INNOVAN-N₂O ANAESTHESIA IN NORMAL MEN EFFECT ON RESPIRATION, CIRCULATORY DYNAMICS, LIVER FUNCTION, METABOLIC FUNCTIONS, ACID-BASE BALANCE, AND PSYCHIC RESPONSES*

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MUNDELEER AND DeCASTRO induced an analgesic and sedative state for surgical procedures, without using barbiturates or volatile anaesthetic agents, which they called neuroleptanalgesia. They employed a combination of drugs developed by Janssen in Belgium to accomplish this state and many anaesthetists are now using this technique in Europe ¹⁻⁶

Of the numerous new analgesic and sedative drugs recently developed by Janssen, the combination of droperidol (R4749, dehydrobenzperidol, Inapsine®) and fentanyl (R4263, phentanyl, Sublimase®) in a 50:1 mixture has been found to provide the most satisfactory anaesthetic conditions in both animals and in man, without causing serious physiological disturbances that cannot be controlled effectively ^{7,8}. The pharmacological properties of these two drugs are summarized in Table I.

TABLE I
SUMMARY OF PHARMACOLOGICAL PROPERTIES OF DROPERIDOL AND FENTANYL

<p>dehydrobenzperidol R4749</p> <p>DROPERIDOL (LACTATE) 1 mg/ml (INAPSINE)</p>	<p>50:1 MIXTURE</p> <p>↓</p> <p>INNOVAN</p>	<p>phentanyl R4263</p> <p>FENTANYL (CITRATE) 0.02 mg/ml (SUBLIMASE)</p>
<p>DROWSINESS & TRANQUILITY POTENT onset 5-10 minutes duration 6-12 hours</p> <p>VASOMOTOR REFLEX SUPPRESSION weak</p> <p>HYPOTENSION weak mild orthostatic response may last several hours</p> <p>ANTIADRENALIN EFFECT POTENT prevents hypertensive response to epinephrine protects dogs against ventricular arrhythmias due to epinephrine during pentobarbital anaesthesia protects rats against drum shock</p> <p>ANTIEMETIC ACTION POTENT</p> <p>POTENTIATION OF THIOPENTAL POTENT</p> <p>EXTRAPYRAMIDAL SEIZURES FREQUENT twitching facial muscles oculogyric seizures stiff neck muscles trembling hands reversed with atropine or cogentin</p> <p>BEHAVIOURAL DISTURBANCES occasional</p>	<p>ANALGESIC ACTION POTENT (>50 x morphine) onset 2-5 minutes duration 30-45 minutes</p> <p>RESPIRATORY DEPRESSION SEVERE onset 5-10 minutes duration 15-60 minutes</p> <p>VAGAL STIMULATION (CENTRAL) causes bradycardia & sweating blocked by atropine</p> <p>CATALEPTIC RIGIDITY OF MUSCLES lead pipe muscles develop with 0.1 mg relieved by curare or succinylcholine</p> <p>EMETIC ACTION very weak</p> <p>DEFECATION RESPONSE present in dogs</p> <p>HISTAMINE IS NOT RELEASED</p> <p>NALORPHINE & ALVALORFAN REVERSE ALL EFFECTS OF FENTANYL</p>	

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Those who have used neuroleptanalgesic mixtures for anaesthesia have found it desirable to add the inhalation of nitrous oxide and oxygen to remove conscious awareness and to ensure a more pleasant anaesthetic^{9 10}

This study was undertaken to determine the effects of intravenous injection of the combination of droperidol and fentanyl in the proportion of 1 mg/ml + 0.02 mg/ml (50 to 1), known as Innovan, followed by the inhalation of nitrous oxide and oxygen (60:40). The effects on circulatory dynamics, pulmonary ventilation, liver function, and acid-base balance were measured in young, normal, male subjects in experiments which were devised to simulate clinical conditions.

PROCEDURES

Volunteer subjects were examined initially and 16 men who were judged to be in excellent health were selected after preliminary laboratory tests were returned and showed normal values (see Table II). The various test procedures to be carried out were explained and a formal consent was obtained from each subject who agreed to participate in the experiments.

Twenty-four anaesthetics were administered. Two subjects received three anaesthetics at one-week intervals, 4 subjects received two anaesthetics a week apart, and 10 subjects received one anaesthetic each.

On the day of an experiment, each subject was admitted, in the fasting state, to the University Hospital of New York State University at Syracuse. After a routine physical examination, a questionnaire was completed to evaluate the mood evoked in the subject by the experimental situation (Table III). Blood pressure, pulse rate, pupil size, minute volume, respiratory rate, and oral and axillary temperature were measured and recorded. A venous blood sample was drawn (without use of a tourniquet) for fibrinolysin estimation, and an infusion of 1000 ml of 0.9 per cent saline was started in a forearm vein. One hour before induction of anaesthesia, the subject was premedicated with 0.3 mg atropine and 0.3 mg scopolamine given by intramuscular injection.

At the appointed time, the subject was transported by cart to the operating room. Blood pressure, pulse rate, respiration rate, minute volume of breathing, lead 2 of the electrocardiogram, pupil size, and skin temperature were measured and recorded again just prior to induction of anaesthesia. Bromsulphalein dye (5 mg/kg) was injected intravenously through the same needle used for the saline infusion and an arterial blood sample was drawn anaerobically from the femoral artery for subsequent measurement of the pH, P_{CO_2} and P_{O_2} .

The minimum total dose of Innovan was set at 10 ml, or 1 ml/15 lb body weight. Anaesthesia was induced in two stages, as follows. Twenty per cent of the total dose was injected into the infusion tubing and the clamp regulating the rate of the infusion was released to ensure rapid absorption of the drugs. The subject was observed closely for ten minutes after the initial injection of Innovan. At 5 minutes and again at 10 minutes, ECG (lead 2), pulse rate, blood pressure, rate of respiration, minute volume, skin temperature and moisture, pupil size, and subjective reactions were checked and recorded. The remaining 80 per cent of the Innovan was then injected. As soon as the subject became unresponsive, an

TABLE II
VITAL PHYSICAL AND LABORATORY DATA OF VOLUNTEER MALE SUBJECTS

	Age	Height, inches	Weight, pounds	Build*	Blood pressure, mm Hg	Pulse rate, per min	Cardiac output,† litres	HGB, gm	HCT, %	Urinalysis	Resp rate, per min	Tidal vol,‡ ml	Min vol, litres
1 A	29	72	231	O	150/80	82	6.5	16.2	41	normal	13	650	8.5
2 A	23	76	202	M	125/70	72	5.2	14.6	42	normal	14	550	7.7
3	21	71	163	L	130/65	84	6.9	17.0	48	normal	20	380	7.6
4	24	68	174	M	115/80	76	4.3	15.8	40	normal	20	390	7.8
5 A	29	66	150	M	130/80	100	6.7	15.9	47	normal	17	390	6.7
6	21	73	146	L	130/75	84	6.0	17.0	50	normal	18	370	6.7
7	25	70	155	L	120/70	76	5.2	14.4	45	normal	20	390	7.8
8	24	70	185	M	118/65	60	4.5	17.2	50	normal	20	400	8.0
9	28	70	156	M	135/75	74	5.1	16.6	50	normal	16	410	6.6
10	21	70	180	M	124/64	84	6.7	16.9	48	normal	16	460	7.4
11 A	26	70	175	M	110/56	64	5.1	14.5	44	normal	22	380	8.4
12 A	25	64	118	L	115/65	76	5.4	12.9	39	normal	19	310	5.9
13	21	72	165	M	120/70	60	4.4	16.7	43	normal	16	420	6.7
14	23	66	130	L	140/70	84	6.7	17.1	46	normal	12	440	5.3
15 A	23	68	144	L	120/70	78	5.5	18.0	50	normal	18	360	6.5
16	23	68	152	M	100/60	60	4.3	16.3	45	normal	16	400	6.4
1 B	29	72	230	O	130/80	86	5.8	17.7	49	normal	16	560	8.9
2 B	23	76	200	M	120/70	76	5.3	15.0	43	normal	12	600	7.2
5 B	29	66	150	M	125/75	104	6.6	17.3	49	normal	16	400	6.4
11 B	26	70	173	M	105/50	64	5.3	15.1	43	normal	20	390	7.8
12 B	25	64	116	L	110/70	72	4.8	13.3	38	normal	16	330	5.3
15 B	23	68	140	L	120/60	90	7.3	17.0	49	normal	18	360	6.5
1 C	29	72	230	O	130/80	86	5.7	17.7	46	normal	14	600	8.4
5 C	29	66	150	M	115/75	96	5.9	17.3	47	normal	14	440	6.2

