COMBINED USE OF NARCOTIC AND NARCOTIC ANTAGONIST IN THE SUPPLEMENTATION OF ANAESTHESIA

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NARCOTIC ANALGETICS and thiopental (Pentothal®) sodium¹ are commonly employed intravenously to supplement nitrous oxide-oxygen anaesthesia. It is often difficult to achieve the optimal balancing of these agents which is a prerequisite to satisfactory anaesthesia. When used in large amounts, thiopental is slowly metabolized and may therefore depress the patient for a period extending well beyond the surgical procedure. Some narcotic analgetics are similarly objectionable because of their long duration of action. Also, these morphine-like compounds may produce severe respiratory depression. It would therefore appear desirable to find some technique which would limit the depressive effects of the anaesthetic and supplementing drugs used to the operative period, lessen the hazard of apnoea, provide good anaesthesia, and yet allow the patient to be easily aroused and free from pain in the immediate postoperative period.

Alphaprodine (Nisentil®) hydrochloride² is a potent, short-acting narcotic analgetic which, according to Siker *et al.* (1), has the advantage of excellent controllability when used as supplementary agent to nitrous oxide-oxygen-thiopental anaesthesia. By replacing meperidine (Demerol®) hydrochloride with alphaprodine, these workers were able to reduce significantly the thiopental requirements and to increase considerably the percentage of patients who reacted to stimuli within 5 minutes after termination of surgery. Their attempt to decrease further the thiopental doses by using larger amounts of alphaprodine failed because of the severe respiratory depression encountered. Swerdlow *et al.* (2, 3) showed in unanaesthetized subjects that alphaprodine-induced respiratory depression can be prevented or antagonized to a considerable degree by the narcotic antagonist, levallorphan tartrate³ (levo-3-hydroxy-N-allylmorphinan tartrate).

Against this background, the idea occurred to Pirk (4, 5) that the combined use of alphaprodine and levallorphan for supplementation of nitrous oxide-oxygen-thiopental anaesthesia may make it possible to administer larger doses of alphaprodine, without producing respiratory depression and thus to reduce further the thiopental requirements. It was anticipated that in a suitable ratio the narcotic antagonist would not interfere with alphaprodine analgesia and that a reduction of the barbiturate doses would increase the percentage of the patients who react to stimulation postoperatively. Foldes *et al.* (4, 5) have recently reported that, with a technique based on these considerations, alphaprodine doses three to six times greater than those used in their control series

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¹To be referred to henceforth as thiopental.

²To be referred to henceforth as alphaprodine.

³To be referred to henceforth as levallorphan (Lorfan Tartrate T^M)

were tolerated without producing significant respiratory depression and that the thiopental requirements were reduced by 50 to 100 per cent. As a consequence, better than 80 per cent of the patients obeyed commands within 5 minutes of termination of surgery.

This report describes our experiences with a combination of alphaprodine and levallorphan⁴ as supplement to inhalation anaesthesia, with a technique which differed somewhat from that employed by Foldes and collaborators (4, 5). The purpose of the study was to determine if these agents would make it possible to obtain safe, adequate anaesthesia, and yet have the patient awake and in a relatively normal state at the conclusion of anaesthesia.

CASE MATERIAL AND METHOD OF ANAESTHESIA

The study comprised 252 patients (174 females and 78 males) whose ages ranged from 15 to 79 years (average, 45.9 years). Patients were classified according to risk, using the ASA method, 1 being the best and 7 the poorest risk. Eight cases were in category 5 to 7. Table I classifies the patients according to site of operation. One hundred and sixty-five of the procedures were major operations.

TABLE I

CLASSIFICATION ACCORDING TO SITE OF OPERATION PERFORMED IN 252 PATIENTS RECEIVING NISENTIL® AND LEVALLORPHAN AS SUPPLEMENT TO INHALATION ANAESTHESIA

<i>Site of operation</i>	<i>Number of cases</i>
Head or neck	38
Thorax	33
Upper abdomen	14
Lower abdomen	48
Abdominal wall	1
Perineum	71
Spine	6
Limbs	41
TOTAL	252

Premedication, given 60–90 minutes before surgery, consisted of 3–15 mg. of morphine sulfate and 0.15–0.4 mg. of scopolamine hydrobromide or atropine sulfate. These drugs were administered hypodermically except with a few patients, scheduled for emergency operations, who received the premedication intravenously.

