

INNOVAR IN SURGICAL ANAESTHESIA

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INNOVAR is the trade name of a mixture of phentanyl and dihydrobenzperidol in a ratio of 1:50. Phentanyl is a potent short-acting narcotic analgesic, and dihydrobenzperidol (or droperidol), a butyrophenone, produces a feeling of detachment, apathy, and akinesia, also called neuroleptosis. Droperidol appears pharmacologically reminiscent of chlorpromazine, particularly in regard to the multiplicity of its actions; it is a tranquillizer, has anti-emetic properties, depresses the response to intravenously administered adrenaline, but lacks some of the undesirable side-effects of the phenothiazine derivative.

Both drugs were synthesized by Jansen¹ and have been introduced into European anaesthesia associated with the concept of "neuroleptanalgesia."²⁻⁵

The aim of neuroleptanalgesia is to produce freedom from pain and a state of psychic indifference and motor sedation (sometimes referred to as "mineralization") through the selective blockade of certain neural systems in the brain. The term is reminiscent of "neuroplegia," which was used to describe the effect of a variety of cocktails centring around chlorpromazine and other phenothiazine derivatives. Supporters of the new concept claim to have overcome the errors of the past by producing only a slight autonomic inhibition, and also to have avoided the reversible intoxication caused by barbiturates and volatile anaesthetic agents, since the state of neuroleptanalgesia is produced without affecting certain areas of the central nervous system which are blocked by "orthodox" anaesthesia.^{3,4}

A variety of neuroleptic agents and combinations with synthetic analgesic have been tried, and the opinion at present appears to be that droperidol and phentanyl represent the most promising combination.⁵ The analgesia and psychic sedation produced by the two drugs is said to be sufficient to permit most extensive surgical procedures, and yet the patient is somehow awake, although the respiratory depression requires intubation and often intermittent positive pressure ventilation. Phentanyl causes muscular rigidity that is counteracted to some extent by droperidol, but a muscle relaxant may be required to make pulmonary ventilation possible.⁶ Under these circumstances the use of a paralysing dose of curare together with controlled respiration is advocated, and the patient is given, somewhat incidentally by some, deliberately by others, nitrous oxide and oxygen in ratios up to 3:1.

A review of the techniques described gives rise to some doubt whether the concept of neuroleptanalgesia, when used for surgical anaesthesia, is really radically different from the concept of "orthodox" anaesthesia. The supporters of neuroleptanalgesia state that for the protection from surgical trauma, four

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modalities must be considered: analgesia, depression of reflexes, hypnosis, and muscular relaxation.⁴ The essential difference between neuroleptanalgesia and "orthodox" anaesthesia seems to be the absence of hypnotic agents in the former. While the "orthodox" anaesthetist relies heavily on the use of short-acting hypnotics such as barbiturates or halothane, the new method attempts to accomplish the same result with long-acting and less controllable neuroleptic agents. Both methods, however, use nitrous oxide, a gas which has significant analgesic and hypnotic properties. The "orthodox" anaesthetist employs it as analgesic and to reduce the dosage of other hypnotics required, while in neuroleptanalgesia, nitrous oxide affords the only hypnotic effect and provides additional analgesia, allowing a reduction in the requirement for long-acting drugs.

To bring these apparently divergent concepts together, a review of the presently prevailing methods of general anaesthesia can be helpful (Table I). Nitrous oxide is by far the most common anaesthetic used; as a weak agent it requires some form of supplementation. Even the so-called potent anaesthetic gases and vapors are mostly used in rather low concentrations as supplements to nitrous oxide anaesthesia. The combinations with analgesic drugs such as demerol, leritine, or nisentil have been known for some time⁷ and intravenously administered local anaesthetic agents have been used.⁸ In England, excellent results have been claimed with a technique using nitrous oxide and muscle relaxants associated with hyperventilation.⁹ Within this framework, Innovar can be considered as another combination of drugs used to supplement nitrous-oxide anaesthesia.¹⁰

In the series reported here, Innovar was used as a supplement to nitrous oxide anaesthesia. Since this combination lacks hypnotic properties, the addition of small doses of a hypnotic, thiopentone, appeared reasonable, particularly for induction. Also during the maintenance, thiopentone, halothane, or methoxyflurane was used in a low dosage when rapid adjustments in the degree of anaesthetic depression were required. This deviation from the techniques described by those promoting neuroleptanalgesia has greatly facilitated surgical anaesthesia employing Innovar. Indeed the combination of Innovar and thiopentone alone has shown interesting possibilities in anaesthesia for endoscopic procedures.

