Clinical Studies with Innovar

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Neuroleptanalgesia (NLA) was introduced a decade ago as another approach to anesthetic management. The technique combines the use of a potent psychomotor sedative and a powerful analgesic agent to render the patient free of pain without affecting certain areas of the central nervous system that are blocked in conventional anesthesia.[1] According to Nilsson,[2] the term was adopted owing to a lack of more exact terminology to describe neurophysiologic effects which the technique provides. As such, it simulates balanced anesthesia and artificial hibernation in representing a change from the conventional methods of anesthesia. While other agents have been studied, the most satisfactory anesthetic conditions have been provided by a 50:1 mixture of droperidol and fentanyl (Innovar *).[3]

Janssen, *et al.*[4-5] and others [6-8] reported on the chemistry and pharmacology of the components of Innovar. Yelnosky *et al.*[9] and Dobkin *et al.*[10-12] have described the pharmacologic actions of Innovar. Many clinical investigations reported from abroad have stimulated studies in this country.[1, 3, 12-21] In essence, the latter indicate that Innovar has a negligible effect on hepatic, cardiovascular, and gastrointestinal function and is, therefore, safe when used as part of a balanced NLA technique. The lack of adverse effects appeared to increase the clinical utility of Innovar in patients in poor physical condition. Innovar possesses advantages and disadvantages. We have evaluated Innovar to reappraise it as an adjunct to nitrous oxide-oxygen anesthesia, and to assess its effect on the liver, kidney, blood count, and the electrocardiogram.

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* Innovar supplied for investigational use only, by McNeil Laboratories, Inc., Fort Washington, Pennsylvania.

Material and Method

A series of 156 patients were studied. Table 1 presents data relative to age, weight, sex and physical status. Sixty-six (42 per cent) patients were over 61 years of age and 51 (33 per cent) were considered to be in physical status 3, 4, or 5. Table 2 lists the operations performed, virtually all major.

In addition to routine physical examination and laboratory tests, the following were obtained, the day before and two days after operation, on 133 of the patients: (a) complete blood count; (b) gross and microscopic urinalysis; (c) alkaline phosphatase; (d) SGOT; (e) ECG (lead 2). In 16 patients lead 2 of the ECG was recorded approximately 20 minutes after induction since we believed this was the time at which changes would most likely occur. One hour prior to operation patients received an intramuscular injection of sodium pentobarbital (Nembutal, 50–200 mg.), and atropine sulfate, 0.6 mg.

Induction of anesthesia consisted of the intravenous injection of Innovar, and administration of nitrous oxide-oxygen (5:2 liters/minute) in a semiclosed system; placement of an endotracheal tube was facilitated by an intravenous injection (20–60 mg.) of succinylcholine. Injections of Innovar were given in 2 ml. (each ml. contained 2.5 mg. droperidol and 0.05 mg. fentanyl) increments at a rate of 1 ml./60–120 seconds; 1 ml. increments were employed in poor risks. Induction doses were given over a period ranging from 3–15 minutes until the patient became somnolent. Hypoventilation was detected by the use of a ventilometer and was corrected by assisting respiration.

TABLE 1. Age, Weight, Sex and Physical Status

Age Range (yrs.)	Total Patients	Weight Range (lbs.)	Sex		Physical Status				
			Women	Men	1	2	3	4	5
10–20	1*	120	1	0	1	0	0	0	0
21–30	3	135–204	2	1	3	0	0	0	0
31–40	15	130–250	7	8	11	1	3	0	0
41–50	32	98–218	10	22	16	12	4	0	0
51–60	39	116–258	14	25	13	19	7	0	0
61–70	35	110–202	19	16	1	19	10	5	0
71–80	21	114–215	12	12	0	7	13	2	2
81–90	7	95–174	3	4	0	2	5	0	0
Totals	156	—	68	88	45	60	42	7	2

* 17 year-old.

Anesthesia was maintained in the first plane with nitrous oxide-oxygen (5:2 liters/minute) and intravenous administration of Innovar and succinylcholine. The indications for the administration of additional doses of Innovar were rises in the pulse rate and blood pressure, suggesting the need for more analgesia.

All patients were brought to the post-anesthesia recovery room and observed for cardiovascular, respiratory, and central nervous system changes until recovery from anesthesia.

