Anesthetic considerations with pheochromocytoma

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Pheochromocytoma is a condition rarely encountered by most anesthetists. Because of the complications that ensue in such a case, the anesthetist should be aware of the problem and know the necessary counteractive measures. The author provides a review of the physiology and pharmacology involved in pheochromocytoma cases, along with reports on recent techniques for their surgical management.

A pheochromocytoma is a chromaffin tumor most commonly of the adrenal medulla, containing a very high proportion of L- and D-noradrenaline with adrenaline. "About 90 per cent of such tumors are benign and 10 per cent are malignant."

"In contrast to other tumors of the sympathetic system, such as the sympathogonioma or neuroblastoma, the clinical significance of the pheochromocytoma lies chiefly in the fact that it is a 'physiologic malignancy' rather than in a tendency to metastasize."2

Normally, the adrenal medulla contains approximately 20 per cent norepinephrine and 80 per cent epinephrine. In pheochromocytoma, this rate may be grossly altered. A tumor of the adrenal medulla may contain up to 90 per cent norepinephrine. Pheochromocytomas usually occur as unilateral, catecholamine-secreting tumors of the adrenal medulla; but, they may be bilateral and may occur in chromaffin tissue, anywhere in the autonomic nervous system.

According to Dr. Goldfein's reference of Gitlow, et al.,2 98 per cent of the tumors found were in the abdominal cavity, and 90 per cent were in or near the adrenal gland, more commonly on the right side. Another frequent site of the tumors was the thorax, with one localized in the intracranial region and one in the cervical region.

Tumors occurring outside the region of the adrenals are usually observed in the paraganglia, the organ of Zuckerkandl at the arch of the aorta, and in the urinary bladder. The localization of tumors in the bladder has been associated with symptoms present in the act of micturition.

Features of predominantly adrenalin-secreting tumors are paroxysmal episodes of headache, vomiting and irritability, severe hypertension, and neural irritability. The normal clinical picture is one of hypertension, which classically is paroxysmal. In an attack, and apart from having a very high blood pressure, the patient will complain of sweating, palpitation, headache, anxiety, angina, dyspnea, and abdominal pain. The presence of nervousness, a high basal metabolism rate, glycosuria, or persistent hypertension in a thin individual should alert the practitioner to the possible presence of this disease. Common findings are intermittent or chronic hypertension, congestive heart failure, acrocyanosis, cardiomegally, ret-
inopathy, diabetes mellitus, and renal insufficiency.

The intense vasoconstriction that these patients get from increased secretion of catecholamines causes them to be chronically hypovolemic. When undiscovered, the presence of pheochromocytoma eventually leads to a high, sustained blood pressure, which makes the disease difficult to differentiate from essential hypertension, but paroxysms in which the blood pressure rises even higher may still occur. Structural changes in the heart and vessels take place sooner or later, and death may follow cardiac failure or a cerebrovascular accident.

The intermittent episodes of hypertension (attacks) may be caused by normal physiologic occurrences such as mild exertion, strain at defecation, and eating or drinking. Pain, worry, or psychological crises may precipitate a serious attack. When the nervous system perceives a serious disturbance, the adrenal medulla secretes both epinephrine and norepinephrine into the blood stream for distribution to distant action sites. Norepinephrine, the chemical mediator responsible for the excitation of adrenergic receptors, is released by the postganglionic fibers of the sympathetic nervous system and exhibits most of its effects at a local level.

The turnover of epinephrine and norepinephrine in the circulation is very rapid, the half-life of these compounds being less than one minute. This rapid removal is due partially to their rapid removal by monoamine oxidase and catechol-o-methyl transferase. Circulating norepinephrine produces widespread vasoconstriction causing increased peripheral resistance and an increase in systolic, diastolic, and mean blood pressure.

The direct effect on the heart is to increase the force and rate of contraction. Increased blood pressure, however, may cause reflex mechanisms to result in bradycardia and decreased cardiac output which may mask the direct cardiac effects. Another very important effect that has a direct bearing on the actual conduct of the surgical management of these cases is the fact that the plasma volume is reduced by prolonged increases in the level of circulating catecholamines.