TECHNIQUE OF ANAESTHESIA

The following technique of nitrous-oxide-Innovar anaesthesia was used in 197 patients. Pre-operatively the patient received a standard medication (consisting of morphine or meperidine combined with atropine or hyoscine, promethazine or promazine). In the operating room, an initial injection of 4-8 ml. of Innovar (one ml. containing 1.0 mg. droperidol and 0.02 mg. phentanyl) was given according to the size and age of the patient. This was followed by the slow injection of about the same quantity of a 2.5 per cent thiopentone solution. When the patient had lost consciousness, the larynx was gently exposed with a McIntosh laryngoscope and sprayed with 4 per cent lignocaine.

Thereafter, intubation was possible in practically all cases, although the patient still had good functioning laryngeal and pharyngeal reflexes. The endotracheal tube was connected to a breathing circle, and a mixture of 2 to 3 litres of nitrous

TABLE I

NITROUS-OXIDE ANAESTHESIA

| Induction | Maintenance | Supplement |
|---------------------------------|-----------------------------------|--|
| Ultra-short-acting barbiturates | Nitrous oxide 50-80% + oxygen, | Inhalation anaesthetic agents: halothane, methoxyflurane, ether, cyclopropane |
| Cyclopropane | partial or non-rebreathing system | Barbiturates: nembutal, thiopentone |
| Halothane | | Analgesics: nisentil, lertine, demerol, morphine. |
| Nitrous oxide | | Intravenous local anaesthetic agents: xylocaine, procaine |
| | | Muscle relaxants + controlled ventilation or hyperventilation |
| | | Phenothiazines and analgesics ("lytic cocktail") |
| | | Butyrophenones and analgesics (Innovar) |

oxide and 1 litre of oxygen was given. Small additional increments of Innovar (1–2 ml.) were injected shortly before surgery began, depending on the response of the patient.

For intra-abdominal and intra-thoracic procedures the patients were paralysed with d-tubocurarine, while spontaneous respiration was maintained in patients undergoing surgery of the head and neck or on the extremities. For maintenance, intermittent doses of 1–2 ml. Innovar were given as required. The need for further Innovar was determined by the degree of respiratory depression in spontaneously breathing patients, and by a rise in blood pressure as well as signs of general stress in paralysed patients.

RESULTS

For further discussion we have divided our patients into those who had been paralysed and ventilated and those who had been allowed to breathe spontaneously and in whom no relaxants were used; a third miscellaneous group contains patients who had occasional respiratory assistance and/or muscle relaxants or who did not receive nitrous oxide. In view of experiences at other centres, we had selected predominantly long operations and had given a certain preference to patients with a reduced operative risk.^{11,12}

Controlled ventilation was maintained during surgery in 75 patients, mostly for major abdominal operations. The average dosages of Innovar, together with the amounts of thiopentone and curare, are listed in Table II. Although d-tubocurarine was used as the main relaxant in all cases, small doses of gallamine were used occasionally and are included in the total dosage listed, equating 20 mg. gallamine with 3 mg. d-tubocurarine.

In 70 patients, spontaneous breathing was allowed throughout the whole surgical procedure (Table III), which in most cases exceeded two hours. The dosages of thiopentone and Innovar are of the same order in this group.

A group of miscellaneous surgical procedures is presented in Table IV. For the bronchoscopies, only Innovar and thiopentone were used in conjunction with topical anaesthesia.

In addition, 24 patients received Innovar as sedation during spinal or epidural analgesia, so that 230 patients who had Innovar are represented in this report.

Unfortunately our presentation has been rendered somewhat obsolete by a change in the manufacturing process of droperidol; the cases reported here were done with Innovar incorporating an unpurified droperidol, which is no longer used. However, at the time of presentation of this report we had administered "new Innovar" with pharmacologically pure droperidol to 45 patients and there appeared to be no clinically recognizable difference between the two agents.

