THE COMBINED USE OF NISENTIL® HYDROCHLORIDE AND LEVALLORPHAN TARTRATE FOR THE SUPPLEMENTATION OF NITROUS OXIDE–OXYGEN ANAESTHESIA

A Preliminary Report

Francis F. Foldes, M.D.,* Mark Swerdlow, M.D., F.F.A.R.C.S.,**
E. Lipschitz, M.D.,* Gertrude Weber, M.D.* and Leo A. Pirk, PH.D.***

The clinical advantages of supplementing N_2O–O_2 anaesthesia with Pentothal® Sodium† and an analgesic of the morphine class, rather than with Pentothal alone, have been adequately demonstrated (1, 2, 3, 4, 5, 6). It has been shown recently by Siker *et al.* (7) that Nisentil Hydrochloride† (1, 3-dimethyl-4-phenyl-4-propionoxy-piperidine hydrochloride), because of its short duration of action and excellent controllability, is the analgesic of choice for this purpose. These workers reported that the mg/min dose of Pentothal was greatly decreased if Nisentil rather than Demerol,® was used for supplementation. However, their attempts to reduce further the Pentothal requirements, by increasing the Nisentil dose, failed because of the marked respiratory depression encountered. Since studies by Swerdlow *et al.* (8) in unanaesthetized patients showed that the narcotic antagonist, levo-3-hydroxy-N-allylmorphinan tartrate (levallorphan tartrate),† offers considerable protection against Nisentil-induced respiratory depression if these agents are used in a 1:50 ratio, the idea occurred to one of us (L.A.P.) that the combined use of Nisentil and levallorphan for supplementation of N_2O–O_2–Pentothal anaesthesia may make it possible to use larger quantities of Nisentil, without producing respiratory depression, and thus reduce further, or eliminate completely, the Pentothal requirements. This seemed desirable in view of the relatively slow rate of degradation of Pentothal in the body (9, 10). Consequently, clinical trials which would utilize Nisentil-levallorphan combinations were initiated.

So far 452 patients, who underwent a variety of surgical procedures, were studied. Of these, 182, who did not require endotracheal intubation, did not receive a muscle relaxant; 78 were given Anectine® (succinylcholine) Chloride for intubation only; and in 192 relaxation was maintained with Anectine throughout anaesthesia. In these three groups 90, 37, and 75 patients, respectively, received Nisentil and levallorphan from a premixed solution and the remaining 250 patients were given levallorphan first followed by Nisentil. By thus combining these two agents, satisfactory operating conditions could be obtained without the use of Pentothal in 58, or 32 per cent, of the 182 patients who did not

*Department of Anesthesia, Mercy Hospital, and the Section of Anesthesiology, Department of Surgery, University of Pittsburgh School of Medicine, Pittsburgh, Pa., U.S.A.

**Department of Anaesthesia, Salford Royal Hospital, Manchester, England.

***Department of Clinical Research, Hoffmann-La Roche Inc., Nutley, N.J., U.S.A.

†For brevity Pentothal Sodium will be referred to hereafter as Pentothal; Nisentil Hydrochloride as Nisentil, and levallorphan tartrate as levallorphan.

require intubation. In the remaining 124 patients of this group and in the 270 patients who were intubated, small amounts of Pentothal were used.

The technique which utilizes the administration of levallorphan before Nisentil will be described.

Patients were premedicated with 50-100 mg. of pentobarbital sodium, given 90-120 minutes before operation, and with a combination of 5-10 mg. of morphine sulfate, or 50 to 100 mg. of Demerol, and 0.3-0.4 mg. of scopolamine hydrobromide, administered subcutaneously 45-60 minutes prior to induction of anaesthesia.

Upon arrival in the operating room, the patient's mouth and pharynx were sprayed with a 1 per cent tetracaine hydrochloride solution and an intravenous infusion was started. All subsequent injections were made into the rubber sleeve of the intravenous tubing.

Levallorphan 0.02 mg/kg was administered, followed, after 3-6 minutes, by an initial Nisentil dose of 1 mg/kg (1:50 ratio). In old and debilitated patients half these amounts were given. A 4 litre to 1 litre N_2O–O_2 mixture was then administered by face mask in a semi-closed circuit for 3-5 minutes and an oropharyngeal airway inserted.