**Alpha- and beta-receptor blocking agents**

“When Dale, in 1906, showed that the sympathetic nervous activity was mediated by two different receptors and Ahlquist named them alpha and beta in 1948, the only blocking agents available were those that blocked alpha-adrenergic receptors.” Since then, drugs blocking beta-receptors have been discovered; and still more recently, drugs that produce blockade by interfering with the release of noradrenaline from stores in adrenergic axons also have become available.

The alpha blockers act as competitive antagonists for catecholamines and sympathetic amines at the alpha-receptors of the sympathetic system. In most cases, both the agonists and antagonists have a comparable affinity for the receptor, and increasing the dose of either of them will overcome the action of the other. “However, this is not the case with phenoxybenzamine. Once an adequate block has been established, a massive dose of sympathomimetic agent is ineffective until the effect of the blocking compound is terminated by metabolism.”

There are four main groups of drugs which block alpha-receptors:

1. Imidazolines, such as tolazoline and phenolamine.
2. Benzodioxans which are chemically related to epinephrine, such as piperoxan.
3. Chlorethylamines, which are chemically related to the nitrogen mustards, including dibenamine and phenoxybenzamine.
4. Ergot-alkaloids whose actions on the central nervous system (CNS) are so great that they have no safe use in treating man.
Except when used in conjunction with ganglion-blocking agents or other hypertensive drugs, these drugs are of little use in the treatment of essential or malignant hypertension mainly because their action is too transient. Also, in the treatment of hypertension a useful reduction of blood pressure cannot be obtained without causing unpleasant side-effects. Such drug groups are, however, effective in treatment of hypertensive episodes which often occur during operations on the adrenals for removal of chromaffin tissue tumors; but, they are rarely used in the tumor diagnosis now that the metabolites of catecholamines can be readily estimated in the urine.

Beta adrenergic receptors block the beta responses of epinephrine and other sympathomimetic amines. In normal subjects, some slowing of the heart may be the only effect observed. Tachycardia will be reduced and atrial and ventricular arrhythmias abolished. Inhibition of dilator muscle in the bronchioles may cause a tendency toward bronchoconstriction. Drugs available in this group are derivatives of isoprenaline, and include dichloro-isoprenaline, pronethalol, and propranolol.

Dichloro-isoprenaline is not used therapeutically because of its strong sympathomimetic action. Pronethalol is a specific beta-blocking drug, but has been displaced by propranolol as it was found carcinogenic in mice. Many compounds with beta-adrenergic receptor blocking activity have been synthesized, and several, including sotalol and practolol, are now in clinical trial. We can probably anticipate that other such agents will become available within the next few years.

**Diagnosis of pheochromocytoma**

Diagnosis of pheochromocytoma may sometimes be made from the patient's history or may even be discovered inadvertently should an attack of hypertension occur during clinical examination. One test for their presence is to compress the area over the adrenals in an attempt to induce such an attack. A small proportion of tumors are discovered by chance during surgery for other conditions, by release of untoward amounts of catecholamine during positioning of the patient, or by manipulation in the abdominal cavity. Marked sweating and tachycardia for no apparent reason are suspicious signs, and a very high blood pressure reading may confirm your suspicions.

Certain tests can be carried out preoperatively in an attempt to establish diagnosis, but all are fallible, and a laparotomy may be necessary to confirm the diagnosis. An assay of noradrenaline in the urine is the best test, but may not be significant if the tumor is quiescent. If paroxysmal hypertension develops in an apparently well patient during the administration of thiopental, pheochromocytoma should probably be considered as a remote but definite possibility.

Diagnosis may be comparatively simple in patients exhibiting obvious manifestations. However, many of the articles that were surveyed contain cases of patients who had been treated for anxiety states and menopausal syndromes for as long as two years. In many patients, the only observation exhibited may be a very paroxysmal hypertension. It is certainly not practical to suggest work-ups on all patients with hypertension presenting themselves for surgery. The diagnosis must be considered, though, in the following: (1) all patients with hypertension under the age of 30; (2) in all patients with hypertension who also have evidence of hypermetabolism such as heat intolerance, sweating, or weight loss; (3) in cases of hypermetabolism in the absence of hyperthyroidism and; (4) in patients with diabetes mellitus with hypertension.