*L = lean, M = medium, O = obese

†Estimated from Jackson nomogram ¹²

‡Estimated from Radford nomogram ¹¹

TABLE III
 QUESTIONNAIRE FOR MOOD EVALUATION
 Questionnaire to be Completed Before Test with Innovan
 for Evaluation of Mood

Circle only Yes or No

Are you

I	anxious	Y	N	II.	itchy	Y	N	III.	drowsy	Y	N
	apprehensive	Y	N		nauseated	Y	N		tired	Y	N
	nervous	Y	N		dizzy	Y	N		sleepy	Y	N
	jittery	Y	N		warm	Y	N		sluggish	Y	N
	self-conscious	Y	N		chilly	Y	N		weak	Y	N
	shy	Y	N		headachy	Y	N		weary	Y	N
	timid	Y	N		hungry	Y	N		indifferent	Y	N
	emotional	Y	N		twitchy	Y	N		relaxed	Y	N
IV.	unhappy	Y	N	V.	cheerful	Y	N	VI.	quiet	Y	N
	sad	Y	N		joyous	Y	N		peaceful	Y	N
	blue	Y	N		enthusiastic	Y	N		satisfied	Y	N
	downhearted	Y	N		talkative	Y	N				
	detached	Y	N		active	Y	N				
	brooding	Y	N		vigorous	Y	N				

anaesthetic face mask was applied to provide inhalation of nitrous oxide and oxygen (60/40) using a semi-closed circuit. The anaesthetic machine was set to deliver at least 12 litres per minute.

During the following 30 minutes, vital signs were checked at least every 10 minutes. If breathing became very shallow or apnoea ensued, pulmonary ventilation was assisted or controlled as judged necessary. Ten minutes after the total dose of Innovan was administered, a second venous blood sample was drawn (without tourniquet) for estimation of fibrinolysin. Forty-five minutes after starting the anaesthetic, a venous blood sample was drawn for estimation of bromsulphalein dye retention. The operating table was tilted, over a one-minute period, to a 45° head-up position and vital signs were recorded at 5-minute

intervals for 15 minutes. The horizontal position was then resumed. Vital signs were checked for an additional 15 minutes, then blood samples were drawn for estimation of serum bilirubin, blood sugar, serum potassium, blood urea nitrogen, SGOT, SGPT, arterial pH, P_{CO_2} and P_{O_2} .

At the end of the period of the experiment (60 minutes after the injection of the 80 per cent dose of Innovan), the nitrous oxide and oxygen were discontinued and the face mask was removed. The subject was asked, in sequence, at about one-minute intervals: Open your eyes! What is your name? What is your address? What time is it? The time at which the subject responded to these correctly was recorded.

The subjects were then transferred to the recovery room, where they were observed closely and their vital signs were checked and recorded at 10-minute intervals. After 20 minutes in the recovery room, each subject was sat up, to check subjective and other responses to the head up posture. When judged to have recovered adequately, they were returned to the ward to dress and were discharged. Each subject was escorted home either on foot or by car and was instructed to return the following day to answer a questionnaire (see Table IV) and to report for follow-up study of his physical condition. They returned for further blood studies and follow-up 5 days after the test.

LABORATORY METHODS

Blood pressure was measured by applying a Riva Rocci cuff to the right arm over a stethoscope secured over the brachial artery pulsation just proximal to the elbow. The standard auscultatory method was used as recommended by Bordley *et al*¹³. The arm was held at heart level throughout the test. Pulse rate was counted at the wrist. The electrocardiogram (lead 2) was observed continuously on a Cambridge operating room cardioscope, from which the heart rate was counted. Recordings were made at regular intervals on a Cambridge "Simple Scribe" direct-writing electrocardiograph. Minute volume of respiration was measured with a Wright Respirometer attached to a snug-fitting face mask. Rate of respiration was counted for one minute at the regular intervals during which measurements of the minute volume were taken.

Arterial blood samples were analysed for pH, P_{CO_2} and P_{O_2} on an Epsco-Medical Blood Parameter Analyzer, Model 101, which utilizes a constant-temperature bath (set at 37° C), a Metrohm constant-temperature pH electrode, a Clark platinum silver membrane-covered electrode for measuring oxygen tension,¹⁴ and a carbon dioxide tension electrode.¹⁵ Haematocrit values were determined by the Natelson micromethod¹⁶ and haemoglobin values were measured on a spectrophotometer using standard solutions of cyanmethaemoglobin.

Plasma bicarbonate was estimated with the Singer and Hastings nomogram¹⁷. Oxygen per cent saturation was derived from the Rahn and Fenn line chart.^{18, 19} Fixed acid accumulation (the change in plasma bicarbonate at pH 7.40) was derived by plotting the blood data on the pH- P_{CO_2} -plasma bicarbonate diagram of Davenport.²⁰ Blood sugar was measured by a photoelectric method²¹ and blood urea nitrogen by the diacetyl method²², serum potassium was measured by the

TABLE IV

QUESTIONNAIRE FOR POSTANAESTHETIC EVALUATION

Questionary to be Completed 24 Hours After Test with Innovan

1. Did anything unpleasant occur before going to sleep ? _____

- 2 Do you remember going to sleep ? _____
3. What's the first thing you recall upon awakening ? _____

4. What time was it when you awakened ? _____
- 5 Did you hear or feel anything after I said you are going to sleep ? _____

- 6 Did you have any kind of discomfort since the test ? _____

C N S			A. N S		
Drowsiness	Y	N	Dizziness	Y	N
Stiffness	Y	N	Faintness	Y	N
Tremors	Y	N	Blurred Vision	Y	N
Drunken	Y	N	Dry Mouth	Y	N
Restlessness	Y	N	Nausea	Y	N
Sleep Disturbances	Y	N	Vomiting	Y	N
Muscle Incoordination	Y	N	Stuffy Nose	Y	N
Muscle Twitching	Y	N	Constipation	Y	N
Muscle Pains	Y	N	Diarrhea	Y	N
Muscle Weakness	Y	N	Urinary Urgency	Y	N
Slurred Speech	Y	N	Excess Perspiration	Y	N
Confusion	Y	N	Sore Veins	Y	N
			Itchy or Red Skin	Y	N

method using a Model 21 Coleman Flame Photometer, and serum glutamic oxalacetic and pyruvic transaminases by a colorimetric method²³ Fibrinolytic (plasmin) activity was estimated by the fibrin plate method,²⁴ and prothrombin

time by the modified method of Quick²⁵ Serum bilirubin was measured quantitatively by the VanDenBergh direct and indirect reactions²⁶ Serum alkaline phosphatase was measured in King Armstrong units²⁷ and serum clearance of 5 mg/kg sulphobromophthalein was measured quantitatively 45 minutes after injection²⁸

The questionnaire that was completed *before* the anaesthetic test was adapted from Smith and Beecher²⁹ to evaluate the psychological response to the test situation, and the questions at the end of the test were intended to time the rate of recovery beyond the "sleep threshold,"³⁰ that is, response to verbal command (Open your eyes!), sluggish verbal response (What is your name?), alert verbal response (What is your address?), and alert visual response (What time is it?)