FINDINGS

Induction. Induction of anesthesia was, on the average, accomplished in five to ten minutes. Postoperatively patients indicated that induction was pleasant. During induction signs consisted of miosis, changes in heart rate, hypotension, hypoventilation, apnea, and rigidity of the thorax and/or lower extremities. Rigidity of the thoracic musculature has been reported to be caused by the fentanyl component of Innovar and in our experience seemed to be related to the rate of administration. Thoracic rigidity occurred in over 90 per cent of the patients to whom the total induction dose was administered within ten minutes. Rigidity did not occur in those patients to whom the induction dose was administered during a 12 to 15 minute period. Succinylcholine administered prior to endotracheal intubation relieved the rigidity. When succinylcholine was administered with Innovar, thoracic rigidity was rarely seen.

Pulse Rate. Baseline pulse rates varied from 60 to 144 per minute. During induction, changes occurred in 95 patients; most were minor, transient, and have no direct relation to changes in blood pressure, although a significant decrease in blood pressure (30 to 40 mm. of mercury systolic) accompanied bradycardia in three cases. Of the 17 instances of change in pulse rate of more than 20 beats per minute, there were 16 instances of bradycardia and 1 of tachycardia.

Blood Pressure. In most patients, systolic blood pressure fell during the initial administration of Innovar and then stabilized at lower than baseline values. Of 98 patients who experienced hypotension, 16 had changes of more than 30 mm. of mercury. Patients with histories of cardiovascular and significant pulmonary problems had a greater tendency toward hypotensive episodes.

Five of the 16 patients required circulatory support as a result of hypotension; prompt

TABLE 2. Surgery Performed with Innovar-Nitrous Oxide Anesthesia

Region	Cases
Head and neck	7
Thoracic	12
Abdomen	100
Retroperitoneal	5
Groin and pelvis	19
Extremities	13
Total	156

TABLE 3. Duration of Postoperative Analgesia as Determined by the Need for Administration of Narcotics

Time Until Administration of Narcotic (Hours)	Patients	Percentage
8+	42	26.9
7–8	22	14.1
5–6	22	14.1
3–4	17	10.8
0–2	20	12.8
None administered	33	21.1

correction resulted from intravenous single or multiple 15 to 30 mg. doses of mephentermine (Wyamine) and, occasionally, intravenous phenylephrine (Neo-Synephrine).

Electrocardiogram. Electrocardiograms recorded in 16 patients 20 minutes after induction were not remarkable; bradycardia occurred in 2 and tachycardia in 3 patients. A comparison of the preoperative and postoperative electrocardiograms for 133 patients showed occasional ventricular extrasystoles and changes in heart rate. Minimal nonspecific changes in T waves appeared in 4 patients.

Maintenance. Total doses of Innovar during maintenance ranged from 5 to 29 ml. (12.5 mg. droperidol and 0.25 mg. fentanyl to 72.5 mg. droperidol and 1.45 mg. fentanyl) for procedures lasting as long as 9 hours. Arrhythmias, bradycardia and hypotension developed during the maintenance period; none of these complications was serious.

Postanesthetic Period. As judged by the ability to respond to visual stimuli and to talk one hundred and twenty-two of 156 patients emerged from anesthesia within 10 minutes, 28 in 10 to 25 minutes, and 6 in 25 to 35 minutes. Rapidity of emergence from anesthesia was independent of the dose of Innovar and the duration of the operation.

Postoperatively, the time until a narcotic was required was considered as the period during which analgesia persisted (table 3). Table 4 presents data on 10 patients who experienced complications. Two of the patients with postoperative complications died and are commented on in the discussion section.

Laboratory Studies. Urine analyses performed postoperatively indicated no significant changes from values preoperative. There were no significant variations in the pre- and postoperative values for hemoglobin, hematocrit, and red cell counts that could be ascribed to the anesthetic. Differential white cell counts tended to show small increases in polymorphonuclear leukocytes two days after operation.