The dosage of Innovar used in each half-hour is presented for patients with controlled ventilation and those breathing spontaneously in Figure 1. Although different criteria were used to assess the need for additional injections in the two groups, the amounts required were almost identical.

In 18 cases it was considered necessary to supplement the anaesthesia with halothane or methoxyflurane. The indication for the use of gallamine was usually

TABLE II
OPERATIONS WITH CONTROLLED VENTILATION

| Operation | Number of patients | Average age | Average duration (min.) | Average dosage | | |
|---------------------------------|--------------------|-------------|-------------------------|----------------|-------------------|--------------|
| | | | | Innovar (ml.) | Thiopentone (mg.) | Curare (mg.) |
| Gastrectomy | 4 | 54 | 130 | 17 | 185 | 30 |
| Biliary tract surgery | 12 | 52 | 117 | 16 | 230 | 25 |
| Bowel resection | 7 | 54 | 170 | 14 | 200 | 29 |
| Ileal loop conduit + cystectomy | 19 | 60 | 235 | 21 | 175 | 39 |
| Wertheim hysterectomy | 15 | 44 | 144 | 16 | 210 | 23 |
| Ventral hernia | 5 | 49 | 160 | 17 | 250 | 34 |
| Other abdominal surgery | 6 | 46 | 70 | 10 | 175 | 16 |
| Thoracotomy | 7 | 53 | 157 | 16 | 270 | 21 |
| | <u>75</u> | | | | | |

TABLE III
OPERATIONS WITH SPONTANEOUS RESPIRATION

| Operation | Number of patients | Average age | Average duration (min.) | Average dosage | |
|--|--------------------|-------------|-------------------------|----------------|-------------------|
| | | | | Innovar (ml.) | Thiopentone (mg.) |
| Thyroidectomy | 9 | 48 | 110 | 12 | 230 |
| Plastic surgery, face, and rhinoplasty | 12 | 30 | 140 | 15 | 265 |
| Radical neck dissection | 7 | 64 | 305 | 23 | 170 |
| Middle ear surgery | 5 | 50 | 160 | 19 | 160 |
| Other E.N.T. surgery | 9 | 34 | 90 | 10 | 175 |
| Mastectomy | 7 | 56 | 112 | 12 | 160 |
| Vein surgery | 11 | 44 | 110 | 12 | 240 |
| Retinal detachment | 3 | 61 | 225 | 13 | 200 |
| Cataract | 4 | 60 | 65 | 14 | 200 |
| Vascular surgery | 3 | 60 | 120 | 10 | 140 |
| | <u>70</u> | | | | |

TABLE IV

MISCELLANEOUS OPERATIONS AND DIAGNOSTIC PROCEDURES

| | Number of patients | Average age | Average duration (min.) | Average dosage | |
|----------------------------------|--------------------|-------------|----------------------------|------------------|----------------------|
| | | | | Innovar (ml.) | Thiopentone (mg.) |
| Operations | | | | | |
| Fractured hip | 10 | 71 | 110 | 10 | 170 |
| Orthopedic surgery (extremities) | 11 | 50 | 72 | 10 | 220 |
| Vaginal surgery | 20 | 45 | 100 | 13 | 250 |
| Other | 8 | 50 | 60 | 9 | 185 |
| | — | | | | |
| | 49 | | | | |
| Diagnostic procedures | | | | | |
| Bronchoscopy | 9 | 53 | 27 | 7 | 230 |
| Radiographic study | 3 | 23 | 80 | 11 | 320 |
| | — | | | | |
| | 12 | | | | |

