

Anesthetic Management of Pheochromocytoma Employing Halothane and Beta Adrenergic Blockade

A Report of Fourteen Cases

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The anesthetic management of 14 patients operated upon for pheochromocytoma is described. Because of its sympatho-adrenal depressing properties, halothane was used as the principal anesthetic. Arterial pressure was controlled by varying the inspired concentration of halothane, though during tumor manipulation, phentolamine was given in addition. Arrhythmias occurred in ten of the patients and were treated with either lidocaine or propranolol. Lidocaine reverted six of eleven arrhythmic episodes while propranolol reversed eleven of thirteen. In addition, propranolol seemed to provide protection against further arrhythmia. Hypotension following tumor resection was treated with intravenous fluid administration; vasopressors were not used. Cardiovascular monitoring was employed and is essential in this operative procedure.

A SIGNIFICANT hazard attending anesthesia during operation for pheochromocytoma is the occurrence of ventricular arrhythmias. This possibility is present when halothane is used as the anesthetic for, among the commonly used general anesthetics, the property of halothane in enhancing the arrhythmic activity of the catecholamines appears to be exceeded only by cyclopropane.¹ To the sustained high blood levels of catecholamines often characterizing this tumor may be added yet more

catecholamines resulting from intraoperative manipulation. The combined effect of these high levels of circulating catecholamine and halothane may be responsible, through an increase in myocardial excitability, for these arrhythmias.

The well-recognized property of halothane in depressing sympatho-adrenal activity² provides a nicely controllable means of moderating the hypertension which too is a hazard during operation for pheochromocytoma. This action on blood pressure, together with the ease of administration, nonflammability, and relatively rapid induction and recovery, recommends it for use in pheochromocytoma. This paper reports the anesthetic management of 14 cases of pheochromocytoma with halothane employed as the principal agent. In ten of these patients a local anesthetic, lidocaine (Xylocaine), and a beta adrenergic receptor blocking agent, propranolol (Inderal), were used to control intraoperative ventricular arrhythmias during the halothane anesthesia. Other aspects of anesthetic management including the use of muscle relaxants, vasopressors, blood and fluid replacement, and patient monitoring are examined.

Patients and Methods

Ten male and 4 female patients, ranging in age between 12 and 65 years, treated within a fifteen month period, comprise the present series. All had clinical and biochemical evidence of pheochromocytoma before operation. Two patients had histories of recent myocardial infarction, one within two months

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Accepted for publication December 12, 1966.

TABLE 1. Preoperative Therapy and Urinary Excretion of Metabolites of Catecholamine

Patient	Interval between Last Dose and Operation		Immediate Preoperative Urinary Catecholamine Metabolites (mg./24 hr.)	
	Phenoxybenzamine	Methyl-para-tyrosine	N.M.N.* M.N.	V.M.A.†
E. D.	24 hr.	3 days	7.7	42.5
A. B.	12 hr.	1 day	9.5	37.1
D. B.	Not used	2 days	1.8	7.4
D. K.	Not used	1 day	9.7	16.2
E. H.	12 hr.	12 hr.	3.6	6.9
E. A.	12 hr.	1 day	17.4	28.5
K. L.	Not used	12 hr.	19.6	30.6
D. L.	Not used	12 hr.	2.3	8.1
R. K.	Not used	1.5 day	2.6	5.4
T. W.	Not used	1 day	2.7	10.2
E. W.	Not used	12 hr.	1.9	7.8
J. L.	Not used	12 hr.	2.2	4.5
A. A.	24 hr.	12 hr.	0.8	3.3
J. D.	Not used	12 hr.	4.7	10.5

* Normetanephrine and metanephrine—normal value, 1.3 mg./24 hours.

† Vanillylmandelic acid—normal value, 6.5 mg./24 hours.

of surgery, and two patients had had recent cerebrovascular accidents.

All patients were treated preoperatively with alpha-methyl-tyrosine (α MPT), an inhibitor of tyrosine hydroxylase,³ to decrease synthesis of catecholamines. Phenoxybenzamine, an alpha adrenergic receptor blocking agent, was also given orally in the preoperative period to 5 patients, to further lower blood pressure. The preoperative use of these drugs as well as the urinary excretion of metabolites of catecholamine on the day before surgery is summarized in table 1.

