and is the least traumatic way to accomplish intubation of the trachea.

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Reversal of Innovar-induced Postanesthetic Somnolence and Disorientation with Physostigmine

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Innovar, a popular intravenous anesthetic, consists of a short-acting narcotic (fentanyl) and a long-acting tranquilizer (droperidol). It is associated with a number of undesirable side-effects, including respiratory depression, prolonged somnolence, and disorientation.1–3 Respiratory depression is easily reversed with nalorphine or naloxone; however, there is no known antagonist for the somnolence and disorientation. Physostigmine is effective in reversing anticholinergic poisoning4–9 and phenothiazine-induced coma.10 It has been suggested that physostigmine might have nonspecific analeptc actions in the central nervous system and thus be of value as an antagonist to other CNS depressants.10 This study was undertaken to evaluate physostigmine as an antagonist to somnolence and disorientation after Innovar–nitrous oxide anesthesia.

METHODS

We studied a total of 169 patients, A.S.A. Class 1 or 2, scheduled to undergo short (<60 minutes) operations and premedicated with pentobarbital (50–100 mg) or hydroxyzine hydrochloride (50–100 mg), meperidine (50–75 mg) and atropine (0.3–0.5 mg) 60–90 minutes prior to operation. In each case, intravenous infusion was begun and routine monitoring (precordial stethoscope, blood pressure cuff, and electrocardiogram) initiated prior to anesthetic induction. Innovar, 1–3 ml, was administered iv, then 1 per cent methohexital was given in 10–20 mg increments, iv, until loss of eyelid reflex occurred. Anesthesia was maintained with intermittent 0.5–1.0 ml increments of Innovar, iv, and 50 per cent nitrous oxide in oxygen administered through a semiclosed circle system with CO2 absorption and a total fresh gas flow of 5–6 l/min. Muscular relaxation was achieved with a solution of 0.1 per cent succinylcholine in 5 per cent dextrose in water administered intermittently. At the end of operation, those patients breathing at a rate of <6 breaths/min received 0.1–0.2 mg naloxone, iv, and were excluded from the study. All patients were then taken to the postanesthetic recovery room. Those who responded to verbal command on arrival in the postanesthetic recovery room and those who needed analgesics or antiemetics at any time in the postanesthetic recovery room were excluded from the study.
The remaining patients were immediately evaluated for somnolence and orientation on a 0-to-4 scale, as follows: 4 = unresponsive to verbal command or painful (pinprick) stimulation; 3 = responds to painful stimulation but not to verbal command; 2 = responds to verbal command and painful stimulation but is disoriented and does not initiate conversation; 1 = responds to all forms of stimulation, is well oriented but feels sleepy and does not initiate conversation; 0 = oriented and initiates conversation. After initial evaluation the patients were alternately assigned to one of two groups. Patients in Group A received physostigmine, 2 mg, iv, within a minute of initial evaluation and 2 mg, im, after one hour. Group B received no further medication. Repeat evaluations were made 5, 15, 30, 60, 120, and 180 minutes after the initial evaluation.

## Results

One hundred patients fulfilled the criteria for inclusion in the study and were equally divided into Groups A and B. There was no significant difference in the ages and weights of the patients in the two groups or in the amounts of Innovar they were given (table 1).

Seventy-eight per cent of the patients in Group A and 80 per cent in Group B were completely unresponsive (somnolence level 4), and the remainder were responsive to painful stimulation only (level 3) on arrival in the postanesthetic recovery room (table 2). Five minutes after physostigmine administration, 60 per cent of Group A patients were at somnolence level 2, 16 per cent at level 1, and 24 per cent were completely awake, oriented and initiating conversation (somnolence level 0). In contrast, after 5 minutes in the postanesthetic recovery room, all patients in Group B were still at somnolence level 3 or 4. Fifteen minutes after administration of physostigmine 62 per cent of Group A patients were at somnolence level 0. None of Group B patients had reached level 0 after 15 minutes in the postanesthetic recovery room; only 8 per cent were at level 1, and 64 per cent remained at level 3.

After 60 minutes the effectiveness of physostigmine began to wear off, and some of the patients in Group A who had been at somnolence level 0 had slipped back to level 1; however, no patient returned to a lower somnolence level, and there was still twice as many patients at levels 0 and 1 in Group A as in Group B. An hour after receiving a second dose of physostigmine (two hours after admission to the postanesthetic recovery room) 68 per cent of Group A patients were at somnolence level 0, while only 6 per cent of Group B patients were at the same level. Two hours after the second dose of physostigmine, some patients who had been at somnolence level 0 had again slipped back to level 1. At this time all Group A patients were at level 1 or 0, while 22 per cent of Group B patients were still disoriented and at level 3. Discharge from the recovery room after 180–240 minutes prevented further careful evaluation of all patients; however, 21 of Group A and 24 of Group B patients were seen 1–6 hours following discharge from the recovery room. No patient in either group was at a somnolence level other than 0 or 1, and all but four in Group A and six in Group B were at level 0.