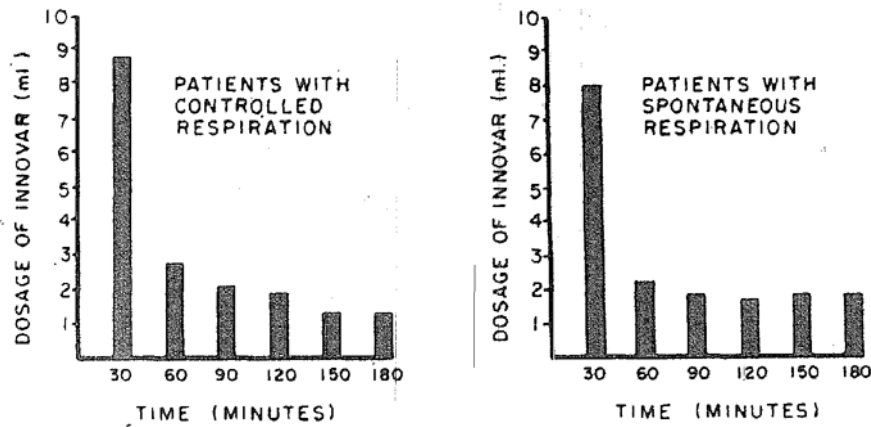


FIGURE 1. Dosage in ml. of Innovar used during successive thirty-minute periods of surgery. Average from patients with controlled ventilation (75) and from those breathing spontaneously (70).

a marked bradycardia encountered in some abdominal cases; under these circumstances gallamine was preferred to atropine. Small doses of vasopressor agents were used in fifteen patients to counteract hypotension (Table V).

There were three deaths postoperatively, one in a terminal cancer patient four weeks following a chordotomy, a second in a patient who had a full course of cobalt treatment followed by a cystectomy and ileal loop conduit, and who died with an intractable infection and complete dehiscence of his wound. A third patient, a 79-year-old woman, had two cataract operations performed within a two-week interval. For the first procedure a chlorpromazine-demerol cocktail was used; for the second, Innovar and nitrous oxide. On the morning following the second operation she was set up in a chair at the bedside to allow the nurses to make the bed. While sitting she collapsed, and all attempts at resuscitation failed.

Although Innovar has been shown to produce no significant circulatory effects,^{6,13} the second postoperative day perhaps deserves more careful consideration in the investigation of this drug, since effects of droperidol have been observed longer than twenty-four hours after its administration.⁶

DISCUSSION

From the point of view of the orthodox anaesthetist this technique of nitrous oxide-Innovar anaesthesia presents the following difficulties and disadvantages:

1. It is a rather inflexible method and does not allow the ready control of the degree of depression that can be obtained with a potent inhalation anaesthetic.
2. Innovar produces a severe respiratory depression. On a few occasions, in

TABLE V
NUMBER OF OPERATIONS WITH EACH ANAESTHETIC AGENT AND WITH SPECIAL DRUGS

| | Total | Gallamine | Halothane | Methoxyflurane | Vasopressors |
|---|-------|-----------|-----------|----------------|--------------|
| Operations with controlled ventilation | 75 | 24 | 5 | — | 6 |
| Operations with spontaneous respiration | 70 | — | 7 | 2 | 2 |
| Miscellaneous | 49 | 10 | 4 | — | 7 |

spontaneously breathing patients, it was difficult to balance the degree of a tolerable respiratory depression with the amount of drug necessary to make the patient tolerate surgery unless thiopentone or a volatile anaesthetic was added. Although the respiratory rate was markedly depressed, the tidal volume was retained and often elevated, so that the alveolar ventilation often remained near normal in spite of the very slow rate of breathing (Fig. 2). In ten patients, breathing spontaneously, the arterial pH and $p\text{CO}_2$ were determined at the end of surgery before the anaesthesia was discontinued. After an average duration of surgery of 165 minutes (range 75 to 255 minutes), an average pH of 7.26 (7.18 to 7.33) and an average $p\text{CO}_2$ of 49 mm. Hg (40 to 59) were observed. Thus the respiratory depression resulted in a rather mild respiratory acidosis, even after long operations.

3. The analgesia produced by Innovar alone is certainly not complete; without the use of nitrous oxide it did not seem possible to give the patient enough of the drug to permit him to tolerate more painful surgical procedures and to avoid side-effects such as apnoea or muscular rigidity.

4. Although the recovery from nitrous oxide anaesthesia is very rapid, the long-acting droperidol produces a state of detachment, apathy, and inertia which lasted in our study from six to twelve hours. The patients studied responded to questions and commands, but there was little spontaneous activity. Some patients, when left alone, would occasionally show signs of airway obstruction, although they obeyed the command to take a deep breath. This state presented no problem in the recovery room but one would be concerned to let such a patient fend for himself.

