"POTENTIATION" OF MEPERIDINE BY PROMETHAZINE

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Many antihistamines and related compounds, when adminsitered to animals in doses which do not produce sleep, will prolong the sleeping time of barbiturate or alcohol narcosis in these same animals.[1-4] This type of drug response has been called potentiation and it was expected these drugs would potentiate the central nervous system depressant effects of hypnotic, narcotic and anesthetic agents in man. Several such compounds (notably diphenhydramine, chlorpromazine, and promethazine) have achieved wide popularity in clinical medicine when used for this purpose. Most commonly they have been used to reduce anxiety preoperatively, to control pain of labor, and to decrease the quantities of anesthetic agents required for surgical anesthesia. Despite abundant clinical reports, few precise pharmacological studies are available to indicate which actions of the central nervous system depressants are potentiated, or to what degree. This study was undertaken to clarify the nature of this potentiation, using the currently popular promethazine and meperidine as the prototypes. The effect of the addition of promethazine on the analgesic, respiratory, and subjective effects of meperidine was the subject of this investigation.

Methods

Analgesic Potency. This was determined in postoperative patients who had had surgical procedures expected to produce moderate to severe postoperative pain. The drug whose potency was to be determined was alternated with a standard drug in individual patients in treatment of their pain.[5,6] Eight groups of patients were studied. In the first three groups meperidine at either 0, 25, or 50 mg. (the test drugs) was alternated in individual patients with 100 mg. of meperidine (the standard). In the next three groups promethazine 25 mg. alone, promethazine 25 mg. plus meperidine 25 mg., and promethazine 50 mg. plus meperidine 50 mg. were alternated with 100 mg. of meperidine. In the seventh group, meperidine 50 mg. plus promethazine 50 mg. was alternated with meperidine 50 mg. In the last group a placebo was alternated with 50 mg. of promethazine. These doses refer to the weights of the salts (both hydrochlorides) and all doses were given per 70 kg. of body weight. All drug solutions were prepared so that 1.0 ml. was the dose per 70 kg. All drugs were coded and the code changed at two-week intervals. All doses were given intramuscularly within the first 30 postoperative hours. The initial dose, either the test drug or the standard, given to successive patients was alternated. Patients were interviewed before and after each medication by technicians who did not know the identity of the drugs. The technicians evaluated the degree of pain relief at 45 and 90 minutes after administration of each drug. A dose was considered analgesic when "most of the pain" was relieved at both interviews. Only paired doses were included in the tabulations. A pair was considered as one dose of test drug and one dose of standard administered successively to the same patient. Patients included in the study received from one to three pairs of doses. The difference in per cent of paired doses which were analgesic between the test drug and the standard in each group of patients expressed relative analgesic potency (table 1).

Respiratory Depression. The respiratory effect of meperidine 50 mg., meperidine 100 mg., and meperidine 50 mg. plus promethazine 50 mg. was determined in five healthy male subjects between the ages of 20 and 30 years. These doses were given per 70 kg. of body weight. All subjects received all drugs in random order on separate occasions with at least four days between successive trials. Measurements of respiration were made at three intervals: before drug, one and three hours after drug. At each period subjects breathed

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gas mixtures which approximated 1, 3, and 5 per cent CO_2 in oxygen through a mouthpiece attached to a nonrebreathing valve with a dead space of 35 ml. Expired gases were passed through a low resistance dry gas meter. Each subject breathed each gas mixture for five minutes to obtain maximum response before data were collected. Expired minute volumes were corrected to 37 C. Alveolar air was sampled continuously by means of a Rahn end-tidal alveolar air sampler and passed through an infrared carbon dioxide analyzer to determine alveolar carbon dioxide tension ($P_{A_{CO_2}}$). Data were collected during two 3-minute periods on each gas mixture. The mean values for these two periods provided the data for further analysis.

Alveolar ventilation (V_A) was calculated from expired minute volume and respiratory rate, assuming a dead space of 150 ml. The data from each subject at each time interval were plotted as $P_{A_{CO_2}}$-V_A curve. The slope of the control curve for each subject was applied to the two post-drug curves and the displacement of this stimulus-response curve at V_A 8.5 l./minute was determined for each subject. This displacement represented in a single expression the degree of respiratory depression produced by the drug.

