ANILERIDINE (LERITINE®):[1] A NEW SYNTHETIC ANALGESIC IN ANAESTHESIA

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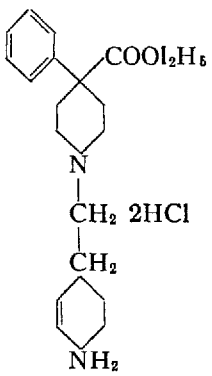
IN SURGERY and anaesthesia it is often necessary to have recourse to opiates for the alleviation of pain. Morphine always remains the drug of choice, but it possesses certain disadvantages, the more important ones being respiratory and circulatory depression, somnolence, nausea and vomiting, constipation, and addiction. These disadvantages explain why there is a continuing search for potent analgesic drugs, the ultimate goal being an ideal compound of a high order of activity and perfectly innocuous. To this end, for several months in the Department of Anaesthesia of Laval Hospital, we have used with great success a new synthetic analgesic named anileridine (ethyl 1-(4-aminophenyl)-4-phenylisonipecotate), available commercially under the trade name of Leritine®.

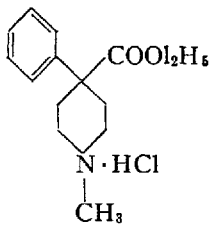
PHARMACOLOGY

Anileridine is a synthetic compound which is a member of the piperidine class of analgesic agents. It differs chemically from meperidine (Demerol®) in that the N-methyl group of meperidine is replaced by N-(p-aminophenethyl). Recent studies, indeed, have demonstrated that phenethyl increases analgesic activity when substituted for methyl on the nitrogen atom, which has been previously considered as the ideal radical.

The pharmacological actions of anileridine have been studied in man (4, 5, 6) and in animals (3), especially in comparison with morphine and meperidine (7, 8).



ANILERIDINE



MEPERIDINE

Pharmacological Action in Animals

In animals anileridine possesses analgesic activity approximating that of morphine but is ten to twelve times more active than meperidine. This pharmacological activity of anileridine is associated with fewer side reactions, and the

[1]Anileridine supplied as Leritine by Merck, Sharp & Dohme, Montreal, P.Q.

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drug is highly effective by the oral route, exhibiting prompt onset of action. The analgesic effect is maximal in 20 to 30 minutes and lasts from 4 to 6 hours. Anileridine like meperidine possesses anticholinergic and antihistaminic properties, and in addition it is effective against experimental cough in animals in contrast with morphine, which exerts little antitussive effect. It does not produce nausea and vomiting nor cause constipation. Its effects on respiration are easily reversible by the narcotic antagonists, such as Nalline® (N-allylnormorphine) or Lorfan® (3-hydroxy-N-allylmorphinane), tolerance to the drug seems to develop more slowly and to a lesser degree than is the case with morphine or meperidine.

We have also experimented with the new drug in dogs in our research facilities at the Centre de Recherches de l'Hôpital Laval. It was employed in premedication in association with atropine in a group of 30 dogs at the dosage of 0.4 mg. per pound of body weight. Its effects, in general, corresponded well with those described above though four of the dogs had nausea and vomiting. It was also administered by the Murphy drip in the same animals following induction of anaesthesia with thiopentone (25 mg/kg body weight), intubation, and maintenance with oxygen and nitrous oxide. Over a period of 3 hours 125 mg. of anileridine in 250 cc. of 5 per cent dextrose were administered. In the course of this study only a very slight hypotensive effect was noted.

Pharmacological Action in Man

In man, the analgesic property of anileridine bears a close resemblance to that of morphine but is two and a half times more active on a weight basis than meperidine. Anileridine exerts a sedative action mainly, and by itself has little hypnotic effect in comparison with equivalent doses of other narcotics. Respiratory rate was depressed and blood pressure was lowered but for a shorter period of time and to a lesser degree than previously noted in animals. It seems to possess in man spasmolytic and antihistaminic effects with diminution of nausea and vomiting, and absence of constipating effect.

Clinical Investigation

Anileridine was employed in 318 different surgical cases in the preoperative, peroperative, and postoperative periods In the course of these studies, we shall consider successively, according to the chronological order followed, the effects of the drug in the postoperative, peroperative, and preoperative periods. Our first clinical trials, in fact, were done during the postoperative period when we first employed anileridine alone, then associated with Lorfan Later, having acquired a better knowledge of the properties of this drug, we used it as a potentiator in the course of anaesthesia. Finally, in the face of the good results obtained, and hoping to verify its efficacy by the oral route, we incorporated it into the premedication regimen.