The questionnaire used 24 hours *after* the test was compiled to gather information of interest and importance to an over-all evaluation of the anaesthetic

All the physiological parameters that were measured were recorded digitally on a table prepared for the experiment for each subject. These individual data, together with the results of the various blood tests, were studied with respect to the normal range of values. They were also analysed statistically to determine mean values and standard deviation in the group, to attempt to expose gross deviations or trends away from normal values. Subsequently, appropriate data were graphed.

RESULTS

Observations during Induction of Anaesthesia

Most of the 16 subjects were obviously nervous when brought to the operating room, in spite of the fact that all participating investigators worked as quietly and quickly as possible in preparing the subjects for the test (see Fig 1 and Table V). Nevertheless, the initial 20 per cent dose of Innovan appeared to be

TABLE V
SUMMARY TABLE SHOWING EFFECT OF TEST SITUATION ON RESPONSES TO MOOD ADJECTIVES IN GROUPS AND TO PHYSICAL SIGNS PRECEDING THE TEST

Yes answer to subjective questions		0	1	2+
I	Fear	8	5	11
II	Discomfort	13	10	1
III	Depression	5	8	11
IV	Dejection	20	4	0
V	Elation	1	7	16
VI	Tranquillity	4	3	17
Objective signs		Normal	Slight	Marked
1	Tachycardia	6	6	12
2	Tachypnoea	13	5	6
3	Hypertension	14	6	4
4	Hyperventilation [*]	9	3	12
5	Dilated pupils [†]	14	4	6

^{*}25% + greater than minute volume predicted by Radford

[†]8 mm + before atropine + scopolamine

FIGURE 1 Summary chart showing response to mood questions *before* the test

enough to render all but two subjects quite drowsy serene and relaxed. One subject (12A) became unconscious after the initial dose and one subject (10) became somewhat belligerent complained of a general feeling of discomfort (closed in feeling) and was not sleepy.

Effect on Respiration

Within 5 minutes of injecting the full dose of Innovan, all subjects became unconscious and virtually apnoeic, and it was deemed necessary to augment their respiration. One subject (5) became semi-conscious again within 15 minutes in three tests and had to be given supplementary doses up to 4 ml of Innovan, in each case, to restore quiet general anaesthesia (see Fig 2). One other subject (13) seemed to be very lightly anaesthetized, as evidenced by slight movements

FIGURE 2 Anaesthetic chart from experiments on subject No 5. Observe that a supplementary dose of Innovan had to be given to maintain smooth quiet anaesthesia even though the subject could not breathe adequately without assistance.

[illegible]

AIRWAY
End tracheal

MAINTENANCE
B₁ = blood sample for fibrinolysis
B₂ = arterial blood sample and BSP dye injected
B₃ = 20 dos Innovan
B₄ = 1st fibrinolysis
B₅ = blood sample for BSP estimate
B₆ = 1 minute 1st arterial and venous blood samples drawn
B₇ = Transfer subject to recovery room
P₁ = Subject sitting
P₂ = Discharged

Min. Vol. liters

Pupils

h

Time (min)

Legend:
B₁ B₂ B₃ B₄ B₅ B₆ B₇
P₁ P₂

FIGURE 3 Anaesthetic charts from experiments on subject No 11. Observe that during the first test his pulse and blood pressure rose when he was tilted, but respiration remained depressed. At the next experiment, his pulse rate rose briefly and there was a sharp increase in the minute volume during the tilt, then these parameters decreased when the table was levelled.

FIGURE 4 Anaesthetic charts from experiments on subject No 12. Observe that this subject received 10 ml of Innovan, which was more than 1 ml per 15 lb body weight. This caused severe respiratory depression during the entire period of the test. The following week, the same dose also caused severe depression, but of shorter duration.

of the extremities and facial muscles throughout the test period, but a supplemental dose of Innovan was not required. In all but four subjects, adequate ventilation returned within 45 minutes, and spontaneous ventilation could be permitted when the operating table was tilted to the 45° head-up position during 16 of the experiments. The rate of breathing was lowered appreciably in all the subjects from the time of the initial dose until well into the postanesthetic recovery period. One subject (11A) did not resume adequate breathing until the end of the test. When the test was repeated one week later (11B), he began to breathe when he was tilted, then moderate respiratory depression recurred when the table was restored to the horizontal position (see Fig 3). One subject (12A) remained apnoeic throughout the test and for 8 minutes after the nitrous oxide was discontinued (see Fig 4). When a second anaesthetic was given to this subject one week later, he was apnoeic until tilted, then resumed breathing (as occurred with subject 11) and his minute volume of breathing was adequate by the end of the test (12B).

In every case, there was a variable period after the full dose of Innovan was given when it was difficult to ventilate the subjects, although the airway seemed to be clear. The thoracic muscles were evidently quite rigid. The cheeks and neck overlying the pharynx were seen to bulge out with each compression of the breathing bag, and even with peak airway pressures of 30–40 mm Hg only slight motion was seen in the epigastrium. Inserting an oral airway was easy, but this did not assist air entry into the lungs. The thoracic rigidity lasted at least 5 minutes in all of the subjects, and as much as 40 minutes, during four tests. It seemed that most of these subjects probably had a moderate amount of laryngeal and bronchial spasm as evidenced by stridor, phonation, and difficulty in inflating the lungs even when the thoracic spasm appeared to relax.

Eye signs Immediately following the initial dose, the pupils became constricted almost to pinpoint size, the conjunctivae became injected, and the subjects had difficulty keeping the eyelids open. The relatively small dose of Innovan apparently was sufficient to produce a bilateral Horner's syndrome.

Skin Skin was warm and dry, and veins were well filled after induction of anaesthesia, and remained so during the tests. None of the subjects had any appreciable visible perspiration. During the early stages of the test, a few subjects developed slight cyanosis because of the difficulty in providing adequate pulmonary ventilation, but the cyanosis cleared rapidly with persistent efforts to produce an adequate tidal volume. It was not necessary to administer a muscle relaxant or other drugs to facilitate restoration of effective breathing.

Effect on Circulation (Figs 5 and 6)

Systolic blood pressure fell very slightly in 11 tests and sharply (34%) in 1, while in the remaining 12 tests, the blood pressure remained virtually constant or rose slightly.

Diastolic blood pressure changed in the same direction as the systolic pressure, so that there was no appreciable alteration in the pulse pressure.

Pulse rate decreased appreciably immediately after induction in 16 subjects, showed little or no change in 4 subjects, and increased moderately in 4 subjects.

FIGURE 5 Summary chart of mean physiological measurements from the 24 experiments

FIGURE 6 Summary of the cardiovascular effects of Innovan

Electrocardiogram In almost all the tests, the lead 2 tracing appeared to be remarkably uniform. Minor non-specific changes in T waves were seen in a few instances, associated with changes in heart rate and, in some subjects, with changes in body position, but none of the changes that were seen warranted concern.

Responses to tilting 45° head up Immediately after tilting, there was a moderate rise in systolic blood pressure during 6 experiments, no change during 10 experiments, a slight fall in 7, and a sharp fall in 1. The diastolic pressure rose in 11 subjects, there was no change in 10 subjects, and a fall in 3 subjects. The over-all effect was a slight decrease in pulse pressure (see Figs 7 and 8). In subject 3, the blood pressure fell sharply below 70/40 within 5 minutes of tilting. The tilt table was reduced to 30°, resulting in a prompt rise of the blood pressure to 84/40, but it fell again shortly thereafter, so the tilt was reduced to 20°, whereupon the pressure rose again to a little over 80/40. There it remained virtually unchanged until the end of the anaesthetic (see Fig 9).

