A Narcotic Analgesic and a Butyrophenone with Nitrous Oxide for General Anesthesia

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For four years, anesthetists in Continental Europe have been using various combinations of narcotic analgesics and butyrophenones intravenously for surgical anesthesia.1-5. 13 Reports on such combinations as palfium plus haloaonine, and phenoperidine plus haloperidol, indicated certain disadvantages, namely profound hypotension, extrapyramidal disturbances, and in a few instances prolonged postoperative psychic changes ranging from diminished powers of concentration to hallucinations. It is now recognized that the latter two undesirable sequelae can be promptly reversed by benztoprine (Cogentin) or atropine.

The synthesis by Janssen of phentanyl in the narcotic series and dehydrobenzperidol, a butyrophenone, appears to have minimized these side effects. This paper describes the intravenous injection of the two drugs in a mixture termed Innovan, which together with the inhalation of nitrous oxide has been used to provide general anesthesia for 400 patients.

Pharmacologic Considerations

Phentanlyl (1-N-2-phenethyl-4-N-propionyl-anilinoipiperidine) is a potent narcotic analgesic approximately 100 times more powerful than morphine milligram for milligram.6 The drug has a high therapeutic ratio. In mice, for example, the ED₅₀ (Eddy hot-plate test) following subcutaneous injection is 0.05 mg./kg., while the LD₅₀ by the same route is 70 mg./kg. A peak intensity of action (analgesia, respiratory depression and tranquility) appears sooner than with most narcotic analgesics after both intravenous and intramuscular injection. For example, maximal respiratory depression is reached twice as rapidly with phentanlyl as with equianalgesic doses of meperidine. Duration of respiratory depression is also less.7 These data were obtained by the CO₂ challenge technique.8 Both rate and depth of respiration may be decreased—apnea may appear. The drug causes almost no hypotension, nor does it liberate histamine. Evidences of a central vagal stimulant action include bradycardia and sweating, both of which are reduced or eliminated by the preoperative doses of atropine in common use, e.g., 0.4 mg. In dogs, phentanlyl, unlike most narcotics, does not cause vomiting although defecation is seen. A minimal incidence of vomiting has been noted in man, but we are currently subjecting this to a double-blind analysis. After the rapid intravenous injection of the drug in 0.1 mg. doses in man, rigidity of the muscles of the arms, legs, abdomen and thorax may result. This has been seen after the intravenous injection of large doses of other narcotic analgesics, such as meperidine, phenaecine and alphaprodine. In pharmacology texts this has been described as "lead-pipe or catatonic rigidity."11 All actions of phentanlyl seem to be effectively antagonized by nalorphine or levallorfan.

Dehydrobenzperidol (4'-fluoro-4-[N-4''-(4-nbenzimidazolono)-Δ3,4-tetrahydropropiperdine]-butyrophenone hydrate) produces sleepiness, and a feeling of detachment in man. These effects develop within five to ten minutes of either intravenous or intramuscular injection. The duration of sleepiness in man may be as long as six to twelve hours after intramuscular administration of a single dose. The drug lowers blood pressure in man and animals. It minimizes the rise in blood pressure caused by intravenously administered epinephrine and norepinephrine. As further evidence of an adrenergic blocking action, it is difficult, if not

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impossible, to produce ventricular arrhythmias with epinephrine given intravenously to dogs given dehydrobenzperidol and anesthetized with pentobarbital. Rats are protected from drum shock by the drug more effectively than by chlorpromazine. Extrapyramidal tract reactions such as oculogyric crises have been noted after single doses (1.0–2.0 mg./10 pounds body weight) in infants and children. These have occurred after the sedation has disappeared, i.e., as late as 12–18 hours after injection. They respond promptly to benztpine or atropine.

It is reasonable to wonder whether a mixture of the two drugs is associated with any antagonistic or potentiating effects so far as either component of the mixture is concerned. Potentiation of the analgesic action of the narcotic by the butyrophenone is suggested by studies in mice. In the dog neither antagonistic nor potentiating effects on blood pressure were seen.