Postoperatively

Anileridine Alone. We first used anileridine in postoperative analgesia. Our observations deal mainly with the period of recovery when the anaesthesiologist

TABLE I

CLINICAL USE OF ANILERIDINE NUMBER OF CASES

Type of surgery	Preoperative (I M or orally)	Peroperative associated with Lorfan (I V)		Postoperative (I M or orally)	
		Before induction	After induction	Leritine only	Leritine Lorfan
Pulmonary surgery Lobectomy Segmentectomy Thoracoplasty Pneumonectomy	30	54	26	48	92
Cardiac surgery Mitral commissurotomy Ligature of the arterial canal Pericardectomy				6	4
General surgery Cholecystectomy Spinal fusion Cystoscopy Cystectomy Incision of abscesses Hip arthrodesis, etc	48	62	18	20	16
TOTAL	78	160		186	

still has the patient under his immediate control. According to our way of thinking, this period extends up to the moment when the patient is perfectly awake, conscious in time and place with regular respiration, with perfect oxygenation, and with blood loss compensated. The dosage used was, in general, less than half the usual recommended dose and ranged from 10 to 25 mg intramuscularly. The usual dose equivalent to 100 mg of meperidine is from 40 to 50 mg. The majority of the patients were chest surgery cases, but cardiac and general surgery cases were also included in this study Age varied from 12 to 61 years.

In all these patients anileridine appeared as a highly effective analgesic, keeping patients calm, fully conscious, and free of unwanted side-effects Pulse and blood pressure were not affected to any significant degree. The relief of pain produced by these doses on the average was complete and lasted from 40 to 60 minutes. The analgesic action proper seemed to last longer, and did not necessitate a new injection within 2 to 3 hours Nevertheless, even at the dose of 25 mg., we have found in many patients a certain degree of respiratory depression (up to 10 respirations per minute in one case), and this unwanted effect incited us to use anileridine in conjunction with Lorfan®.

Anileridine Administered Concurrently with Lorfan. Lorfan (3-hydroxy-N-allymorphinane) is related to Levo-Dromoran® (3-hydroxy-N-methylmorphinane) to the same extent that Nalline (N-allylnormorphine) is to morphine. Lorfan and Nalline act in the same way, but it seems that the antagonistic action of Lorfan is superior to that of Nalline (9). The mode of action of the narcotic and antagonist is still a matter of controversy, and it seems that there is a sort of competition between the two for the possession of the sensory and respiratory centres (10). Narcotics have a greater affinity towards the receptors of the

sensory cortex whereas the antagonists possess affinity mainly towards the respiratory centres. The latter, therefore, replaces analgesics inside the respiratory cells and lowers, toward the normal, the sensivity threshold to the stimulus of carbon dioxide. However, this substitution by the antagonist is also directly related to the concentration in the receptors of the sensory cortex, producing along with the diminution of respiratory depression a certain decrease in analgesia. We have, therefore, combined Lorfan with anileridine to ward off the respiratory depression caused by the anileridine used alone. Moreover, this association was made in the proportion of 50 to 1 (i.e., 50 parts Leritine to 1 part Lorfan), in which proportion the antagonist did not seem to oppose the analgesic properties of the narcotic. In all the cases where we employed this combination, no respiratory depression has ever been observed, and the analgesic properties remained as effective as with the use of the narcotic alone.

Peroperatively

Potentialized anaesthesia (11) in our immediate circle is a term in very current usage, considering the very nature of thoracic surgery. By this term is meant a technique whereby, owing to the use of certain pharmacological agents, the organism is placed in such a state that it is possible to maintain anaesthesia at the same time superficial but effective with the use of minimal doses of the usual anaesthetics (thiopentone, nitrous oxide) Thus, with the use of this technique, it is possible to keep the patient perfectly oxygenated and without major neurovegetative or vasomotor reactions, throughout the course of the surgical intervention. It permits us also in the immediate postoperative period to obtain with rapid if not immediate awakening, a conscious patient able to expectorate and not depressed from the respiratory point of view, and also able to react to minimal painful stimuli. The clinical investigation of the anileridine Lorfan combination in the postoperative period having produced very satisfactory results, we then used it during the peroperative period as potentiator. The intravenous route alone was utilized, and the doses of anileridine used ranged from 0.3 to 0.4 mg./kg. body weight. The age of the patients varied from 12 to 57 years.

Technique

Premedication as usual comprised the administration of a non-barbiturate hypnotic (Noludar®) and of a phenothiazine derivative (Phenergan®) on the evening before surgery. In the morning, 1½ hours before surgery, a phenothiazine derivative was administered followed a half-hour later by a narcotic and a vagolytic agent. The doses of these drugs were determined on the basis of age, body weight, and tolerance of the individual. Induction was effected by the use of a barbiturate (thiopentone) and of a relaxing drug of short action (succinylcholine) to permit intubation and aspiration bronchoscopy if necessary in the very beginning. Maintenance was effected by means of oxygen, nitrous oxide, and by the azeotropic mixture of Fluothane and ether (12) and a relaxant of short action administered by the Murphy drip. In certain cases, the anileridine-Lorfan combination was employed prior to induction. The injection was done

about 10 minutes prior to the use of the barbiturate, the dose of the latter being decreased by half. In other cases it was administered after induction during the period of maintenance while the degree of anaesthesia was still superficial. It should be noted that "anileridine" does not mix with thiopentone (flocculation) because of pH difference.

