tion of even small amounts of material should be prevented whenever possible. Pressure exerted against the tracheal wall by a cuff should be high enough to prevent significant aspiration yet low enough to allow adequate capillary mucosal blood flow. Nordin reports that large cuffs will not decrease mucosal blood flow until cuff-to-tracheal wall pressure exceeds 40.5 cm H_2O.[10]

Intracuff pressure in large-diameter cuffs approximates cuff-to-tracheal wall pressure until the cuff wall is stretched.[11] We assume that regulated pressures in the large-diameter cuffs studied approximated lateral tracheal wall pressures because cuff diameters were large and filling volumes small. However, large-diameter cuffs initially filled to minimal occluding volume with air may become "high-pressure" cuffs due to N_2O diffusion.[12]

Intracuff pressure at minimal occluding volume in the small-diameter Rusch latex cuff (approximately 250 cm H_2O in our study) is assumed to be higher than cuff-to-tracheal wall pressure because the cuff has to be stretched to seal the trachea. Wu *et al.* report that cuff-to-tracheal wall pressure at minimal occluding volume is above 243 cm H_2O for these small-diameter, thick-walled latex cuffs.[13] Since small-diameter (high-pressure) cuffs stop the microcirculation in the mucosa on top of tracheal cartilages at cuff-to-tracheal wall pressures exceeding 40.5 cm H_2O,[10] use of tracheal tubes with this type of cuff should probably be limited to special circumstances.

Endotracheal tubes with *large-diameter, thin-walled cuffs,* such as American/National Catheter Corporation or Lanz tubes, should be used whenever possible. When a reservoir-type inflation pressure-regulating valve is not used in the operating room, the cuff should be filled with anesthetic gases injected simultaneously into the cuff and a pressure manometer as described by Lewis *et al.*[7] Controlling intracuff pressures in large-diameter thin-walled cuffs between 25 and 34 cm H_2O should prevent significant aspiration and still allow adequate capillary mucosal blood flow. This can be done with a pressure-regulating valve or by periodically measuring intracuff pressure and adjusting intracuff volume and pressure through a three-way stopcock.

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Innovar-induced Hypertensive Crises in Patients with Pheochromocytoma

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The butyrophenone compounds (droperidol and haloperidol) have many pharmacologic similarities to the piperazine-substitute phenothiazines. In normal man, these compounds induce a feeling of tiredness and reduce blood pressure, pulse rate, and body temperature.[1]

From 1972 to 1977, we encountered nine patients in whom sudden, severe hypertension developed after Innovar® had been administered iv. In some patients marked tachycardia occurred as well. Another patient had received fentanyl and droperidol separately. After the iv administration of droperidol, hypertension and tachycardia developed. Three of these pa-

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TABLE 1. Cardiovascular Responses to Intravenously Administered Innovar in Patients with Pheochromocytoma

	Before Innovar		Innovar (ml)	Time of Response	After Innovar	
	Blood Pressure (torr)	Pulse (Beats/Min)			Blood Pressure (torr)	Pulse (Beats/Min)
Unrecognized pheochromocytoma						
Patient 1	140/75 before angiography	88	1	5 min*	>300/110	140†‡
Patient 2	150/90 before arthrography	80	1.5, 1	2 min*	230/110	72
Patient 3	180/100	90	1	1 min	230/110	90
Suspected pheochromocytoma—before angiography						
Patient 4	160/120	120	1	5 min*	270/170	160†
Patient 5	150/90	80	1	5 min*	210/120	80
Patient 6	110/80	84	1	5 min*	200/100	160†§
	160/120 before anesthetic induction	84	1	2 min*	250/130	130§
Known pheochromocytoma—before anesthetic induction						
Patient 7	160/130	82	2	5 min*	>300/150	120¶
Patient 8	180/100	96	1	35 sec¶	230/120	170†

* First blood pressure recorded by auscultation after drug administration.
† Sinus tachycardia.
‡ Occasional premature ventricular contractions.
§ Premature atrial contractions, ventricular premature contractions.
¶ Recorded by continuous intra-arterial monitoring.

tients were suspected of having pheochromocytomas, three were known to have pheochromocytomas, and three were undergoing evaluation for other unrelated conditions (table 1).

REPORT OF NINE CASES

Patient 1. A 58-year-old man sought medical advice because of the chief complaints of upper abdominal pain and pain in the right shoulder of six weeks' duration. Two similar attacks, each lasting several hours, had occurred in the preceding year. The past history was unremarkable.

Physical examination revealed a blood pressure of 130/80 torr and a pulse rate of 80/min. A large, grapefruit-sized epigastric mass was present on abdominal palpation. No other abnormality was found. Intravenous pyelography showed deviation of the upper portion of the right ureter to the right, suggesting a huge retroperitoneal mass. Results of all laboratory studies were within normal limits.