Pre- and postoperative values for serum glutamic oxalacetic transaminase and alkaline phosphatase tests appear in table 5. Elevation of these values occurred in 14 patients. Elevations in SGOT and serum alkaline phosphatase are considered to have arisen from either the patient's disease or from the operation performed.[22]

TABLE 4. Data Concerning Patients and Their Postoperative Complications

Case	Age	Physical Status	Operation	Minutes	Complication	Remarks
1	33	1	Cholecystectomy	95	Hypotension	Recovered spontaneously
2	68	2	Thyroidectomy	35	Hypotension	Neo-Synephrine or ephedrine injection; recovered
3	73	2	Inguinal hernia	70	Hypotension	Recovered spontaneously
4	53	1	Cholecystectomy	145	Hypotension	Recovered spontaneously
5	85	3E	Cholecystectomy	195	CV and respiratory depression	Died 36 hours postoperatively
6	73	4E	Drain subphrenic abcess	80	CV and respiratory failure	Died 10 hours postoperatively
7	45	1	Cholecystectomy	40	Apnoea	Reintubated, recovered
8	79	3	Colostomy	75	Hypoventilation	Administered O_2, recovered
9	62	3	Gastrectomy	170	Severe coughing	Administered O_2, aerosol inhalations,
10	65	3	Closure of colostony	130	Muscular rigidity	Transient, recovered

TABLE 5. Data on Patients Who Had Abnormal Values for Liver Function Tests

Case No.	Age (yrs.)	Physical Status	Operation	SGOT* Serum Glutamic Oxalacetic Transaminase			Alkaline Phosphatase†	
				Minutes	Preop.	2nd day Postop.	Preop.	2nd day Postop.
30	74	3	Abdominal laparotomy, biopsy liver (CA)	78	10	52	12	75
31	40	1	Gastrectomy	210	5	60	4	4
37	44	2	Cholecystectomy, hiatal herniorrhaphy	114	15	64	3	4
46	58	3	Abdominal laparotomy, gastroenterostomy, liver biopsy	90	19	46	6	5
54	82	2	Cholecystectomy, cholangiogram	126	36	48	4	2
57	42	1	Cholecystectomy, cholangiogram	120	12	64	2	2
60	71	3	Abdominal laparotomy, gastrojejunostomy, omental biopsy	78	42	49	4	6
62	71	3	Cholecystectomy, common duct expl., pancreatic biopsy	188	17	64	8	4
74	59	2	Abdominal laparotomy	120	7	65	3	7
22	50	2	Cystectomy, ileal bladder	555	28	46	6	3
27	36	1	Trans-abdominal colotomy, polyectomy	105	12	52	4	3
26	60	2	Vagectomy, gastroenterostomy	165	18	22	6	8
93	64	2	D & C, laparotomy, ovarian cystectomy	135	10	17	3	10
44	67	2	Whipple procedure	330	216	126	35	10
53	65	2	Cholecystectomy, hiatal herniorrhaphy	150	96	39	4	4
71	62	2	Cholecystectomy, cholangiogram	120	320	145	30	20

* SGOT—Sigma colorimetric method—normal <45.
† Alkaline phosphatase—modified Gomori method—normal 1–6.

DISCUSSION

The results of the study substantiate those of previous investigators in that a variety of surgical procedures can be performed safely and effectively with the use of Innovar, nitrous oxide, and succinylcholine. Emergence from anesthesia was rapid and of the same order as from N_2O–curare. Analgesia was excellent. There was a small incidence (3 of 156 patients) of nausea, retching, and/or emesis during the 24 hours postoperatively. Gastric tubes were used where indicated.

Two of the patients died postoperatively. The first was an 85 year old white woman, physical status 3E, with chronic cholecystitis, acute pancreatitis, severe jaundice, generalized arteriosclerosis, coronary insufficiency and right bundle branch block. She underwent a 195 minute operation during which the abdomen was explored and the gallbladder removed. Operation and anesthesia proceeded uneventfully and she was brought to the recovery room; 120 minutes thereafter, she had a marked drop in blood pressure and experienced respiratory insufficiency. Despite energetic supportive therapy, cardiovascular and respiratory depression continued. She died thirty-six hours postoperatively of cardiovascular collapse. Permission for autopsy could not be obtained.