If the patient resisted the insertion of the airway, 2 to 8 cc. of a 2½ per cent Pentothal solution were administered in 1 to 2 cc. increments until the airway was readily accepted. A few cc. of Pentothal solution were used before insertion of the airway in all patients who were to be intubated. Endotracheal intubation was facilitated by the intravenous administration of a single dose of Anectine (11) in patients who did not require prolonged muscular relaxation and by continuous intravenous infusion of this agent in instances in which muscular relaxation was to be maintained throughout surgery. Patients were manually hyperventilated with 100 per cent O_2 before intubation. Following the insertion of the oropharyngeal airway, or the endotracheal tube, the bag of the anaesthesia machine was washed out three times with the 4 litre to 1 litre N_2O–O_2 mixture. Thereafter, the flow rates of N_2O and O_2 were each reduced to 500 cc. per minute, according to a previously described technique (12).

If the depth of anaesthesia was not sufficient at the beginning of surgery, additional doses of Nisentil were administered in 10-20 mg. increments, 2-3 minutes apart, until the desired depth of anaesthesia was obtained. When this could not be accomplished without depressing the respiratory rate below 12, additional Pentothal was given in 1-2 cc. increments, 2-3 minutes apart. On occasion, when the duration of the surgical procedure exceeded 2-3 hours, an additional dose of 0.4-0.6 mg. levallorphan was injected. The administration of additional 5-10 mg. doses of Nisentil was governed by signs of lightening of anaesthesia (voluntary movements, breath holding, irregular breathing, tachypnea).

To ensure adequate alveolar ventilation, respirations were assisted by manual compression of the breathing bag throughout anaesthesia.

Table I summarizes the average doses (mg/min) of Pentothal and Nisentil used in the three groups of patients who received levallorphan prior to Nisentil and in comparable groups of patients who were not given levallorphan.

TABLE I

COMPARISON OF THE AVERAGE PENTOTHAL SODIUM AND NISENTIL HYDROCHLORIDE REQUIREMENTS OF PATIENTS ANAESTHETIZED WITH N_2O–O_2, WITH OR WITHOUT THE PREVIOUS ADMINISTRATION OF LEVALLORPHAN TARTRATE

Muscle relaxant	Levallorphan tartrate	Pentothal sodium (mg/min)	Nisentil HCl (mg/min)	Patients reacting (%)
Not used	Used	4 11	2 74	98
	Not used	9.8	0 49	77
For intubation only	Used	3 83	1 92	94
	Not used	8.4	0 48	87
For maintenance	Used	3 37	2 17	95
	Not used	6.4	0.41	84

As is seen, the administration of levallorphan permitted an approximately 50 per cent reduction of the Pentothal requirements as compared with the requirements when no levallorphan was employed. Conversely, when levallorphan was given, the Nisentil doses could be markedly increased. In spite of the four- to fivefold increase of the Nisentil doses, no serious respiratory depression was encountered when Nisentil was preceded by levallorphan. The initial and terminal respiratory rates of the patients who received levallorphan were of the same order of magnitude. Of the 182 patients who did not receive a muscle relaxant only a very few developed apnea which lasted 2-10 minutes. In the majority of patients in this group, the unassisted tidal volume was between 300 and 400 ml. No postoperative respiratory depression was observed in any of the patients.

The average initial and terminal pulse rates and the average initial and terminal blood pressure readings of the patients included in this study were practically identical. No marked increase of pulse rate and no significant fall of blood pressure were observed that could not be explained by the operative procedure. However, in spite of adequate CO_2 removal, a marked increase of the systolic blood pressure occurred in approximately 5 per cent of the cases during anaesthesia. This was usually observed in patients with hypertension, hyperthyroidism, or duodenal ulcers. In these instances, the administration of one or two 5 mg. doses of Hexameton® (hexamethonium) Chloride returned the blood pressure to preoperative levels.

Irrespective of the duration of anaesthesia, over 90 per cent of the patients reacted to auditory or tactile stimulation within 5 minutes after discontinuation of N_2O–O_2 (see Table I). On recovery, patients seldom complained of pain and over 50 per cent did not require analgesics for 8 hours after surgery.

More extensive studies with Nisentil-levallorphan combinations are under way. We are prompted to publish this preliminary report in order to invite the attention of other workers to this promising approach to balanced anaesthesia.

SUMMARY

A technique is described which utilizes the combined administration of Nisentil Hydrochloride and levallorphan tartrate, in a 50:1 ratio, for supplementation of N_2O–O_2–Pentothal Sodium anaesthesia. The possibility of employing large doses of Nisentil, without producing respiratory depression, was demonstrated in 452 patients. In 32 per cent of the patients, who did not require endotracheal intubation, the use of Pentothal could be eliminated. In the remaining 68 per cent, who did not require intubation, and in the patients who required muscular relaxation, the Pentothal requirements were reduced by approximately 50 per cent, as compared with patients who received Nisentil without levallorphan. Over 90 per cent of all patients reacted to stimulation within 5 minutes after discontinuation of N_2O–O_2 and 50 per cent did not require analgesics during the first eight postoperative hours.

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