Our interest in the combination of these two drugs stemmed in part from a belief that certain of the commonly used anesthetic agents and adjuncts have undesirable properties. Thiopental is not a good analgesic agent. Morphine has a long action, liberates histamine, and may produce hypotension. Meperidine causes tachycardia and nausea and vomiting in many patients to a greater extent than do other drugs of similar nature. Hypotension, occasionally troublesome, follows the use of halothane. Tachypnea commonly accompanies trichlorethylene anesthesia. We have therefore studied phentyl and dehydrobenzperidol in combination with nitrous oxide to see if this technique would obviate some of the disadvantages outlined above. Although the technique to be described also was found to have disadvantages, it offers certain interesting features, including profound analgesia, minimal hypotension, protection against epinephrine-induced ventricular rhythms, and an apparently lessened incidence of postoperative nausea and vomiting.

The Study

Four hundred patients ranging in age from 15 to 92 years were studied. One hundred eighty-five were men. According to our classification, 197 were grade 1 in physical status, 152 grade 2, 48 grade 3, and 3 grade 4. The operations performed are listed in table 1. There were no deaths during anesthesia, but there was one postoperative death in the series, a patient dying with a massive pulmonary embolus two days after an uneventful pneumonectomy.

Composition of the Mixture. The optimal mixture appeared to contain dehydrobenzperidol 1 mg./ml. and phentyl 0.02 mg./ml., or 50:1. This was used in 356 cases; our current technique will be described. We have also used a 100:1 mixture in seven patients, and a 25:1 mixture in 37 others. With the decreased amount of analgesia in the 100:1 mixture it was difficult to prevent movement in response to surgical stimuli. Depressed respiration was the primary undesirable complication with the 25:1 mixture.

The fixed ratio of 50:1 was used as a matter of convenience rather than attempting to individualize doses of the two drugs for each patient.

Preanesthetic Medication. Preanesthetic medication was deliberately varied, and included secobarbital, amitriptyline, and dehydrobenzperidol. Narcotics were not used. In patients given atropine only, induction time was prolonged and large amounts of Innovane were required. Bradycardia and sweating occurred during induction in the majority of patients in whom atropine had been omitted.

Induction of Anesthesia. Four to 5 ml. of the mixture (50:1) were given rapidly intravenously. After a few minutes the patient would become somewhat drowsy but could answer questions appropriately. If after three to four minutes an appreciable sedative effect was not observed, a further 2–3 ml. dose was given. Inhalation of N₂O::O₂ (3:1) was begun after the first 5–8 ml. This drug was used to
produce unconsciousness. Total gas flows of 8–9 liters per minute were used in a semi-
closed circle system. Nonrebreathing systems
are now being studied. This technique should
provide a more intense effect with a quicker
onset of action.

Unconsciousness usually occurred about three
minutes after the nitrous oxide had been
begun. If not, an additional 2 ml. of the mix-
ture was given. Thus, the total induction dose
was usually 5–10 ml. Mild to moderate ex-
citement was noted in 10 per cent of the
patients and was partially related to the time
of starting nitrous oxide. If inhalation was
begun too early, before sedation had de-
veloped, there was a greater likelihood of excite-
ment. If on the other hand, nitrous oxide
was started too late, too much of the mixture
might have been given in an effort to produce
sleep.

**Maintenance of Anesthesia.** (1) **Operations
Not Requiring Muscular Relaxation:** For
these procedures respiration was spontaneous.
Additional doses of 1–2 ml. of the mixture
were given if there was a rise in respiratory
rate, an increase of blood pressure, coughing,
or movement by the patient. Some patients
required additional doses every 15 minutes,
while in others dose intervals exceeded 60–75
minutes. The usual total dose for a two hour
procedure was from 10 to 15 ml. Tolerance of
a tracheal tube was increased by use of a topi-
cal spray of a local anesthetic. If this was
omitted, coughing was likely during operations
on the neck.

(2) **Operations Requiring Muscular Re-
laxation:** The trachea was intubated, after
intravenous injection of succinylcholine. Ven-
tilation was controlled throughout and d-
tubocurare given for muscular relaxation in doses
similar to those used in thiopental–N₂O–curare
techniques. Additional doses of Innovar were
infrequently needed.