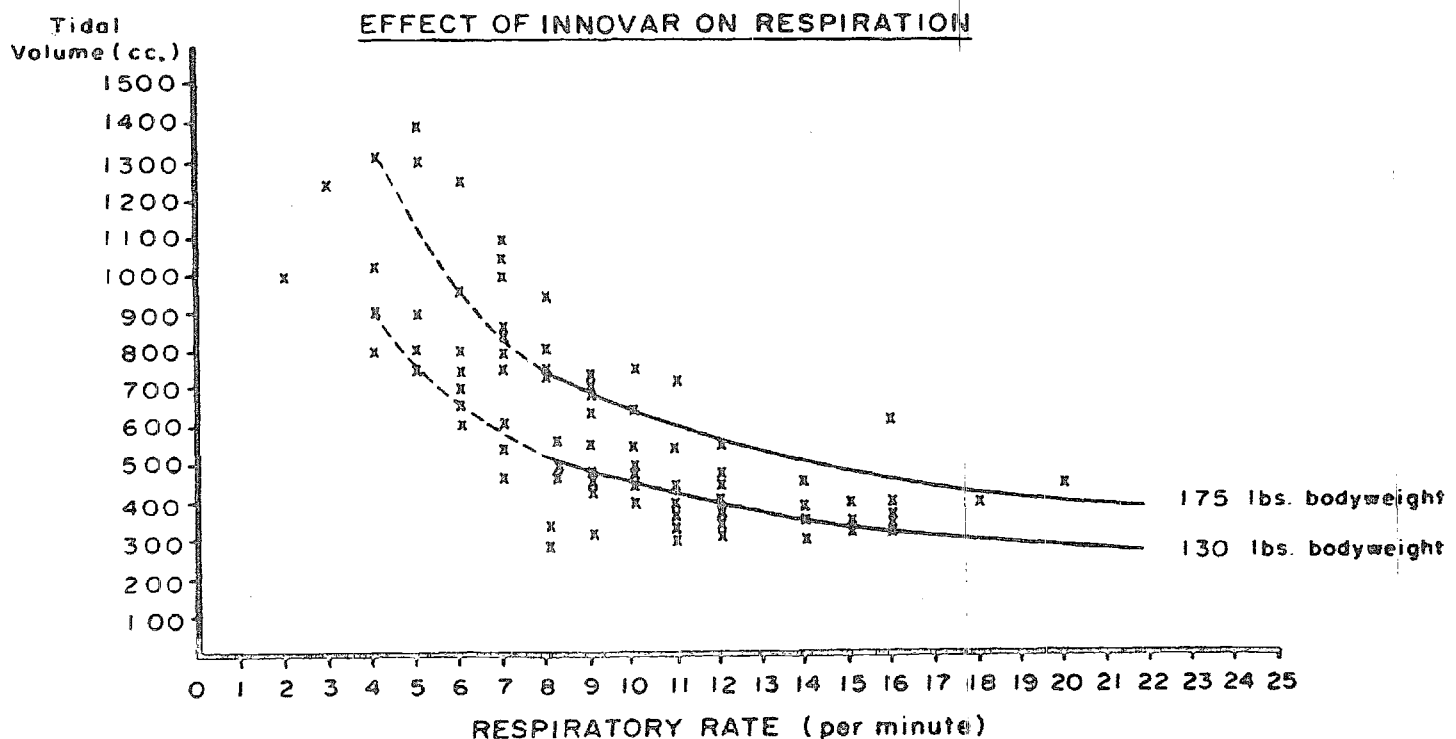


FIGURE 2. Tidal volumes observed in 12 patients at varying respiratory rates under nitrous-oxide-Innovar anaesthesia and orotracheal intubation. A Wright respirometer was used to measure the respiratory minute volume. The lines represent the tidal volumes in the same range of body weights, taken from Radford's nomogram (uncorrected); in the range of the broken lines the values were extrapolated.

5. It has been stated that the amount of postoperative analgesia required is reduced.^{11,14} Since there are individual differences in requirements and one has to contend with a wide variety of anaesthetic techniques, it is rather difficult to find suitable controls. There is a divergence of opinion as to whether to give a depressant agent of long duration which extends into the postoperative period, or to use a short-acting agent whose effect ends after surgery and then give analgesic drugs as required postoperatively. Droperidol is not an analgesic; often patients did state on questioning that they had severe pain, but they did not complain spontaneously and therefore were not given pain-relieving drugs. Whether this is a desirable state remains to be determined. Three patients complained about transient unpleasant sensations several hours after surgery, but no regular inquiry into this was made. The possibility of extrapyramidal symptoms must be kept in mind,⁶ although none were observed in our patients.