Subjective Effects. These were estimated in four groups of female patients who were awaiting elective surgery, most commonly gynecological. Patients were considered suitable for study if they were not seriously ill and were not receiving other medications. On the afternoon before operation, patients were given either promethazine 50 mg., meperidine 50 mg., promethazine 50 mg. plus meperidine 50 mg. or meperidine 100 mg. intramuscularly by the ward nurse without explanation as to the purpose of the injection. These doses were per 70 kg. of body weight. A technician randomly assigned successive patients to one of the four drugs until 30 patients were obtained in each group. All drugs were coded in identical vials and the code changed frequently. All patients were interviewed by one technician before and at 30, 60, and 120 minutes after injection. Three types of data were collected. (1) Subjective: The presence or the absence of a variety of symptoms was recorded, such as dizziness, sleepiness, and nervousness. A list of signs and symptoms of special interest was used by technicians as a

TABLE 1

ANALGESIA FOLLOWING SEVERAL DOSE LEVELS OF MEPERIDINE WITH AND WITHOUT PROMETHAZINE (TEST DRUG) COMPARED TO MEPERIDINE 100 MG./70 KG. (STANDARD DRUG) IN THE SAME PATIENTS

No. of Patients	No. of Paired Doses	Test Drug			Standard	Test Drug Minus Standard Per Cent Analgesic Doses
		Meperidine, mg. per 70 kg.	Promethazine, mg. per 70 kg.	Per Cent Analgesic Doses	Per Cent Analgesic Doses	
					Meperidine, *100 mg./70 kg.*	
18	44	0	0	27.3	81.8	−54.5
17	24	25	0	50.0	75.0	−25.0
18	42	50	0	66.7	78.6	−11.9
12	29	0	25	44.8	96.5	−51.7
14	24	25	25	66.7	91.7	−25.0
18	35	50	50	71.4	80.0	− 8.6
					Meperidine, *50 mg./70 kg.*	
20	45	50	50	66.7	71.7	− 4.4
					Promethazine, *50 mg./70 kg.*	
13	24	0	0	8.3	12.5	− 4.2

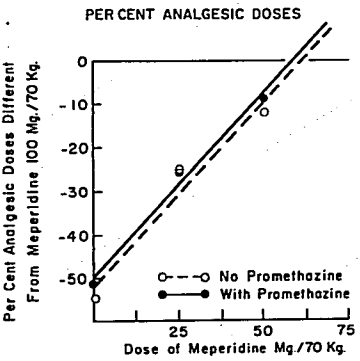

FIG. 1. Dose-effect curves for analgesia following meperidine alone and meperidine combined with promethazine. The standard for comparison of analgesia was 100 mg./70 kg. of meperidine. These curves are not significantly different.

guide for recording drug effects. Information was obtained in response to non-specific questions only, such as "How do you feel?" (2) Objective, such as restlessness, sweating, vomiting. (3) Value judgments. The technician estimated the following: depressed or cheerful, sedated or stimulated. No patient received more than one drug or drug combination. The occurrence of any sign or symptom at one or more observation periods contributed only once to the incidence reported for the group (table 3).

To estimate intensity of subjective effects as well as incidence, a scoring system was used. At each observation period all reported signs or symptoms were graded numerically as follows: 1=slight, 2=moderate or 3=marked. For each effect observed a total score could then be calculated for each patient. The mean of the 30- and 60-minute score was added to the 120-minute score to obtain a two-hour effect score. These scores provided the basis for statistical comparisons between drug effects (table 4) and for construction of time effect curves (fig. 4).

RESULTS

Analgesia. The differences in the frequency of analgesia following the test drug and standard drug in the eight groups of patients are presented in the last column of table 1. These differences (relative analgesic potency) have been plotted as a dose-effect curve for meperidine with and without promethazine (fig. 1) and their equations calculated. If promethazine increased the analgesia provided by meperidine, a displacement of the promethazine-meperidine curve to the left would be expected. The two curves were not significantly different when tested by covariance analysis,[7] indicating that analgesia produced by promethazine-meperidine mixtures was due entirely to their meperidine content.