The pulse rate increased immediately after tilting during 20 of the experiments, it did not change in 3 subjects, and it slowed gradually in 1 subject. During the rest of the period of tilt, the pulse rate continued to rise in 2 subjects, remained steady in 9, and fell gradually to the rate before tilting in 9 subjects.

Spontaneous breathing was judged to be adequate at the time of tilting during 11 experiments, of the remainder, 5 were being assisted and the other 8 had to be controlled. There was little or no change in the spontaneous respiratory rate in response to tilting. Three subjects, who were virtually apnoeic just prior to the time of tilting, began to breathe within 5 minutes after the tilt. The subject who had a sharp fall in blood pressure in response to tilting (No 3) was apnoeic at the time and did not resume spontaneous breathing until the last 5 minutes of the tilt test. When tilted, 8 of the 11 subjects who were breathing adequately had a marked increase in the minute volume of breathing, 2 subjects had no change, and 1 had a sharp fall in the first 5 minutes (10.8 to 6.1 litres) but, in the following 5 minutes, the minute volume rose again to 8.4 litres and then gradually stabilized at approximately 7.0 litres.

LIVER FUNCTION TESTS

The results of these tests are shown in Table VI. In none of the subjects did the tests show a change which might indicate an appreciable deleterious effect on liver function. Subject 1A, B, C, who was the only obese subject in the group and who was expected to have some abnormal control tests, had no disturbing effect even after three anaesthetics. The only other subject (5A, B, C) to have three anaesthetics (at weekly intervals) had normal values in all of the serial tests.

Metabolic Effects (see Table VII)

Haemoglobin and haematocrit did not alter appreciably during any of the tests. Fibrinolysin (plasmin) estimations did not alter appreciably or consistently except that they appeared to follow the small alterations in the haematocrit values.

TABLE VI

EFFECT OF INNOVAN ANAESTHESIA ON LIVER FUNCTION TESTS, SUMMARY OF DATA

		Serum bilirubin (Van den Bergh reaction)			Prothrombin level (% of normal)	Bromsulphalein retention test (% dye retention, 45 min)	Alkaline phosphatase (King-Armstrong) (units/100 ml serum)	Serum glutamic oxalacetic transaminase (units)	Serum glutamic pyruvic transaminase (units)
		Direct	Indirect	Total					
1 A	Control	0.2	0.1	0.3	90-100	0	12.8	31	23
	End	0.2	0.4	0.6	75	6.3	9.0	50	16
	5 days	0.2	0.1	0.3	80-90	0	12.8	20	16
2 A	Control	0.1	0.9	1.0	55-65	0	5.4	28	13
	End	0.2	0.6	0.8	80-85	<2.5	4.9	14	10
	5 days	0	0.9	0.9	75-85	0	5.3	19	14
3	Control	0.2	0.2	0.4	80-90	0	9.0	36	30
	End	0.2	0.2	0.4	85-90	4.3	6.3	17	11
	5 days	0.2	0.6	0.8	75-85	0	7.9	33	16
4	Control	0	0.7	0.7	80-90	0	4.1	39	18
	End	0.4	0.2	0.6	85-90	4.5	3.1	17	16
	5 days	0.1	0.7	0.8	90-100	0	4.0	27	13
5 A	Control	0.1	0.1	0.2	85-95	0	8.1	39	33
	End	0.2	0.2	0.4	85-95	0	4.0	34	23
	5 days	0.1	0.5	0.6	90-100	0	7.5	35	21
6	Control	0	0.4	0.4	80-90	0	5.3	16	13
	End	0	0.6	0.6	80-90	0	4.0	30	16
	5 days	0	0.3	0.3	85-95	0	5.3	20	11
7	Control	0.1	0.5	0.6	80-90	0	6.8	32	24
	End	0	0.5	0.5	80-90	0	5.4	9	16
	5 days	0	0.2	0.2	85-95	0	7.1	25	18
8	Control	0.1	0.5	0.6	80-90	0	9.0	37	41
	End	0.1	0.5	0.6	75-85	Trace	4.5	35	25
	5 days	0.1	0.5	0.6	90-100	0	7.5	35	23
9	Control	0	0.8	0.8	90-100	0	8.5	26	23
	End	0.1	0.5	0.6	90-100	0	6.7	33	22
	5 days	0	0.3	0.3	85-95	0	9.3	24	18
10	Control	0.1	0.1	0.2	80-90	0	8.5	19	23
	End	0	0.5	0.5	85-95	4	6.3	31	18
	5 days	0	0.2	0.2	85-95	0	7.5	28	14

11 A	Control	0	0 5	75-85	0	7 2	24	11
	End	0 1	0 3	85-90	0	6 6	19	13
	5 days	0	0 3	85-95	0	6 6	24	18
12 A	Control	0 2	0 3	75-85	0	5 6	29	14
	End	0 1	0 4	90-100	0	5 4	32	15
	5 days	0	0 5	90-100	0	7 5	28	21
13	Control	0	1 2	85-95	0	4 9	30	18
	End	0 2	0 9	75-85	0	7 1	26	11
	5 days	0 1	0 9	90-100	0	8 6	25	17
14	Control	0	0 5	85-95	0	9 7	26	19
	End	0 1	0 3	85-95	0	9 3	18	13
	5 days	0 2	0 4	85-95	0	9 7	31	23
15 A	Control	0	0 6	80-90	0	6 2	22	14
	End	0 1	0 5	85-95	0	5 7	19	17
	5 days	0 1	0 5	85-95	0	5 3	24	14
16	Control	0 1	0 3	85-95	0	6 4	31	19
	End	0 1	0 6	90-100	0	4 4	29	24
	5 days	0 1	0 3	85-95	0	5 7	38	34
1 B	Control	0 2	0 1	80-90	0	12 8	20	16
	End	0 1	0 3	70-80	2 0	11 0	22	14
	5 days	0 2	0 2	90-100	0	12 4	32	25
2 B	Control	0	0 9	75-85	0	5 3	19	14
	End	0	1 1	85-90	0	5 7	21	11
	5 days	0 1	0 8	85-95	0	4 4	26	16
5 B	Control	0 1	0 5	90-100	0	7 5	35	21
	End	0	0 3	85-95	0	6 6	40	25
	5 days	0 1	0 3	90-100	0	5 7	45	25
11 B	Control	0	0 3	85-95	0	6 6	24	18
	End	0 1	0 2	85-95	0	5 3	26	18
	5 days	0 1	0 2	90-100	0	6 6	29	21
12 B	Control	0	0 5	90-100	0	7 5	28	21
	End	0	0 5	90-100	0	5 3	28	25
	5 days	0	0 2	75-85	0	7 5	34	18
15 B	Control	0 1	0 5	85-95	0	5 3	24	14
	End	0	0 6	75-85	0	4 4	21	15
	5 days	0 2	0 4	65-75	0	4 4	21	13
1 C	Control	0 2	0 2	90-100	0	12 4	32	25
	End	0 1	0 3	70-80	2 0	10 6	33	29
	5 days	0 1	0 1	85-95	0	11 5	30	26
5 C	Control	0 1	0 3	90-100	0	5 7	45	25
	End	0 2	0 2	90-100	0	5 3	35	19
	5 days	0 2	0 4	80-90	0	8 4	34	25

FIGURE 9 Anaesthetic chart from experiment on subject No 3. Observe the sharp fall in blood pressure in response to tilting, after an initial fall due to Innovan anaesthesia, requiring a reduction of the angle of tilt.

