ANALGESIC AND ANAESTHETIC PROPERTIES OF LEVOMEPROMAZINE (NOZINAN®) (R.P. 7044)*

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THE STRUGGLE against pain has always been one of the major objectives of medicine. Even nowadays, the pain felt by the patient is an important factor in the urge to consult a physician. In some cases pain is merely the symptom of a disease and disappears when the latter is adequately treated. But in others the causative factor cannot be eliminated as, for instance, a progressive inoperable cancer, in which case symptomatic therapy of the pain is warranted.

There has been an astounding increase in the number of antalgic drugs during the last few years. Some of them have proved to have a high therapeutic effectiveness but to have also the serious drawbacks of high toxicity, absence of any effect on psychic activity, or a tendency to produce addiction, which often develops quite rapidly.

In the course of an anaesthesiological study of a new neuroleptic, levomepromazine, we had noted that this phenothiazine reduced pain. In addition to this antalgic property we also noted that it had anaesthetic properties since it reduced sensibility and raised the threshold of pain.

This phenothiazine proved of considerable interest in anaesthesiology and its applications can now be extended into the broad fields of sedation of pain and participation in general intravenous anaesthesia as a main anaesthetic agent. We had already noted this ataraesthetic property during our first studies on Nozinan®, but in view of the increasing interest in this property we wish to discuss it again in greater detail.

J. Du Cailar, A. Decourt, and J. Rioux[1] also demonstrated the ataralgesic properties of levomepromazine, which can even permit the elimination of barbiturates.[2,3]

Sigwald was the first to discover the analgesic properties of phenothiazine derivatives in the treatment of herpes zoster (zona).[11,12]

MATERIAL

Levomepromazine possesses pharmacological properties that are quite interesting in anaesthesiology and that are quite appreciably differentiated from those of the other phenothiazines. We shall refer to them again in discussing the mechanism of action of levomepromazine on pain and on the threshold of sensitivity.

In order to study the two properties, namely, ataralgesia and ataraesthesia, we selected cases where pain was acute or lancinating, where it was due to an

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incurable condition, and where narcotics were required. We also wished to determine the surgical role of levomepromazine as co-anaesthetic in prolonged surgery, and as an intravenous anaesthetic for deep hypothermia with circulatory arrest (method of Negre, DuCailar, Drew, Keen, and Benazon) during experimental extracorporeal surgery.

We used levomepromazine in the following cases:

1. As local anaesthetic, at a dilution of 1 mg./ml. in normal saline, in 12 patients.

2. As local anaesthetic during sympathetic ganglion infiltration, at the same dilution as above in normal saline, in 14 cases (2 stellate ganglion infiltrations and 12 lumbar sympathetic infiltrations).

3. As analgesic in rheumatology in 46 rheumatic and arthritic patients in the Rheumatology Department of Ste-Foy Hospital (during the past 8 months these patients received levomepromazine, or are still receiving it).

4. As sedative in neuritis, neuralgia, causalgia, and pruritus in 16 cases (6 cases of herpes zoster of which one was ophthalmic, 4 cases of causalgia, 1 case of facial neuralgia, 4 cases of pruritus, and 1 case of lichen planus).

5. As antalgic in cancer pains in 39 cases of generalized cancer (of which 18 were at the anticancer clinic of the St. Francis of Assisi Hospital, 2 at Ste-Foy Hospital, and 19 non-hospitalized patients included on the recommendation of the treating physicians).

6. In thoracic, nerve, and plastic surgery by intravenous infusion, in 312 patients (see Table I).

7. As postoperative antalgic in over 1800 cases.

8. As anaesthetic for deep hypothermia with circulatory arrest in 2 cases. These operations were done in collaboration with Doctors Jobin, Caron, and Beaulieu of the Department of Anatomy, Laval University.

The results are therefore concerned with two very specific properties of levomepromazine. The first is its action against pain (antalgic or ataralgesic according to the term used by DuCailar). The second is the reduction of sensitivity (anaesthetic or ataraesthetic). In order to meet the problem of pain and sensitivity we are looking for an ideal agent that will calm without depressing respiration or circulation, that will not be habit-forming, that will not injure any organic function, that can, if need be, reduce or correct thermogenesis, that reduces the dose of general anaesthetics required during prolonged surgery, that will reduce electrolyte disturbances and loss of blood during certain operations, and finally that will act as central sedative and as sedative of nervous tension and anxiety. Because of its pharmacological properties, levomeprosmazine can meet these requirements and it is for that reason that we wished to study its antalgic and anaesthetic effects.