To confirm this, two additional groups of patients were studied. In one, meperidine 50 mg. plus promethazine 50 mg. was alternated with meperidine 50 mg. and no significant difference in analgesia found (table 1). Similarly no significant difference was found in the analgesia which followed promethazine 50 mg. compared to a placebo.

To investigate the possibility that promethazine may prolong meperidine analgesia without increasing its intensity of effect, a scoring system for analgesia was also used in the group in which meperidine 50 mg. plus promethazine 50 mg. was compared to meperidine 50 mg. Prior to the injection of either drug, pain was graded as: 0=no pain, 1=slight, 2=moderate pain; and 3=severe.

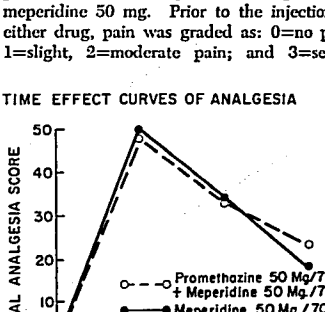

FIG. 2. Time-effect curves of analgesia for meperidine alone and meperidine combined with promethazine. Forty-five doses of each drug were administered to the same 20 patients. The difference between the two curves at three hours post drug was not statistically different.

pain. Pain was graded on the same scale at each hour following every dose for three hours. The difference between the pain score before and at each hour after injection was used as the index of analgesia. The sums of scores at each hour for the 45 doses of each drug were plotted as a time-effect curve (fig. 2). The curves were identical except at three hours when the analgesia of the promethazine-meperidine mixture exceeded meperidine alone. However, the difference between the means at three hours was not statistically significant.[7]

Respiration. The mean data for V_A and $P_{A_{CO_2}}$ of the 5 subjects are presented in figure 3 as a stimulus response curve. The pre-drug curve was calculated from the three pre-drug determinations on each of the 5 subjects (means of 15 determinations). The post-drug curves were calculated from the means of 5 subjects on each drug. The displacements of the stimulus response curve at V_A 8.5 l./minute for each subject from his control of the day of study are presented in table 2. The significance of the differences between mean displacements was tested by the *t*-test for paired replicates.[7] The respiratory depression produced by 100 mg. of meperidine was significantly greater than that following the other two drugs at one hour ($P < 0.01$). Three hours after administration the respiratory depression caused by meperidine 100 mg. remained significantly greater than that resulting from meperidine 50 mg. ($P < 0.01$) but not greater than that following the meperidine-promethazine combination. The respiratory depression caused by the meperidine-promethazine mixture was not significantly different from that after meperidine 50 mg. either at one or three hours after administration. There is the suggestion, however, that promethazine prolonged the respiratory depressant effect of meperidine.

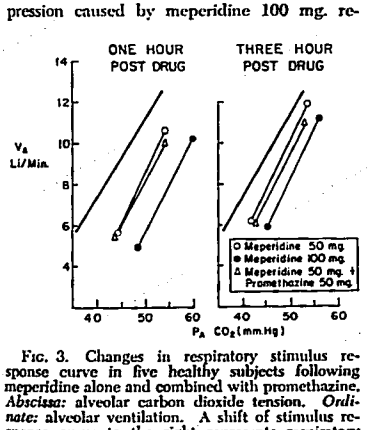

FIG. 3. Changes in respiratory stimulus response curve in five healthy subjects following meperidine alone and combined with promethazine. *Abscissa:* alveolar carbon dioxide tension. *Ordinate:* alveolar ventilation. A shift of stimulus response curve to the right represents respiratory depression.

