THE ANALGESIC PROPERTIES OF ANILERIDINE, MEPERIDINE, AND MORPHINE: A COMPARATIVE STUDY[1]

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THE EVALUATION of a new drug requires that its effects be tested under controlled conditions in large numbers of clinical cases. This is particularly true of analgesic drugs since none of the methods proposed for objective measurement of the value of these drugs in man can be considered wholly satisfactory.

Although the analgesic effectiveness of anileridine (Leritine®) has been previously recorded by a number of investigators (1–5), we believe that the addition of yet another study to this series may help to orientate the usefulness of this drug among the established analgesic agents. We have, therefore, compared the analgesic activity of anileridine with the effectiveness of morphia and meperidine in a series of unselected patients in the immediate postoperative period.

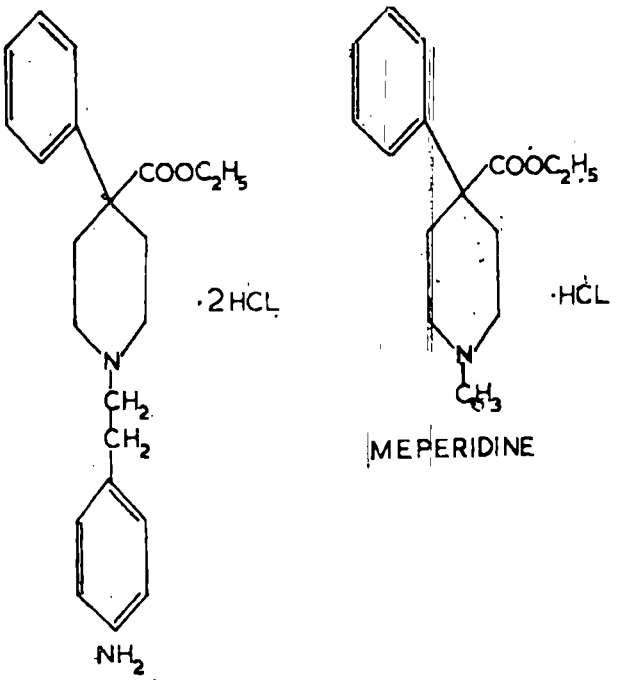

FIGURE 1

Anileridine resembles meperidine in chemical structure. The two drugs are represented by the formulae in Figure 1. Anileridine was first described by Weijlard *et al.* (6) in May 1956.

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Method and Material

Anileridine, meperidine, and morphine were administered to unselected postoperative patients in the recovery room in a blind study. Stable solutions of each drug were prepared in identical multiple dose bottles, each containing 30 cc. Each bottle was labelled by a code number only, and the code was not broken until the study had been completed. Since earlier reports had indicated that the analgesic potency of anileridine is approximately twice that of meperidine, and that of meperidine approximately one-tenth of morphine, weight for weight, the solutions were made to contain:

Anileridine	25 mg. per cc.
Meperidine	50 mg. per cc.
Morphine	5 mg. per cc.

These drugs were administered by experienced recovery room nurses who have for some years judged the requirement of postoperative patients for sedative. We consider these nurses to be our most reliable observers in this matter. The information supplied to the nursing staff was simply that each cubic centimetre of solution was equivalent to 50 mg. of meperidine.

The drugs were administered by intramuscular injection, and blood pressure, pulse, and respiratory rate were recorded at the time of administration. The administration of an analgesic drug was indicated in each case by complaint of pain, or by restlessness judged to be produced by pain. Effect of the drug in the dose given, blood pressure, pulse rate, and respiratory rate were recorded thirty minutes after administration. Patients requiring further sedation in the recovery room received the same code number as the original dose, except for a few cases in which the recovery room staff failed to carry out this plan. Time elapsed from the last administration of sedative in the recovery room to the first sedative required after return to the floor was recorded from the patients' records on the following day.