Oral secobarbital, 100 to 200 mg., was the sole premedicant in every patient but one, a 12 year old child to whom morphine, scopolamine, and secobarbital were given. Induction of anesthesia was carried out with thiopental given intravenously in doses ranging from 100 to 250 mg. Anesthesia was then maintained with halothane, 0.25 to 2.00 per cent, added to a 50 per cent mixture of nitrous oxide in oxygen in a total flow of 4 liters per minute into a semiclosed circle absorber system. Tracheal intubation performed after the patient was well anesthetized, was facili-

tated with succinylcholine, 60 to 100 mg. intravenously. Ventilation was controlled using a Bird Mark 4 ventilator, and end-tidal CO₂ concentration was measured in three patients with a Godart Capnograph. Muscle relaxation was produced with *d*-tubocurarine; the total dose varied from 9 to 90 mg. for operations lasting from 3 to 9 hours. Intravenous phentolamine (Regitine) was used as an adjunct to halothane to moderate hypertension. Repeated doses of 1 to 5 mg. were given depending upon the response of the blood pressure to an initial dose of 1 to 2 mg. Ventricular arrhythmias lasting longer than 15 to 30 seconds were treated first with lidocaine, 50 to 100 mg. intravenously. Those arrhythmias persisting longer than one minute following the administration of lidocaine were treated with propranolol,* 1 to 5 mg. intravenously. Arrhythmias which occurred following this sequence of therapy were treated with propranolol only. Patients undergoing bilateral adrenalectomy received supplemental hydrocortisone, 100 mg. intravenously, during anesthesia. Fluids administered during operation included whole blood, 5 per cent albumin in saline and lactated Ringer's solution.

Before induction of anesthesia, an indwelling catheter or needle was placed in either the brachial or radial artery, using local anesthesia. This was then connected to a Statham strain gauge and a Gilson polygraph recorder for continuous monitoring of arterial pressure. The electrocardiogram was similarly recorded before induction and displayed simultaneously on an oscilloscope and the recorder throughout the operative procedure. Venous pressure was measured with a saline manometer connected to an 8.5 inch catheter inserted into the external jugular vein just superior to the clavicle. Blood loss was estimated by direct measurement of the volume in suction bottles and by a conductimetric method on blood extracted from sponges.

Results

Seventeen episodes of arrhythmia were treated in 10 patients (table 2). Arrhythmias included bigeminy (ten), ventricular tachycardia (one), multifocal ventricular premature

* Supplied by Ayerst Laboratories.

contractions (five) and supraventricular tachycardia (one). Lidocaine, given in 50–100 mg. dosage, reverted six arrhythmias and failed to do so in five others. In those cases where lidocaine was effective, the apparent duration of action was short, ranging from 15 seconds to 10 minutes (table 2, fig. 1). Propranolol in 1.0 to 5.0 mg. dosage terminated eleven of thirteen arrhythmic episodes. The apparent duration of action of propranolol was longer than that of lidocaine; in some cases no arrhythmia recurred for over an hour even though the tumor was being continuously handled. No adverse effects were noted with either lidocaine or propranolol except as described below (case 1).

Case 1. T. W. was a 65 year old man with an intrathoracic pheochromocytoma. He had a past history of congestive heart failure for which he had received digitalis. Anesthesia was maintained with nitrous oxide, oxygen, and halothane supplemented with tubocurarine. During the first 90 minutes of operation, he developed three episodes of arrhythmia, bigeminy twice, and a supraventricular tachycardia (rate 150). For these he received a total dose of propranolol of 7 mg., and of lidocaine 150 mg. In the course of dissecting the tumor, a large (2,000 ml.) blood loss occurred, followed by extreme hypotension and the development of ventricular fibrillation. A contributing factor to the hypotension might have been the action of propranolol which diminishes the cardiac response to sympathetic stimulation. Direct manual systole of the heart and electrical defibrillation through the thoracotomy incision re-