**Effects on Respiration.** Both rate and depth
of breathing were reduced, the greatest effect
occurring during induction. Both respiratory
parameters returned to preinjection levels
within 8 to 12 minutes. In ten patients, how-
ever, analysis of arterial blood samples at this
time revealed an elevation of P₇CO₂ (44–54
mm. of mercury) in six, suggesting a decreased
sensitivity of the central respiratory mecha-
nisms to CO₂. How often this would be noted
during spontaneous respiration with such re-
spiratory depressant anesthetic agents as thiop-
ental, cyclopropane and halothane is under
study. Preliminary results with the latter re-
veal an average rise of end-respiratory P₇CO₂
of 9–10 mm. of mercury during respiration of
a 1.5–2.0 per cent concentration of the drug.

**Rigidity of Skeletal Muscles.** This phe-
nomenon was noted in 32 (8 per cent) of the
400 patients. The muscles affected varied
but included those of the extremities, thorax
and abdomen. Sometimes only a few muscle
groups were involved; at other times the re-
ponse was widespread. Rigidity of thoracic
musculature developed only when profound
respiratory depression had been produced.
When positive pressure was then applied to
the airway to assist ventilation, marked resis-
tance was encountered. A small dose of re-
laxant intravenously, e.g., 20 mg. succinyl-
choline, produced flaccidity promptly. The
offending drug in the mixture was the nar-
cotic analgesic, for the syndrome could be
reproduced by administering the analgesic
alone. It was not seen after butyrophenone
alone.

**Cardiovascular Effects.** (1) **Pulse Rate:**
A heart rate of between 50 to 60/minute re-
duced from a control rate of 75–85/minute was
noted in seven cases, but in four of these
instances atropine had been deliberately
omitted preoperatively. For the rest there
was either no change in pulse rate or a tran-
sient rise of 20–30 beats per minute.

(2) **Blood Pressure:** A sharp decrease in
blood pressure to 50 mm. of mercury followed
the initial 5-ml. dose of the combination in
one patient. This was accompanied by a
pulse rate of 56/minute. These changes were
reversed promptly by 0.2 mg. atropine intra-
venously. In 22 cases during induction there
was a gradual decrease in systolic blood pres-
sure of approximately 25 per cent of the pre-
operative level.

**Postoperative Period.** Apnea was present
at the end of operation in one patient and was
promptly reversed by 0.5 mg. of levallorphan
intravenously. This occurred in a healthy
patient who would open her eyes and breathe
on command at the end of operation, but
would not breathe if left undisturbed.
The time of response to command after discontinuance of N₂O is shown in Table 2.

As a rule emergence from anesthesia was smooth, the patients awakening peacefully, free of pain, and able to converse rationally. Although consciousness and orientation returned soon after discontinuance of the nitrous oxide, many patients were drowsy for a number of hours thereafter, sleeping lightly unless aroused, at which time they could converse intelligently. Twenty patients mentioned mental depression and inability to concentrate during the remainder of the day of operation.

Three patients required an analgesic within the first four postoperative hours.

Postoperative nausea occurred in 23 patients. In no cases did this last longer than 12 hours. Five of these patients vomited once or twice during the first 12 hours.

**Discussion**

The mixture of narcotic analgesic and butyrophenone used together with nitrous oxide in this series provided hypnosis and analgesia, but the third component of complete anesthesia, muscular relaxation, was lacking. d-Tubocurare was required for intra-abdominal operations, for example. The technique, therefore, resembled that involving thiopental and/or narcotic analgesics and nitrous oxide, although onset of anesthesia was slower.

The stability of the cardiovascular system during Innovan–nitrous oxide anesthesia was notable. Alteration in pulse rate and blood pressure was uncommon, particularly after induction had been completed. Because of the adrenergic blocking action of dehydrobenzperidol, hypotension can be expected to occur in some patients. We recorded marked hypotension only once in this series, although it was present when Innovan was given as a supplement in approximately one third of a group of patients receiving spinal or halothane anesthesia. This series is not included in this paper.

Electrocardiographic tracings were taken infrequently, and although the anesthetic combination was given to one patient for removal of a pheochromocytoma and to 32 others receiving epinephrine by local infiltration for hemostasis without the development of ventricular arrhythmias, the data permit few conclusions. Animal studies, however, indicate epinephrine protection. Thus the combination should prove useful when epinephrine is part of the surgical approach.