Serum potassium decreased slightly during 16 experiments and increased slightly in the other 8. Changes were not consistent among those who had more than one test and all values were within normal limits.

Blood urea nitrogen did not change appreciably during the test and was within normal limits for all.

Blood sugar rose slightly during 14 experiments, decreased in 7, and remained the same in 3. There was no consistent change among those subjects that had

TABLE VII

SOME METABOLIC EFFECTS OF INNOVAN ANAESTHESIA IN NORMAL MEN, SUMMARY OF DATA FROM METABOLIC TESTS

	Haemoglobin			Haematocrit			Potassium			Blood urea nitrogen			Blood sugar			Body temperature		
	(gm)			(%)			(mg %)			(mg %)			(mg %)					
	Before	After	+5 days	Before	After	+5 days	Before	After	+5 days	Before	After	+5 days	Before	After	+5 days	Before	After	After
1A	16.2	17.5	17.7	41	44	49	4.7	4.2	5.2	10	11	18	110	88	90	98.8	97.2	97.4
2A	14.6	13.6	15.0	42	39	43	5.2	4.3	4.4	18	17	14	84	113	58	97.1	97.1	97.0
3	17.0	16.8	16.7	48	52	47	4.6	4.5	4.5	12	12	11	80	83	80	98.0	98.2	97.2
4	15.8	15.0	14.6	40	47	43	4.6	4.3	5.3	13	16	16	90	90	64	99.0	98.0	97.4
5A	15.9	17.1	17.3	47	46	49	5.0	4.4	4.6	15	10	12	90	76	68	98.7	98.0	97.8
6	17.0	16.3	17.0	50	48	53	5.0	5.3	4.8	16	14	13	88	86	84	98.2	96.8	96.6
7	14.4	12.8	15.3	45	36	44	4.7	4.3	5.4	15	12	13	100	94	96	99.0	98.0	96.4
8	17.2	13.9	16.3	50	40	48	4.6	4.2	4.9	23	18	18	76	88	70	97.8	98.0	97.2
9	16.6	14.3	16.7	50	42	48	4.8	4.5	5.2	18	19	19	86	96	90	98.2	98.0	97.0
10	16.9	14.1	15.6	48	39	45	4.8	4.5	5.0	20	18	19	82	104	86	98.4	97.0	97.0
11A	14.5	14.5	13.3	44	44	38	4.7	4.9	4.0	13	14	14	96	116	116	98.4	96.4	96.4
12A	12.9	12.9	15.1	39	39	43	5.0	4.5	3.6	7	13	11	68	84	84	98.4	97.8	96.0
13	16.7	17.0	17.0	43	46	46	4.8	5.2	4.8	15	16	15	82	84	84	98.4	97.2	96.4
14	17.1	15.3	17.3	46	41	46	5.0	4.1	4.9	18	16	13	68	82	68	98.4	98.8	97.0
15A	18.0	16.3	17.0	50	45	49	4.3	4.0	4.8	14	13	13	66	98	98	97.8	98.2	96.4
16	16.3	14.3	15.6	45	40	45	4.5	3.9	4.4	18	17	17	78	110	78	98.0	96.4	95.4
1B	17.7	15.8	17.7	49	44	46	5.2	4.8	4.6	18	15	14	90	96	100	98.0	98.2	97.8
2B	15.0	14.6	14.6	43	41	40	4.4	4.7	5.2	14	15	14	58	86	86	98.2	97.2	96.0
5B	17.3	18.0	17.3	49	47	47	4.6	4.8	4.6	12	13	16	68	80	94	98.0	97.0	97.2
11B	13.3	14.5	14.3	38	40	45	4.0	4.7	4.6	14	12	18	116	108	84	97.8	95.2	96.0
12B	15.1	13.9	15.0	43	37	41	3.6	4.3	5.1	11	8	12	84	76	82	98.4	97.2	97.0
15B	17.0	15.3	18.0	49	45	49	4.8	4.0	5.1	13	12	11	98	84	68	97.6	96.8	96.4
1C	17.7	16.3	16.3	46	45	45	4.6	4.8	5.4	15	12	16	78	78	98	97.6	97.0	96.6
5C	17.3	17.3	17.3	47	49	49	4.6	4.5	5.0	16	12	15	94	80	92	97.4	96.8	95.0
Mean	16.1	15.3	16.2	46	43	46	4.7	4.5	4.8	15	14	15	84	91	83	98.0	97.4	96.7
SD	1.6	1.6	1.3	4	4	3	0.37	0.44	0.51	3.4	2.8	2.5	14	12	14	0.6	2.9	1.6

repeated tests and all values were judged to be in the normal range for a fasting subject

Body temperature There was a slight decrease in oral and axillary temperature during most of the tests, as was expected would follow exposure to an air-conditioned operating room and a general anaesthetic

Acid-Base Changes (see Table VIII and Fig 10)

Arterial blood pH decreased in 23 of the 24 experiments and increased in 1. However, the change exceeded 0.1 pH units in only 3 subjects, and then only slightly

TABLE VIII

SOME METABOLIC EFFECTS OF INNOVAN ANAESTHESIA IN NORMAL MEN, SUMMARY OF DATA FROM METABOLIC TESTS RELATED TO ACID-BASE BALANCE

	pH		P_{CO_2} (mm Hg)		HCO_3^- (mM /L)		P_{O_2} (mm Hg)		O_2 (% sat)	
	Before	After	Before	After	Before	After	Before	After	Before	After
1 A	7.31	7.25	35.5	37.7	17	17	40	146	75	100
2 A	7.29	7.26	39.9	43.0	18	18	46	192	80	100
3	7.32	7.27	39.4	39.4	19	17	38	140	72	100
4	7.34	7.33	37.1	36.1	19	19	96	227	97	100
5 A	7.41	7.34	38.9	43.6	24	22	80	186	95	100
6	7.36	7.30	42.8	45.3	23	21	36	163	69	100
7	7.39	7.32	42.1	49.2	24	24	113	266	98	100
8	7.35	7.32	40.5	47.3	21	23	44	60	78	88
9	7.37	7.30	40.7	43.4	22	21	55	157	87	100
10	7.41	7.35	37.5	43.7	23	23	105	187	98	100
11 A	7.45	7.34	31.6	45.7	21	23	113	216	99	100
12 A	7.38	7.35	39.4	44.7	22	23	93	252	97	100
13	7.36	7.46	40.5	29.0	22	20	87	120	96	100
14	7.41	7.30	36.0	41.5	22	20	63	198	91	100
15 A	7.44	7.35	41.7	48.7	26	26	69	144	92	100
16	7.40	7.31	35.9	46.6	21	22	119	262	99	100
1 B	7.32	7.23	42.8	51.3	21	20	77	108	94	98
2 B	7.34	7.30	45.1	46.4	23	22	68	232	91	100
5 B	7.42	7.38	34.2	38.2	21	22	96	136	98	100
11 B	7.43	7.31	36.0	49.4	23	24	130	231	100	100
12 B	7.44	7.33	37.2	53.9	24	27	107	171	98	100
15 B	7.39	7.37	40.0	46.1	23	25	61	187	90	100
1 C	7.41	7.35	37.1	41.0	22	22	93	195	98	100
5 C	7.44	7.34	36.5	47.2	24	24	76	120	95	98
Mean	7.38	7.32	38.8	44.1	22	22	79	175	87	100
S D	0.05	0.05	3.2	5.4			28	59		

P_{CO_2} increased during 22 experiments. The increase was slight in most subjects, but was as much as 15 mm Hg in three. One subject had no change and one had a decrease of 11 mm Hg.