Smith enumerates some of the diseases which can be confused with pheochromocytoma. These include: essential hypertension, hyperthyroidism,
diabetes mellitus, toxemia of pregnancy, acute congestive heart failure, severe cardiovascular collapse after the stress of surgery, massive gastrointestinal bleeding, and terminal renal tubular necrosis.3

The two most commonly used tests when paroxysmal hypertension is present are the histamine and adrenolytic tests. The most provocative test consists of the administration of 0.5-1.0 mg of histamine. This will elicit a hypertensive attack in the patient with pheochromocytoma. This test has been condemned by many authors since it can be quite dangerous when the blood pressure rises excessively. A somewhat safer method, but still dangerous, is the adrenolytic test. The patient must be hypertensive at the time of this test when phentolamine (Regitine®) is administered IV or IM. If pheochromocytoma is present, the systolic pressure will fall approximately 35 mmHg and the diastolic will fall approximately 25 mmHg within two to five minutes. Several writers felt that the demonstrations of the tumor by intravenous pyelography, insufflation of CO₂ or N₂O retroperitoneally, or aortography involve too great a risk and suggest these tests be omitted if possible. The use of specialized noradrenaline drugs such as benzodioxane, and dibenamine only can be expected to confirm the diagnosis by inducing hypotension when the pressure is well above normal.

Surgical mortality

Surgical mortality in cases of pheochromocytoma was reported to be as high as 25-45 per cent in the pre-1950 era but is now relatively low. In Dr. Goldfein’s article,2 it is stated that Apgar and Pappar, in 1951, estimated the operative mortality rate to be 24 per cent for patients where the presence of pheochromocytoma had been established or suspected preoperatively. In contrast, they reported a mortality rate of more than 50 per cent in patients with unsuspected tumors undergoing unrelated surgical procedures. These observations clearly point out the necessity for diagnosis and surgical removal of such tumors even though the symptoms may be mild at the time.

The 1950-1960 period resulted in an overall mortality figure of about 13 per cent, and recent papers suggest that current operative mortality may be as low as 1-5 per cent. This favorable trend is due to general improvements in surgery and anesthesiology techniques, better diagnostic methods, the development of more effective drugs for control of the hypertensive episodes, and a heightened awareness of the problems of hypovolemia in these patients.

The majority of operative mortalities has been caused not from the effects of hypertension, but from irreversible hypotension following the tumor’s removal. In the past, this hypotension was believed to have been caused by the resetting of pressoreceptors or an acquired resistance to the increased levels of epinephrine. It is now commonly thought that such hypotension is actually caused by the sudden reduction of blood volume which occurs when the tumor is removed. Expansion of the blood volume with oral phentolamine preoperatively greatly reduces the need for transfusion at this particular time.

Tumor removal

According to Dr. Shields,6 the following problems arise with surgery for the tumor’s removal:

1. Stimulation from the anesthetic or from handling the tumor may result in excessive secretion of epinephrine and norepinephrine, producing dangerous hypertension. This should probably be treated with Regitine® 5mg given intravenously.

2. These patients tolerate anoxia and changes in position extremely poorly.

3. Because of the possibility of excessive circulating epinephrine, cyclopropane should never be used.

4. After the tumor has been removed, and especially in the postoper-
ative period, there may be severe hypotension, for which an infusion of Levophed® is given (4 ml in 500 ml D/saline). The mortality from surgical removal of these tumors is extremely high.

Further problems, which may be encountered are enumerated by R. H. Smith: ¹

1. The characteristic hypertension is not subject to therapy with any drug but an adrenalytic one.
2. An overworked heart may be found, the severity of the changes depending upon the severity of the disease.
3. There is a tendency toward severe cardiac dysrhythmias of ventricular origin. Both of the catecholamines increase myocardial irritability and shift the pacemaker away from the S-A node. This tendency may prohibit the use of some anesthetic agents which increase the severity of ventricular dysrhythmias.
4. The rise in metabolic rate necessitates a definite plan to avoid respiratory depression or myocardial depression in the selection of techniques and agents.
5. The elevated heat production may result in heat retention unless preventive steps are taken.
6. There is always the danger of a CVA (cerebrovascular accident).
7. The blood volume is low. It is assumed that this is caused by the high head of pressure transmitted to the capillaries, blocking return from the tissues. When pheochromocytoma is diagnosed and surgery is scheduled for removal of the tumor, much of the difficulty can be resolved by building the blood volume and red cell mass to normal before the actual operation itself.

