Pheochromocytoma crisis: The Use of Magnesium Sulfate

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Pheochromocytoma crisis is a rare life-threatening event that may appear with a variety of clinical symptoms. We present three cases of life-threatening crisis in which magnesium sulfate was particularly beneficial in controlling symptoms and signs when more conventional forms of therapy had failed. Two patients presented with hypertensive encephalopathy, and the third presented with catecholamine-induced cardiomyopathy. All three patients successfully underwent tumor excision with magnesium sulfate used as the sole drug for control of hemodynamic disturbances during surgery. The problems of pheochromocytoma crisis and the potential benefits of magnesium sulfate in this condition are reviewed.

Pheochromocytoma crisis is a relatively rare condition in which the patient presents with rapid acceleration in the frequency and severity of potentially life-threatening catecholamine-induced hemodynamic disturbances. The condition is often fatal (1,2), and early diagnosis with aggressive, accurate management is required if the patient is to survive. This report deals with three cases of pheochromocytoma crisis, none of which responded well to conventional attempts at hemodynamic control but which were effectively controlled by infusions of magnesium sulfate (MgSO₄) as the main drug in combination with α-adrenergic antagonists.

Case Reports

The first patient was a 27-yr-old woman who presented to a peripheral hospital with a 1-wk history of headaches, sweating, and palpitations 6 wk after delivery of a healthy baby. Investigation of a suspected pheochromocytoma was commenced, but the next day she presented again with severe intermittent headaches accompanied by abdominal pain and nausea and markedly increased arterial blood pressure (ABP) (systolic arterial blood pressure >300 mm Hg). A diagnosis of pheochromocytoma crisis was made, and the patient was transferred to the surgical intensive care unit (ICU) at Groote Schuur Hospital.

On admission to the ICU, at around midnight, the patient had severe paroxysms of hypertension, headaches, clouding of consciousness, and nausea with retching every 10 min. During these cycles, mean ABP increased to 200–250 mm Hg and then gradually subsided to a mean of 90 mm Hg (Fig. 1). A left radial arterial line and a right internal jugular catheter were inserted. Central venous pressure (CVP) did not change significantly during these episodes.

Initial therapy was instituted with an infusion of sodium nitroprusside in increasing doses to a maximum of 8 μg · kg⁻¹ · min⁻¹ and with intermittent doses of phentolamine 5 mg. By the next morning, despite the nitroprusside infusion and the administration of 80 mg of phentolamine, there was no improvement in the patient’s condition. Laboratory results revealed a hemoglobin concentration of 12.5 g/dL and a urea concentration of 11.4 mmol/L (normal range [NR], 4–7 mmol/L); other laboratory results were unremarkable. The initial electrocardiograph (ECG) recording on admission was normal, but over the first 8 h, 2-mm horizontal ST segment depression and T-wave inversion developed in the lateral chest leads. In view of the failure of sodium nitroprusside and phentolamine to control the crisis, magnesium therapy was instituted with an initial bolus of MgSO₄ 4 g IV followed by an infusion starting at 1 g/h. This produced a respite from the crisis for approximately 20 min, but the symptoms then returned, although the peak ABP reached in each paroxysm was lower and the mental and gastrointestinal manifestations abated. Still, the frequency of the paroxysms remained unchanged. Phenoxybenzamine, at a dose of 10 mg orally twice daily, was commenced, and the infusion of MgSO₄ gradually increased to 3 g/h. This combination produced further improvement in ABP control, but the 10-min cyclical swings in ABP continued. The increased dose of MgSO₄ resulted in a plasma magnesium concentration of 3.9 mmol/L, at which the patient complained of feeling weak, so no further increase in the dosage of MgSO₄ was considered. Multiple crystalloid fluid challenges of 200 mL each, together with a background infusion of 125 mL/h, were administered to maintain the CVP constant during the pharmacological attempts at ABP control. Blood samples were obtained for the determination of plasma catecholamine concentrations on the morning after admission;
these showed very large concentrations of both norepinephrine and epinephrine of 31,687 pg/mL (NR, 200–400 pg/mL) and 2,687 pg/mL (NR, 0–80 pg/mL), respectively, but the concentrations were significantly smaller 24 h later (norepinephrine, 16,420 pg/mL; epinephrine, 1,094 pg/mL).

Over the next day, gradual resolution of the symptoms was achieved, and the magnesium infusion was gradually withdrawn. The periodicity of swings of ABP persisted for most of that time, although these were no longer of such a magnitude as to give cause for clinical concern. The fluid balance was 4 L positive, and the serum urea concentration rapidly decreased from its initial high value to 1.4 mmol/L; this was accompanied by a reduction in hemoglobin concentration to 8.8 g/dL, indicating a marked expansion of plasma volume. After 3 days in the ICU, the patient was hemodynamically stable and was returned to the ordinary ward.

