STUDIES OF ANALGESIC DRUGS: ANILERIDINE DIHYDROCHLORIDE

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CURRENTLY used potent analgesics possess certain important therapeutic disadvantages. Depending on the clinical situation in which they are used, the major disadvantages include respiratory depression, sedation, nausea and vomiting, circulatory instability, constipation, and addiction. The discovery of an analgesic of the effectiveness of morphine without one or more of the above side actions would represent a significant contribution to the therapy of pain. Toward this end we have recently studied a new synthetic analgesic, anileridine dihydrochloride (Leritine).

Anileridine (ethyl 1-(4-aminophenethyl)-4-phenylisonipecotate) is a derivative of meperidine (Demerol) in which a phenethyl group has been substituted for a methyl group in the meperidine molecule. Weijlard *et al.* (1) reported that the addition of a phenethyl group to some analgesic compounds including meperidine increased the analgesic potency of these compounds. In rats and dogs, Orahovats, Lehman, and Chapin (2) found anileridine to be a more potent analgesic than meperidine by both parenteral and oral routes. However anileridine produced considerably milder side actions (sedation, respiratory depression, hypotension) than morphine in these animals and somewhat milder side actions than meperidine. Neither vomiting nor constipation was observed following anileridine. Because of the high potency and low side action liability of anileridine in animals, the following studies were undertaken in man.

METHODS

Analgesia.—An estimation of analgesic potency was made in postoperative patients by the method described in detail by Keats, Beecher, and Mosteller (3). Postoperative patients of all surgical services were eligible as subjects for study. Only those patients who had had a surgical procedure warranting moderate to severe postoperative pain and who were sufficiently oriented to respond to simple questions were included. In treatment of their pain, anileridine dihydrochloride was alternated in individual patients with 50 mg. of meperidine hydrochloride. The dose levels of anileridine studied were 10 mg., 20 mg., 40 mg., 50 mg., and 75 mg. These doses refer to weight of the respective

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salts per 70 kg. of body weight. In addition, one group of 30 patients, 50 mg. of anileridine was alternated with 100 mg. of meperidine. All drugs were administered intramuscularly within the first thirty postoperative hours. Patients were interviewed before and after each medication by trained technicians who evaluated the degree of pain relief at forty five and ninety minutes after administration of each dose of each drug. A dose was considered analgesic when "most of the pain" was relieved at both evaluations. No attempt was made to evaluate degrees of severity of pain other than that the pain be of sufficient intensity to warrant a narcotic. No attempt was made to grade degrees of pain relief. Only paired doses were included in the tabulation. Analgesic potency was expressed as the difference in the per cents of total paired doses which were analgesic.

Respiratory Depression.—The respiratory effects of 40 mg. of anileridine and 100 mg. of meperidine (per 70 kg. of body weight) were determined in 2 male and 3 female healthy subjects between the ages of 20 and 30 years (mean body area of 1.75 ± 0.09 m^2). All subjects received both drugs but in random order with at least five days between drug trials. Subjects breathed through a mouthpiece attached to a Kirchoff nonrebreathing valve. Total dead space of this system was 25 cc. Expired gases were passed through a low resistance dry gas meter. Expired minute volume and respiratory rate were measured for 3 minute periods. Alveolar air was sampled continuously during the 3 minute periods by means of a Rahn end-tidal alveolar air-sampler attached to the expiratory tube. The sample was dried, passed through an infrared carbon dioxide analyzer, and percentage of carbon dioxide determined directly. Carbon dioxide values were discarded when tidal volumes fell below 200 cc. Measurements were made at three intervals: before drug administration, and one and 3 hours after administration. At each interval subjects first breathed room air, then 3 per cent to 4 per cent carbon dioxide in oxygen. Data were collected during two three-minute periods on each gas mixture. The mean values of these two periods provided data for further analysis. All volumes were corrected to 37 C. at standard atmospheric pressure.

For ease in handling these data, the following transformations were made. Alveolar ventilation (V_A) was calculated from expired minute volume and respiratory rate assuming a deadspace of 150 cc. for males and 100 cc. for females. Alveolar ventilation was converted to alveolar ventilation ratio (V_AR), using pre-drug alveolar ventilation on room air as unity. Alveolar carbon dioxide tension (P_ACO_2) was converted to increase or decrease carbon dioxide tension from the pre-drug value on room air. For statistical treatment the data of each subject at each time interval on each drug were plotted as a respiratory stimulus (P_ACO_2)-response (V_AR) curve. For each curve (6 curves for each subject) the alveolar ventilation ratio at a hypothetical 4 mm. increase in carbon dioxide tension from the pre-drug room air value was esti-

mated (alveolar ventilation ratio at + 4 mm. of mercury for all three curves in each half of figure 2). The differences in these values between pre-drug and post-drug measurements represented drug effect in a single expression. This was primarily a measure of displacement of the curve. The significance of such changes could then be determined by the *t*-test for paired replicates (4). Similar probability values were obtained when differences were analyzed by covariance analysis techniques (5). Comparisons between drugs were similarly made. No attempt was made to evaluate differences in the slopes of these curves since only two points determined each curve.