The patient was scheduled for exploratory laparotomy. He received pentobarbital, 100 mg, morphine, 10 mg, and atropine, 0.4 mg, im, 90 min before operation. In the operating room the blood pressure was 140/75 torr and pulse, 88/min. Innovar®, 1 ml, was given iv. Within 5 min blood pressure was greater than 300/110 torr. The pulse rate at this time was 140/min. The patient did not experience any symptom, and slept soundly. An infusion of sodium nitroprusside reduced blood pressure to 150/100 torr. Electrocardiography demonstrated sinus tachycardia with occasional premature ventricular beats and a shift in the axis. A left anterior hemiblock followed this pattern. Arterial blood-gas values with $F_{I_{O_2}}$ 0.4 were: P_{O_2}, 59 torr; P_{CO_2}, 47 torr; *p*H, 7.33; HCO_3^-, 22 mM/l. Roentgenograms of the chest revealed bilateral pulmonary infiltrates. The surgical procedure was canceled. The patient was treated with digoxin, furosemide, and sodium nitroprusside, iv. A suspected myocardial infarction was subsequently confirmed by enzymatic analysis.

The next day, arterial blood-gas values with $F_{I_{O_2}}$ 0.21 were P_{O_2}, 61 torr; P_{CO_2}, 32 torr; *p*H, 7.47. Vanillylmandelic acid was reported as 178 mg/24 hours (normal, 2–10 mg/24 hours) metanephrines, 28 mg/24 hours (normal, <1 mg/24 hours); catecholamines, 6,240 mg/24 hours (normal, <100 mg/24 hours). The patient was given phenoxybenzamine and propranolol. The electrocardiographic pattern revealed a nontransmural inferolateral myocardial infarction.

TABLE 2. Cardiovascular Responses to Intravenously Administered Fentanyl and Droperidol in a Patient with Pheochromocytoma

	Before Fentanyl–Droperidol		Agent	Time of Response*	After Fentanyl–Droperidol	
	Blood Pressure (torr)	Pulse (Beats/Min)			Blood Pressure (torr)	Pulse (Beats/Min)
Known pheochromocytoma—before anesthetic induction						
Patient 9†	158/79	80	Fentanyl, 1 ml (0.05 mg)	10 min‡	158/79	80
	158/79	80	Droperidol, 1 ml (2.5 mg)	90 sec	175/80	100
				4 min	230/110	100

* Recorded by continuous intra-arterial monitoring.
† 10-min continuous baseline values were obtained.
‡ Pressures were continuously recorded for 10 min.

Seven days later increasing abdominal pain and enlargement of the abdominal mass suggested hemorrhage into the pheochromocytoma, and the patient was scheduled for emergency laparotomy. That evening an intra-aortic balloon assist device was inserted, with some difficulty as the mass was compressing the aorta. The patient successfully underwent excision of a huge, right suprarenal pheochromocytoma. A partial vena caval resection was necessary for removal of the tumor. The patient was subsequently discharged 14 days later.

Patient 2. Another asymptomatic patient, being prepared for left-hip arthrography, experienced severe hypertension 2 min after the administration of Innovar, 1.5 ml, iv. Further medical evaluation was undertaken, and a large left suprarenal pheochromocytoma was excised seven months later.

Patient 3. Hypertension developed 5 min after administration of Innovar during a planned transurethral prostatic resection with use of spinal analgesia. The procedure was terminated, and a search for a possible pheochromocytoma was undertaken.

Patients 4, 5, and 6. In three patients similar hypertensive responses developed after administration of Innovar before selective angiography for possible pheochromocytomas. The tumors were demonstrated and subsequently excised. Before excision of a pheochromocytoma, one patient (Patient 6) received Innovar again during induction of anesthesia, and hypertension recurred.

Patients 7 and 8. Two patients had chemical and roentgenographic evidence of pheochromocytoma. Before induction of anesthesia for removal of their tumors, they received Innovar. Hypertension was seen within 35 sec in one (continuous intra-arterial recording) and within 5 min (by auscultation) in the other.

Patient 9. Since the hypertensive response to Innovar had been recognized, it was decided that droperidol and fentanyl should be administered separately under controlled conditions to verify which of these substances initiated the response. Patient 9 sought treatment for intermittent episodic hypertension and classic symptoms of pheochromocytoma (table 2). Laboratory studies confirmed the existence of the tumor. Intravenous pyelography and selective angiography demonstrated a large right cystic suprarenal pheochromocytoma. After premedication with pentobarbital, 100 mg, meperidine, 100 mg, and atropine, 0.4 mg, im, two intravenous catheters and an indwelling radial-artery catheter were established. We obtained 10-min continuous baseline values for blood pressure and pulse rate (158/79 torr and 82 beats/min). No alteration in these vital signs was seen during this time. Fentanyl, 0.05 mg (1 ml), iv. was given and the recording continued for another 10 min without change in blood pressure or pulse rate. Droperidol, 2.5 mg (1 ml), was then injected iv. Within 90 sec blood pressure rose to 175/80 torr, and within 4 min it had reached 230/110 torr. Pulse rate increased to 100 beats/min (sinus tachycardia). Infusion of sodium nitroprusside was begun. General anesthesia proceeded without complication, and the tumor was successfully excised.

