ANAESTHETIC MANAGEMENT OF PHEOCHROMOCYTOMA*

E. R. ENGELBRECHT, M.D., J. T. HUGILL, M.D., AND
H. B. GRAVES, M.D., C.M., F.R.C.P.(c)†

AT THE VANCOUVER GENERAL HOSPITAL, a pheochromocytoma tumour has been seen in approximately one case per 100,000 admissions. Over the past ten years seven patients have come to surgery, requiring thirteen anaesthetics for the removal of ten tumours.

It is the purpose of this paper to present briefly our anaesthetic experiences with these cases, and the changes in their management during this period. No attempt will be made to present a detailed discussion of the physiology, pharmacology, clinical picture, and specific diagnostic tests relevant to the disease. This has been reviewed in several recent articles.¹⁻⁵

Table I summarizes these cases. Patients 1 and 7 of our series illustrate many of the interesting pharmacological and physiological problems which the anaesthetist must face. All of the patients presented with paroxysmal hypertension, palpitations, and sweating. Four had cardiac arrhythmias. Patient 1 and patient 5 were father and daughter. In patient 6 the onset of symptoms commenced during pregnancy. Only in patient 2 was the location of the tumour diagnosed prior to surgery, and all the tumours were located in the adrenals initially.

Patient 1—W.W.

In 1955 a forty-three year old white male presented with a ten-year history of episodic tachycardia, accompanied by sweating and nervousness. Examination revealed a blood pressure of 180-230/100-120 and a pulse rate of 80-152. The electrocardiogram showed T-wave depression, episodes of paroxysmal atrial tachycardia, and ventricular bigeminy. Haemoglobin was 17.8; N.P.N. was normal. Phentolamine and benzodioxane tests were positive, and 24-hour catecholamine urinary excretion was 100 µg. The patient was placed on quinidine and digoxin to control the arrhythmia. Three weeks after admission he was presented for surgery.

Premedication was meperidine 100 mg. and hyoscine 0.4 mg. one hour pre-operatively. A phentolamine drip was started on the ward immediately before the patient was brought to the operating room, to stabilize the blood pressure. Induction was with thiopentone followed by succinylcholine for endotracheal intubation. The patient was maintained on nitrous oxide, meperidine, and succinylcholine. In spite of intermittent phentolamine, the blood pressure fluctuated widely, with rises to 240-300 systolic on manipulation of the adrenal glands;

*Presented at the Annual Meeting of the Canadian Anaesthetists' Society at Banff, June 6-10, 1966.

†Department of Anaesthesiology, Vancouver General Hospital and the Faculty of Medicine, University of British Columbia.

TABLE I

Patient	Year	Age	C.E.*	Preparation	Anaesthetic†	Other agents	Outcome
1. W.W.	1955	43	100	quinidine digoxin	T.S.O.N.	phentolamine 13 mg.	Improved for 11 months, with B.P. 140-160/80
	1957	44	450	"	T.O.N. gallamine	phentolamine 8 mg.	Severe paroxysmal tachycardia after palpation of tumour; surgery discontinued
2. B.W.	1960	47	400	digoxin	T.O.N. gallamine	phentolamine 3 mg.	Severe tachycardia after induction; surgery cancelled
					tribromoethanol S.N. ether	phentolamine 9.5 mg. hydrocortisone norepinephrine blood 500 cc.	Slow recovery, then well for 3 years
	1959	14	250	T.S.O.N. ether tribromoethanol	phentolamine drip procainamide cortisone	Ventricular tachycardia (short); norepinephrine and methoxamine for 3 days; steroid gastric ulcer; discharged well	
				T.S.O.N. promethazine	phentolamine drip phenylephrine drip blood 500 cc.	Well postoperatively	
3. S.B.	1959	24	—	—	T.S.O.N. chlorpromazine	phentolamine drip phenylephrine norepinephrine blood 500 cc.	Well for 3 years
	1962	27	150	—	T.S.O.N.	phentolamine drip norepinephrine	Well for 2½ years
4. G.B.	1965	30	160	—	T.S.O.N.	phentolamine 5 mg.	Extensive metastasis found; discharged on beta-blockers
	1960	18	100	—	T.S.O.N.	phentolamine 30 mg. phenylephrine norepinephrine blood 500 cc.	Well 3 years later
5. P.W.	1960	22	1500 2000	—	T.S.O.N.	phentolamine 6 mg. hydrocortisone norepinephrine blood 500 cc.	Dilutional hyponatremia 48 hours postoperatively Well 5 years later
6. S.C.	1964	30	180 326	phenoxybenzamine cortisone	T.S.O.N.	phentolamine 10 mg. hydrocortisone metaraminol blood 1000 cc.	Discharged well
7. S.S.	1965	30	280 16798	phenoxybenzamine phentolamine hydrocortisone	T.S.O.N.	phentolamine 40 mg. blood 2000 cc.	Discharged well