The changes in pH and P_{CO_2} showed a general trend to a mild respiratory acidosis which undoubtedly would have been severe if breathing had not been augmented particularly during the early part of each experiment.

The mean plasma bicarbonate calculated at pH 7.40 did not change. The slight changes that occurred in individual tests were not consistent, so that there was no significant evidence of a trend to metabolic acidosis.

The P_{O_2} rose considerably as would be expected from the administration of 40 per cent oxygen (with nitrous oxide) during the experiments. The rise in

FIGURE 10 Effect of Innovan-N₂O on acid-base balance
 A = blood sample before anaesthesia, B = blood sample at end of anaesthesia. Observe that a mild respiratory acidosis is present at the end of the anaesthetic period

oxygen tension was reflected in the increase in oxygen saturation which reached 100 per cent at the end of the test in all but 3 subjects. However, there were a few instances in which the oxygen tension undoubtedly became low enough to be alarming during the early part of the experiment, as evidenced by slight cyanosis during several of the tests.

Recovery from Anaesthesia

All but one subject were awake enough to respond to the requests (Open your eyes! What is your name? What is your address? What time is it?) within 10 minutes after discontinuing inhalation of nitrous oxide and oxygen at the end of the test. The exception (12A) opened his eyes in 6 minutes but could not answer the questions for another 16 minutes. At a subsequent test, he recovered as rapidly as the rest.

When the subjects were placed in the sitting position 20 minutes after arriving in the recovery room, they did not become dizzy or nauseated, and there was no appreciable change in blood pressure, pulse rate, or breathing. The one subject (12A) who recovered slowly vomited a small amount of clear brown fluid immediately after he sat up. He admitted to having had some black coffee before coming to the hospital for the test. None of the other subjects had nausea or vomiting while in the hospital after the test. All the subjects remained very drowsy for at least one hour after the test, but they were all able to carry on a conversation during this time, and were able to drink coffee or water without difficulty within an hour after completion of the test. Fourteen subjects found it necessary to "sleep it off" for several hours after returning home. Subject 12A

was the only one who was unable to stand unsupported immediately after reaching home

Twenty four Hour Follow up

A few subjects had some complaints referable to the period immediately preceding induction of anaesthesia. Four recalled feeling pain when the arterial blood sample was drawn, one felt everything was vibrating and one had a closed in feeling."

After full anaesthesia was induced two subjects 12A and 5A thought they heard people talking but this apparently occurred only after the initial dose of Innovan. One subject (3) thought he dreamed during the test but couldn't recall any details. One subject (2A) felt the needle puncture at the end of the test.

In response to the questions regarding their first memory and the time on the clock it was evident that there was a period of amnesia after 14 experiments. This lasted about 15 minutes. After 10 tests the subjects had immediate total recall and no evidence of amnesia.

There were a variety of minor discomforts after the test. Most of these had disappeared when the subject was seen the following day (see Table IX). The only troublesome complaints that lasted longer were referable to the extra

TABLE IX
SUMMARY CHART SHOWING INCIDENCE OF POSTANAESTHETIC COMPLAINTS

pyramidal system mainly affecting the neck and face muscles, and irritation of veins due to repeated injections of bromsulphalein dye. One subject (14) was given cogentin to relieve twitching of muscles of the face. Two subjects had torticollis. In one, this occurred after 2 tests, but it cleared without drug therapy. Two subjects required treatment of phlebitis for several days.

Discounting complaints referable to the laboratory tests, only two subjects considered the anaesthetic experience very unpleasant (3 and 10). Both of these subjects had hallucinations. In subject 3, these lasted several days. Persistent drowsiness (12 hours +) after the test was the commonest complaint. This occurred after all but one test. Restlessness, lasting at least one day after the test, occurred 14 times among 9 of the subjects. Three subjects (6, 7, 9) felt they were "groggy" too long after the test (more than 24 hours). Two subjects (2 and 14) said they felt "jittery" and unable to concentrate on their work. The employer of one of these was not aware that a test had been done, and observed that the subject was quite incapable of doing his work for a few days. Only one of these subjects (2) consented to a second test. The remaining 7 subjects considered having the anaesthetic a rather pleasant experience and, of these, five had additional anaesthetic tests. The other two consented to additional tests but could not be accommodated for reasons unrelated to the test procedure.

DISCUSSION

The carefully designed and rigidly controlled evaluation of anaesthetic drugs in man presents a complex situation because the utmost safety measures must be enforced. In addition, one must avoid the use of some of the ordinary measures that facilitate the maintenance of anaesthesia, so as not to risk obliterating some effects of the drugs under investigation, but without jeopardizing the comfort or safety of the subject. These aspects were all reviewed in minute detail by the authors before proceeding with this study, and it was recognized that the projected studies would have to be restricted to those within the realm of tests that would cause the least psychic and physical trauma. The reader must, therefore, make certain reservations in evaluating the data presented, for there is obviously in experimental procedures an artificial atmosphere, and one cannot reproduce the clinical situation in which a patient is going to have an operation for a disease and where the chosen anaesthetic procedure would always be manipulated fully to fit the rules of safety and comfort to the patient, the ease of maintenance for the anaesthetist, the facility of operating by the surgeon, and to ensure the smooth rapid recovery from the anaesthetic by the patient.

Psychic Effects

The preliminary questionnaire that was used to evaluate the mood of the subjects immediately preceding the preparations for the anaesthetic test was applied to obtain the kind of subjective data that would help to evaluate any excesses in parameters we planned to observe closely, namely—sweating, pulse and heart rate, rate and depth of breathing, blood and pulse pressure, and pupil size. The individual word responses elicited before medication indicated that some of the subjects were apprehensive, as summarized in Figure 1. This shows

how frequently the subjects responded affirmatively to the nurse who asked the questions in each instance. We recognized, of course, that these men would only tell the nurse what they were willing to admit, and not necessarily what they felt, whereas the physiological measurements taken immediately after the questionnaire, while the subject was reclining in bed, would be affected by his actual physical or mental condition.

We were able to utilize several subtle aids in evaluating the responses without resorting to specious reasoning. One was to evaluate the positive responses in groups (as shown in Table I) as recommended by Wendt, Nowlis, and Nowlis, who developed the questionnaire, and by Smith and Beecher who studied this kind of an evaluation.²⁹⁻³¹ The other was to equate the group answers with the measurement of the vital signs while the subject was in the resting state away from the area where the anaesthetic tests were to be carried out, as shown in Table I. We were able to conclude that virtually all of the subjects were frightened to some degree. The six subjects who returned to have additional tests were less apprehensive, but a study of their subjective responses and vital signs still showed that none were completely relaxed and calm as they would usually be if they were merely reclining to take an undisturbed rest or ready to go to sleep.

Premedication

All of the subjects were premedicated with both atropine (0.3 mg) and scopolamine (0.3 mg). The reason for using belladonna derivatives was to reduce the expected sweating and bradycardia that occurs with Innovan⁷ and for the antisialogogue action that is desired with any anaesthetic. Atropine was not used alone because it has cerebral irritant properties and might augment the psychic stimulation inherent in the experimental situation, and increase the amount of Innovan necessary to produce smooth general anaesthesia, whereas scopolamine has calming and amnesic properties and would tend to cancel out the stimulant effect of atropine. It was decided not to use scopolamine alone because atropine was felt to be more effective in blocking noxious vagal stimuli to the heart. No other premedicants were used in order to avoid confusion with the effects of the test drugs. No troublesome secretions were encountered either during the test or during the recovery period and, in fact, many complained of a dry mouth lasting several hours after discharge from the hospital.