Results

Clinically, levomepromazine gave us the following results:

1. Intradermal infiltration of undiluted Nozinan is painful and produces erythema. At a dilution of 1 mg./ml. in isotonic normal saline or in redistilled water, it is not painful and produces an analgesia that permits incision of the

TABLE I

DETAILS OF SURGERY IN WHICH LEVOMEPROMAZINE WAS USED AS INTRAVENOUS ANAESTHETIC

Nature of surgery	Average duration	Average quantity, c.c.	Age range, years	Anaesthetic value of sol. N_1 alone, %	Supplementary agents	Number of operations
Bone grafts and laminectomies	2h. 40m.	275	18–56	42	Spinal Peridural Fluother	94
Mastoidectomy	2h. 15m.	425	8–57	78	Fluothane 0.5%	39
Rhinoplasty	2h. 20m.	360	12–55	100		69
Strabismus and dacryocystectomy	1h.	110	18–33	70	Fluother 0.5% Fluothane	5
Repair surgery: skin graft	1h 45m.	175	12–57	80	Fluothane 0.5% Fluother	28
Cataracts	50m.	110	67–77	100		8
Thyroidectomies	1h. 35m.	220	30–46	50	Fluother 0.6% Ether, 1 case	6
Thoracic surgery	3h. 05m.	180	26–57	55	Fluothane 0.6% Peridural	18
Biopsy—larynx	45m.	100	18–37	100		4
Other surgery:						
Hernias	45m.	150	28–45	70	Fluother 0.5–0.7%	11
Meniscectomies	55m.	125	18–47	76	Fluother 0.5–0.8%	6
Abdominal	1h. 10m.	160	26–51	26	Fluother and curarization	24
Total						312

skin. A dilution of 1 mg. of Nozinan per ml. in 1 per cent procaine solution is painless, does not cause any cutaneous reaction, and produces satisfactory local anaesthesia, which lasts more than two to three times longer than that produced by procaine alone. These local anaesthetic properties are superior to those of promethazine (Phenergan®) and the tolerance is good.

2. Infiltration of the lumbar sympathetic ganglion with an indiluted solution (0.3 per cent, with a pH of 4.3) produces vasodilatation of the lower extremities. Infiltration of the stellate ganglion produces the Horner-Bernard syndrome. Diluted to 1 mg./ml. in normal saline, the response is also positive but its onset is slower.

3. In rheumatology, ambulant patients rarely tolerate more than 15 mg. of levomepromazine daily in three divided doses, whereas hospitalized patients can take up to 75 mg. daily. Administration is by the oral route. The evaluation furnished by Doctor Rousseau is as follows: Nozinan reduces pain but does not remove it entirely. Specific medication is continued but is reduced in 18 per cent of the cases. Vasoplegic and central effects prevent the use of high dosages in ambulant patients; but there is noted in these patients, even with low dosages, a decrease in nervous tension and anxiety. It is advantageous to combine levomepromazine with the specific medication. Treatment can be prolonged *ad libitum* without causing addiction or injury. This has been confirmed by haemotalogical and liver-function tests (Table II).

4. The antalgic effect of levomepromazine is dramatic in the treatment of the herpes zoster type of infectious neuritis, of some neuralgias of undetermined origin, and of pruritus. Relief of cancerous algias is typical (Table II).

TABLE II

DETAILS OF CASES WHERE LEVOMEPROMAZINE WAS USED AS ANTALGIC AND ANALGESIC

Nature of pain or disease	No. of cases	Route of administration	Average quantity	Relief alone	Potentiation of narcotics and other antalgics
Generalized cancer	39	Oral 92% Parenteral 8%	25 m.g. t.i.d.	86%	80%
Neuritis and neuralgia herpes zoster	16	Oral 90% Parenteral 10%	75 mg. I.D. in 3 doses	92%	80%
Rheumatism and arthritis	46	Oral 100%	15 mg. I.D. in 3 doses	40%	20%
Postoperative analgesic	1800	Parenteral I.M. 100%	75 mg. I.D. in 3 doses	60–70%	60%
Local anaesthesia and infiltration agent	26	Parenteral	10–25 mg.	100%	Potentiates procaine

Administration of 25 mg. intramuscularly or orally one to three times daily as required permits the almost complete elimination of the use of narcotics. Levomepromazine permits a 90 per cent reduction in the quantity of narcotics used in patients who were already receiving them, and total suppression of their use in 10 per cent of these patients.