The phenoxybenzamine dosage was gradually increased over the next 10 days to a maximum of 100 mg twice daily, with excellent hemodynamic control; however, the ST segment depression and T-wave inversion that had developed during the initial phases of treatment persisted. Computed tomography of the abdomen revealed a large (10-cm) right adrenal mass.

Examination of the patient’s obstetric records confirmed a completely normal pregnancy, with the ABP ranging between 110/60 and 120/80 mm Hg. She had undergone elective cesarean (for previous cesarean delivery) delivery under spinal anesthesia in the maternity unit of Groote Schuur Hospital. During this procedure, the patient remained entirely hemodynamically stable. The patient reported typical pheochromocytoma symptoms between pregnancies, with frequent episodes of headache, sweating, and heat intolerance. The symptoms had persisted for 2 yr between pregnancies but disappeared completely for the duration of her second gestation.

In view of the severity of the crisis and the large size of the tumor, it was decided to proceed with surgery, despite persistent ECG changes. However, cardiac enzymes (myocardial band isoenzyme of creatine phosphokinase) were found to be normal, and transthoracic echocardiography did not reveal any dyskinetic areas. Before surgery, the patient’s ABP remained stable in the region of 120/80 mm Hg, and she displayed moderate postural hypotension. The heart rate was in the range of 70 to 80 bpm without beta blockade. Phenoxybenzamine was continued at a twice-daily dosage of 100 mg until the night before surgery.

On the morning of the operation, the patient received premedication of phenoxybenzamine 50 mg and temazepam 10 mg. In the operating room, a radial arterial catheter and a 14-gauge peripheral cannula were inserted under local anesthesia; five-lead ECG monitoring with ST segment trend recording was established. Anesthesia was induced by using fentanyl, thiopental, and vecuronium for muscle relaxation. The induction of anesthesia was followed by an immediate surge in mean ABP from its preinduction level of 110 mm Hg to 160 mm Hg. An arterial blood sample was immediately obtained for catecholamine concentration measurement, and this sample subsequently showed a markedly increased norepinephrine concentration of 12,035 pg/mL. A bolus of 4 g of MgSO4 was administered and resulted in an immediate reduction in mean ABP to 80 mm Hg; this was not affected by the subsequent tracheal intubation. Anesthesia was maintained with 60% nitrous oxide in oxygen with end-tidal isoflurane partial pressure maintained in the range of 1–2 kPa and fentanyl 100 μg/h. Additional hemodynamic control was obtained solely with MgSO4 as an infusion of 2 g/h and intermittent administration of 2 g whenever the ABP started to increase. A transesophageal echocardiography probe was inserted, and the left ventricular shape and size were monitored continuously. Surgery was uneventful, with good intraoperative ABP control (peak mean ABP, 110 mm Hg). Tumor excision was accompanied by rapid blood loss and hypotension (mean ABP, 45 mm Hg). MgSO4 was withdrawn, and the ABP responded well to IV administration of 1 g of calcium chloride and aggressive fluid replacement. Neuromuscular blockade was reversed without difficulty, and the patient’s trachea was extubated at the end of the procedure, 4 h after the induction of anesthesia. Throughout the procedure, there was no evidence of myocardial ischemia or dysfunction either on ECG or on transesophageal echocardiography. A total of 24 g of MgSO4 was administered. Catecholamine estimations performed throughout the operation showed high levels of both epinephrine and norepinephrine, with a very large surge at the time of tumor excision (Fig. 2).

The patient was admitted to the ICU for 2 days postsurgery, but the subsequent course both in the ICU and afterward was unremarkable, and she was discharged home 10 days after surgery. On follow-up, she appeared to have made a complete recovery, although she had some residual hypertension (ABP 150/100 mm Hg) for which she was given α-methyl dihydroxyphenylalanine.

The second case was a 19-yr-old man, approximately 1.7 m tall, weighing 31 kg, who presented to a peripheral hospital after a long illness in gross congestive cardiac failure with severe tachycardia (heart rate, 145 bpm) and increased ABP (180/110 mm Hg). The ECG indicated marked left atrial enlargement, left ventricular hypertrophy, and signs of ventricular strain, but no myocardial ischemia (Fig. 3). The chest radiograph showed bilateral pulmonary edema, an enlarged heart with a straight left heart border, and an elevated left main bronchus. On the basis of the pulmonary edema, radiological picture, and left atrial enlargement, an initial diagnosis of mitral stenosis was made. The patient’s trachea was intubated and his lungs were ventilated, and then he was transferred to the cardiac ICU at Groote Schuur Hospital. In the cardiac ICU, a glyceryl trinitrate infusion (increasing from 1 to 5 μg · kg−1 · min−1) and IV furosemide 10 mg every 8 h were initiated, but the ABP remained very difficult.