In all, 1,117 patients are included in this study. The distribution of these patients by drug given is shown below:

Anileridine	382
Meperidine	389
Morphine	346
	1,117

Age Distribution

The youngest patient in this series was 15 years of age, and the oldest 86 years. Age distribution of patients receiving each drug is represented in Table I. It is so similar in each instance that it can play no significant part in the assessment of the results.

TABLE I

	Age group (years)			
	15–29	30–49	50–69	70+
Anileridine	63	151	133	35
Meperidine	57	176	121	35
Morphine	56	156	103	31

Operative Site

It is generally recognized that the operative site greatly influences the requirement of the patient for sedative. We have, therefore, examined the distribution of operative site in this series and this is represented for each drug in Table II. The full range of general surgery and surgical specialties has been abundantly covered, with the exception of cardiac surgery. Here again we find that in most instances the distribution for each drug is sufficiently similar that this factor is unlikely to influence the assessment of the effectiveness of drugs in the comparison.

TABLE II

	Anileridine	Meperidine	Morphine
Intracranial	—	—	2
Head and neck	24	20	26
Thoracic	12	8	12
Abdominal			
Upper	63	54	53
Lower	97	114	78
Perineal	42	42	33
Transurethral	21	25	27
Plastic	13	12	20
Extremities	70	59	54
Back	25	36	31
Breast	15	19	10

Average Dose

In recording the dosage of drugs in this series, simple notation of the number of cubic centimetres given was made in the record. It is of interest in examining these records that the nursing staff quickly established an average effective dose, and that this varied from 1 to 2 cc. of the coded solutions, the dose being based on the assessment of the status of the patient and the individual requirement for sedative. It has been of interest to determine the comparative average dose of these three drugs since we feel that this gives some expression of the relative potency of the preparations. Average dose in milligrams of the three drugs for the patients in the series is shown below:

Anileridine	38.8 mg.
Meperidine	73.6 mg.
Morphine	8 mg.

Sedative Effect

The sedative effect of the drugs was judged by the recovery room nurses at a period of thirty minutes after intramuscular administration. The assessments recorded for each dose are shown in Table III. A good effect was one in which it was evident that no further sedative was required at the end of thirty minutes, a fair effect was one in which relief was probably adequate, but left something to be desired, while a poor effect is recorded in the patient who required additional sedative after the first thirty minutes. It is interesting to note that, in the group having a poor effect from the sedative, there are several who are reported to have had a poor effect from additional sedative. It is probable that, in some of these cases, some other factor was contributing to restlessness.

TABLE III

	No. of patients	No. of doses	Sedative effect		
			Good	Fair	Poor
Anileridine	382	392	350	38	4
Meperidine	389	403	343	45	13
Morphine	346	349	265	64	18

It is of interest to note that there are more good and fair effects recorded for anileridine and meperidine than for morphia. We feel that this firmly establishes the analgesic value of anileridine, and we believe that the differences shown in Table III between anileridine and meperidine are not significant in a study of this kind. It is possible that the potency of anileridine is something greater than twice that of meperidine, so that the standard solutions used in this study did not actually represent equipotent doses, volume for volume. In this regard, it is of interest that Dripps and his collaborators in a similar study (3) calculated that 40 mg. of anileridine was equivalent to 100 mg. of meperidine in analgesic potency. Our study does not permit an accurate calculation of this kind, but the results shown in Table III might tend to bear out this assumption.

It might also be suggested from the data shown in Table III that the generally accepted therapeutic equivalents of 10 mg. of morphine and 100 mg. of meperidine may not be quite accurate, but that meperidine is somewhat more potent than this in relation to morphine.

Duration of Sedative Action

An attempt was made to compare the duration of sedative action of the three drugs by recording the time from the last administration of sedative in the recovery room to the next sedative required by each patient after return to the ward. The time of the first sedative on the ward was taken from the patient's record on the day following operation. The data so derived are shown in Table IV.