In cases of cancer it must be administered continuously and permanently. The initial dosage is 10 mg. with increase up to 25 mg. two to three times daily according to individual tolerance. It is advisable that such patients remain in bed for the first few days in order to establish tolerance satisfactorily and prevent lipothymia and postural hypotension. After a few days these side-effects disappear and levomepromazine is well tolerated. Some of these patients have shown a tolerance permitting the administration of 150 mg. daily without any trouble (Table II).

Levomepromazine seems to be specific in the treatment of herpes zoster. In six patients we obtained consistently good results with relief of sharp pains, and it was possible to continue therapy until the disappearance of the skin lesions, which coincides with the disappearance of ganglionic oedema. The average dosage is 25 mg. every 8 hours. The patient should be hospitalized, because, in addition to the antalgic effects, he also benefits from a central hypnotic effect featured by calm sleep without respiratory depression and with presence of reflexes and a state of semiconsciousness. The patient answers questions correctly and then very soon falls into a state of complete indifference.

We cite the case of a female patient who had become addicted to meperidine after having received two injections daily for one month. Not only was this patient immediately broken of her addiction by levomepromazine, but the pain for which meperidine had been prescribed also disappeared.

(5) In surgery, levomepromazine is combined with meperidine in 500 ml. of 5 per\cent glucose in saline (solution N_1) and intravenous infusion permits tolerance of endotracheal intubation and a degree of general anaesthesia adequate for plastic, nerve, or orthopaedic surgery and for eye, nose, and ear surgery. A compilation of these cases is presented in Table I. The patient is preferably given levomepromazine–meperidine premedication; intravenous drip is infused during surgery at a rate ranging from 20 to 60 drops per minute. Anaesthesia is calm, hypothermic, and mildly hypotensive and bradycardic. Ventilation is facilitated by the weakening of the Hering-Breuer reflex. The electrocardiographic tracing is normal and the electroencephalographic tracing shows a surgical stage not exceeding the first degree. The patient is on semi-open circuit and no other anaesthetic, except nitrous oxide and oxygen, is given in over 91 per cent of the following cases: rhinoplasty, skin graft, laminectomy, bone graft, plastic surgery, mastoidectomy. A concentration of 0.5 per cent Fluothane or Fluother is adequate in the other 9 per cent of cases.

In the two cases of rapid (15 minutes) deep hypothermia at 16° C. that we performed on dogs by means of a pump, anaesthesia with solution N_1 was adequate and it was discontinued when the temperature had reached 28° C. This technique is worthy of consideration in this type of hypothermia because, apart from its physiobiological advantages, it has the merit of maintaining a very light general anaesthesia, even lighter than with other anaesthetic agents.

Recovery is rapid after levomepromazine–meperidine anaesthesia and is characterized by full, regular respiration, excellent capillary circulation, and complete freedom from nausea, vomiting, and pain. Constant hyperkalicitia shows that neuromuscular repolarization is more rapid, resulting in reduced postoperative fatigue.

Intravenous infusion of solution N_1 was also used during regional, peridural, and subarachnoid anaesthesia to maintain light sleep, either when there was a psychic indication, or to permit the introduction and retention of an endotracheal tube, or to facilitate control of respiration during endothoracic surgery.

Interpretation and Discussion

The physiology of pain is a subject that is as important and as broad as it is poorly known. We do not claim to have found an integral solution to the problem, but the solution that we suggest to the treatment of medicosurgical pain or for the prevention of surgical pain by reducing sensitiveness at least constitutes an approach.

The theories advanced may appear daring, but they are contrary neither to physiology nor to reason. While they may be vulnerable, this very vulnerability will have furnished an approach to an urgent problem that medicine must tackle, and we do not claim to do anything else than stimulate efforts that will aid in the solution of the problem of the most acceptable sedation of pain. We are advancing some hypotheses regarding the physiological and pharmacological processes in which levomepromazine seems to play an integral part and thus enters into the treatment of pain.