Figure 1. Mean arterial blood pressure fluctuations during the initial admission period of Case 1 (redrawn from the original printed monitor trend record).

<table>
<thead>
<tr>
<th>Time (hrs)</th>
<th>ABP (mmHg)</th>
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<tbody>
<tr>
<td>0-0.5</td>
<td>160-180</td>
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<tr>
<td>0.5-1</td>
<td>150-160</td>
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<tr>
<td>1-1.5</td>
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<tr>
<td>1.5-2</td>
<td>130-140</td>
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Figure 2. Catecholamine concentrations in Case 1. Initial values of those measured at the time of the original admission. The remaining measurements were performed at intervals during anesthesia for tumor excision. Epinephrine concentrations are multiplied five times to show them on the same scale as the norepinephrine concentrations.

Anesthesia was induced with fentanyl, thiopental, and vecuronium, and, after endotracheal intubation, anesthesia was maintained with isoflurane in oxygen-enriched air. An MgSO\textsubscript{4} infusion was used to control hemodynamic disturbances and provided excellent control throughout the procedure, although 1 g of calcium chloride was needed after the tumor was removed to maintain a satisfactory ABP. A total of 10 g of MgSO\textsubscript{4} was administered during the procedure. At the end of surgery, spontaneous ventilation was readily established, and the cardiac index had improved markedly to 3.7 L·min\textsuperscript{-1}·m\textsuperscript{-2}. The patient was transferred to the surgical ICU, where he made an uneventful recovery. At medical review, 6 mo later, the patient was hemodynamically stable, with a normal ABP and receiving no drug therapy; his weight had increased to 41 kg, and he had a normal chest radiograph. Transthoracic echocardiography showed normal left ventricular measurements with an ejection fraction of 70%.

The third patient was a 13-yr-old boy who was transferred from a peripheral hospital to the Inkosi Albert Luthuli Central Hospital with a presumptive diagnosis of a catecholamine-induced hypertensive crisis. His initial presentation was with a left-sided tonic-clonic seizure, blurring of vision, headache, and malaise. He had an ABP of 240/145 mm Hg, and an abdominal ultrasound scan revealed a 5- to 6-cm left suprarenal mass. A brain computed tomography scan showed enhancement of white matter that was suggestive of encephalopathy. On arrival in the pediatric ICU of Inkosi Albert Luthuli Central Hospital, the patient had a very high ABP, systolic pressures in the range of 201–245 mm Hg, diastolic pressures in the range of 124–164 mm Hg, and tachycardia of 150 bpm. The child was tachypneic but was awake and fully orientated, had a normal arterial oxygen saturation, was apyrexial, and had a normal blood sugar content. Physical examination revealed no other abnormalities. The ECG showed left atrial enlargement and left ventricular hypertrophy on voltage criteria. On admission, the child was receiving an infusion of sodium nitroprusside at 4 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}. A right radial arterial line and a right internal jugular catheter were inserted. A bolus dose of 2 g of MgSO\textsubscript{4} was given by slow IV injection followed by an infusion of 1 g/h. This produced a rapid improvement in ABP, with almost immediate reduction in the diastolic pressures to <100 mm Hg and a gradual reduction in heart rate over the next 12 h. Doxazosin was administered in a dose of 2 mg every 12 h. The sodium nitroprusside infusion was rapidly reduced to 2 μg·kg\textsuperscript{-1}·min\textsuperscript{-1}, was then further reduced as the ABP responded to the MgSO\textsubscript{4} infusion, and was stopped altogether approximately 8 h after admission. Twelve hours after admission, the APB was 160/72 mm Hg, and the heart rate was 112 bpm. The plasma magnesium concentration at this time was 2.0 mmol/L, and all other biochemical measurements were normal. Urinary catecholamine estimations showed a markedly increased urinary norepinephrine excretion of 2263 μg/24 h (NR, 0–104 μg/24 h), whereas epinephrine (10 μg/24 h, NR, 0–16 μg/24 h) and dopamine (315 μg/24 h; NR, 0–580 μg/24 h) were normal.