TABLE 2. Effect of Treatment on Arrhythmias Occurring During Operation

Patient	Arrhythmia	Blood Pressure before Treatment (mm. Hg)	Pulse	Treatment (mg.)	Effect	Blood Pressure after Treatment (mm. Hg)	Pulse	Arrhythmia-free Interval (min.)	Interrupted by
K. L.	V.T.	220/180	170	L 50	none	—	—	—	—
	M.V.P.C.	140/100	96	P 5	N.S.R.	200/150	95	42	A
				L 50	N.S.R.	140/100	96	5	T
D. B.	B	140/100	130	P 7	N.S.R.	180/100	60	12	T
A. B.	B	190/100	120	L 50	N.S.R.	180/100	120	15 sec.	A
	B	180/100	120	P 2.5	N.S.R.	190/120	132	33	T
E. D.	B	180/100	120	P 1.0	none	—	—	—	—
				L 50	N.S.R.	210/120	110	5	T
D. K.	M.V.P.C.	180/120	130	L 50	none	—	—	—	—
	B	180/120	130	P 4	N.S.R.	160/100	100	13	A
				P 5.5	N.S.R.	170/120	120	69	T
A. E.	B	230/140	100	L 50	N.S.R.	220/150	100	7	A
	B	190/110	110	P 5	N.S.R.	180/120	120	16	A
	M.V.P.C.	210/110	110	P 5	N.S.R.	200/140	110	2	T
D. L.	M.V.P.C.	240/190	170	L 50	none	—	—	—	—
				P 5	N.S.R.	200/120	60	63	T
E. W.	M.V.P.C.	220/160	144	L 50	none	—	—	—	—
				P 3.5	N.S.R.	230/180	120	30	T
T. W.	B	140/180	84	L 100	N.S.R.	130/80	66	10	A
	B	100/50	72	P 5	none	—	—	—	—
					N.S.R.	80/50	60	10	A
	S.V.T.	130/100	150	P 2	S.V.T.	110/70	120	15	A
J. D.	B	200/100	144	L 100	none	—	—	—	—
				P 1.5	N.S.R.	150/120	126	15	T

V.T. = Ventricular tachycardia; M.V.P.C. = Multifocal Ventricular Premature Contractions; B = Bigeminy; T = Tumor excision; A = Further arrhythmia; L = Lidocaine; P = Propranolol.

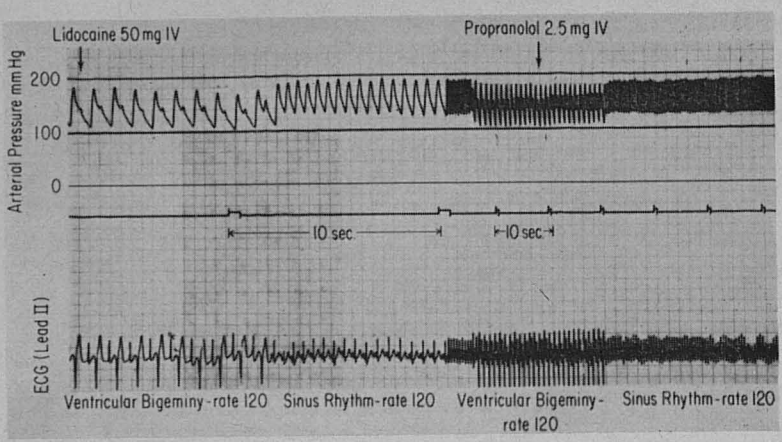


FIG. 1. Reversion of ventricular bigeminy by intravenous lidocaine showing recurrent arrhythmia treated with propranolol. Note that the paper speed has changed at mid-chart.

TABLE 3. Blood Loss and Fluid Replacement During Operation

Patient	Estimated Blood Loss (ml.)	Blood Replaced (ml.)	Lactated Ringer's & Albumin/ Saline (ml.)		Total Replaced (ml.)	Excess (ml.)
			A	L/R		
E. D.	—	1,500	—	500	2,000	—
A. B.	750	2,000	—	300	2,300	1,550
D. B.	2,000	2,000	—	1,000	3,000	1,000
D. K.	1,500	2,500	500	600	3,600	2,100
E. H.	1,200	1,000	—	1,000	2,000	800
E. A.	700	1,000	—	1,500	2,500	1,800
K. L.	3,500	4,000	250	3,000	7,500	4,000
D. L.	1,500	2,500	500	2,500	5,500	3,000
R. K.	3,000	2,000	1,000	2,000	5,000	2,000
T. W.	8,000	9,000	—	250	9,250	1,250
E. W.	3,000	2,500	1,250	2,000	5,750	2,750
J. L.	1,500	500	1,000	1,500	3,000	1,500
A. A.	26,000	30,000	3,500	2,000	35,500	9,500
J. D.	500	800	750	600	2,150	1,650