*C.E. = Twenty-four-hour urinary catecholamine excretion in µg.

†T.S.O.N. = Thiopental, succinylcholine, opiate (meperidine and/or alphaprodine), nitrous oxide.

there also occurred one short episode of ventricular tachycardia which was controlled with procaine amide HCl. Following removal of a large left adrenal tumour the blood pressure levelled off to 130-160/70-80 with a pulse rate of 80-100. The patient did well postoperatively and did not require vasopressors. His symptoms were relieved and the urinary catecholamine excretion returned to normal; blood pressure remained elevated at 140-160 systolic.

In February, 1957, he returned with a recurrence of symptoms and investigation confirmed the diagnosis of recurrent pheochromocytoma. The anaesthetic was similar to that used for the first procedure, with the exception that gallamine was administered for relaxation. This produced a rise in blood pressure and a tachycardia. On manipulation of the tumour a further severe rise in pressure and an intractable tachycardia developed, and further surgery for the removal of the tumour was discontinued. One month later the patient was again brought to surgery, anaesthetized by the same method, and given gallamine after induction. He again developed a severe tachycardia, and surgery was cancelled. Two days later he was presented for surgery. On this occasion he was induced on the ward with tribromoethanol, intubated after succinylcholine, and maintained on nitrous oxide and ether. No meperidine was given. Phentolamine was used only to control the blood pressure elevation on manipulation of the tumour. Hydrocortisone was administered before, during, and after surgery. Postoperatively the blood pressure remained at 120-140 systolic, with only small amounts of noradrenaline required in the first 24 hours. The patient was discharged well, with a normal catecholamine excretion.

In 1960 he returned with a second recurrence of pheochromocytoma. He was given cortisone prior to surgery, and a phentolamine drip was started on the ward immediately prior to induction with tribromoethanol. Agents used for maintenance were nitrous oxide, ether, meperidine, and succinylcholine. On being moved from the anaesthetic room to the operating room the patient developed a ventricular tachycardia which was quickly controlled with procaine amide. Blood pressure rose sharply on manipulation of the left adrenal gland, and a large left adrenal tumour was found and removed. No blood was given. In the postanesthetic room the patient became hypotensive and required increasing doses of phenylephrine, noradrenaline and methoxamine. He also had another episode of ventricular tachycardia, controlled with procaine amide. Blood pressure finally stabilized at 130/80 on the third postoperative day. Haemoglobin dropped from 19 gm. preoperatively to 11 gm. five days postoperatively. The patient had also been given cortisone, and ten days postoperatively he developed an acute gastric ulcer, thought to be due to the cortisone. He was finally discharged well and has remained so since, with moderate essential hypertension (150/90) but good kidney function.

Patient 7—S.S.

This 30-year-old white male was referred from an outside hospital with a history of episodes of headache, retching, palpitations, and sweating. On admission he was acutely ill, sweating profusely, with a blood pressure of 260/160, and a pulse rate ranging from 70 to 170. He had anuria of two days'