The patient received the magnesium infusion for the next 7 days, and doxazosin was increased to 2 mg every 8 h. On Day 8, the patient had an ABP of 140/75 mm Hg, and an attempt was made to wean the patient off the magnesium infusion. However, the APB rapidly increased to 190/146 mm Hg, and the magnesium infusion was restarted; 24 h later, the ABP was 130/72 mm Hg. At the time of recommencement of the magnesium infusion, the plasma magnesium concentration had decreased to 0.79 mmol/L.
Surgery was performed on Day 13. After premedication with lorazepam and doxazosin, the patient was brought to the operating room, and radial arterial and right internal jugular vein catheters were inserted. After a standard induction of anesthesia, an epidural catheter was placed at the L2-3 interspace, and epidural analgesia was established. The MgSO₄ infusion from the ICU was continued at 1 g/h and increased to 1.2 g/h at the skin incision. Additional bolus doses of MgSO₄ were given with intubation, skin incision, and tumor handling, and a total of 7 g of MgSO₄ was administered during the procedure. At tumor devascularization, the MgSO₄ infusion was stopped, and the ABP was supported with fluid infusions. Thereafter, the mean ABP was maintained at a stable value of 52–58 mm Hg. The excised tumor weighed 52 g, and the largest measured intraoperative magnesium concentration was 1.70 mmol/L. After surgery, the patient was hemodynamically stable, and his pain was well controlled with an epidural infusion of bupivacaine and fentanyl. He was discharged to the general ward on postoperative Day 4 and went home 4 days later.

Discussion

The management of pheochromocytoma crisis has not been widely reported, and where it occurs, it appears to be associated with significant mortality, with one survey reporting 85% mortality (1). The clinical picture of pheochromocytoma crisis may be extremely variable, ranging from severe hypertension (3) to circulatory failure and shock (2,4,5). Acute myocardial infarction (6,7), pulmonary edema (8), encephalopathy (9), and multiorgan failure (10,11) have all been reported. These three cases all presented with hypertensive crisis, with evidence of hypertensive encephalopathy in two cases and cardiac dysfunction in the other. The first case also showed acute signs of myocardial strain. MgSO₄ was effective in all three cases, and, although the use of this drug has previously been reported in the anesthetic management of pheochromocytoma resection, these reports are the first in which the drug has been deliberately used for the management of nonsurgical crisis.

The first case is particularly interesting because of the highly unusual periodicity of the ABP changes. There is no immediately obvious, simple explanation, but a number of assumptions can be made. There is little doubt that the plasma volume in this patient was markedly reduced. The prerenal dysfunction and the 25% decrease in hematocrit without evidence of blood loss that followed fluid administration both strongly suggest that the patient was significantly fluid depleted. The nature of the ABP changes resembled that of a “hunting system,” and a possible sequence of events is that the sharp increase in ABP inhibited sympathetic outflow, resulting in a reduction in catecholamine release; the consequent decrease in ABP resulted in a stimulation of the aortic baroreceptors, with a consequent increase in sympathetic tone and further release of hormones. The marked swings in ABP would have been accentuated by the state of relative hypovolemia. These events disappeared with the expansion of plasma volume, as shown by the rapid decrease in hematocrit, supporting the concept that relative hypovolemia, which has previously been described in pheochromocytoma patients (12), was the background to this unusual pattern of ABP disturbance. Paroxysmal hypertension with hypovolemia has been described, but not in patients with pheochromocytoma (13,14), although the diagnosis was originally considered in the first of these reports. Inappropriately severe reflex vasoconstriction was thought to
be the mechanism (13), and this could well have applied in our first patient. The second patient was also markedly volume depleted despite the presence of pulmonary edema. Once vasodilator therapy with MgSO4 had been well established, renal function returned to normal, and there was a marked decrease in hematocrit.

The failure of nitroprusside to control the hemodynamic disturbances in either of the two cases in which it was used as first-line therapy is important, because sodium nitroprusside is widely recommended in these circumstances. Sodium nitroprusside dilates both arterioles and venules and, in a patient already significantly hypovolemic, could conceivably worsen the hunting process postulated previously, with the venu dilation from sodium nitroprusside worsening the reflex vasoconstriction and thus increasing catecholamine release. Failure of nitroprusside to control hypertensive crises in association with pheochromocytoma has been reported (15,16), and the third of our cases showed a similar failure of response of the hypertensive crisis to this drug. Severe, labile hypertension where a combination of sodium nitroprusside, phenoxybenzamine, and phentolamine was unable to prevent a fatal result has been reported (2). Magnesium decreases catecholamine release (17), and there was some evidence of this effect in the first of our three cases. It is also a highly effective α-adrenergic antagonist and antiarrhythmic when large-dose epi nephrine infusions are being given (18). Furthermore, magnesium appears to be predominantly an arteriolar dilator, reducing peripheral resistance but with minimal effects on venous return or pulmonary capillary wedge pressure (19), and this may have been especially beneficial in the first patient. Magnesium has also been shown to be effective in controlling a post-delivery hypertensive crisis with pulmonary edema and encephalopathic signs, originally thought to be due to preeclampsia but subsequently found to be due to a pheochromocytoma presenting for the first time after delivery (20).