Subjective Effects.—These were estimated in preoperative patients who were free of pain and awaiting elective surgery. We have previously found such patients to be especially responsive to drug effects and useful for assessing the subjective effects of narcotic drugs (6). Patients who had been hospitalized for long periods or who had received narcotic or sedative drugs in the recent past were not studied. On the day before operation, suitable patients were given either 50 mg. of anileridine or 100 mg. of meperidine by the ward nurse without explanation as to the purpose of the injection. All doses were per 70 kg. of body weight. All data were collected by technicians who were unaware of the drugs being used but who were aware of the changes to be observed. These were defined as rigidly as possible. Patients were interviewed prior to drug administration and at thirty, sixty, and one hundred twenty minutes after the drug. Three types of data were collected: (1) Subjective—the presence or absence of the following were recorded: lightheaded, drunk, headache, dizzy, hard to concentrate, groggy, shaky, palpitations, heavy limbs, nervous, "blue," nausea, difficulty focusing eyes, itchy, and dry mouth. A check list of these symptoms was used as a guide by the technicians but patients were not questioned specifically for each symptom. All data were obtained from patients' statements made in response to such questions as, "How do you feel?" "Do you feel any different?" (2) Objective—such as restlessness, hiccups, tremor, pallor, sweating, vomiting, or unusual behaviour. A check list was also used as a guide. (3) Value judgments—the technicians estimated the following: friendly or unfriendly, groggy or clearheaded, depressed or cheerful, calm or nervous. The technician also summarized the total drug effect as sedation or stimulation or both, and as pleasant or unpleasant drug effect. Only signs and symptoms which represented a change from the pre-drug interview were attributed to the drug. No patient received more than one drug. Estimates of the significance of the differences in frequency of these effects between drugs were made by the rank method for paired replicates of Wilcoxon (7). The significance of the differences between frequencies of a single symptom was estimated by the method outlined by Treloar (8) for determination of the significance of the difference between two proportions.

TABLE 1

FREQUENCY OF ANALGESIA FOLLOWING ANILERIDINE COMPARED TO MERPERIDINE IN THE SAME PATIENTS

Number of Patients	Total Paired Doses	Anileridine		Meperidine		Difference in Analgesic Doses (per cent)
		Dose (mg./70 kg.)	Analgesic Doses (per cent)	Dose (mg./70 kg.)	Analgesic Doses (per cent)	
28	73	10	52.1	50	64.4	−12.3
44	81	20	70.4	50	76.5	− 6.1
29	56	40	85.7	50	58.9	+26.8
37	78	50	85.9	50	60.3	+25.6
33	60	75	86.7	50	70.0	+16.7
30	50	50	92.0	100	78.0	+14.0

The analgesic equivalent of 50 mg. of meperidine was estimated (method of least squares) to be 21.3 mg. of anileridine (fig. 1).

RESULTS

Analgesia.—The differences in the frequency of analgesia following several dose levels of anileridine compared to 50 mg. of meperidine in the same patients are presented in table 1. These differences were plotted as a dose-effect curve (fig. 1) which breaks sharply at 40 mg. per 70 kg. of anileridine. The equation for the first three points of this plot was calculated by the method of least squares. The intersection between this curve and the line representing the analgesia of 50 mg. meperidine represents the point of analgesic equivalence. This

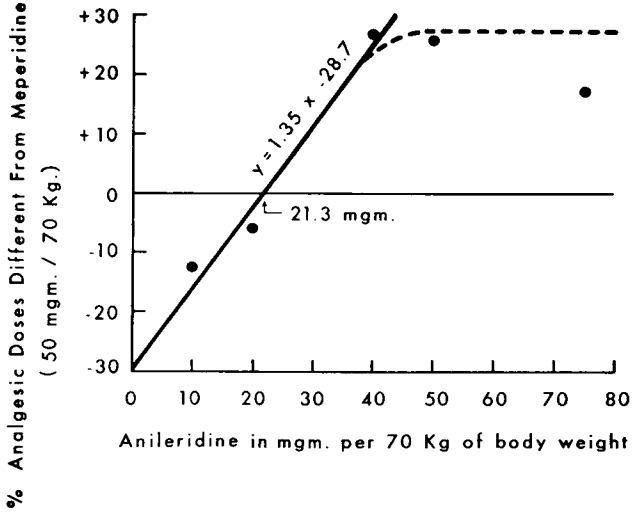

FIG. 1. Dose effect curve of analgesia following anileridine compared to meperidine. The intersection of the two curves represents the point of analgesic equivalence. Thus 21.3 mg. of anileridine produced analgesia equal to 50 mg. of meperidine.