duration. N.P.N. was 36 mg./100 ml. and haemoglobin was 18 gm./100 ml. Twenty-four-hour urinary catecholamine excretion was 280 μ g. two weeks prior to admission, and 16,798 μ g. after admission. A phentolamine test dropped the blood pressure to zero, but it quickly responded to vasopressor administration. The electrocardiogram showed T-wave inversion, left axis deviation, and wandering pacemaker. The patient was placed on a very dilute phentolamine drip but his blood pressure was difficult to control, ranging from 0 to 230. Intramuscular phentolamine was also given. Two days later he was placed on phenoxybenzamine 30 mg. b.i.d. His condition improved: after one week of treatment the blood pressure stabilized at 110–130/70 and the pulse rate 80–100. He was also sedated with promethazine 25 mg. q.i.d. A central venous pressure catheter was inserted into the external jugular vein the day before surgery, and recorded a pressure of 18 to 19 cm. H₂O. Phenoxybenzamine was discontinued one day before surgery, and cortisone 100 mg. was given. Premedication consisted of secobarbital, morphine sulfate, and hyoscine. A phentolamine drip was started on the ward, and hydrocortisone was also given. On the patient's arrival in the operating room an E.C.G. for continuous monitoring was set up. He was induced with thiopental, intubated after succinylcholine, and maintained on nitrous oxide, meperidine, alphaprodine, and succinylcholine, with intermittent doses of phentolamine to control the blood pressure. On manipulation of the right adrenal gland, the blood pressure rose sharply to 230 systolic, and then dropped to the 110–120 range after removal of the tumour. Figure 1 shows the course of anaesthesia. Blood was administered to replace the loss until the tumour was removed; when the blood pressure dropped, 1000 c.c. of blood was given rapidly. The central venous pressure dropped to zero after removal of the tumour but rapidly returned to 6–8 cm. H₂O with the administration of the blood. A total of 2000 c.c. of blood was given—1000 c.c. above the estimated loss. Postoperatively the patient was given hydrocortisone. The central venous pressure was monitored for 48 hours after surgery. Blood pressure remained stable postoperatively at 110/70; pulse rate was 90 and central venous pressure was 6–8. In spite of the increased blood administration, haemoglobin dropped to 9 gm./100 ml. on the second postoperative day, but rose to 12 gm./1000 ml. by the time of discharge two weeks later. The patient has remained well.

DISCUSSION

These cases outline the common problems arising from the over-production of epinephrine and norepinephrine by pheochromocytoma tumours. The problems are basically:

1. *Vasoconstriction*, producing sustained or paroxysmal hypertension and the resulting cardiac failure, pulmonary oedema, renal failure, and cerebral haemorrhage.
2. *Vasodilatation*, producing severe hypotension.⁶
3. *Sensitization* of the myocardium, producing severe and fatal arrhythmias.
4. *Stimulation* of the production of epinephrine and norepinephrine by manipulation of the tumour, or by the pharmacological action of the anaesthetic drugs.⁷

FIGURE 1

The development of the alpha blocking agents, phenoxybenzamine and phentolamine, and clinical experience with them, have contributed to a more successful management of patients with these tumours.^{1,4,8} Phenoxybenzamine is a long-acting blocking agent, and must be discontinued at least 24 hours prior to surgery. Phentolamine is a rapid, short-acting drug, and is therefore useful during surgery. Preoperative treatment with these drugs for several days prior to surgery decreases the severe vascular constriction, allowing the vascular bed to dilate to a more nearly normal capacity, and enabling the blood pressure to stabilize.

It has been demonstrated that the patients in this series have a decreased blood

volume and red cell mass.^{9,10} As patient 7 indicates, haemoconcentration and haemoglobin may be initially high, only to drop precipitously pre- and postoperatively. Where preoperative blood replacement is necessary, packed cells are probably better than whole blood. The hyponatremia in patient 5 could probably have been avoided by the use of blood instead of glucose.

Patients with marked preoperative cardiac arrhythmias indicate the following observations: (1) that their tumours are secreting epinephrine; (2) that their tumours are more likely to be located in the adrenal glands, and (3) that cardiac arrhythmias are more likely to occur at surgery. Recently, the beta-blocking agents, pronethalol, propranolol, and dichloroisoproterenol, have been advocated in this group.^{4,7,11-16} These drugs were not immediately available when our cases were done. Patient 3 is now controlled on pronethalol.