The second death was that of a 73 year old white woman, physical status 4E, with marked jaundice, hyperpyrexia (103° F.), impending liver failure, and acute pancreatitis. She underwent an 80 minute operation during which a subphrenic abscess was drained. The postoperative course was stormy, initiated by gradual cardiovascular depression, then collapse and subsequent respiratory failure. She died 10 hours postoperatively. Death was believed due to pancreatitis, sepsis, and septic shock. An autopsy was not performed.

Most of the cases of hypotension observed in the study were of little significance with no association between the hypotensive episodes and the cumulative dose of Innovar. Significant hypotension was believed to be due to preoperative hypovolemia and to surgical manipulation or hemorrhage.

Laboratory test results reinforced the impression of Tornetta and Boger [16] and of Dobkin *et al.*[1] that Innovar is non toxic to the liver and does not have adverse effects on blood cells or urinary function.

The thoracic rigidity observed during induction constituted a problem. Our experience suggests that the rigidity may be related to the speed with which the induction dose is administered. Further studies are recommended to determine the association between speed of injection and the occurrence of thoracic rigidity and hypotensive episodes.

Summary and Conclusions

One hundred and fifty-six patients were anesthetized for a variety of operations with Innovar (droperidol 2.5 mg. and fentanyl 0.05 mg./ml.) and nitrous-oxide, oxygen, and succinylcholine. Anesthesia was characterized by an induction time of 3–15 minutes (average 5 minutes) and was accompanied by hypoventilation, apnea, thoracic muscular rigidity, changes in heart rate and miosis. Respirations were controlled.

Maintenance of anesthesia was adequate for operation but accompanied by 7 instances of hypotension, one severe. Recovery from anesthesia was prompt, almost free of nausea and retching, and accompanied by relatively long periods of analgesia and amnesia. Significant postoperative complications consisted of respiratory depression (3 cases) and hypotension or vascular collapse (6 cases). Two poor-risk patients died 10 and 36 hours postoperatively.

There were no toxic effects on the liver as determined by the SGOT and alkaline phosphatase and no significant changes in urinary composition, hemograms and electrocardiograms.

These findings suggest that Innovar can be used successfully in a balanced anesthetic technique as an adjunct to nitrous oxide-oxygen anesthesia for a wide variety of operations with patients in all physical states.

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An Effective Method for the Treatment of Hiccups During Anesthesia

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Effective treatment of hiccups during anesthesia is important for many obvious reasons. Hiccup is seen more frequently during light anesthesia when muscle relaxation is produced by neuromuscular blocking agents. It is often associated with the slow return of diaphragmatic activity as relaxation starts to wear off.[2]

The afferent limb of the reflex arc producing hiccups is the vagus nerve and, possibly, the phrenic nerve and the sympathetic chain from the sixth to twelfth thoracic segments. The center is located at cervical cord levels 3 to 6.[1, 2] Other afferent pathways may also exist. The efferent limb is the phrenic nerve.[1, 2] Afferents may arise from almost any part of the body but, during anesthesia, are most frequently associated with stimulation of the diaphragm by irritating fluids such as blood, pus, or gastric juice.[3] It may also occur in disorders of the esophagus, dilatation of the stomach, inflation of the stomach with anesthetic gases, intestinal obstruction, ileus, pancreatitis, peritonitis, pericarditis, traction on viscera and nerves, and in toxic conditions such as uremia.[3, 4]

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Various methods of treating hiccups have been described[3, 4]: deepening the anesthesia, incremental doses of a muscle relaxant, pressure on the eyeballs, pressure on the common carotid artery, vagal blockade by local anesthesia, phrenic nerve block, electrophrenic stimulation, relieving distention if present, carbon dioxide inhalation, and hyperventilation. Amyl nitrite, ether, intravenous edrophonium, atropine, chlorpromazine, and other central nervous system depressants have been used with varying results. None of these procedures can be considered totally effective in the management of hiccups.

It occurred to me that the presence of an oral endotracheal tube might possibly be a triggering mechanism of hiccups and I was able to observe that the spraying of lidocaine around the endotracheal tube in the pharynx through a catheter resulted in cessation of the hiccups in a few cases. Dr. Anis Baraka of Cairo University, Egypt, suggested to me that it has been his experience that the mere passage of a catheter through the nose into the nasopharynx frequently abolished hiccups.* Following Baraka's suggestion, nasopharyngeal

* Baraka, A.: Personal communication.