TABLE IV

	Time to next sedative (hours)		
	Shortest	Longest	Average
Anileridine	0.5	17	5.4
Meperidine	0.5	17	4.73
Morphine	0.5	20*	5.46

There appears to be no significant difference between the three drugs. We are aware that these figures may be open to question since we were unable to control the administration of the sedative on the floor, and we are aware that it is a habit of some nurses to administer an analgesic to every postoperative patient immediately he comes under their care. We do feel, however, that we may assume from these figures that the three drugs have approximately the same duration of action.

A number of patients required no further sedative after leaving the recovery

room Of these, 43 had been given anileridine, 39 had received meperidine, and 48 had received morphine.

Cardiovascular Effects

As we have previously noted, blood pressure and pulse rate were recorded at the time of administration of the analgesic drug, and after thirty minutes. It is interesting that there is no consistent pattern in the changes which were recorded after the administration of sedative drugs. Blood pressure increased by 10 mm. of mercury systolic as frequently as it decreased by the same amount, and in all but two patients remained within normal limits for the patient at that time. In the patients who received anileridine, blood pressure rose ten or more points on 78 occasions, and was reduced more than 10 mm. of mercury systolic on 91 occasions. In the morphine series, blood pressure rose on 95 occasions and was reduced in 85 patients. In the patients receiving meperidine, blood pressure rose on 75 occasions and was reduced on 99 occasions. Only two patients in this series had declines of blood pressure following the administration of an analgesic drug which caused any concern. Both the patients had received meperidine. The first of these was a postoperative mastectomy whose blood pressure dropped to 75 mm. of mercury within thirty minutes of receiving the sedative. Someone ordered Lorfan® for this patient, although there is no record that the respiration had shown any change, and her blood pressure promptly rose to 100 mm. Hg systolic. The second patient had a cholecystectomy and within the thirty-minute period after receiving meperidine had a drop of blood pressure to 60 mm. mercury. This patient received a vasopressor drug, the foot of the bed was elevated, and the blood pressure returned to normal limits.

There were no cases of circulatory depression in the anileridine series or the morphine series.

We have been interested in the fact that in many cases blood pressure rose following the administration of analgesic drugs. We feel that the changes in blood pressure have been related rather to the relief of pain than to specific cardiovascular effects of the drugs in the doses used in this series. We have examined these changes in blood pressure in relation to operative site, and it is apparent that there is an outstanding tendency for the pressure to rise following the use of analgesics in patients who have had abdominal operations, and a tendency for it to fall from higher than normal to normal levels in other patients. We would infer from this experience that the original pressure levels have been influenced by the stimulus of pain, and that there has been a tendency for the pressure to return towards the patient's normal level when the pain was relieved

Effect on Respiration

Depression of respiration is a pharmacological property which is common to all three of the drugs in this comparison. We were interested, therefore, to record changes in respiration in the patients of this series. As our criterion of a significant change, we adopted an increase or decrease of respiratory rate of four or more breaths per minute. We were interested to find that respiration increased almost as often as it decreased following the administration of these drugs. In nearly every

instance where respiration was decreased, the decrease represented a change from a faster than normal respiratory rate to a rate in a more normal range. One patient who received anileridine had a decrease from 18 per minute to 14 per minute. Two patients who received meperidine had a similar decrease while two patients who received morphine had respiratory rates decreased from 20 per minute to 16 per minute. There was no case of marked respiratory depression in this series.

Discussion

It is evident from examination of the records of this series of 1,117 patients who have received anileridine, meperidine, or morphine for the relief of postoperative pain that all three drugs will produce satisfactory analgesia in doses which do not produce any significant change in cardiovascular or respiratory function. Anileridine (Leritine®) has been found to be a most satisfactory analgesic drug with a therapeutic potency somewhat greater than twice that of meperidine. It has been found satisfactory in all age groups for the relief of pain in the postoperative period.