Premedication in the majority of cases consisted of a barbiturate, a narcotic, and an anti-cholinergic drug (hyoscine). Some anaesthetists prefer to avoid morphine sulfate due to its histamine-releasing action. This has not been a problem in our cases. Conversely, in our patients with tachycardia we have observed that morphine sulfate has the advantage of producing a slight bradycardia. Atropine has been avoided because of its tachycardia-producing effect and its potentiation of cardiac arrhythmias.¹⁷

Phenothiazine derivatives, especially chlorpromazine, have been used, but these drugs have not proved to be as specific and as reliable as the blocking agents.¹⁷ They can produce severe tachycardia and hypotension.¹⁸ Promethazine has been advocated for its antihistamine effect.¹⁹ It provided a good sedative effect for patient 7, where it was also used for its anti-emetic action.

During the conduct of anaesthesia, stressful situations which stimulate the production of catecholamines must be avoided. These include emotional upsets, improper selection of anaesthetic agents, haemorrhage, hypotension, histamine release, hypoxia, hypercarbia, and acidosis. Constant vigilance, with adequate ventilation, complete carbon dioxide absorption, continuous or repeated blood-pressure monitoring, electrocardiogram, and central venous pressure monitoring, is mandatory. Temperature recording is important, especially in children. We have observed that patients with this disease are thin and do not require deep anaesthesia, and therefore large doses of relaxants are not necessary. However, they do require anaesthesia that is rapidly reversible.

Practically all the anaesthetic agents available have been used in various centres. Thiopentone, which does not produce adrenaline stimulation, is preferred for induction. Maintenance of anaesthesia with nitrous oxide and intermittent doses of meperidine or alphaprodine or a combination of both, with controlled respiration, is our method of choice for these cases. Meperidine tends to produce a slight tachycardia and is longer-acting than alphaprodine. The latter is a more potent analgesic and tends to produce bradycardia. This technique also has the advantage of being non-explosive.

Cyclopropane, chloroform, and trichlorethylene sensitize the myocardium, producing arrhythmias and fibrillation in the presence of catecholamines, and are therefore contra-indicated.^{11,20,21}

Ether was used in our first case and has been used in many other centres.

However, it is explosive and does not seem to have any advantage over our preferred technique. It is recommended by some²² as the agent of choice for children.

Halothane is the agent of choice of some anaesthetists since it does not stimulate the production of catecholamines and also tends to counteract vasoconstrictor action.^{2,18,23} However, we do know that halothane sensitizes the myocardium to catecholamine-induced arrhythmias.^{11,24} In patients who are receiving alpha and beta blockers, it is probably safe.²⁵ During manipulation of the tumour, the circulation may receive a sudden large endogenous infusion of the catecholamines,⁴ upsetting the balance with the blocking agents. In patients 1 and 7, who were difficult to control, the use of halothane would have added an unnecessary risk.

Methoxyfluorane has the disadvantage of being a slow agent for induction, and its excretion is prolonged. It is not readily reversible. Regional anaesthesia has been employed but is not now recommended.

Various relaxants have been used, but our choice, and the one most widely accepted, is succinylcholine. A slight rise of blood pressure may occur on the initial dose but this has not been a problem. A single dose of decamethonium has been used initially for opening the peritoneum in some cases. With the use of controlled respiration, and a wide surgical incision, relaxation has not been a problem except for opening and closing the abdomen. Gallamine may produce tachycardia and arrhythmia, as occurred in our first case, and d-tubocurarine has generally been avoided due to its histamine-releasing action.^{17,20} We also feel that large doses of competitive blocking relaxants necessitate the use of atropine and prostigmine-reversal, which may upset the cardiovascular balance. A few authors feel that all relaxants should be avoided in these cases.¹⁹

The drugs which we have ready to use before anaesthetizing a patient are: (1) narcotics, i.e., meperidine 20 mg./c.c. or alphaprodine 12 mg./c.c.; (2) phentolamine, 10–50 mg./500 c.c. depending on the patient's sensitivity; 1 mg./c.c. in syringe; (3) hydrocortisone, an intravenous preparation 100 mg./20 c.c.; (4) vasopressor, noradrenaline 4 mg./500 c.c. or phenylephrine 8 mg./500 c.c.; (5) calcium gluconate or calcium chloride; (6) digoxin and procainamide.

