Pheochromocytoma: The use of labetalol hydrochloride for management of intraoperative effects of circulating catecholamines

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Following a concise review of the physiology and effects of pheochromocytoma, a case report is presented. This case report presents the clinical findings, illustrates how the diagnosis was made, follows the clinical course and treatment, and shows the problems of anesthetic management of a patient with pheochromocytoma.

After a thorough review of the literature and consultation with Glaxo, Inc., the author believes this case to be the first reported intraoperative use of labetalol hydrochloride as the sole antihypertensive agent for a case of pheochromocytoma in the United States.

In this case, the use of labetalol hydrochloride proved effective in lowering blood pressure intraoperatively, and perhaps may present an alternative to traditional therapy after further study.

Introduction
Pheochromocytoma, a catecholamine-secreting tumor, is a disease characterized by hypertension that may be sustained or intermittent. Symptoms may consist of a mildly elevated blood glucose, headache, palpitations, tachycardia, sweating, angina, abdominal pain, irritability and weight loss. Physical findings can include hypertension, postural hypotension, and cardiomegaly. Rarely is this tumor palpable in the abdomen. Ninety percent are found in the medulla of the adrenal gland.

Pheochromocytoma was first described by Frankel in 1886, and the first successful removal was by Charles Mayo in 1926. This tumor was not diagnosed preoperatively; that was accomplished by Pincoffs in 1929.

The exact incidence of pheochromocytoma is not known. However, it is not as rare as previously thought. The occurrence among the hypertensive population of the United States is estimated at 0.1-0.2% or 35,000-70,000 cases. Age incidence ranges from 5 to 82 with the peak age in the fifth decade. Sex distribution is equal between men and women.

The clinical signs of pheochromocytoma are caused by the release of catecholamines from the tumor. Usually, epinephrine and norepinephrine are present in the tumors, although they may produce epinephrine alone, but this is rare. The manifestations of these two substances cause the recognizable symptoms of hypertension and tachycardia. Hypertensive crises have been precipitated by drugs, anesthetics, and surgery. The early diagnosis of pheochromocytoma is important to cure the hypertension, prevent possible malignant metastasis, and to stabilize the resulting metabolic derangements. Unrecognized pheochromocytomas are potentially lethal.

A diagnosis of pheochromocytoma must be made on more than physical signs and symptoms. A 24-hour urine sample for catecholamines, metanephrines, and vanillylmandelic acid, as well as plasma catecholamines is considered to be a very
accurate diagnostic confirmation.\textsuperscript{7} These tests are commonly available. When the 24-hour urine test presents a hardship, as with children, practitioners have bracketed 2-4 hour samples and have obtained accuracy as reliable as the 24-hour sample.\textsuperscript{2} If the urine is negative, then pheochromocytoma is unlikely. If it is positive, then the plasma level is obtained.

After a diagnosis is made, localization of the tumor is attempted with computed tomography (CT) scan, which has been shown to be 97% accurate.\textsuperscript{8,9} Magnetic resonance imaging (MRI) has been shown to be accurate in pregnant patients and others in whom x-rays are contraindicated.\textsuperscript{10}

Although symptoms can be treated with varying degrees of success, surgery is virtually the only cure for these patients.\textsuperscript{1} Preoperative stabilization of these patients is essential. Phentolamine or phenoxybenzamine are the two alpha blocking agents that have been used historically.\textsuperscript{1,2} In recent years, another drug, metyrosine, has become available as an alpha blocking agent, but it has many possible side effects including sleepiness, diarrhea, and crystalluria, which then must be treated.\textsuperscript{2}

Only after alpha blockade is achieved, is the beta blockade established. Propranolol has been the drug of choice for beta blockade.\textsuperscript{2} Alpha blockade is achieved prior to beta blockade to avoid an acute, severe, hypertensive episode that may occur if beta blockade is instituted first.