Nitrous oxide–oxygen was used for 243 patients. Of these, 144 received no other inhalation anaesthetic. Of the 99 patients in whom nitrous oxide–oxygen was supplemented by other agents, 82 were given cyclopropane and 17 ethyl ether. Nine operations were performed under local blocks.

Ten to fifteen minutes before initiation of anaesthesia, alphaprodine and

⁴Supplied for this study as "Rol-7700" through the courtesy of Dr. M. J. Schiffman, Hoffmann-La Roche Inc.

levallorphan were given intravenously as a premixed solution which contained 12 mg. of the former and 0.24 mg. of the latter agent per cc. (50:1 ratio). The size of the initial dose of this mixture—usually 2.5 to 5 cc. (corresponding to 30 to 60 mg. of alphaprodine)—depended on the age and physical status of the patient. Subsequent doses of 12 mg. of alphaprodine and 0.24 mg. of levallorphan and/or a 2½ per cent solution of thiopental were administered intravenously as required during the operative procedure.

Succinylcholine was used in 53 patients for relaxation or intubation.

The duration of surgery ranged from less than 1 hour to 9¼ hours. It was less than 1 hour in 58, 1 to 2 hours in 83; 2 to 3 hours in 63; 3 to 4 hours in 20; 4 to 5 hours in 15; 5 to 6 hours in 8, and 6 to 9¼ hours in 5 cases.

RESULTS

The total amount of alphaprodine used per patient ranged from 6 to 240 mg. with an average of 73.3 mg. The total amount of thiopental, which was used in but 207 of the 252 cases, ranged from 50 mg. to 775 mg. with an average of 194 mg.

The 53 patients who received succinylcholine required continuous assisted respiration. In 154 patients of the 199 who did not receive succinylcholine, respiration was adequate during the entire surgery. The remainder of 45 (22.6 per cent) experienced different degrees of respiratory depression. Thus, in 15 instances the respiratory rate was temporarily reduced to 8 to 12 per minute; and in 30 cases, marked depression occurred which required manual assistance. This depression of respiration usually occurred after administration of the first dose of the combined alphaprodine-levallorphan solution, but subsequent doses of the combination did not produce this effect. Respirometer studies indicated that the first dose often reduced the minute-volume exchange by as much as 50 per cent for 5 or 6 minutes. The minute volume then increased, approaching control levels. Depression of minute volume tended to be minimal with additional doses of combined alphaprodine-levallorphan.

One hundred and sixty-four patients (65 per cent) were awake and reacted within 3 minutes, and 229 (91 per cent) responded within 5 minutes after completion of surgery. Thus only 23 patients (9 per cent) required more than 5 minutes to react. There were no cases of postoperative respiratory depression. In two instances hives developed at the site of injection of the combined drugs.

DISCUSSION

As mentioned, the technique of the combined use of alphaprodine and levallorphan employed in this study differed somewhat from that devised by Foldes *et al.* (4, 5). These workers, in the great majority of their cases, did not use a premixed combination of alphaprodine and levallorphan but administered 0.02 mg./kg. of the narcotic antagonist first, followed after several minutes by 1 mg./kg. of the analgetic. Subsequent alphaprodine doses were given without the conjoint use of levallorphan. Additional doses of the antagonist were administered only when the duration of surgery exceeded 2 to 3 hours or when there was respiratory depression at the end of surgery. While the initial

alphaprodine-levallorphan ratio was thus always 50:1, the ratio of the total doses of these two agents varied between 60:1 and 120:1, depending on the total dose of alphaprodine and the duration of anaesthesia. Since alphaprodine is metabolized more promptly than levallorphan, it is possible that the ratio of the two agents in circulation at any given time approximated 50:1. On the other hand, it must be assumed that with our technique this ratio was smaller, particularly in instances in which several doses of the mixture of the two drugs were given in the course of anaesthesia. However, this did not lead to an interference with the analgetic effect of alphaprodine or to respiratory depression after operation which might be expected from a cumulative effect of levallorphan, known to depress respiratory function by itself. Probably such consequences did not arise because alphaprodine in the form of the mixture was used more sparingly than the analgetic by Foldes *et al.* (5). For instance, the largest total amount of the premixed drugs given to one patient in our series was 240 mg of alphaprodine and 4.8 mg. of levallorphan. This maximal analgetic dose is considerably less than 780 mg. used in one case by the other workers. Similarly, the average amounts of alphaprodine and levallorphan employed in our patients, whose surgery lasted more than three hours, was 0.38 mg./min. and 0.0076 mg./min., respectively. In contrast, the average analgetic doses used by the other group ranged from 0.9 (± 0.1) to 1.2 (± 0.2) mg./min. Had such large doses of alphaprodine been given with our technique, which utilizes a premixed combination of the two drugs, obviously a much greater total dose of levallorphan would have been administered than was the case.