TABLE 2

DRUG EFFECTS ON MEAN EXPIRED MINUTE VOLUME AT 37 C., RESPIRATORY RATE, AND ALVEOLAR CARBON DIOXIDE TENSION IN 5 SUBJECTS BREATHING ROOM AIR AND A MIXTURE OF CARBON DIOXIDE AND OXYGEN

	Room Air			3 Per Cent Carbon Dioxide in Oxygen		
	Mean Expired Minute Volume ±S.E. (liters)	Respiratory Rate ±S.E. (per min.)	P_ACO_2 ±S.E. (mm.Hg)	Mean Expired Minute Volume ±S.E. (liters)	Respiratory Rate ±S.E. (per min.)	P_ACO_2 ±S.E. (mm.Hg)
	Demerol 100 mg. Intramuscularly					
Control	6.25 ± 0.35	11.4 ± 0.6	33.5 ± 1.4	16.83 ± 0.47	15.5 ± 0.9	40.0 ± 1.1
1 Hour	4.42 ± 0.42	11.1 ± 0.4	38.8 ± 1.5	11.22 ± 0.39	13.6 ± 0.6	46.7 ± 2.2
3 Hours	5.87 ± 0.82	11.9 ± 0.8	37.6 ± 1.3	14.45 ± 0.38	14.7 ± 1.4	42.2 ± 1.5
	Anileridine 40 mg. Intramuscularly					
Control	6.54 ± 0.64	11.5 ± 0.5	36.5 ± 1.4	15.65 ± 0.75	14.9 ± 1.5	43.8 ± 1.6
1 Hour	4.69 ± 0.65	10.6 ± 0.7	41.2 ± 1.2	11.85 ± 0.43	14.6 ± 1.3	47.9 ± 1.3
3 Hours	5.65 ± 0.56	10.9 ± 0.7	37.9 ± 1.1	15.06 ± 0.34	14.5 ± 1.7	43.1 ± 1.2

S.E. = standard error of mean. Both anileridine and meperidine significantly depressed respiration 1 hour post-drug ($P < 0.02$). Respiration remained depressed 3 hours post-drug following meperidine ($P < 0.05$), but not following anileridine ($P > 0.05$).

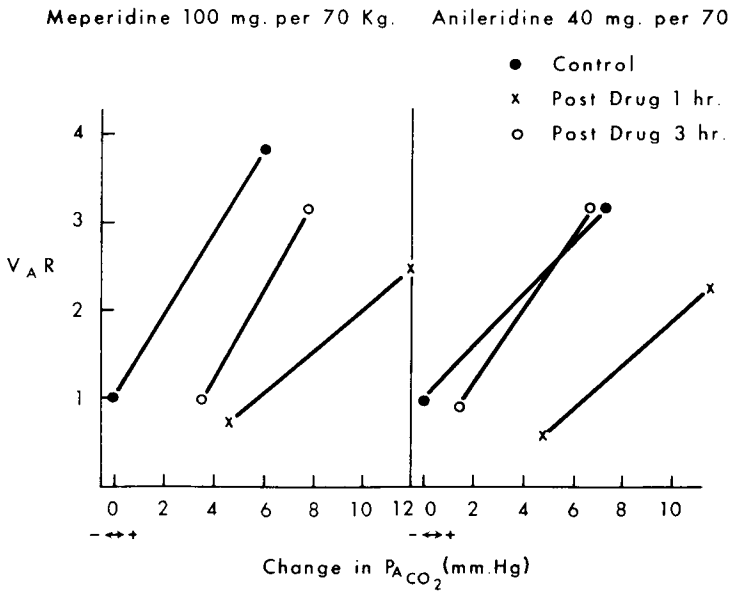

FIG. 2. Effect of meperidine and anileridine on the respiration of 5 normal subjects. Abscissa: change in alveolar carbon dioxide tension. Ordinate: alveolar ventilation ratio. A shift of the curve to the right represents respiratory depression. Both drugs depressed respiration to the same degree one hour after drug administration. Depression persisted at three hours after meperidine but not after anileridine.

was calculated to be 21.3 mg. Anileridine was therefore estimated to be two and one-half times as potent as meperidine and 40 mg. of anileridine to be the analgesic equivalent of 100 mg. of meperidine. The placebo point (0 mg. of anileridine) of — 29 per cent agrees well with that found in previous studies by this technique (9). When 50