TABLE 2

DISPLACEMENTS OF $P_{A_{CO_2}}$–V_A CURVES AT V_A 8.5 L./MINUTE IN FIVE HEALTHY SUBJECTS BY MEPERIDINE WITH OR WITHOUT PROMETHAZINE (IN MM. HG $P_{A_{CO_2}}$)

Subject	Meperidine, 50 mg./70 kg.		Meperidine, 50 mg./70 kg. + Promethazine, 50 mg./70 kg.		Meperidine, 100 mg./70 kg.	
	1 Hour	3 Hours	1 Hour	3 Hours	1 Hour	3 Hours
1	7.5	2.8	7.3	2.7	12.0	5.5
2	6.8	3.5	7.0	3.5	10.8	5.0
3	4.8	2.2	7.2	5.7	11.0	6.2
4	6.5	3.5	7.8	6.0	10.8	5.8
5	5.0	2.0	6.5	4.7	8.5	4.8
Mean	6.1	2.8	7.2	4.5	10.6	5.5

Subjective Effects. Since a crossover study was not possible, only female patients were used to provide more homogeneous samples. The per cent frequency of the most prominent subjective effects which followed the four drugs are presented in table 3. These data, expressed as mean two-hour scores (multiplied by 10 to facilitate statistical comparisons), are presented in table 4. In the categories of sleepy, nervous, restless, and cheerful, patients could report either an increased (positive) or a decreased (negative) effect. Reports of increased nervousness and decreased sleepiness were rare and therefore omitted from table 3. Increased restlessness was included because previous observers[8, 9] have noted a high frequency of restlessness among normal subjects given promethazine. This was not true in our patients in whom the net effect of promethazine with or without meperidine was to decrease restlessness (table 4).

Although all patients studied were in an anxiety laden situation, *i.e.*, preoperative, the

TABLE 3

INCIDENCE (PER CENT) OF SUBJECTIVE EFFECTS IN FOUR GROUPS OF FEMALE PATIENTS (30 PATIENTS PER GROUP)

Drug Effect	Promethazine, 50 mg./70 kg.	Meperidine, 50 mg./70 kg.	Promethazine, 50 mg./70 kg. + Meperidine, 50 mg./70 kg.	Meperidine, 100 mg./70 kg.
Per cent White	29	23	13	43
Per cent over 40 years	26	37	33	46
Drunk	3	7	20	17
Groggy	40	7	13	17
Sleepy	73	70	93	86
Hard to Concentrate	3	7	13	13
Less Nervous	29	10	33	36
Restless	3	3	13	3
Dizzy	33	60	70	86
Sight Difficulty	26	23	30	13
Heavy Feeling	13	30	36	40
Perspiration	3	13	13	30
Feels Hot	3	27	17	33
Nausea	0	17	13	20
Vomiting	0	3	3	3
Dry Mouth	3	3	3	3
Disliked Drug Effect	37	40	63	53
Evaluation By Technician				
More Cheerful	3	7	10	23
Less Cheerful	13	13	26	23
Sedation	70	70	93	83

TABLE 4

MEAN SCORE (× 10) PER PATIENT FOR SUBJECTIVE EFFECTS

Drug Effect	Promethazine, 50 mg./70 kg.	Meperidine, 50 mg./70 kg.	Promethazine, 50 mg./70 kg. + Meperidine, 50 mg./70 kg.	Meperidine, 100 mg./70 kg.
Drunk	0.7	0.5	3.3†	1.8
Groggy	5.3	1.7	3.3	6.7†
Sleepy	16.0	14.5	26.0†	22.8
Hard to Concentrate	0.7	0.3	3.0	1.7
Nervous	−12.0	− 3.3	−12.0*	−12.7
Restless	− 2.0	− 1.3	− 4.0	− 2.0
Dizzy	5.2	12.7†	15.8	18.0
Sight Difficulty	4.3	2.8	4.7	2.7
Heavy Feeling	2.3	4.8	7.3	7.8
Cheerful	− 4.7	− 1.3	− 7.3	− 1.5
Perspiration	0.7	2.2	1.8	2.5
Feels Hot	0.3	3.8*	2.2	2.8
Nausea	0	2.0*	1.5	3.3
Vomiting	0	0.3	0.3	1.0
Dry Mouth	0.2	0.7	0.3	0.3

Statistical comparisons were made by the *t*-test for significance of the difference between means.[7] For each drug effect, the means were compared as follows: meperidine 50 mg. versus promethazine 50 mg.; promethazine 50 mg + meperidine 50 mg. versus meperidine 50 mg.; meperidine 100 mg. versus promethazine 50 mg. + meperidine 50 mg. * = $P < 0.05$, † = $P < 0.01$.

data on relief of nervousness must be interpreted with caution because of the difficulty in quantitating "nervousness" before drug injection by our interview technique of nonspecific questions. A "heavy feeling" usually referred to the extremities, but at times to the head or "all over." "Sight difficulty" included double vision, difficulty focusing eyes or extreme dizziness.