sulted in the restoration of normal sinus rhythm. A norepinephrine infusion was required for a period of 30 minutes; thereafter a satisfactory arterial pressure was maintained without the use of pressor amines.

Estimated blood loss for these operations ranged between 500 and 26,000 ml. and blood replacement ranged from 500 to 30,000 ml. The median amount by which the total blood, albumin, and lactated Ringer's solution infused exceeded the estimated blood loss was 1,800 ml. (table 3).

Discussion

Halothane was chosen as the principal anesthetic in these patients because of its property of depressing sympatho-adrenal activity.² Halothane acts centrally and peripherally on the autonomic nervous system, on the myo-

cardium and peripheral vasculature to either decrease sympathetic activity or obtund the response to catecholamine. These properties provide a ready means of control of arterial pressure by varying the inspired concentration of halothane. Acute hypertension periods did occur however, and were coincident with periods of tumor manipulation. At these times we chose to lower the arterial pressure quickly by giving phentolamine rather than by the slower means of increasing the inspired concentration of halothane.

In contrast to the experience of others who have used halothane in the operation for pheochromocytoma,^{5, 6, 7} the arrhythmias encountered in this series were neither transient nor infrequent. Several investigators indicate that a significant increase in cardiac irritability re-

sults from the infusion of catecholamine in animals anesthetized with halothane.^{1, 8} Administration of catecholamines to animals anesthetized with halothane has demonstrated a definite increase in susceptibility to ventricular arrhythmias over the thiopental-anesthetized and the unanesthetized animal.¹ Epinephrine and norepinephrine are approximately equal in their capacity to induce ventricular arrhythmias.^{9, 10} Accordingly, chromaffin tumors of both adrenal and extra-adrenal origin may provoke arrhythmias during halothane anesthesia.¹¹

Both lidocaine and propranolol are of demonstrated value in the treatment of cardiac arrhythmias though their mode of action probably differs. Sprouse *et al.*¹⁷ showed that the lowering of the ventricular diastolic threshold to stimulation caused by epinephrine could be returned to normal by the simultaneous administration of lidocaine. A more recent investigation has shown lidocaine to be a myocardial depressant, this being the basis for the antiarrhythmic activity.¹³ Lidocaine was effective in slightly more than half of the instances in which it was used. It might well have been more successful had the dosage been larger; greater than 1 mg./kg. body weight. The reported duration of antiarrhythmic action is between 10 and 20 minutes,^{14, 15} though in our patients, the apparent duration of action was usually less. Hypotension which can be produced by rapid intravenous administration of lidocaine was not noted.

The cardiac adrenergic stimulating activity of catecholamines appears to be specifically antagonized by propranolol; in this manner cardiac arrhythmias are reverted.¹⁶ However, there is evidence that there is a nonspecific depressant effect of propranolol on cardiac muscle, similar to lidocaine, and this action too may be of importance in reversion of arrhythmias.^{17, 18} Our present series provides further evidence for reversion of catecholamine-induced arrhythmias with propranolol. When given in amounts greater than 0.05 mg./kg. body weight, all arrhythmias except one were converted to normal rhythm. In addition, there may have been protection by propranolol against recurring arrhythmias during subsequent manipulation (table 2).

Unlike previous investigators who have used

beta adrenergic blocking agents in the operative management of pheochromocytoma,^{19, 20, 21} we used propranolol for the reversion of ventricular arrhythmias, not supraventricular tachycardia. Though our patients often had sinus tachycardia of 100–120 beats per minute, it was not thought necessary to treat this since blood pressure and peripheral circulation were well maintained. Also after propranolol had been given any pre-existing sinus tachycardia often continued and did not usually subside until the pheochromocytoma had been removed.