TABLE 3

FREQUENCY (PER CENT) OF SUBJECTIVE EFFECTS PRODUCED BY MEPERIDINE AND ANILERIDINE IN HOSPITALIZED PATIENTS

	Meperidine (100 mg. intramuscularly)	Anileridine (50 mg. intramuscularly)
Number of Subjects	40	40
Per cent male	30	28
Per cent white	30	50
Per cent over 40 years	43	40
Drunk	18	33
Lightheaded	55	68
Dizzy	65	60
Shaky	8	10
Visual difficulties	15	28
Nervous	5	10
Restless	0	8
Psychic depression ("blue")	3	20
Relief of depression	8	0
Cheerful	15	5
Absence of cheerfulness	0	8
Heavy limbs	13	5
Unpleasant dreams	8	0
Sweating	53	38
Nausea	25	43
Vomiting	5	13
Itchy	5	28
Dry mouth	48	23
Dislikes drug effect	37	62
Technician Evaluation:		
"Euphoria"	8	3
Little drug effect	13	10
Sedation	23	48
Marked sedation (sleep)	65	30
Stimulation	8	15
Increased talkativeness	30	60
Unpleasant drug effect	50	70

The over-all incidence of symptoms following these two drugs was not significantly different by rank analysis ($P > 0.05$). The incidence of sedation and sleep following meperidine was significantly greater than that following anileridine ($P < 0.05$).

mg. of anileridine and 100 mg. of meperidine were compared, the frequency of analgesia following anileridine exceeded that of meperidine by 14 per cent (table 1), providing a good check on the estimate of analgesic potency previously made.

It is of interest that 75 mg. per 70 kg. of anileridine produced less frequent pain relief than did 40 mg. or 50 mg. We have observed this

previously in studies of other potent analgesics by this technique (9). Although we have no explanation for this decrease in analgesia, it does suggest that an optimal dose for analgesia has been exceeded.

Respiration.—The data as collected (table 2) and the mean carbon dioxide sensitivity curves pre-drug and post-drug are presented (fig. 2). Displacement of the curve to the right represents respiratory depression. In equipotent doses, both drugs depressed respiration to the same degree. However, after three hours, respiration had returned to normal following anileridine whereas respiration remained depressed following meperidine. The following statistical comparisons were made and the probability ratios are indicated: anileridine pre-drug, compared to anileridine one hour post-drug ($P < 0.02$); meperidine pre-drug, compared to meperidine one hour post-drug ($P < 0.02$); anileridine one hour post-drug, compared to meperidine one hour post-drug ($P > 0.05$); anileridine pre-drug, compared to anileridine 3 hours post-drug ($P > 0.05$); meperidine pre-drug, compared to meperidine 3 hours post-drug ($P < 0.05$) (4).

Subjective Effects.—The frequency of the most prominent subjective effects which followed meperidine and anileridine together with some of the characteristics of the patient samples are presented in table 3. It should be noted that in this comparison 50 mg. of anileridine was administered instead of the analgesic equivalent of 40 mg. The higher incidence of subjective effects observed in many symptom categories following anileridine could therefore be the result of the 25 per cent excess in dose of anileridine. Despite this, the over-all incidence of subjective effects following anileridine is not significantly greater than that following meperidine ($P > 0.05$). Despite the difference in dose, meperidine produced sedation and sleep more frequently than anileridine ($P < 0.05$). This difference is supported by the higher incidence of nervousness, restlessness, and stimulation which followed anileridine. The patients found anileridine a more unpleasant drug at this dose; the technicians concurred. This observation may be of some importance with regard to the development of psychic drug dependence to these drugs (6). The differences in the incidence of nausea, vomiting, and sweating were not significant.

Discussion

The initial step in the proper study of any analgesic drug must be the establishment of a dose which is equivalent in analgesic effectiveness to some dose of a standard drug. Once this is established, the relative respiratory, subjective, gastrointestinal, circulatory, or other effects of the drugs can then be compared. In this study, anileridine was found to be two and one-half times as potent an analgesic as meperidine on a milligram basis. However when given in equivalent analgesic dose, anileridine was remarkably similar to meperidine in its

respiratory effects and in its subjective side action liability. From these data the only differences between these two drugs are: sedation is less marked following anileridine, and based on the respiratory data, anileridine is slightly shorter acting than meperidine. These characteristics might be advantageous in some clinical situations; for example, in the treatment of postoperative pain. In other clinical situations, anileridine can be considered an adequate substitute for meperidine, with both the safety and hazards of meperidine.

Summary

Anileridine, a phenethyl meperidine, was administered to normal subjects, preoperative and postoperative patients and compared to meperidine. The analgesic, respiratory, and subjective effects of these two drugs were studied.

The data collected indicate that: (1) Forty milligrams of anileridine is the analgesic equivalent of 100 mg. of meperidine. (2) Anileridine depresses the respiration of normal subjects to the same degree as meperidine, but respiration returns to normal more rapidly after anileridine. (3) Anileridine is capable of producing the same subjective side actions as meperidine; however, sedation was less marked following anileridine.

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