The average alphaprodine dose we needed was probably so much smaller because in over 40 per cent of the cases in which nitrous oxide-oxygen was used, this was supplemented with cyclopropane or ethyl ether. Foldes, on the other hand, limited inhalation anaesthesia to nitrous oxide-oxygen. Yet we used doses of alphaprodine considerably larger than could be given safely without the conjoint administration of levallorphan.

The incidence of depression which required assisted respiration in our patients, who had not received succinylcholine, was 15 per cent. This is a somewhat higher figure than that of 8 per cent reported by Foldes' group. Since respiratory depression usually occurred after the first dose of the alphaprodine-levallorphan solution, one might conjecture that a more complete protection against the respiratory depressing effect of alphaprodine may be assured if the narcotic antagonist is administered several minutes prior to the initial alphaprodine dose.

As for thiopental requirements, satisfactory operating conditions were obtained in 45 patients without the use of barbiturate. The average thiopental dose of 194 mg. was considerably less than that needed with other techniques. For instance, Ausherman *et al* (6), who used meperidine by continuous drip, employed approximately six times as much thiopental as we did.

The most rewarding aspect of this study was the postoperative course of the patients, which was very similar to that described by Foldes *et al* (5). Indeed, the fact that over 90 per cent of our patients responded to stimulation with 5 minutes after completion of surgery is an unusual experience. No doubt, this

could be accomplished only by reducing the thiopental requirements, and this in turn was made possible by the use of larger alphaprodine doses which were tolerated without undue respiratory depression because of the conjoint administration of levallorphan.

SUMMARY AND CONCLUSIONS

1. Alphaprodine (Nisentil®) hydrochloride and levallorphan tartrate were used in a 50:1 ratio as supplement to inhalation anaesthesia in 252 patients.

2. In the dosage employed, this combination is safe and provides good analgesia with a minimum of undesirable effects.

3. The reduction of thiopental requirements and the very high proportion of patients awake and responding within 5 minutes after completion of surgery make the use of this combination desirable in the conduction of balanced anaesthesia.

RÉSUMÉ

C'est d'usage courant d'employer, par voie intra-veineuse, et des analgésiques narcotiques et du pentothal, pour compléter l'anesthésie au protoxyde et oxygène. On peut toutefois s'objecter à l'emploi de ces agents à cause de la dépression prolongée qu'ils entraînent chez le patient. De là ressort la nécessité de trouver une technique qui, tout en procurant une anesthésie adéquate, limiterait au temps opératoire les effets dépressifs de ces agents, permettrait un réveil facile du patient et protégerait ce dernier contre la douleur dans la période post-opératoire immédiate.

On a employé, chez 252 patients, un mélange de chlorure d'alphaprodine (Nisentil) et de tartrate de lévallorphan dans une proportion de 50:1 comme complément à l'anesthésie par voie d'inhalation. On s'est servi d'une solution contenant un mélange de 12 mgm. d'alphaprodine et de 0.24 mgm. de lévallorphan par cc. Selon l'âge et l'état physique du patient, on administrait de 2.5 à 5 cc du mélange, dix à quinze minutes avant le début de l'anesthésie. Par la suite, au cours de l'intervention, on répétait des doses de 1 cc. du mélange ou des doses adéquates de pentothal, suivant la nécessité. Chez 53 patients, on a également employé de la succinylcholine, soit au moment de l'intubation, soit pour obtenir un meilleur relâchement musculaire au cours de l'opération; et chez tous ces patients, on a dû recourir à la respiration assistée.

Chez 45 des patients qui n'ont pas reçu de succinylcholine, i.e. 22.6 pour-cent, on a constaté une dépression de la respiration; 30 de ceux-ci ont présenté une dépression assez importante pour nécessiter une assistance manuelle. Cette dépression de la respiration se produisait généralement après l'administration de la première dose du mélange alphaprodine-lévallorphan. Seulement 23 patients ont pris plus de 5 minutes à réagir, une fois l'opération terminée; il n'y eut aucun cas de dépression respiratoire post-opératoire. Dans l'ensemble, les patients ont eu besoin de doses moindres de pentothal.

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