The introduction of a new agent into anaesthesia seems justified if it offers advantages over the previously used agents and techniques. In our study, Innovar showed the following possible advantages:

1. In small to moderate doses it appeared to provide an excellent supplemental sedation to regional anaesthesia. The patients were calm, relaxed, and detached. However, they could be aroused to answer questions or respond to commands. In operations with minimal pain, and these include surgery on the brain and in the open heart,¹¹ the combination of Innovar and nitrous oxide is reported to provide satisfactory conditions. It may be the method of choice when intra-operative communication with the patient is required.¹¹ We have been disappointed in our attempts to use Innovar to overcome the pain caused by inadequate regional anaesthesia or by a tourniquet.

2. The combination of Innovar and thiopentone made laryngoscopy and endotracheal intubation possible without the use of relaxants. This can be done at a depth of anaesthesia where patients appear to have all the protective reflexes; we believe accidental aspiration to be virtually impossible with this technique. In two patients in whom severe facial injuries and fractures made the application of a mask impossible, intubation was accomplished without incident using this method. Innovar and thiopentone, in conjunction with topical application of 4 per cent lignocaine to the larynx, trachea, and bronchi, were used for laryngoscopies and bronchoscopies in a technique similar to the one described for intubation without relaxants (Table IV). Spontaneous respiration was maintained, and small supplementary doses of thiopentone were administered as required to provide a light sleep throughout the procedure. Excellent conditions for bronchoscopy were obtained by this approach. With this technique, the potentiating effect of Innovar on thiopentone must be considered¹⁵ and the dosage must be kept small (Table IV).

3. Droperidol has an adrenergic blocking effect similar to chlorpromazine. According to more recent concepts in the prevention of shock, an adrenergic blockade should be beneficial.^{11,16} Although one has the impression that after long and traumatizing operations under nitrous-oxide-Innovar anaesthesia, patients look better clinically, and have a better peripheral circulation than when other techniques of general anaesthesia are used, there is no reliable objective evidence available to substantiate this.

4. The stability of the cardiovascular system and the lack of depression of the myocardium and the vasomotor system have been cited as advantages. At our dosage level the need for additional injections of Innovar could be guided by the blood-pressure and heart-rate response. In our series of patients with abdominal surgery, hypotension and bradycardia, presumably caused by traction reflexes, were rather prominent features. Gallamine in doses of 20–60 mg. was used in 30 per cent of the abdominal cases to counteract excessive bradycardia, and vasopressors were required occasionally (Table V).

5. The rapid recovery from anaesthesia is impressive, and so are the absence of restlessness and the calm and detached attitude of the patient postoperatively. In this state the patient appears to be readily following commands, particularly the one to take a deep inspiration. Whether the impression is correct that these patients are more readily inclined to breathe deeply following abdominal or thoracic surgery than patients recovering from other types of anaesthesia requires further and more detailed investigation.¹⁷ If the impression is substantiated, Innovar would certainly be of considerable value in the management of older patients with abdominal surgery.

CONCLUSION

It is certainly desirable to describe the unique effect of the drugs combined in Innovar, and the term "neuroleptanalgesia" serves the purpose. However, it does not seem helpful to use the term to describe an anaesthetic technique which uses agents in dosages required for already well-known anaesthetic techniques, and adds really only one new drug, droperidol, to it. To think of Innovar as another drug that is useful in the context of a "balanced anaesthesia" avoids the application of a rigid concept of anaesthetic management and makes it easier to overcome the shortcomings of a technique based on theoretical considerations.

We believe that Innovar in its present form, as a combination of drugs that complement each other in some aspects, deserves further study. The impression that certain anaesthetic procedures could be carried out better with Innovar signifies the need for its existence and justifies its continued use.