As when other narcotic analgesics are used as adjuvants, reduction of respiratory minute volume was noted in this series. Double-blind comparisons of phentanlyl and meperidine currently underway in our laboratories confirm the clinical impression that the respiratory depressant action of the former is statistically significantly briefer than with meperidine. The tachypnea associated with trichlorehylan, ether and other volatile liquid anesthetics was not seen. With the exception of one patient early in the series, when larger doses of Innovan than necessary were used, pulmonary gas exchange was believed adequate in all cases at the end of operation. Of concern, however, has been the ventilatory insufficiency caused by rigidity of thoracic and abdominal musculature. Although relaxation followed intravenous injections of succinylcholine, rigidity was an undesirable complication unless tracheal intubation had been planned. This example of the catatonic rigidity seen in laboratory animals after narcotic analgesics has not been observed by us after intramuscular administration of phentanlyl for analgesia to more than 1,000 patients. It appears to be related to the greater concentration of the drug in the central nervous system as the result of intravenous injection. It has been noted after the intravenous administration of other narcotic analgesic drugs.

The postoperative somnolence was gratifying in patients uncomfortable because of gastric suction tubes, urinary catheters, and incisional pain. It was not desirable in patients subjected to short operations or in whom postoperative discomfort was minimal. The incidence of postoperative vomiting was low.

**Table 2. Time of Awakening after Discontinuing Nitrous Oxide**

<table>
<thead>
<tr>
<th>Time after discontinuation</th>
<th>Number of Patients</th>
</tr>
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<tbody>
<tr>
<td>Within 3 minutes</td>
<td>195</td>
</tr>
<tr>
<td>Within 5 minutes</td>
<td>309</td>
</tr>
<tr>
<td>Within 10 minutes</td>
<td>345</td>
</tr>
<tr>
<td>Within 15 minutes</td>
<td>376</td>
</tr>
<tr>
<td>Within 30 minutes</td>
<td>381</td>
</tr>
<tr>
<td>Within 35–120 minutes</td>
<td>7</td>
</tr>
<tr>
<td>No data</td>
<td>12</td>
</tr>
</tbody>
</table>
Analgesia appeared to extend into the immediate postoperative period for at least four hours in the majority of instances.

Transient central nervous system reactions (Parkinson-like, akathisia and dystonia) of an extrapyramidal tract type have been reported after use of phenothiazines and butyrophenones. These undesirable neuromuscular reactions have been noted more commonly in the younger age group. Of concern is the fact that they may occur after a single dose, and with a time interval after ingestion or injection of between 24 to 48 hours. Although we have not observed such responses after Innovar-nitrous oxide anesthesia a larger series and greater experience with children are necessary before conclusions are possible, for dehydrobenzperidol alone in large doses can cause these effects.

This report is purely clinical in nature. It is difficult to compare anesthetics in controlled series, but our findings will have to be substantiated by measurements of such aspects as alveolar ventilation, cardiac output, organ blood flow, and hepatic and renal function. Most of these are underway.

We have no data on a possible antishock effect, an action which has been attributed to other adrenergic blocking agents. Nor could we determine whether the technique afforded protection from reflexes aroused by surgical manipulation. These aspects deserve study.

Summary

A technique of general anesthesia using phentany, a potent analgesic, and dehydrobenzperidol, a butyrophenone derivative, intravenously, together with the inhalation of nitrous oxide has been utilized to anesthetize 400 patients for general surgical procedures. The method affords excellent analgesia and hypnosis for operations not requiring muscular relaxation. For the latter a relaxant must be added. Circulatory stability was impressive during and after operation. Respiratory depression resembled that seen when other narcotic analgesics are used as adjuvants to anesthesia, but was of lesser duration than with most. Rigidity of skeletal muscles, occasionally making pulmonary ventilation difficult but responding promptly to small doses of relaxants, was seen primarily when excessive amounts of the mixture had been given by vein.

Profound analgesia, minimal hypotension, probably protection against epinephrine-induced ventricular arrhythmias, and a smooth postoperative course constitute some of the appealing features of this technique with non-explosive agents which appears to merit further exploration.

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References