Being a subjective symptom, pain does not lend itself readily to a precise description. Each patient feels it in his own way, according to his temperament

and imagination, and expresses his impressions according to the richness of his vocabulary. There are, however, two features of pain that have a certain objectiveness, namely, duration and localization. According to its localization, pain may be of two types: superficial, i.e., at the surface, and deep, i.e., located in the muscles, bones, or viscera. Neuritides and neuralgias are pains located in the region of a specific nerve. It is impossible to determine accurately the nature of pain; the important point from the objective and scientific standpoint is that the psychic reaction to pain is related to anatomical and physiological disturbances that are accessible to experimental study. At what level does the psychological fact of pain, or in other words its awareness, originate from a physiological disturbance? For a combination of reasons, it can be supposed that it is at the hypothalamic level; experimentally, after section below the thalamic level, it is found that a very painful stimulus applied at any point of the body no longer produces the phenomenon of pain. It is therefore plausible to assume that the thalamus is involved in the genesis of pain. The thalamus appears to be the seat of affectivity and the cortex to be the seat of mental discrimination. The cortex is aware that something abnormal has occurred whenever injury is produced and *pain is mediated by the thalamus*. The mechanisms of physical pain therefore operate at different levels, namely, at peripherial levels with transmission, after the action of the stimuli, by conduction paths leading to the thalamus, and at psychophysiological central levels consisting of the cortex and thalamus. Pain consists in a sensory excitation of sufficient intensity to reach or exceed the threshold.

There is pain when cellular damage occurs. It is assumed that this lesion, whether it be systemic, in the skin, joints, viscera, or nerves, liberates a substance called "*substance H*" by Lewis, and which may be *histamine*. This substance gives rise in the nerve endings to a current of action by the standard process of progressive depolarization.

The pains of arthritis, neuralgias, and cancerous transformations, as well as surgical cutaneous pain, seem to proceed according to the same physiological process. Pain is conditioned by the stimulation of nerve endings, which are to be found in all the tissues, organs, vessels, muscles, and joints. In their normal state these endings are at rest, and they come into action as soon as any morbid cause sensitizes them. It is impossible to make a complete analysis of the pathology of each pain and of their medical and surgical variations. But it would seem that all painful states bring into play *similar systems* leading to the *same centres* by stimulating conduction and producing pain. It is possible to study by what methods and with what drugs impulses from the periphery can be interrupted, or how synaptic tranmissions to the cortex or, even better, to the hypothalamus can be blocked. It is evident that the conduction paths extend from the excitation mechanisms, in whatever tissue they may be located, to the higher thalamocortical centres.

Apart from its sensation, pain causes various reactions: cardiac acceleration, a rise or lowering of blood pressure, peripheral vasoconstriction, sweating, etc., by acting on the neuro-endocrine system, particularly the catabolic and defensive adrenergic sympathetic system; for even if it may be doubted that the sympathetic really plays a part in the conduction of sensation, there can be no doubt

as to the existence of a close interrelation between the autonomic system and the sensory system and that any disturbance in either one definitely influences *sensitiveness*.

Painful impulses, if they are not blocked at some stage or other of conduction, will reach the central elements of pain, namely, the thalamus and cortex, *where the sensation of pain arises*. These central elements are of great importance in the mechanism of pain and account for all the various and erratic characteristics of pain according to races, individuals, and their physical, emotional, or moral condition. Variations in painful sensations can be explained by the state of receptivity of the centres; any decrease will help to lower the intensity of pain, whereas stimulation will increase the intensity. In brief, in the genesis of pain there are peripheral elements and central elements. The combined thalamus and cortex creates pain, irrespective of the location of the lesion from which it originates. The dolorogenic impulse may be an enzyme or some chemical mediator, such as *histamine*, serotonin, or other, which produces a corticothalamic imbalance. Most often there is a peripheral irritative pain spike, and even in algias designated as psychic there is a reaction to an emotional stimulus which conditions the strong reaction of the centres. The point of attack in the mental patient obsessed with pain, and who complains of severe resistant pains without any detectable cause, is the *centre*. That is the point at which the attack should be directed, either surgically by severing the nerve bundle connecting the anterior thalamic region with the frontal cortex, or chemically by blocking the dolorogenic impulses at the hypothalamus. And it is found that, by the use of levomepromazine during leukotomy, for instance, on being questioned the patients state they feel the same pains, but immediately afterwards they lapse into indifference and the anxiety component of the pain seems to have disappeared. In ordinary practice there is a tendency to use general analgesics, such as morphine or other opium alkaloids, which act by depressing the pain centre but which offer the disadvantages of also depressing vital functions and of leading to addiction, not to mention the frequently serious depression of respiratory exchange.