**Drug usage during surgery**

During surgery, both an antinoradrenaline compound and noradrenaline must be available for immediate use. One is to control an excessive rise of blood pressure (since this may lead to a cerebral hemorrhage or acute pulmonary edema from left ventricular failure), and the other is to maintain a normal blood pressure once the tumor is removed. Since the peripheral circulation will have become accustomed to the high level of the pressor agent, marked hypotension is likely at, or soon after, the time when the tumor is removed. Then, the intravenous Levophed® infusion should be started, but care must be taken that the use of noradrenaline does not mask the bleeding from the operative site, particularly in the postoperative period. ²

During surgery for pheochromocytoma, several specific adrenergic blockers which effect each type of receptor site are usually administered for the management of symptoms. The alpha- and beta-adrenergic receptor sites coupled with the affinity of norepinephrine for the alpha-sites and epinephrine for the beta-sites play a large part in determining the clinical picture of the disease. In most cases, both catecholamines are released, but in some cases, both catecholamines may be in excess or one or the other may predominate.

The two drugs currently available as alpha-blocking agents are phenoxybenzylamine (Dibenzyline®) and phentolamine (Regitine®). The first drug has a duration of action of 12-24 hours and may be given IV or orally. Regitine® has a 5-10 minute duration of action and is usually given in increments or by infusion. It has a short onset of action and is valuable for use during surgery when the reactions it produces may be required quickly. Alpha-adrenergic blocking drugs exert an effect antagonistic to drugs such as epinephrine. Alpha-adrenergic blockers lower the blood pressure by extensive vasodilatation, increased muscular tone, and activity of gastrointestinal organs, but inhibit the action of the heart only after very large doses.

Agents used for beta-adrenergic blockade include propranolol and practolol. Propranolol is being used less frequently because of its depressant effect on cardiac output and on beta-receptors.
in the bronchial tree and peripheral vessels. Bronchial constriction and peripheral vasoconstriction have proved to be its undesirable effects. Practolol has been relatively free of these drawbacks. It is also (in contrast to propranolol) not lipid soluble to any great extent, is excreted unchanged in the urine, and does not cross the blood-brain barrier. “Given orally it has a chemical half-life of about ten hours as compared to two for propranolol, is devoid of local anesthetic or quinidine-like effects, and is rather less potent.”

Preoperative medication

All of the patients in the Cooperman, Engleman, and Mann series were treated preoperatively with alpha-methyltyrosine (alpha-MPT), an inhibitor of tyrosine hydroxylase, to decrease synthesis of catecholamines. Oral phenothiazines as they exhibit pro-

mended avoiding chlorpromazine and obtund this response. biturates (Seconal and Nembutal®) and respiratory depressant effects. The preanesthetic visit, which establishes personal rapport with the patient and provides him with a thorough explanation of everything that is to take place, greatly allays any apprehension. Such communication does much to avoid the patient’s undesirable psyche response for the contemplated anesthesia and operation. Drugs are a poor substitute for understanding between the patient and his anesthetist.

The series done by Crout and Brown consisted of 16 operations performed on 14 patients since 1964. Phenoxybenzamine was administered to 12 patients before surgery. They recommended this regime for its value in bringing the blood pressure under control and expanding plasma volume. Blood pressure increases still occurred during manipulation of the tumor and supplemental phentolamine was required in most patients.

Preanesthetic medications in this particular series included atropine (0.3-0.6 mg) and various combinations of pentobarbital (2-3 mg/kg). Succinylcholine (0.75-1.25 mg/kg) was used for tracheal intubation. “It is an interesting fact that the administration of atropine (0.3-0.6 mg) does not produce an alarming tachycardia in pheochromocytoma patients.” In the Crout-Brown series, no patient came to the operating room with a heart rate greater than 110/min, and atropine was omitted in only one case. This patient, however, developed sinus bradycardia and first-degree heart block after succinylcholine was administered, and 0.4 mg of atropine had to be administered IV.