The anaesthetist starts a dilute phentolamine drip on the ward before bringing the patient to the operating room. The blood pressure is closely monitored to control sudden changes with the excitement of movement. On arrival in the anaesthetic room, the electrocardiogram is set up and a large-bore intravenous catheter is inserted. A central venous pressure catheter is inserted, preferably the day before surgery; or, if preoperative blood transfusions are given, it is used as a monitor of the blood volume.²⁶ The patient is slowly induced with thiopentone and intubated after succinylcholine. Small doses of narcotic are given as necessary during the surgery. Generally, after the tumour is removed, only nitrous oxide and a relaxant are necessary for closure. Patients are awake on return to the recovery room.

Phentolamine is given as required to control blood pressure, the more concentrated doses being required on manipulation of the tumour. Blood is replaced as it is lost up to the time the tumour is removed, then rapidly as the blood pressure

drops. Cortisone is given before, during, and after surgery, and is repeated if the blood pressure falls or is unstable in the recovery room. A vasopressor drip of phenylephrine or noradrenaline is given to keep the systolic blood pressure above 100 mm. Hg.

Postoperatively patients need intensive care for 24 to 72 hours until their condition is stable. Our patients remain in the recovery room and also have special nursing care. Failure to maintain adequate blood pressure without a vasopressor indicates the need for more blood and cortisone. Fluid intake and output should be carefully recorded.

SUMMARY

From our experience, the following are important requirements in the successful management of pheochromocytoma cases. (1) Adequate hospital treatment with the blocking agents for at least one week prior to surgery. (2) Adequate blood replacement during surgery, and preoperatively if necessary. (3) Adequate cortisone before, during, and after surgery. (4) Our anaesthetic of choice is thiopentone, opiate, nitrous oxide, with succinylcholine for relaxation, and controlled respiration. Careful monitoring of the blood pressure, central venous pressure, and electrocardiograph are mandatory.

The general surgical mortality rate reported elsewhere for the period 1952-65 was thirteen per cent.⁴ There were no deaths in our series. We predict that in the future this operation will be a relatively safe procedure. The knowledge, diagnostic investigation, and therapeutic drugs at our command are available to accomplish this.

RÉSUMÉ

Au cours des dix dernières années à l'Hôpital Général de Vancouver, on a pratiqué chez sept malades treize anesthésies pour l'ablation de dix phéochromocytomes. Un malade à sa troisième opération avait des métastases multiples. On expose l'usage de différents médicaments et de techniques variées d'anesthésie. Les points importants qui assurent le succès dans le traitement de ces malades sont: (1) Soins appropriés à l'hôpital durant au moins une semaine avant l'opération: agents bloqueurs de récepteurs alpha et, s'il y a indication, agents bloqueurs de récepteurs bêta; cependant l'utilité de ces derniers n'a pas été établie de façon évidente. (2) Remplacement du sang de façon minutieuse durant l'opération, et si nécessaire avant l'opération pour établir le volume sanguin normal. (3) Traitement adéquat à la Cortisone avant, pendant et après l'intervention. (4) Pour l'ablation chirurgicale, notre choix d'anesthésique est pentothal, opiacés, protoxyde d'azote, succinylcholine comme agent myorésolutif et respiration contrôlée. Le milieu physique doit être maintenu aussi normal que possible. Il est essentiel d'enregistrer attentivement la pression artérielle, la pression veineuse centrale, l'électrocardiogramme.

REFERENCES

1. HUME, D. M. Pheochromocytoma in the Adult and the Child. *Am. J. Surg.* 99: 458 (1960).
2. GOLDFIEN, A. Pheochromocytoma: Diagnosis and Anesthetic and Surgical Management. *Anesthesiology*. 24: 462 (1962).