The over-all effect of promethazine was sedation manifested by sleepiness and relief of nervousness. The high incidence of "groggy" following promethazine alone was in contrast to its low score, indicating that it was not marked in the patients who reported it. Dizziness, a heavy feeling, a hot feeling, perspiration, nausea, and vomiting were more characteristic of meperidine effects. Neither restlessness nor dry mouth reported by others[5, 9] as common after promethazine was prominent in these patients.

In table 4, statistical validation of the differences between scores have been made between drugs whose comparison would be most meaningful. Thus, meperidine 50 mg. produced significantly more dizziness, hot feeling, and nausea than did promethazine alone. Promethazine-meperidine produced more drunkenness, sleepiness, and relief of nervousness than did meperidine 50 mg. alone. Meperidine 100 mg. was different from the meperidine-promethazine combination only in producing more grogginess. The nausea and vomiting produced by meperidine was not prevented by the addition of promethazine.

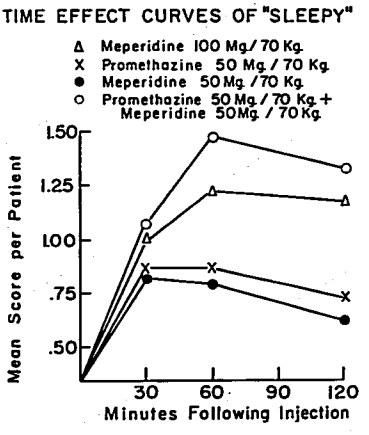

FIG. 4. Time-effect curves for "sleepy" expressed as mean score per patient at each interview. The sum of the scores for meperidine 50 mg. and promethazine 50 mg. given separately exceed the score for the drugs when given together.

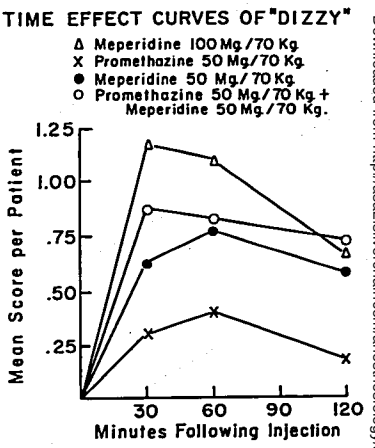

FIG. 5. Time-effect curve for "dizzy." Both doses of meperidine produced significantly more dizziness than did promethazine alone. The dizziness of meperidine 50 mg. could account for most of the dizziness seen following promethazine-meperidine combined.

The data on table 4 permit a quantitative comparison of the subjective effects of meperidine and promethazine alone and in combination. For most effects recorded, the sum of the mean scores of columns 1 and 2 are greater than those of column 3. In the case of the exceptions (drunk, hard to concentrate, restless, heavy feeling and cheerful) the sums of the scores of promethazine alone and meperidine alone are not much different from the score for the meperidine-promethazine mixture.

These data were further analyzed by construction of time-effect curves of the prominent subjective effects (nervous, drunk, nausea,

heavy limbs, dizzy, sleepy, and sight difficulty). Time-effect curves of sleepy and dizzy are presented in figures 4 and 5. The sum of effects of promethazine alone and meperidine alone were either equal to or more than the effects of the drugs given together. In all time-effect curves constructed, drug effects were decreasing at the two-hour observation period. There was no evidence that promethazine prolonged meperidine effects. However, the observation period was only two hours.