For what reasons do we use levomepromazine as an antalgic and anaesthetic? Levomepromazine does not produce addiction. It has local anaesthetic properties, it produces deep local anaesthesia of the sciatic nerve, it has an anaesthetic effect on peripherial nerves, on the nerve endings of the afferent sensory pathways of the reflex arc. It has a psychomotor depressing action on the hypothalamus, which has been identified as a leukotomizing action at the centre of pain. Moreover, to satisfy the neurovegetative theory of the genesis of pain advanced by some authors, levomepromazine has a powerful sympathicolytic action. When administered previously, it prevents epinephrine-induced hypertension, as we have consistently observed during blocks when we used local anaesthetics with epinephrine concentrations as high as 1:60,000. It reverses epinephrine-induced hypertension in a greater proportion of cases than does chlorpromazine. And if the theory that histamine is the chemical mediator of the dolorogenic impulse is accepted, it is easy to guess the role of levomepromazine with its very high antihistamine potency. As an example, by the Bovet-Staub test, a subcutaneous dose of 20 mg./kg. of levomepromazine can protect the mouse against 2,000 lethal doses of histamine. Levomepromazine has a marked potentiating action:

it reinforces by about 60 per cent the effects of barbiturates, halothane, morphine, meperidine, pyrrolamidol, and other narcotics. Furthermore, levomepromazine has a much greater protective antishock action than all other analgesics and neuroleptics.

Conclusion

The pharmacological study of levomepromazine reveals analgesic and anaesthetic properties in accord with the physiopathogenesis of pain. Clinical studies showed that levomepromazine has a local anaesthetic action, a central analgesic action on the thalamic pain centre, an antihistamine action in accord with Lewis' theory on histaminogenic impulses, and an effective neurovegetative action.

All these antalgic properties are evident in the treatment of cancerous pains and neuritic pains and are beneficial in the treatment of rheumatic pains. Its anaesthetic properties enable prolonged surgery to be performed with a minimum of other anaesthetic agents. In the relief of postoperative pain, with levomepromazine the amount of narcotics used can be reduced by more than 80 per cent.

Sympathetic ganglion infiltration with 0.3 per cent levomepromazine solution at pH 4.3 produces an immediate vasoplegic response. When diluted in normal saline, it produces a positive but slower response.

We believe that the analgesic and anaesthetic aspects of levomepromazine should be emphasized and that the drug has a place in the relief of pain.

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REFERENCES

1. Cailar, J. Du; Decourt, A.; & Rioux, J. Intérêt de la lévomépromazine (7044 R.P.) en anesthesiologie. Presse Médicale *44* (Sept. 1959).
2. Cailar, J. Du; Vermette, M.; Rioux, J.; & Herail, J. Une technique standard d'anesthésie veineuse sans barbiturique: intérêt de l'association ataralgésiante: pyrrolamidol et lévomépromazine. Anesth. & Analg. *4*: 797–808 (Sept.–Oct. 1959).
3. Decourt, A. La lévomépromazine en anesthésiologie. Anesth. & Analg. *4*: 808–820 (Sept.–Oct. 1959).
4. Laborit, G. Etude physico-biologique de la lévomépromazine chez l'homme. Anesth. & Analg. *4*: 820–833 (Sept.–Oct. 1959).
5. Hazard, R. Actualités pharmacologiques, Troisième série, p. 183. Paris: Masson & Cie.
6. Guillaume, J.; DeSeze, S.; & Mazars, G. Chirurgie cérébrospinale de la douleur.
7. Paradis, B. La lévomépromazine en anesthésie. Anesth. & Analg. *16*: 185–193 (1959).
8. Paradis, B.; Plante, G.; Aubut, J.; & Tardif, A. La lévomépromazine (Nozinan ou 7044 R.P.) Etude clinique, pharmacologique et biochimique portant sur 1000 observations. Laval Méd. *28*: No. 4 (Nov. 1959).
9. Paradis, B.; Lamontagne, A.; Gagne-Desrosiers, R.; & Lamarche, Y. Association Nozinan-Fluothane en anesthésie. Laval Méd. *28*: No. 3 (Oct. 1959).
10. Rhône-Spécia-Poulenc (pub.) Applications du Nozinan en anesthésiologie.
11. Sigwald *et al.* Le traitement du zona et des algies zostériennes—Etude des résultats obtenus avec la lévomépromazine. Thérapie *14*: 818–824 (1959).
12. Sigwald *et al.* L'action anti-algique des phénothiazines. Thérapie *14*: 978–987 (1959).