In addition to receptor blockade, preparation involves correcting any existing hypovolemia and electrolyte imbalance.\textsuperscript{2}

Anesthesia and intraoperative management of these patients must be carefully planned. All necessary equipment and drugs must be readily available for possible use. Adequate large bore IV’s or central lines are essential. Since release of catecholamines is the potential problem, an arterial line for monitoring beat-by-beat blood pressure readings during all phases of anesthesia for these patients is essential. Any movement, undue stress, surgery itself, and manipulation of the tumor can increase the amount of circulating catecholamines dramatically.\textsuperscript{8} The anesthetist’s objective is to monitor the signs of circulating catecholamines, and keep the physiologic state of the patient as normal as possible.\textsuperscript{1}

Nitroprusside has historically been used for the control of intraoperative hypertensive episodes.\textsuperscript{11} The availability of labetalol hydrochloride, a drug with both alpha and beta adrenoreceptor blocking activity has raised the possibilities of its use in the anesthetic management of patients with pheochromocytoma.\textsuperscript{12}

**Case summary**

A 36-year-old white female was admitted through the emergency room in extreme distress with nausea, vomiting, cough, and fever. She had a 19-year history of alcoholism, and significant history revealed a right thoracotomy at age 16 for a benign granuloma. In addition, the patient had a 15-year history of cigarette smoking, poor diet, and IV drug abuse. Functionally, she was ambulatory, able to care for the household, involved in family therapy for her alcoholism, but had recurrent abdominal symptoms with nausea and a “queasy feeling” in her stomach. There was slight, intermittent, abdominal pain. Recent history showed intermittent fever 3 or 4 days prior to admission with shortness of breath and disorientation.

Physical examination revealed a temperature of 101° F, blood pressure at 140/102 after hydration in the emergency room, shallow respiration of 32, and an irregular pulse of 130. X-ray findings were bilateral pneumonitis in the superior segments of the lungs. Pertinent laboratory results revealed the following: white count 71,000 with a marked left shift; hemoglobin 17.0; hematocrit 54; glucose 175; potassium 3.3; amylase 293; and arterial PO\textsubscript{2} 73 with respiratory alkalosis.

The diagnostic problem upon admission, besides the obvious pneumonitis, was the etiology of the severe leukemoid reaction. She was admitted to the intensive care unit (ICU) with a central line and placed on antibiotics. She remained in the ICU for several days and began to markedly improve.

Because of the suspicion of an underlying abdominal process, a gastrointestinal workup was done, including an ultrasound and abdominal CT scan. A general surgeon was consulted for the possibility of a pancreatic abscess or pseudocyst.

The CT scan revealed a pseudocyst or adrenal mass. Percutaneous drainage of 35 ml of fluid from this mass was done. During this procedure, blood pressure elevated to 135 diastolic and the pulse rate increased to 140. Phentolamine (5 mg) was given intravenously for blood pressure control. At the time, a probable diagnosis of pheochromocytoma was made. The amylase of the fluid was 56, so a pseudocyst was ruled out.

As the diagnosis of pheochromocytoma became more firm, the patient was placed on phenoxybenzamine (10 mg per day). Blood pressure ranged from 130/80 to 150/100 with pulse around 110. The 24-hour urine results showed metanephrines 7.5 mg (normal is 0.3-0.5 mg), vanillylmandelic acid 30.4 mg (normal is 1.8-7.1 mg), and serum results were even more dramatic: epinephrine 1,969 \textmu g, (normal is less than 200 \textmu g), norepinephrine 2,754 \textmu g (normal is less than 900 \textmu g), with free catechol-

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amines 4,766 \mu g (normal is 200-825 \mu g). A clonidine suppression test was positive for pheochromocytoma.

Alpha blockade was achieved by increasing the phenoxybenzamine to 30 mg per day. Beta blockade was maintained with long-acting propranolol (80 mg per day). Vital signs were stable for approximately one week preoperatively. Systolic blood pressure ranged from 90 to 105 mmHg. Heart rate was stable at 80 beats per minute in normal sinus rhythm. Preoperative evaluation showed laboratory studies normal, nutritional status was much improved from total parenteral nutrition, and the lungs were clear.

Medication was given one hour preoperatively and consisted of the phenothiazine methotrimeprazine 30 mg, ranitidine 50 mg, and hydrocortisone 100 mg intramuscular (IM). The patient was calm and drowsy when she arrived in the operating room. Vital signs showed blood pressure 140/80, pulse 130, and respirations 16. A triple lumen central line was in place. A peripheral line was started with an 19-gauge catheter. A radical arterial line was placed to continuously monitor blood pressure.