Results

The combination anileridine-Lorfan has enabled us to use superficial anaesthesia, in thoracic surgery mainly, without undesirable side-effects. During anaesthesia the restricted use of barbiturates, especially in patients with hepatic insufficiency, the reduced quantity of relaxants, and the absence of respiratory and circulatory depression have asserted themselves as very important advantages Moreover, while obtaining highly effective anaesthesia with the minimum of toxic effects, this potentialized anaesthesia adds considerably to safety, especially in being non-inflammable and allowing the use of electrocautery.

The obvious action of the anileridine-Lorfan combination by the intravenous route is observed simultaneously 2 to 5 minutes after the injection and is generally of 25 to 40 minutes duration This explains why we did not meet with respiratory depressions in the beginning such as were obtained with the Nisentil-Lorfan combination, because of the more rapid action of Nisentil. Awakening is calm and prompt The patient becomes rapidly conscious, answers to questions, and all his reflexes have returned to normal after a few minutes. At this state it seems that anileridine possesses somewhat prolonged analgesic activity extending even throughout the immediate postoperative period, that is to say during the first two hours. As a matter of fact, during this period, except in rare cases, no narcotics have been administered in this series to patients who have received the anileridine-Lorfan combination during anaesthesia. In the doses used no nausea or vomiting were encountered.

Preoperative Treatment

Finally, anileridine was used as premedication in the average dose of 25 mg by intramuscular injection. However, the oral route was also used and anileridine proved to be highly effective by this route Its effects as premedication are in general comparable to those of meperidine. One must, however, always associate with it the drying effects of atropine

Conclusion

Anileridine (Leritine®) a new synthetic analgesic offers certain advantages over other opiates. Possessing analgesic activity comparable to that of morphine, it soothes the patient but keeps him conscious without precipitating him into profound sleep. The respiratory and circulatory depression in the usual doses is minimal. Owing to its anticholinergic and antihistaminic activity, nausea and vomiting are only rarely seen. Moreover, this new analgesic agent is highly effective orally and seems to have brought about no constipating effects up to the present stage of investigation. These advantages certainly are very valuable

and anileridine will become a very important tool in the therapeutic armamentarium against pain. Nevertheless, one should not be led to believe that it will eventually replace morphine entirely.

Summary

Anileridine (Leritine®) is a new synthetic analgesic drug and is a member of the piperidine class of analgesic agents It differs from meperidine (Demerol) in that the N-methyl group of meperidine is replaced by an N-aminophenethyl group, which increase its analgesic activity.

In this study, we have discussed the efficacy of the new drug in the periods immediate to anaesthesia, which are, chronologically, the postoperative, the peroperative and the preoperative periods.

In the postoperative period, even at half the usual dosage, it proved itself to be a potent analgesic with few undesirable secondary effects Nausea and vomiting are rare. The patient is without pain and remains conscious without hypnosis. When associated with Lorfan, higher dosage may be used without respiratory depression.

In the peroperative period, a light and highly effective potentialized anaesthesia has been possible with the association anileridine-Lorfan with minimum respiratory and circulatory depression. A calm, painless, and prompt awakening is observed The patient is without pain, because the analgesic action of anileridine (Leritine) seems to extend over a period of 2 to 3 hours. In the preoperative period, anileridine by mouth was found very effective Its effects as a whole are similar to those of meperidine We must, however, associate with it the drying effect of atropine.

Anileridine has proven to be a very advantageous new narcotic and will certainly deserve high consideration.

Résumé

L'aniléridine (Léritine) est un nouvel analgésique synthétique de la famille de la pipéridine Un groupement N-(p-aminophénétyl) au lieu du groupement N-méthyl le différentie de la mépéridine (Démérol) et en augmente la puissance analgésique.

Dans ce travail, nous avons voulu exposer les résultats efficaces obtenus avec le Léritine dans les périodes immédiates de l'anesthésie, à savoir, selon l'ordre chronologique suivi, post-opératoirement, per-opératoirement et pré-opératoirement.

Dans la période post-opératoire, il s'est montré, même à un dosage réduit de moitié, un analgésique puissant sans effet indésirable important. Les nausées et vomissements apparaissent rarement et le patient est calme et conscient sans être plongé dans un sommeil profond. Son association avec le Lorfan empêche la dépression respiratoire que peuvent causer les doses plus élevées.

Durant la période per-opératoire, l'association Léritine-Lorfan a favorisé l'emploi d'une anesthésie potentialisée légère et hautement efficace avec le

minimum de dépression respiratoire et circulatoire Elle a aussi favorisé un réveil prompt et calme avec le minimm de douleur, car le "Léritine" semble posséder une puissance analgésique assez prolongée s'étendant sur une période de 2 à 3 heures.

En prémédication, l'aniléridine (Léritine) a donné d'heureux résultats par la voie orale, ses effets se comparant à ceux de la mépéridine (Démérol). Toutefois, il faut lui associer les effets asséchants de l'atropine.

Avec tous ces avantages, l'anilériding (Léritine) sera un atout précieux dans l'arsenal thérapeutique.

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