Induction of Anaesthesia

Anaesthesia was induced in two stages for a number of reasons. The initial 20 per cent of the total dose was given first to determine whether approximately 2 ml of Innovan (containing 2 mg droperidol and 0.04 mg fentanyl) was sufficient to produce adequate sedation within 10 minutes. The time was also utilized to measure physiological responses and question the subject as to any change in his feelings. It was also considered essential to follow this procedural technique to avoid the acute cardiovascular depression that frequently occurs rapidly following intravenous injection of potent anaesthetic drugs,³² to avoid the occurrence of acute tolerance to the ingredients of the mixture,³³ and to

reduce the degree of adrenergic blocking action at alpha receptors that is likely to occur with droperidol^{3 34} It was obvious that Innovan can in fact produce very marked sedation rapidly (within 10 minutes) when given intravenously, and 2 ml is a dose which is quite adequate even for vigorous, healthy subjects As noted above, one subject (who received more than 1 ml/15 lb) was rendered unconscious with the 2 ml of Innovan, and all but one of the subjects became drowsy and quite relaxed mentally Breathing rate, tidal volume, pupil size, pulse rate, and blood pressure were all reduced somewhat in most of the subjects at this time, but these changes were considered to be consistent with the onset of psychic depression or a combination of neuro and hypnotic sedation, rather than heralding severe physiological depression

Maintenance of Anaesthesia

The second dose of Innovan (8 to 13 ml) was sufficient to produce unconsciousness in all the subjects within less than 5 minutes, and this state could be maintained with 60/40 nitrous oxide-oxygen for an hour in 14 of the 16 subjects One of the two remaining subjects (5) was a very strong man and required supplementary doses at each of the three anaesthetics he had The added dose was sufficient to restore quiet anaesthesia each time The other subject was also very vigorous, but he did not appear to become semi-conscious until the last few minutes of the test, when the blood sample was being drawn from an artery, so a supplementary dose of Innovan was not given.

Respiratory Effects and Muscular Rigidity

In many instances, it would have been desirable to administer a muscle relaxant (e.g. succinylcholine or gallamine) to facilitate the provision of controlled ventilation when rigidity of the thoracic and abdominal muscles caused difficulty We decided to refrain from doing this as long as we could maintain adequate ventilation by other means This decision was made so that we could measure the duration of the catatonic effect, and also be able to identify whether some of the difficulty in ventilating the subjects was due to lower airway obstruction Some degree of rigidity appeared to develop in all of the subjects, but ventilation was not always severely affected, so that only those with a measured low tidal volume were assisted or controlled In most of the subjects, the muscle rigidity lasted only a short time (<20 minutes), while it continued almost to the end of the hour in two In four subjects, we experienced difficulty in extending the head on account of rigidity of the sternocleidomastoid and trapezius muscles, but the masseters did not become especially rigid so that an oral airway could be inserted easily In four other subjects, after the thoracic and abdominal muscles seemed to have relaxed, we still had difficulty in maintaining air entry and, in these, the difficulty appeared to be internal Phonation and stridor pointed to laryngeal and perhaps bronchial spasm as the probable causes for difficulty

These observations are important because they emphasize that although an operative procedure may not require a muscle relaxant, the maintenance of adequate pulmonary ventilation during Innovan anaesthesia cannot be ensured easily without it It is not logical, therefore, to employ Innovan-N₂O anaesthesia

unless a muscle relaxant is to be used by choice, particularly for the purpose of facilitating the operation

Circulatory Effects

There were no instances in which the circulatory response to Innovan became alarming, even when the subjects were tilted 45° head-up during the anaesthetic, and when they were sat up 20 minutes after recovering consciousness, so the adrenergic blocking action of droperidol is perhaps sufficiently weak or short-acting to allow the normal compensatory responses to be protective. A hypertensive response and increase in pulse rate was in fact seen in several of the subjects when they were tilted. This vasomotor response to tilting undoubtedly depends mainly on the general good health of the subject, a healthy cardiovascular system with an adequate circulating blood volume, and on the rate of administration and the total dose of droperidol administered. As with chlorpromazine and other phenothiazine derivatives, one should be very careful when administering these drugs to the elderly patient who has a less resilient circulation, or whose circulating blood volume is lowered^{35 36}. In the present study, only one subject developed significant hypotension when tilted during the anaesthetic, and the angle of tilt had to be reduced appreciably to insure a satisfactory blood pressure. Six subjects had more than a 20 mm drop in blood pressure (systolic) when sat up 20 minutes after the anaesthetic, but in none did the fall require supportive measures.

No arrhythmias occurred in these subjects although minor T wave changes were observed in response to changes in position, and it is apparently safe to use epinephrine in the presence of Innovan anaesthesia^{7 37}.

Liver Function

There were no disturbances in liver function in any of these subjects even after two or three anaesthetics. However, the total doses used in these tests were not a severe test of the drug mixture as far as the liver is concerned. It is desirable, therefore, to see how patients with liver disease respond to the anaesthetic before one can be certain that it is safe to use it under all circumstances.

Metabolic Effects

Undesirable metabolic effects were absent but, here again, one would have to study patients with azotaemia or diabetes to be certain that Innovan is perfectly safe in this respect. The trend to respiratory acidosis was consistent with a prolonged hypnotic effect after the general anaesthetic effect was worn off, and possibly as an aftermath to the difficulty with ventilation during the anaesthetic.

The results of these tests were not all the same as those found in a similar evaluation in dogs, in which we found a consistent decrease in serum potassium and a consistent rise in the blood sugar. The change in serum potassium was attributed in part to the hyperventilation that was used in the animals, but the rise in blood sugar could not be explained adequately⁸.

Recovery from Anaesthesia

Recovery of consciousness was surprisingly fast. Even more remarkable was the rapidity with which the subjects seemed to lose the mental sluggishness that invariably follows immediately after a general anaesthetic with all commonly used agents. On the other hand, it soon became evident that a very strong hypnotic sedative effect persisted in most instances for at least another 8 hours and, in a few subjects, for more than 24 hours. One might attribute part of this effect to the mental exhaustion that is not unexpected after a stressful experience, but hypnotic depression after intravenous as well as inhalational anaesthesia is more likely to be caused by the slow rate of excretion or metabolism of the drugs.

The absence of vomiting during recovery was outstanding and speaks for use of this agent. Aside from one episode mentioned above, none of the subjects vomited after the anaesthetic, and only four subjects had nausea—which was attributed to early ambulation, with the undoubted attendance of moderate hypotension, in each case. Since none of these subjects underwent a surgical operation, and the anaesthetic period was relatively short, the incidence of nausea and vomiting requires further study. Other observers have remarked on the low incidence of these symptoms with Innovan anaesthesia, and the same was observed in dogs.^{7,8}

Three disturbing aspects of the recovery period are worthy of comment.

Extrapyramidal symptoms. Tremors and/or a “jittery” feeling were described by 5 subjects. In 3 of these, they were attributed to extrapyramidal effects affecting mainly the facial and neck muscles. One was relieved with cogentin, and in the others the response subsided spontaneously. Hallucinations and behavioural upsets were described by two subjects. One of these subjects was considered to be a rather stable individual and the disturbance was attributed directly to the Innovan anaesthesia. The other subject was the only one in the group who was thought to be rather less sedate, and we might have discounted his complaints, but he asserted that he had experienced similar hallucinations during tests with LSD 25. In the present case, the hallucinations lasted a few days and were associated with periods of psychic depression. During the week following the test, this subject lost 9 lb in weight.