Crandell and Brown also stated that the administration of phenoxybenzamine preoperatively caused a fall in the hematocrit value due to expansion of the plasma volume. In fact, it provides a simple means of detecting a patient with a diminished erythrocyte mass. The patient who experiences a sharp fall in hematocrit as a result of phenoxybenzamine therapy may then be trans-

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fused with packed erythrocytes before surgery.

During the initial exploration, if the tumor has not been localized preoperatively or if multiple tumors are suspected, complete adrenergic blockade should probably be avoided. This is so that manipulation of masses containing catecholamines will produce a rise in blood pressure and facilitate their localization. Also, two typical signs of diagnostic usefulness to the surgeon still remain intact: (1) the blood pressure increase during manipulation of the tumor, and (2) the blood pressure fall when the tumor is removed.

When phenoxybenzamine causes the alpha blockade, compensatory tachycardia ensues because the beta-adrenergic system is still functional. This receptive beta-adrenergic response is still capable of full potential reaction upon stimulation of circulating catecholamines. For this reason, dangerous dysrhythmias and tachycardia can result from manipulation of the tumor, even though the blood pressure is now in the “safe” range. With concurrent use of a beta-adrenergic receptor blocking agent, the chances of misadventure should be less. Goodman and Gilman report on a study done by Ross and co-workers in England on 27 patients managed with this regime. In that study, the combined use of these agents was preferred, over all the others that were investigated.

Bingham, Elliott, and Lyons also concurred with the use of specific alpha- and beta-adrenergic blocking agents, both in the operative and preoperative periods to modify the intensity of the reactions resulting from raised plasma adrenaline-noradrenaline levels. They listed reports of a series by four different British anesthesiologists who obtained a definite value from using phenoxybenzamine and propranolol toward this effect.

They went on to state that “suppression of the sympathoadrenal activity by these potent drugs deprives the cardiovascular system of an important homeostatic mechanism designed to meet fluctuating demands upon it. The sudden transition from an abnormal state of intense and varying sympathetic stimulation during dissection of the tumor, to partial or complete withdrawal of this stimulus when the tumor is removed, creates a stimulation in which the need for suppression of the abnormal state is suddenly replaced by a need for reestablishment of normal mechanisms of cardiovascular control.”

For this reason, Bingham and his associates attacked the problem from the standpoint of: how can we modify this highly liable state and give it some element of stability which avoids the undesirable extreme responses? The chief method they used to solve this problem was the administration of chlorpromazine in the preoperative period.

The basic preoperative medication used in their series was chlorpromazine 50 mg every six hours for the three days prior to surgery. This regime was reported to result in a mildly sedated patient with reasonable adrenergic suppression but not a complete blockade of adrenergic activity. The chlorpromazine generally brought the blood pressure and pulse rate gradually down to a range of 130–150 mmHg systolic and 100–110 beats/min by the time of operation.

Six out of eight of the patients in their series also received Pethidine 50–100 mg, chlorpromazine 25–50 mg, promethazine, 25–50 mg, and hyoscine 0.4 mg IM one hour before the operation. Hyoscine was preferred to atropine because of its weaker vagolytic action. With this regime, patients arrived deeply sedated, allowing intravenous and intra-arterial cannulation to be carried out without disturbing them too much. Many of the patients for the period immediately before surgery were, thus, medicated and had total retrograde amnesia.

Chlorpromazine is valuable as a preoperative sedative in these cases be-
cause it is a phenothiazine with adrenergic blocking, antiarrhythmic, and sedative properties. It is relatively free of side effects. In experiments with dogs, it has been shown to reduce adrenaline-induced hypertension, prevent ventricular fibrillation brought on by adrenaline in the presence of chloroform, and antagonize local vasoconstriction caused by adrenaline.