SUMMARY

Innovar, a mixture of phentanyl and droperidol (0.02 mg./c.c. and 1 mg./c.c. respectively), was used to supplement nitrous oxide and other forms of anaesthesia. In contrast to the techniques of neuroleptanalgesia, small doses of thiopentone were used for induction and as a hypnotic when required. With this technique, the dosage of Innovar could be reduced, minimizing side-effects.

Innovar was given to 230 patients. In 24 it was used to provide sedation during regional anaesthesia; nine bronchoscopies were done using a combination of thiopentone, Innovar, and topical anaesthesia, with superior results.

The remaining 197 patients received Innovar to supplement nitrous-oxide anaesthesia. The dosages required were similar in curarized patients on controlled ventilation and patients breathing spontaneously. Innovar induced a marked slowing of the respiration, although most patients were able to maintain their

alveolar ventilation by a corresponding increase in tidal volume; only a mild respiratory acidosis (average $p\text{CO}_2$, 49 mm. Hg) was found in 10 patients after an average of 165 minutes of anaesthesia.

Although the technique described lacked the flexibility of inhalation anaesthesia, certain advantages deserve further consideration. Among them, the possibility to intubate the patient without loss of reflexes and without relaxants, the lack of circulatory depression, the possible benefit of a mild adrenergic blockade, the rapid return of responsiveness, and the calm postoperative period with reduced drug requirements were particularly noticed. At the same time, the postoperative "neuroleptosis" may require a closer supervision of the patient.

None of the three postoperative deaths in this series can be related to Innovar; however, one circulatory collapse occurred within the possible duration of action of droperidol.

Although the term "neuroleptanalgesia" describes the unique effect of this combination of drugs, the justification to apply the term to a technique of general anaesthesia is questioned. The use of Innovar within the framework of the present concept of anaesthesia has shown promising results and should be actively continued.

RÉSUMÉ

Nous avons employé l'innovar, un mélange de phentanyl et de dropéridol (0.02 mg./ml. et 1 mg./ml. respectivement) pour compléter l'anesthésie au protoxyde d'azote et aux autres mélanges d'agents. Contrairement à ce qui se fait lorsque les techniques de neuroleptanalgesie sont utilisées, nous avons employé de petites doses de thiopentone pour faire l'induction et comme hypnotique selon le besoin. De cette façon, il est possible de réduire la quantité d'innovar, ainsi que les effets secondaires.

Nous avons donné de l'innovar à 230 malades. Chez 24 malades, nous l'avons employé comme sédatif au cours d'anesthésies régionales; nous avons pratiqué 9 bronchoscopies en employant un mélange de thiopentone, d'innovar et d'anesthésie locale et avons obtenu des résultats de toute première qualité.

Les 197 autres malades ont reçu de l'innovar pour compléter une anesthésie au protoxyde d'azote. Il nous a fallu donner les mêmes quantités aux malades curarisés dont la ventilation était contrôlée qu'aux malades qui respiraient spontanément. L'innovar produit un ralentissement marqué de la respiration; toutefois la plupart des malades ont réussi à maintenir leur ventilation alvéolaire en augmentant leur air courant; nous avons trouvé une très légère acidose respiratoire ($p\text{CO}_2 = 49$) chez dix malades après 165 minutes d'anesthésie.

Bien que cette technique anesthésique n'ait pas la souplesse de l'anesthésie par inhalation, nous attirons l'attention sur certains avantages. Parmi ces avantages, signalons la possibilité d'intuber le malade sans qu'il ait perdu ses réflexes et sans qu'il ait reçu des substances curarisantes, l'absence de collapsus circulatoire, l'avantage possible d'un léger blocage adrénergique, un retour rapide à la capacité de répondre et une période post-opératoire calme où il faut donner moins de médicaments. En même temps, la neuroleptose post-opératoire peut exiger une surveillance plus étroite du malade.

Aucune des trois mortalités post-opératoires survenues au cours de cette série n'est attribuable à l'innovar; un collapse circulatoire est survenu alors que l'action du dropéridol se faisait encore probablement sentir. Signalons aussi que le terme "neuroleptanalgesie" décrit l'effet unique de ce mélange de médicaments; nous nous demandons s'il est justifiable de donner ce nom à une technique d'anesthésie générale. L'emploi de l'innovar dans le cadre du présent concept de l'anesthésie nous a donné des résultats prometteurs; il faudrait continuer de l'employer de façon régulière.

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