The failure of phentolamine in the first of these cases probably reflects the extremely large norepinephrine concentrations. Phentolamine is a competitive antagonist at the α-adrenergic receptor and would probably have been ineffective with such massive adrenergic stimulation. Phenoxybenzamine is a noncompetitive α-adrenergic antagonist and is effective regardless of the concentrations of circulating catecholamines. However, oral phenoxybenzamine has a very variable absorption, and its peak effect occurs no earlier than three to four hours after administration (21). Thus, although it is an ideal drug in terms of its mode of action, it is of little use in the immediate management of a hypertensive crisis associated with pheochromocytoma. Doxazosin, a longer-acting drug that has been favorably reviewed (22,23), is probably preferable to phentolamine, but is also a competitive antagonist. In the third case, the recurrence of severe hypertension on withdrawal of the magnesium infusion demonstrated that doxazosin in a relatively large dose of 6 mg/d in this child was inadequate to control the hemodynamic disturbances on its own.

Since the first description of the use of magnesium infusions in the management of pheochromocytoma anesthesia (24), there have been numerous reports of its successful use in this condition (25–34), and this has been recently reviewed (35). The ability of MgSO4 to control hemodynamic disturbances in the presence of extremely large catecholamine concentrations is demonstrated by the excellent cardiovascular control obtained during surgery in these cases, despite norepinephrine concentrations that were larger than those seen during the initial crisis in the first case. Some of this control is undoubtedly attributable to the assistance of the α blockade produced by phenoxybenzamine, but the absence of complete α blockade is demonstrated by the fact that the first patient had a significant hypertensive response to the induction of anesthesia that was not seen again once MgSO4 infusions had been instituted, despite much larger plasma catecholamine concentrations during tumor handling. In the third patient, recurrence of hypertension occurred when the magnesium infusion was withdrawn during the preoperative phase, and this patient also showed excellent intraoperative hemodynamic control with MgSO4 as the sole intraoperative hemodynamic drug in the absence of phenoxybenzamine.

The cardiomyopathy evident in the second case is a well described feature associated with pheochromocytoma and has been extensively reviewed (21). It is an important diagnosis to make, because the condition is generally reversible (36,37), as indicated in the excellent outcome in our case. Unfortunately, cardiac transplantation has been performed for cardiomyopathy where the diagnosis of pheochromocytoma was missed until after the transplantation (38). Of interest is the fact that our second and third cases both showed left atrial enlargement in the presence of normal mitral valve function, strongly suggesting left ventricular diastolic dysfunction with subsequent left atrial hypertrophy.

Beta blockade is seldom necessary in the management of pheochromocytoma in the absence of arrhythmias (39,40). In the management of a crisis, there is the additional risk of decreased left ventricular performance, and, in the absence of adequate α1 -blockade, it may worsen the hypertension and precipitate pulmonary edema (41). Labetalol, which has α-blocking properties, has also precipitated hypertensive crises (42). Because none of our patients had problems with arrhythmias and because heart rate was adequately controlled without resorting to β blockade, we elected not to use these drugs in our patients. The only patient
with significant tachycardia was the second patient, in whom the presence of poor left ventricular performance made the use of β-blockade potentially problematic. Magnesium is as effective an antagonist of catecholamine-induced arrhythmias as propranolol (43), and, in the absence of unresponsive tachycardia, the use of β-blockade in pheochromocytoma crisis is probably not advisable. Where these drugs are considered, good vasodilator therapy must be established first.

It is of interest that the first patient went through a completely normal pregnancy with an apparent resolution of her pheochromocytoma symptoms. Although pheochromocytoma is frequently regarded as being worsened by pregnancy, cases present frequently during labor or immediately after delivery (7,20,28). However, complete resolution of the typical syndrome, as appears to have happened in the first of these cases, does seem to be unusual, and the only references we could find to this are nearly 70 years old (44,45).

In summary, we present three cases of pheochromocytoma crisis in which severe hypertension and cardiomyopathy with cardiac failure presented life-threatening risks to the patients. In the two cases in which it was used, sodium nitroprusside was ineffective, whereas MgSO₄ infusions provided good hemodynamic control and facilitated hemodynamic control during the operative removal of the tumors. MgSO₄ provides an inexpensive, simple, and safe option in the management of these cases.

References