Discussion

By definition, potentiation of drug action occurs when the total effect of two drugs given together is greater than the sum of their individual effects. When the combined effect is simply the algebraic sum of their individual effects, this is known as summation.[10] Despite the common clinical observation in man that both chlorpromazine and promethazine enhance the hypnotic actions of narcotics and decrease the amount of intravenous barbiturate necessary for anesthesia, no quantitative data are available to determine whether this represents summation or potentiation. A review of the evidence for a potentiating action of the phenothiazine derivatives on the other actions of narcotics is equally disappointing.

Both Dundee[11] and Jackson and Smith[12] have claimed that chlorpromazine potentiated the analgesic effects of morphine in man, since satisfactory analgesia could be obtained with a lower dose of morphine when combined with chlorpromazine. However, in both studies, chlorpromazine alone produced some analgesia and the data were not sufficiently quantitative to determine whether this was summation or potentiation. Others[13, 14] have been unable to demonstrate increased analgesia when morphine was combined with chlorpromazine. Similar studies with promethazine have not been done.

Wendel, Lambertsen and Longenhagen[15] investigated the respiratory effects of chlorpromazine alone and in combination with meperidine in man. The degree of respiratory depression following the combination of drugs suggested additive effects, but chlorpromazine significantly prolonged the respiratory depression of meperidine. In the sense of total effect, this represented potentiation. Eckenhoff and associates[8] found no respiratory depression following promethazine alone in man. Their data even suggest that stimulation of respiration occurred. However, this may be an artifact due to restlessness produced by the drug in their subjects. Further studies by these investigators[9] showed that the combination of promethazine and meperidine did not reduce minute volume any more than the same dose of meperidine alone. However, alveolar or arterial P_{CO_2} was not measured.

Although there is good evidence that the hypnotic effects of central nervous system depressants are potentiated by phenothiazines in animals, there is little evidence that this occurs in man. Since chlorpromazine alone possesses hypnotic, analgesic and respiratory depressant activity, and promethazine possesses potent hypnotic activity, the evidence suggests that these effects are additive in man. At least this is true with regard to intensity of effect, although it is still possible that these drugs may prolong the effects of narcotics.

This study demonstrated that the effects of promethazine were simply added to those of meperidine and that promethazine by itself was a potent sedative without analgesic or respiratory depressant activity. This observation is of significance in the management of the pain of labor and in preanesthetic medication. By the addition of 50 mg. of promethazine to 50 mg. of meperidine, the sedative or psychic effects of 100 mg. of meperidine can be achieved with the respiratory depression of 50 mg. of meperidine. However, it would also be true that if such a combination were used for analgesia alone, profound sedation with little analgesia might result, since it has been demonstrated that sleep or sedation is not necessarily associated with pain relief.[16]

Summary

The analgesic, respiratory depressant and subjective effects resulting from meperidine were measured in man and compared to the effects produced when identical doses of meperidine were given in combination with promethazine. It was found that the addition of promethazine to meperidine did not increase the analgesic activity of meperidine, did

not increase the respiratory depression of meperidine, did not prevent the nausea and vomiting of meperidine, but markedly increased the sedative effects of meperidine. Expressed quantitatively these data indicated that promethazine did not potentiate the meperidine actions measured. Their effects were simply additive.

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THIOPENTAL SLOUGH Thiopental injected intra-arterially or para-arterially in experimental animals causes tissue slough and gangrene. Protection is afforded against this by prior treatment with reserpine and prior sympathectomy, procedures which decrease artery wall stores of noradrenaline. Tolazoline which abolishes the constrictor action of noradrenaline also abolished that of thiopental. The action of thiopental in causing constriction of aortic strips is similar to that of noradrenaline and it is similarly potentiated by cocaine and abolished by pretreatment with reserpine. It is suggested that the gangrene caused by intra-arterial injection of thiopental in humans as well as the skin sloughs caused by infiltration of thiopental solution is similarly due to release of norepinephrine in humans with consequent intensive vasoconstriction. (*Burn, J. H.: Why Thiopentone Injected Into an Artery May Cause Gangrene, Brit. Med. J. 2: 414 (Aug. 6) 1960.*)