average for all treatments	4.60	2.96	2.73	

TABLE 2. Alveolar Ventilation (Liters/Minute)—6 Per Cent CO_2 in Room Air

(Average of Six Subjects)

Treatment	Time of Observation—Minutes			
	0	30	60	Average for all Observation Times
MTM	14.39	15.29	16.08	15.25
MS	14.13	10.80	10.99	11.97
MTM + MS	13.19	9.64	8.13	10.32
Average for all treatments	13.90	11.91	11.73	

TABLE 3. Alveolar Ventilation (Liters/Minute)—CO_2

(Average of Six Subjects)

Time of Observation (minutes)	Treatment		
	MTM	MS	MTM + MS
0	14.39	14.13	13.19
30	15.29	10.80	9.64
60	16.08	10.99	8.13

The mean values underscored by a common line are not significantly different ($P \leq 0.05$).

End-expiratory Carbon Dioxide Concentration. Analysis of values of end-tidal carbon dioxide levels under the varying conditions of the test gave no definite indication of any relation to drug treatment.

Subjective Effects. Nausea was common when MS was given. Drowsiness was common when MTM was the treatment, and two subjects complained of giddiness. When MTM + MS were given, all subjects became heavily sedated, and this condition lasted about 24 hours. There seemed to be less nausea when MTM + MS were given than with MS alone. Several subjects complained of nasal stuffiness with no definite association with a particular treatment. We thought the nasal stuffiness was due to the effect of the nose clip during the respiratory measurements. Orthostatic hypotension did not occur in any of the volunteers.

Discussion

It is evident that phenothiazine compounds form a peculiar group of drugs. Among properties ascribed to various phenothiazine compounds are antihistaminic activity, sedation, tranquilization, analgesia, and antishivering and antiemetic properties. Yet some compounds, such as promethazine, have antianalgesic activity. A brief and succinct review of phenothiazines was published by Dundee.[7] Few clear and significant structure-activity relationships are apparent in this class of compounds. For example, the difference between promethazine, an antianalgesic, and trimeprazine, an analgesic, lies only in an intermediate CH_2 group in a side-chain. Methotrimeprazine and chlorpromazine, as well as trimeprazine, are among phenothiazines with analgesic activity. As in the case of opioids, the explanation of analgesia is obscure.

The results shown in table 1 would seem to indicate that methotrimeprazine causes some depression of respiration when room air was being breathed, but not with a mixture of 6 per cent carbon dioxide in room air. We believe the explanation is that the drowsiness and sedation produced by methotrimeprazine cause a diminution of alveolar ventilation when this is not being strongly stimulated. However, when a potent stimulus, 6 per cent carbon dioxide, is present the action of methotrimeprazine is not strong enough to overcome the normal physiological response, table 2. We were able to show the well-accepted depression of respiration with 10 mg. of morphine. The evidence indicated that methotrimeprazine does not significantly potentiate the respiratory depressant action of morphine, although it does potentiate the sedation. If in the course of more extensive studies it can be shown that methotrimeprazine is a clinically excellent analgesic of the same order of potency as morphine, the absence of respiratory depressant properties would be a most useful characteristic of methotrimeprazine.

Summary

A study was made of respiratory depression in human volunteers produced by a new phenothiazine analgesic, methotrimeprazine.

There was no significant respiratory depression from 15 mg. of methotrimeprazine. There was depression of respiration with 10 mg. of morphine sulfate, and with a combination of morphine and methotrimeprazine. No potentiation by methotrimeprazine of the morphine effect on respiration was seen.

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