In order to avoid a hypertensive episode immediately before induction, it is often advisable to perform intravenous cannulations or cutdowns the night before surgery.11

The induction phase

The induction phase of the anesthetic for a patient with pheochromocytoma presents some very special problems. Many studies have demonstrated a highly significant rise in the arterial blood pressure of normotensive patients following endotracheal intubation under sodium pentothal, nitrous oxide and oxygen, and succinylcholine. This reflex sympathetic response is due to the mechanical stimulation of the larynx and trachea. This same rise observed in hypertensive patients may lead to left ventricular failure or cerebrovascular accident. In the case of pheochromocytoma, where hyperexcitability of the sympathetic system already exists, this mechanical stimulation could possibly lead to a very dangerous sudden rise in blood pressure. Intra-abdominal pressure increase from the fasciculations of succinylcholine or bucking on the tube can also lead to the direct same effect.

In the past, it has been suggested that succinylcholine induces arrhythmias because of its chemical similarity to acetylcholine. Other hypotheses proposed range from increases in serum potassium, postganglionic parasympathetic stimulation, and direct myocardial effect to direct stimulation of the adrenal gland. Stoner and Urhack12 presented an interesting case report on a patient who developed a ventricular bigeminal rhythm that could be reproduced each time a succinylcholine drug was started during surgery, but was not reproducible after her tumor was removed, nor 24 hours later when the same anesthetic technique was used for a second operation. They, therefore, assumed, that in this particular case, the arrhythmias were associated with the high catecholamine levels. They concluded their article with a call for caution in the use of succinylcholine in the presence of a pheochromocytoma. Many of the other series reviewed, however, reported use of succinylcholine with no untoward effects.

Three to five mg of d-tubocurarine preceding the intubation dose of succinylcholine or the administration of a full relaxing dose of a nondepolarizing relaxant to begin with is, therefore, advised by most anesthetists. The main factor in this rise, however, seems to be the reflex sympatho-adrenal response and preventive, suppressive measures can be taken beforehand by injecting 30 mg of Xylocaine® followed by 5 mg of Regitine® before inducing anesthesia. This is designed to start a fall in blood pressure.

When the fall occurs, anesthesia may be induced with Brevital® and a relaxant (d-tubocurarine or pancuronium) is given. The rest of the steps of laryngoscopy, spraying of the trachea with 4 per cent topical Xylocaine® and intubation, should probably be carried out in a relaxed, unhurried manner so that adjustments to the speed of the Regitine® infusion can be made as indicated by the blood pressure response to each act.

Since hypoxia also increases myocardial irritability, it is best avoided by rapid intubation and the insurance of optimum ventilation levels through use of a ventilator.

Two separate infusion lines—one for blood or other fluid therapy and one for central venous pressure—is advised by most anesthetists. Some people go ahead and set up a 1 mg/ml infusion of phentolamine (Regitine®) and a 1
mg/ml infusion of lidocaine (Xylocaine®) and plug them into the injection rubber or stop cock at the end of two separate blood infusion lines. This provides for their immediate use and may even decrease the incidence of "grey-hair" production on the part of the anesthetist. The radial artery is frequently cannulated to permit a continuous arterial pressure read-out during surgery. Patients are catheterized to facilitate hourly estimation of urinary output by means of a urometer. A continuous ECG is also essential because of rapid changes in cardiac rate and rhythm. Venous pressure monitoring is of obvious importance when the patient is receiving large volumes of fluid.

Although the patient is most often in the supine position, occasionally a thoraco-abdominal incision is used, for which the patient must be in a lateral position. Positioning the patient in this manner often results in hyperventilation and a Regitine® drip with 25 mg/1,000 ml Ringers Lactate Solution may have to be used to lower the blood pressure. ¹¹

Maintenance during the operation

Cardiovascular stability during the operation is also significantly influenced by the choice of anesthetic agent. Many authors tend to choose halothane for its hypotensive effect, ⁷, ¹⁴ while others lean toward the freedom from dysrhythmias which is a feature of methoxyflurane anesthesia. ¹⁰, ¹³ Most of the authors reviewed seem to use the basic maintenance of anesthesia by using a ventilator with nitrous oxide, oxygen, and a relaxant, along with the addition of another agent (such as Fluothane® or Penthrane®) to add to the therapeutic management, as well as to the anesthesia.