3. CAHIES, G. F. & PAPPER, E. M. Surgical Removal of Pheochromocytoma. *J. Urology*. 76: 467 (1956).
4. CROUT, J. R. Pheochromocytoma. *Pharmacol. Rev.* 18: 651 (1966).
5. GIFFORD, R. W. JR.; KRALE, W. F.; MAHER, F. T.; ROTH, G. M.; & PRIESTLEY, J. T. Clinical Features, Diagnoses and Treatment of Pheochromocytoma: A Review of 76 Cases. *Proc. Mayo Clin.* 39: 281 (1964).
6. RICHMOND, J.; FRAZER, S. C.; & MILLAR, D. R. Paroxysmal Hypotension due to an Adrenaline-Secreting Phaeochromocytoma. *Lancet*. 2: 904 (1961).
7. RIDDELL, D. H.; SCHULL, L. G.; FRIST, T. F.; & BAKER, T. D. Experience with Pheochromocytoma in 21 Patients. *Ann. Surg.* 157: 980 (1963).
8. GRIMSON, K. S.; LONGINO, F. H.; KERNODLE, C. E.; & O'REAR, H. B. Treatment of a Patient with Pheochromocytoma—Use of an Adrenolytic Drug before and during Operation. *J.A.M.A.* 140: 1273 (1949).
9. SCHNELLE, N.; FERRIS, D. D.; & SCHIRBER, A. The Use of Blood Volume Determination in Patients Undergoing Surgery for Pheochromocytoma. *Anesth. & Analg.* 43: 641 (1964).
10. BRUNJES, S.; JOHNS, V. J.; & CRANE, M. G. Pheochromocytoma: Post-operative Shock and Blood Volume. *New England J. Med.* 263: 393 (1960).
11. JOHNSTONE, M. Beta-adrenergic Blockade with Pronethalol during Anaesthesia. *Brit. J. Anaesth.* 36: 224 (1964).
12. BLACK, J. W. & STEPHENSON, J. S. The Pharmacology of a New Adrenergic Blocking Compound (Nethalide). *Lancet*. 2: 311 (1962).
13. ALQUIST, R. P. Beta-adrenergic Receptor Blockade by Naphthylisoproterenol. *Fed. Proc.* 22: 449 (1963).
14. DORNHORST, A. C. & LAURENCE, D. R. Use of Pronethalol in Phaeochrome Tumour. *Brit. Med. J.* 2: 1250 (1963).
15. BLACK, J. W.; CROWTHER, A. F.; SHANKS, R. G.; SMITH, L. H.; & DORNHURST, A. C. A New Adrenergic Beta-receptor Antagonist. *Lancet*. 1: 1080 (1964).
16. HELLEWELL, J. & POTTS, M. W. Propranolol and Ventricular Arrhythmias with Malothane. *Anaesthesia*. 20: 269 (1965).
17. ROBERTSON, A. I. G. Anaesthetic Management of Phaeochromocytoma. *Proc. Roy. Soc. Med.* 55: 432 (1962).
18. BRODY, I. A. Shock after Administration of Prochlorperazine in Patients with Pheochromocytoma. *J.A.M.A.* 169: 1749 (1959).
19. ROLLASON, W. M. Halothane and Phaeochromocytoma. *Brit. J. Anaesth.* 36: 251 (1964).
20. MUSHIN, W. The Adrenals and the Anaesthetist. *Anaesthesia*. 12: 15 (1957).
21. MATTEO, R. S.; KATZ, R. L.; & PAPPER, E. M. The Injection of Epinephrine during General Anesthetics with Halogenated Hydrocarbons and Cyclopropane. *Anesthesiology*. 23: 360 (1960).
22. STACKPOLE, R. H.; MILICOW, M. M.; & USON, A. C. Pheochromocytoma in Children: a Report of 9 Cases and Review of the First 100 Published Cases with Follow-up Studies. *J. Pediat.* 63: 315 (1963).
23. MURPHY, M.; PRIOR, F. M.; & JOSEPH, S. Halothane and Blood Transfusion for Phaeochromocytoma. *Brit. J. Anaesth.* 36: 813 (1964).
24. ANDERSON, N. & JOHANSON, S. H. Incidence of Catecholamine-Induced Arrhythmias during Halothane Anesthesia. *Anesthesiology*. 24: 51 (1963).
25. MURRAY, W. J.; MCKNIGHT, R. L.; & DAVIS, D. A. Antagonism of Hydrocarbon-Anaesthetic-Epinephrine-Induced Arrhythmias in Dogs by Nethalide, a Tichloroisoproterenol Analogue. *Proc. Soc. Exper. Biol. & Med.* 113: 439 (1963).
26. SYKES, M. K. Venous Pressure as a Clinical Indication of Adequacy of Transfusion. *Ann. Roy. Coll. Surg. Engl.* 33: 185 (1963).