Marked restlessness occurred after 14 of the 24 tests, involving 11 of the subjects. The complaint was rather marked in 3 subjects, and it lasted as much as 3 days in 8 subjects. One subject described the feeling as “I felt very tired, but couldn’t lie still, and when I got up, I felt like lying down.” He lost 7 lb in body weight during the week following the test. Such restlessness is characteristically seen after some of the phenothiazine derivatives, such as promethazine, prochlorperazine, and perphenazine, but not after methotrimeprazine, promazine, and chlorpromazine.^{38,39,40}

A dry mouth was a common complaint, but this did not last beyond one day, and was attributed to the atropine and scopolamine premedication. Sore veins occurred in 9 subjects and were due, in most instances, to multiple punctures, but, in a few, they were due to the BSP dye.

In spite of the numerous minor complaints by these volunteers and some of

the disturbing side-effects that we observed, Innovan-N₂O anaesthesia apparently has now been administered safely and without special problems to a considerable number of patients, including many elderly people who were considered to be poor risks^{4 5 6 7 41} This anaesthetic mixture, therefore, warrants further careful study and extensive clinical evaluation

SUMMARY AND CONCLUSIONS

The experimental evaluation of intravenous Innovan anaesthesia in healthy male subjects showed that this drug mixture, in a low dose, exerts a marked neuro and hypno sedative effect and, in higher doses, with N₂O-O₂ supplementation, produces unconsciousness accompanied by depression of the sympathetic nervous system, as shown by the Horner's syndrome, warm, dry extremities, engorged veins, and moderate depression of blood pressure Cardiovascular depression appears to be minimal and of short duration and, in most of the subjects, the cardiovascular system remained remarkably stable during the action of this agent Respiratory depression is intense for a short period and mild for a much longer period Hypertonic reactions, affecting the neuromuscular system, appear early as spasm of the thoracic, abdominal, and neck muscles, which would probably necessitate the use of muscle relaxants to ensure adequate pulmonary ventilation, and later as restlessness and dyskinesia of the muscles in the face and neck—which may require treatment with anticholinergic drugs such as atropine or cogentin Two subjects complained of the occurrence of hallucinations which lasted several days in one case Whether or not this disturbance was due to Innovan alone could not be established Representative liver function and metabolic tests indicate that Innovan is a relatively non-toxic substance in the dose range required for approximately one hour of general anaesthesia The incidence of nausea and vomiting appears to be negligible after this anaesthetic

On the basis of these experiments, it is difficult to say whether general anaesthesia with Innovan-N₂O has many great advantages over the use of thiopental, cyclopropane, halothane, methoxyflurane, or trichlorethylene and their combinations with nitrous oxide, but it appears worthy of extensive trial

RÉSUMÉ

Le but de ce travail a été d'étudier, chez l'humain, les effets physiologiques, biochimiques et psychiques de l'Innovan, produit d'un mélange de fentanyl et de dropéridol dans une proportion de 1/50, médication sédatrice et analgésique, mise au point récemment et pleine de promesse

Seize jeunes volontaires du sexe masculin ont subi un examen de routine des urines et du sang, des épreuves hépatiques et un examen clinique, puis, ils ont reçu en tout 24 anesthésies à l'Innovan et au protoxyde d'azote

Le jour de l'expérience, chacun des sujets a répondu à un questionnaire destiné à évaluer son état psychique, on a aussi enregistré leur tension artérielle, leur pouls, le diamètre de leurs pupilles, la fréquence de leur respiration et le volume-minute Un goutte à goutte de chlorure de sodium à 0.9 pour cent a été installé, et 0.3 mg d'atropine et 0.3 de scopolamine ont été donnés par voie

intramusculaire une heure avant le début de l'expérience. Après le transport des sujets au bloc opératoire, on a répété les analyses précédentes et l'on a appliqué la dérivation II de l'électrocardiogramme, des échantillons de sang veineux et de sang artériel ont été prélevés, et le colorant B S P a été injecté par voie intraveineuse.

On a injecté l'anesthésique en deux temps : la dose d'Innovan fut de 1 ml par 15 livres de poids d'un mélange contenant 0.02 mg de fentanyl et de 1 mg de dropéridol par ml. Vingt pour cent de cette dose a été donnée par voie intraveineuse et, après 10 minutes d'observation des signes vitaux, le reste, soit 80 pour cent, fut injecté, on a alors administré à l'aide d'un masque 60 pour cent de protoxyde d'azote et 40 pour cent d'oxygène. Pendant l'heure suivante, on a observé les signes vitaux en assistant ou en contrôlant la respiration, selon le cas. Quarante-cinq minutes après la première dose d'Innovan, on a prélevé un échantillon de sang pour un dosage du B S P, puis les sujets furent placés en position de Fowler à 45° durant 15 minutes au cours desquelles les signes vitaux furent constamment observés, on remit alors les malades en position horizontale. Quinze minutes plus tard, d'autres échantillons sanguins furent prélevés pour le dosage de la bilirubine et du potassium dans le sérum, pour le dosage du sucre sanguin, de l'azote uréique, des transaminases du sérum et des pH, $p\text{CO}_2$ et $p\text{O}_2$ artériels. A ce stade, on cessa l'inhalation du protoxyde d'azote et de l'oxygène, et l'on tint compte du temps qui s'écoula à partir de ce moment jusqu'à celui où les sujets purent répondre à quelques questions-types. Après le transfert à la salle de réveil, les signes vitaux furent observés durant 20 minutes, puis les sujets furent assis. Dès que leur état l'eut permis, les sujets ont été conduits à leur demeure, on leur demanda de revenir 24 heures plus tard pour répondre à un nouveau questionnaire puis, au bout de cinq jours, pour subir des analyses de sang et répondre à d'autres questions.

Les résultats sont résumés dans les tableaux. Les sujets, bien que nerveux avant l'expérience, ont été calmés par la dose de 20 pour cent, et tous sont devenus inconscients et pratiquement apnéiques après la dose de 80 pour cent, la ventilation a été appliquée dans chaque cas.

Le système nerveux sympathique fut déprimé ainsi que l'ont indiqué le syndrome de Horner, les extrémités chaudes et les veines engorgées. Un des sujets qui était très robuste a eu besoin de doses supplémentaires d'Innovan pendant l'expérience. Sauf une exception, tous les sujets ont repris une respiration lente mais suffisante à la fin de l'expérience. La présence de spasmes des muscles abdominaux et thoraciques fut presque constante après la dose de 80 pour cent, ce qui rendait la ventilation difficile dans plusieurs cas, il y avait probablement aussi un certain degré de broncho- et de laryngo-spasmes.

La tension artérielle fut peu modifiée par l'anesthésique, et un seul sujet a présenté une hypotension posturale importante. Les changements électrocardiographiques furent presque nuls, et la fréquence du pouls eut tendance à diminuer à l'induction, et à augmenter après le changement de position de la table.

Les épreuves sur la fonction du foie, l'hémoglobine et l'hématocrite, le potassium dans le sérum, l'azote uréique et le sucre sanguin ne se sont pas éloignés sensiblement de la normale. Comme on s'y attendait, la température a légèrement baissé au cours de l'expérience.

L'équilibre acide-base a penché vers une légère acidose respiratoire sans changements appréciables du métabolisme et la pO_2 a été élevée par l'inhalation de 40 pour cent d'oxygène, sauf pendant les brèves périodes de difficulté respiratoire

Le retour à la conscience a été rapide, et les sujets ont répondu correctement aux questions moins de 10 minutes après la fin de l'expérience, cependant, un état de somnolence a généralement persisté durant 12 heures ou plus. Un seul sujet qui n'était pas à jeun, a vomé pendant le réveil. Après l'épreuve, on a observé fréquemment de l'agitation et une dyskinésie des muscles de la face et du cou, deux sujets ont souffert d'hallucinations.

Les propriétés analgésiques de l'Innovan sont suffisamment sûres et non toxiques pour justifier des essais cliniques plus importants.

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