Induction was slow and deliberate with 500 \mu g of fentanyl in divided doses, thiopental 300 mg and atracurium 34 mg. Anesthesia was maintained with \(O_2\)-2L, \(N_2O\)-4L, and enflurane 0.5-1.5% as needed.

After induction, the patient was intubated and placed in the lateral position. Blood pressure remained at 140/80 and pulse was 120 instead of the expected drop. During the next 15 minutes, blood pressure had dropped to only 130/80 and pulse remained high at 110. At this point, 5 mg of labetalol was given to lower vital signs before surgery and manipulation of the tumor. Within 5 minutes, blood pressure was 120/70 and pulse was 90. As surgery proceeded labetalol was given as needed to maintain pulse and blood pressure at acceptable levels. One additional dose of methotrimeprazine (20 mg) was given IM to help blunt the effects of circulating catecholamines. Blood pressure was held very stable at 120/80 and pulse at 90-100, even during manipulation of the tumor.

As the veins to the tumor were clamped and the supply of catecholamines abated, the anticipated drop in blood pressure to 90/70 had occurred. A small dose of ephedrine (6 mg) was given to slightly boost the blood pressure before a further drop, as fluids were increased. After 3 minutes, the blood pressure quickly returned to preclamp levels and remained stable at 120/70 for the remainder of the operation. Enflurane was discontinued, and no additional labetalol was required. The surgery was uneventful, blood loss was less than 200 cc, and urinary output 1,050 cc. The patient was reversed in the usual manner. Metoclopramide (5 mg) was given intravenously to help prevent postoperative nausea, and buprenorphine (0.15 mg) was given for anticipated postoperative discomfort. The patient was suctioned, extubated, and transferred to the recovery room awake, aware and in very stable condition after 3 hours and 45 minutes of anesthesia. Blood pressure and pulse remained very stable in the recovery room.

Discussion

Labetalol hydrochloride is a new adrenergic receptor blocking agent that is relatively short acting and has both selective alpha and nonselective beta adrenergic receptor activities. Its unique properties of confirmed beta blockade and vasodilatation make it a possible alternative to combined therapy. Because of the sensitivity of these patients to abrupt changes in circulating catecholamines, the doses of labetalol were kept low and given more frequently in this case; the alpha blockade and vasodilatation were easily managed with a small dose of ephedrine and increased fluids once the supply of catecholamines was absent.

Although this is the author's first use of labetalol in a case of pheochromocytoma, with this particular case, it seemed to be less cumbersome, more accurate, more predictable and with less side effects than with the previous use of nitroprusside. Although both drugs work quickly and are short acting, nitroprusside must be administered very carefully by an unpredictable intravenous drip and titrated to the desired effect, which can take valuable time during a hypertensive episode in these patients. Nitroprusside is also potentially toxic in higher doses when free cyanide is formed leading to excess plasma thiocyanate levels which can be fatal.

Summary

The experience of others in Europe and Asia has shown labetalol to be effective in lowering blood pressure and relieving symptoms in pheochromocytoma patients. Labetalol is particularly useful when given intravenously for the rapid control of blood pressure; and has provided satisfactory coverage during surgery at the time of removal of the tumor. This case seemed to parallel those results.

Preoperatively, this patient was well controlled with a combination of phenoxybenzamine and propranolol, but that was not sufficient to prevent a marked increase in pulse and blood pressure at the time of the operation.

There have been a few reports of paradoxical
hypertensive response after labetalol administration in patients with pheochromocytoma. 25-27 In these cases, large doses (50-400 mg) were given for control of hypertension before the operation. Therefore, although most studies have shown labetalol can effectively lower blood pressure in these patients, the reports of possible problems with its use require that caution should be used when administering labetalol to patients with pheochromocytoma.

Nitroprusside will continue to be the standard by which rapid, intraoperative, antihypertensives are judged. However, the experience gained with this patient indicates the intraoperative, intravenous use of labetalol may be an alternative therapy to consider.

REFERENCES


AUTHOR

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