Discussion

During the past ten years Innovar has become increasingly popular as a premedicant in the preparation of patients undergoing diagnostic procedures. Neuroleptanalgesia has been one of the methods of choice in anesthetizing patients with pheochromocytomas[2–4] because, in normal patients, it provides remarkable cardiovascular stability.[5,6] Droperidol has also been shown to prevent epinephrine-induced dysrhythmias in dogs.[7] In his review, Tammisto[8] found inconclusive evidence that fentanyl and droperidol affected the plasma levels of epinephrine or norepinephrine. He also reported that during surgical stimulation catecholamine release was increased markedly, and postulated that neuroleptanalgesia may promote cardiovascular stability by blocking catecholamine action on vascular smooth muscle.

So far as can be determined, six isolated cases of development of extreme hypertension in patients with pheochromocytoma after administration of Innovar or droperidol have been reported. Yusa *et al.*[9] reported the cases of two patients, both of whom received droperidol, 12.5 mg, iv, and experienced sudden hypertension. The patient of Maddern *et al.*[10] experienced sudden hypertension after iv administration of 7.5 mg droperidol. Sumikawa and Amakata[11] reported two cases in which much smaller doses of droperidol were given iv. One patient had the sudden onset of hypertension after administration of 1.25 mg droperidol, and the second experienced hypertension 3 min after a similar dose. Sumikawa and Amakata[12] reported the case of one patient who received a test dose of 1.25 mg droperidol, iv. Within 30 sec blood pressure fell from 190/120 to 160/108 torr. Sixty seconds later blood pressure rose to 216/160 torr, and within 10 min it reached 232/160 torr. Six days later, droperidol, 1.25 mg, iv, was given. Within 3 min blood pressure rose from 160/108 to 188/110 torr. Another 1.25 mg droperidol was given, and within 1 min blood pressure reached 206/100 torr.

It is apparent from these studies and our nine cases that droperidol caused hypertension in some patients who have pheochromocytoma. This response is somewhat paradoxic, for when the drug is administered to patients without pheochromocytoma, hypotension may be induced. Many believe that this hypotensive response may be due to alpha-adrenergic receptor blockade.[1,13,14] The mechanism of the hypertensive response is unknown. Sumikawa and Amakata[12] dismiss a centrally mediated site of action of droperidol in eliciting this response. Our study tends to confirm this, as all of our patients remained calm and symptom-free and were very drowsy after the administration of either Innovar or droperidol.

Sumikawa and Amakata[12] also stated that a positive-feedback mechanism may play a role, as their patient experienced a reduction in blood pressure initially after the first dose of droperidol. Three of our patients in whom indwelling radial-artery catheters were present did not have reductions in blood pressure after the administration of Innovar or droperidol. In the remaining six patients blood pressures were measured by auscultation, and it could not be determined from the anesthetic record whether a decrease in blood pressure occurred immediately before the

hypertensive response. It seems unlikely, therefore, that a positive-feedback mechanism is responsible for this hypertensive response. Two unproven mechanisms may then play roles. Droperidol may directly stimulate the tumor cells or sympathetic nerve endings to release catecholamines, or it may inhibit catecholamine reuptake into the nerve terminals.[12]

The hypertensive response to the iv administration of droperidol or Innovar does not seem to be dose-related, as the response has been demonstrated with both small (1.25 mg)[11] and large doses (12.5 mg).[9] It is not apparent from Yusa and associates' report, however, whether the smaller doses of droperidol did indeed evoke the response. In most clinical situations, doses of droperidol of 1.25 or 2.5 mg would be considered small but, as has been demonstrated, the hypertensive response can be evoked in this dose range.

Because droperidol can evoke a hypertensive response in patients who have pheochromocytomas, we evaluated three patients who experienced unexpected hypertension after the administration of Innovar. In two of these patients unrecognized pheochromocytomas were discovered and excised. In the third (Patient 3) a pheochromocytoma was not demonstrated. In our experience, negative results do not preclude the discovery of a tumor later. One patient (Patient 7) in the group known to have pheochromocytomas had had hypertension for 16 years. After ten years of repeated evaluations, the tumor was identified and removed.

Yusa and associates[9] suggest that neuroleptanalgesia or droperidol be avoided in management of patients with pheochromocytoma. Furthermore, these drugs should not be given parenterally unless blood pressure is carefully monitored. The hypertensive crisis can readily be controlled with an infusion of sodium nitroprusside. However, as one of our cases (that of Patient 1) demonstrated, the hypertensive crisis may be fraught with extreme cardiac difficulties.

Nine patients experienced hypertension immediately after the intravenous administration of Innovar or droperidol. Eight of these patients were found to have pheochromocytomas and the tumors were excised. It is suggested that Innovar or droperidol not be given to patients with suspected or known pheochromocytomas, and patients having any severe hypertensive response after administration of these drugs should be investigated for possible pheochromocytoma.

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