## Discussion

Innovar has become popular as a sedative, premedicant, anesthetic induction agent and supplement during general anesthesia. One problem that frequently arises after its use is prolonged drowsiness and disorientation. This has been shown to be due primarily to long duration of action of droperidol. An agent that could reverse this undesirable effect of droperidol after termination of anesthesia would have enormous clinical usefulness.

Physostigmine has been found to be effective as a reversery agent after overdoses of anticholinergic drugs, phenothiazines, and tricyclic antidepressants. The results of our study demonstrate physostigmine is also effective as an antagonist to droperidol-induced CNS depression. We found that patients who were unresponsive or only slightly responsive to verbal command and painful

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<th>Table 1. Preoperative Data (Mean ± SD)</th>
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<tr>
<td><strong>Group A</strong></td>
</tr>
<tr>
<td>Age (years)</td>
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<tr>
<td>37 ± 14</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>63 ± 10</td>
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<tr>
<td>Innovar received (ml)</td>
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<td>4.6 ± 1.2</td>
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<tr>
<td><strong>Group B</strong></td>
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<tr>
<td>Age (years)</td>
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<td>33 ± 17</td>
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<tr>
<td>Weight (kg)</td>
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<tr>
<td>60 ± 12</td>
</tr>
<tr>
<td>Innovar received (ml)</td>
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<td>4.5 ± 1.2</td>
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stimulation and were disoriented became aware of their person, place of being, and the date within 3–11 minutes of intravenous administration of phystostigmine. This effect usually lasted more than 30 minutes, after which some of them again became somewhat more somnolent. Repeat intramuscular administration of phystostigmine after an hour completely reversed the returning somnolence, and the majority of the patients remained alert for an additional hour. Thereafter, some patients felt sleepy but none became disoriented or fell back to a somnolence level of more than 1.

The mechanism of action of droperidol and other butyrophenones is unknown, but is believed to depend on the ability to alter transmission at CNS membranes excited by dopamine and possibly also norepinephrine and hydroxytryptamine. It has been demonstrated that certain butyrophenones increase dopamine synthesis and synaptic release in CNS dopamine neurons. It has also been suggested that these drugs occupy postsynaptic dopaminergic receptors. All of these actions lead to a build-up of transmitter (dopamine) in the intersynaptic cleft and may, as a result, upset the balance of dopamine and acetylcholine in certain key sites in the brain, e.g., perhaps in the extrapyramidal nigrostriatal system, and lead to depression.

Physostigmine, a tertiary amine acetylcholinesterase inhibitor, causes stimulation of behavior and activation of the electroencephalogram in conscious rabbits. When given in high doses the drug can cause signs of bizarre motor activity. Presumably, this is the result of increased CNS acetylcholine synthesis or release, and possibly it also upsets the balance of dopamine and acetylcholine in certain areas of the CNS. While our data in this study do not demonstrate the mechanism of phystostigmine reversal of postoperative Innovar-induced somnolence, they do suggest that one action may be resetting the balance of CNS dopamine and acetylcholine concentrations originally upset by droperidol. However, another mechanism may be a nonspecific analeptic action of phystostigmine, as has been suggested by Bernard and others. Reported complications of phystostigmine treatment of overdosages of phenothiazines and anticholinergic drugs have included the usual side effects of anticholinergic administration, i.e., bradycardia, nausea and vomiting, bronchial constriction, etc., but have been minimal. Only one of our patients in this study sustained a heart rate of less than 50/min, while six complained of nausea and seven had vague abdominal cramps. Although the incidence of these undesirable effects is low, their potential seriousness demands that phystostigmine be given in areas where intensive monitoring and care is present.

The relatively short duration of action of phystostigmine after either intravenous or intramuscular administration is somewhat disconcerting. However, while some patients became somewhat sleepy after initial arousal following phystostigmine, all of them could be easily aroused with stimulation, and none re-
turned to a disoriented state in the post-anesthetic recovery room, or (in those observed), after discharge from the postanesthetic recovery room.

In summary, our data in this study demonstrate that physostigmine is an effective antagonist to the disorientation and somnolence that frequently follow the use of large doses of Innovar, and suggest that its use in the postanesthetic recovery room will shorten the durations of patient stays in this unit.

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