In the series done by Cooperman, Engleman, and Mann ¹⁰ on the anesthetic management of 14 patients operated on for pheochromocytomas, halothane was chosen as the principal agent because of its sympato-adrenal depressant properties. Arterial pressure was controlled by varying the inspired concentration of halothane, but Regitine® had to be given during the tumor manipulation. Dysrhythmias occurred in ten of the patients. The dysrhythmias included many different forms, as mentioned earlier, and were treated with lidocaine or propranolol. Lidocaine reversed 6 out of 11 arrhythmic episodes, while propranolol reversed 11 out of 13. They made the observation that propranolol seemed to afford protection against further dysrhythmias.

Etsten and Shimosato¹⁴ also chose halothane because of its sympato-adrenal suppression. Preanesthetic catecholamine levels on the patient studied were 1600 µg/l for norepinephrine and 2540 µg/l for epinephrine. These levels decreased, however, to 358 and 326 µg/l respectively, and progressively decreased even during tumor manipulation. They experienced two episodes of cardiac dysrhythmia which consisted of bigeminy and pvc's within 7-9 minutes after the start of anesthesia.

It was interesting to note that the authors also deliberately had the surgeon squeeze the tumor during the administration of 0.5 per cent halothane, and again after the concentration was increased to 1.0 per cent. Catecholamine release was decreased during the deeper level of halothane concentration. It was concluded that this reaction was directly attributable to the suppression of the sympato-adrenal response by halothane, and that the agent does not cause any more sensitization of the myocardium in the presence of increased catecholamine levels than it does when used in patients without hormonal pathology.

In the series done by Bingham, Elliott, and Lyons, ⁷ methoxyflurane was used in a concentration of 0.2-0.5 per cent because of its freedom from arrhythmias. Many of the authors who used or advocated the use of halothane reported several cases of arrhythmias. ⁸, ¹⁴ Some of these people maintained that using halothane results in a smoother,
steadier anesthetic without the accompanying greater fluctuations in arterial pressure found in some cases of methoxyflurane anesthesia. On the other hand, the fluctuations can usually be controlled with the Regitine®/Xylocaine® technique.

Hypotension is common following the removal of the tumor, and many of the earlier authors advocated the use of a vasopressor at this point. The most recent authors tend to support the constant monitoring of CVP and the prompt expansion of the blood volume at this particular point in order to avoid the use of vasopressor agents. Another case for the methoxyflurane advocates appears to exist in the fact that, in dogs, the beta-adrenergic blockade with propranolol during halothane anesthesia has a deleterious effect on cardiac performance in the presence of hypovolemia.

Crout and Brown used methoxyflurane in 12 operations, halothane in three, and the combination of nitrous oxide-meperidine-succinylcholine in one. None of their patients anesthetized with methoxyflurane developed cardiac arrhythmias during surgery, although each of the other four showed frequent premature ventricular contractions, and one had ventricular tachycardia. They used norepinephrine to combat hypotension in only one case of the phenoxybenzamine-treated patients for longer than 15 minutes. They seemed definitely in favor of this regimen, stating that, "the findings indicate that the combination of phenoxybenzamine pre-treatment and methoxyflurane anesthesia is useful in patients with pheochromocytoma; patients so treated have a relatively stable blood pressure course and a low incidence of cardiac arrhythmias during surgery."

Postoperative phase

The postoperative course is somewhat altered by the fact that a patient must be gradually weaned from the noradrenaline, as the blood pressure stabilizes itself as an adequate level; and this weaning process may take from a few hours to several days.

Patients who have had their pheochromocytomas a very long time—particularly if structural changes have developed in their vessels—may very well retain their hypertensive blood pressure and never revert to normal.

The prognosis also depends, to a large extent, on the fact that if a fall in blood pressure does not occur at the time of removal of the tumor, the presence of additional tumor tissue is suggested. A histamine or phentolamine injection may be used in an attempt to substantiate this. Often, a second elevation of blood pressure occurs within a few days, which may last for only a few weeks or as long as 3-4 years.

Other than the difficulty in establishing presence of additional tumors, the postoperative problems of these patients are not radically different from those of other hypertensive patients undergoing surgery. Most of the patients are followed for a long period to insure against recurrence. The prognosis is excellent for those patients where the tumor has been diagnosed and removed before permanent cardiac damage or cerebrovascular changes have occurred.

REFERENCES

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