There are certain precautions in the use of propranolol. In common with the beta adrenergic blocking agents, it probably should not be used in the presence of heart failure, asthma or bradycardia.²² Dornhorst has suggested that the use of pronethalol (Nethalide) in pheochromocytoma be restricted to those patients pretreated with phenoxybenzamine, because of the danger of unopposed constrictor (alpha) action of high blood levels of epinephrine.²⁰ Presumably the same caution should be applied to the use of propranolol. We saw no consistent change in blood pressure with the administration of propranolol, though some patients had not been pretreated with phenoxybenzamine and had epinephrine-producing tumors. The maximum total dose of propranolol in our patients was 10 mg. and no serious untoward effects were noted except perhaps in Case 1. One patient developed A-V dissociation following the intravenous administration of atropine 0.5 mg. and prostigmine 2.0 mg. This was readily corrected with the use of additional atropine. Perhaps larger than the usual doses of atropine should be used when an anticholinesterase is given in the presence of a beta receptor blocking agent.

Although manipulation of the chromaffin tumor appeared to be the chief stimulus for arrhythmias, several other factors may be of importance. Hypoxia and hypercarbia are known potent stimuli for arrhythmias as well as for the release of catecholamines. Though arterial oxygen tensions were not measured, the inspired concentration of oxygen was maintained at 50 per cent. Periodic hyperinflation of the lungs was carried out at regular and frequent intervals to help prevent

E. W. 27 Y ♂
RECURRENT PHEOCHROMOCYTOMA

Est Blood Loss	3000 ml
Blood Replaced	2500 ml
5% Albumin/Saline	1250 ml
Lactate Ringers	2000 ml
5% Dextrose/Water	1100 ml

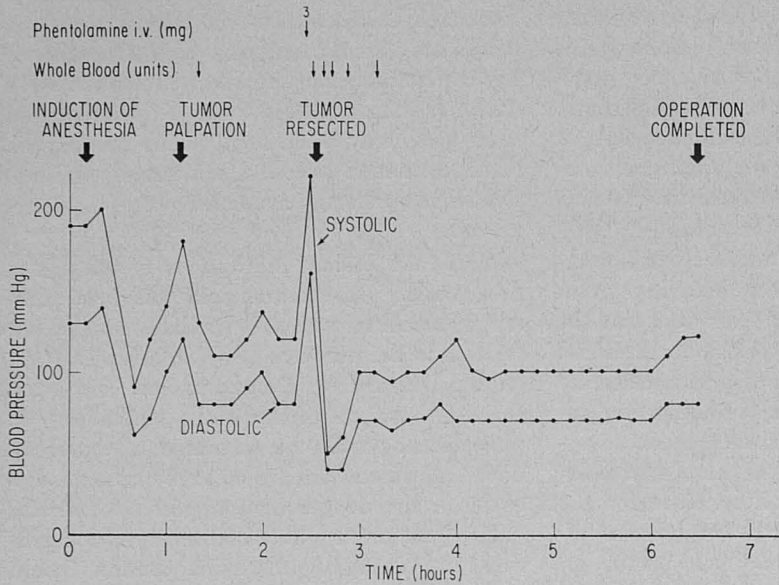


FIG. 2. A typical blood pressure recording demonstrating sharp upswing in pressure requiring phentolamine in addition to halothane to achieve control. The fall in blood pressure following tumor resection is evident.

atelectasis. End-expired carbon dioxide concentrations monitored in 3 patients ranged between 2.5 and 4.0 per cent.

In spite of considerable diversity among the patients in their clinical characteristics, a remarkable similarity was noted in their anesthetic course (fig. 2). Premedication, though usually consisting of an oral barbiturate alone, produced adequate sedation and a compliant patient in the majority of instances. This relative preoperative tranquillity was thought to result not only from the premedication employed but, in considerable measure, from careful preoperative explanation of the intended procedures over the course of many days prior to surgery, and the pharmacologic effects of the α MPT. The anxiety so characteristic of patients with functioning chromaffin tumors thus proved to be unimportant. Preanesthetic atropine in patients already prone to tachycardia was thought to be inadvisable.