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Résumé

Au cours d'une étude avec des produits non identifiés, nous avons administré dans les suites opératoires, à la salle de réveil, à des malades non choisis, de l'anileridine, de la mépéridine et de la morphine. Chacun des médicaments était préparé en solution stable dans des bouteilles identiques à doses multiples et chacune de ces bouteilles ne portait qu'un chiffre correspondant à une légende. Les solutions étaient ainsi préparées que chaque ml contenait soit l'Anileridine (Leritine®) 25 mg., soit mépéridine (Demerol®) 50 mg., soit morphine 5 mg. Ces médicaments ont été administrés par des garde-malades d'expérience dans la salle de réveil qui n'avaient, comme seule information, que chaque millilitre de solution équivalait à 50 mg. de mépéridine. On a noté, trente minutes après l'administration du médicament, l'effet du médicament à la dose donnée sur la tension sanguine, le rythme cardiaque et respiratoire. Le lendemain, on a noté également le temps écoulé entre le moment de la dernière injection à la salle de réveil et le moment de la première sédation à la chambre du malade.

Cette étude a été faite sur 1,117 malades. Le premier tableau nous fait voir le partage des malades selon le médicament donné. En ce qui concerne l'âge et le site opératoire, le partage des trois médicaments a été semblable. Les chiffres au page 33 nous font connaître la dose moyenne de chaque médicament au cours de l'étude.

L'effet sédatif de ces médicaments a été apprécié par les garde-malades de la salle de réveil, trente minutes après leur injection intramusculaire. Nous voyons dans le tableau III le résultat de chacune des injections. Les effets jugés "bons" et "passables" sont plus nombreux pour l'anileridine et la mépéridine que pour la morphine. Cela est fortement en faveur de la valeur analgésique de l'anileridine Cela nous fait croire également que les équivalences thérapeutiques généralement acceptées, de 10 mg. de morphine et de 100 mg. de mépéridine, peuvent bien ne pas être aussi exactes que nous le croyons.

En ce qui concerne la durée d'action, il ne semble pas exister de différence importante entre les trois médicaments. Nous n'avons pas observé d'effets cardio-vasculaires particuliers chez aucun malade et, au cours de cette étude, aux doses employées, nous n'avons noté aucune dépression respiratoire. L'anileridine (Leritine®) s'est avérée une médication analgésique des plus satisfaisantes.

REFERENCES

1. Orahovats, P. D., Lehman, E. G., & Chapin, E. W. Pharmacology of ethyl-1-(4-amino phenethyl)-4-phenylisonopecatate, Anileridine: A New Potent Synthetic Analgesic. J. Pharmacol. & Exper. Therap. *119*:26–34 (Jan. 1957).
2. Chang, F. F. C., Sofar, P., & Lasagna, L. Comparison of the Analgesic Potency and Side Effects of Anileridine and Demerol in Man. Fed. Proc. 16:288 (March 1957).
3. Dripps, R. D., Millar, R. A., & Kneale, D. H. A Comparison of Anileridine, Morphine and Meperidine in Man. Surg., Gynec. & Obst. *105*:322–326 (Sept. 1957).
4. Keats, A. S., Telford, J., & Kurosu, Y. Studies of Analgesic Drugs: Anileridine Dihydrochloride. Anesthesiology *18*:690–697 (Sept.–Oct. 1957).
5. Wallenstein, S. L., & Houde, R. W. Clinical Evaluation of Relative Analgesic Potencies of Anileridine, Meperidine and Morphine. J. Pharmacol. & Exper. Therap. *122*:81A (Jan. 1958).
6. Weijlard, J.; Orahovats, P. D.; Sullivan, A. P., Jr.; Purdue, G.; Heath, F. K.; & Pfister, K., III. A New Synthetic Analgesic. J. Am. Chem. Soc. 78:2342–2343 (May 1956).