Intubation of the trachea, despite the use of topical anesthesia, was accompanied by a rise in blood pressure in all but 3 patients. The blood pressure returned to its previous level in 5 to 10 minutes, perhaps in part as

a result of increased inspired concentrations of halothane and improved pulmonary ventilation. Phentolamine was administered during this period in 3 patients but in the doses employed did not appear to hasten the return of blood pressure to base line. No blood pressure change or arrhythmia was noted after the administration of succinylcholine in contrast to the belief that the fasciculations accompanying its use cause catecholamine release from the tumor.⁵

Notwithstanding the theoretical disadvantage of histamine-release attending the use of curare, neither arrhythmia nor significant change in blood pressure followed its administration in our patients. Paralysis, where it persisted at the termination of operation, was reversed with atropine and neostigmine.

Interruption of the venous drainage from the tumor was invariably followed by a fall in systolic blood pressure to levels below 100 mm. of mercury. Halothane was then decreased to minimum concentrations, and blood, 5 per cent human serum albumin in saline solution, and lactated Ringer's solution were infused until the systolic blood pressure approximated 100

mm. of mercury and the pulse pressure increased.^{23, 24} In no case did the venous pressure rise over 15 cm. of saline even though the average total volume of blood, plasma, and balanced salt solution administered exceeded the median measured blood loss by a volume of 2,000 ml. and all patients had come to operation with normal blood volume (table 3).²⁵ The administration of vasopressors for the support of blood pressure in the operative and postoperative periods was not necessary with the sole exception of case 1. Hypotension was treated successfully in all cases with intravenous blood and fluid administration.

The rapid and wide fluctuations in blood pressure which characteristically occur during the operation for pheochromocytoma make continuous arterial pressure monitoring mandatory. Endovascular techniques employing intra-arterial needles or catheters to provide continuous measurements are so superior to the sphygmomanometer cuff in this condition that they appear to be essential. Simple devices requiring a minimum of time and equipment are available for use in conjunction with the indwelling needle or catheter when electronic monitors are not available.^{26, 27} Similarly, a continuous electrocardiogram is essential because of rapid changes in cardiac rate and rhythm. Venous pressure monitoring is of obvious importance in the patient receiving large volumes of fluid, especially so in cases where underlying cardiac disease may be present.²⁸

Summary

The successful use of halothane anesthesia for the surgical resection of pheochromocytoma in 14 patients is reported. The use of halothane to moderate the characteristic hypertension occurring during operation proved to be a valuable adjunct. Ten of 14 patients developed ventricular arrhythmias or supraventricular tachycardia. Lidocaine (0.75 mg./kg. body weight) and/or propranolol (0.5 mg./kg. body weight) were used in the treatment. Lidocaine terminated 6 of 11 episodes, propranolol eleven of thirteen. Propranolol seemed useful in the reversion of ventricular arrhythmia though in one patient it may have potentiated the hypotension following large blood

loss. Lidocaine was not as successful though the dosage might have been too small. Other important factors in the management of such patients include continuous monitoring of cardiovascular function and adequate intravenous replacement of fluid following tumor resection to maintain satisfactory blood pressure.

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Drugs

HYPNOTICS The sedative effects of four hypnotic drugs was determined. The drugs were: Ro 4-5360 (Mogadon), 5 mg. and 10 mg.; methypylon (Noludar), 200 mg.; secobarbital sodium (Seconal), 100 mg. and a placebo. The active preparations were all effective in terms of length and quality of sleep. Differences among them were not statistically significant. Each drug was statistically significantly different from the placebo. The length of action of the various drugs appeared to be similar. Ro 4-5360 in both dosages had a somewhat longer period of activity. The use of Ro 4-5360 in the 10-mg. dose was followed by the largest number of complaints of morning drowsiness, followed in rank order by Ro 4-5360, 5 mg., secobarbital sodium and methypylon. The hypnotics gave the patients about 1 hour more sleep on the average than the placebo, and to obtain this they experienced certain side effects, which may, however, have been quite acceptable to them. (*Harding, W., and others: A Clinical Trial of Four Hypnotic Drugs, Canad. Med. Ass. J.* 95: 300 (Aug.) 1966.)