Clinical Reports

Use of magnesium sulphate in the anaesthetic management of phaeochromocytoma in pregnancy

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The anaesthetic management of two patients with phaeochromocytoma complicating pregnancy is presented. In one patient, the operative delivery was followed by elective tumour resection at a later stage. Magnesium sulphate was used as an adjunct to all three anaesthetics, with notable success on two occasions. In one of the operative deliveries, it proved impossible to achieve adequate blood levels of magnesium, due to severe pre-existing magnesium deficiency. Hypomagnesaemia is likely to be present in such cases and must be corrected preoperatively. Magnesium sulphate is a useful adjunct to the anaesthetic management of the pregnant patient with a phaeochromocytoma provided that adequate serum levels of magnesium can be established.

The perioperative management of a patient with a phaeochromocytoma requires adequate adrenergic blockade and the minimizing of stimuli that may provoke catecholamine release. The pregnant patient with a phaeochromocytoma poses additional problems, in that anaesthetic techniques advocated for the non-pregnant patient may be hazardous to the fetus. Magnesium (Mg) has been shown to inhibit the release of catecholamines from both the adrenal medulla^{1,2} and peripheral adrenergic nerve terminals.³ It also blocks catecholamine receptors

directly in addition to a direct dilator effect on vessel walls.⁴ Its successful use in phaeochromocytoma has been previously described,⁵ and the agent has particular appeal in the obstetric field as its actions in pregnancy are well known. We present two cases in whom $MgSO_4$ was used in conjunction with other agents to control cardiovascular disturbances during delivery. In one case the delivery and tumour excision were handled on separate occasions, allowing for a comparison of the pregnant and non-pregnant state.

Case reports

Case 1

A 26-year-old pregnant woman presented with unstable hypertension at 32 weeks gestation. The presence of a phaeochromocytoma was demonstrated by a raised urinary VMA excretion and a markedly elevated plasma norepinephrine level of $1164 \text{ pg} \cdot \text{ml}^{-1}$. Over the next five days, blood pressure was stabilized in the range 140/80–150/100 mmHg from an admission level of 180/120 mmHg with oral prazosin 4 mg twice daily and atenolol 50 mg daily. No significant changes occurred in haematocrit or electrolyte levels during this period. Once fetal maturity was confirmed it was decided to attempt vaginal delivery under epidural anaesthesia. Insertion of monitoring lines and induction of labour provoked severe cardiovascular instability (BP 220/110 mmHg) and fetal distress which made immediate operative delivery imperative.

In view of the failure of the epidural anaesthetic to control symptoms, general anaesthesia was chosen. Prior to induction, oral antacids were given and a 4 g bolus of $MgSO_4$ was administered IV over 15 minutes, followed by a continuous infusion of $1.5 \text{ g} \cdot \text{hr}^{-1}$. This produced little improvement in the control of blood pressure. Blood pressure was reduced to 105/60 mmHg with an infusion

Key words

IONS: magnesium; SURGERY: phaeochromocytoma;
PREGNANCY: hypertension, delivery; COMPLICATIONS:
hypertension.

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of sodium nitroprusside at $0.27 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$ which was maintained throughout the induction sequence. A rapid-sequence induction and intubation was performed using thiopentone $6 \text{ mg}\cdot\text{kg}^{-1}$, 60 mg lidocaine and succinylcholine $1 \text{ mg}\cdot\text{kg}^{-1}$ while cricoid pressure was applied. Intubation produced a dramatic rise in BP to 265/165 mmHg which required an increase in the nitroprusside infusion rate to $0.8 \mu\text{g}\cdot\text{kg}^{-1}\cdot\text{min}^{-1}$. Anaesthesia was maintained with 50 per cent oxygen in nitrous oxide with 0.75 per cent enflurane and intermittent succinylcholine. A healthy 2730 g baby (Apgar scores 8/10) was delivered rapidly. Immediately after delivery, a precipitous fall in BP to 90 mmHg systolic necessitated temporary withdrawal of the nitroprusside. Thereafter the patient maintained a SBP on nitroprusside in the range 180–230 mmHg into the postoperative period. Heart rate ranged between 80 and 120 $\text{beats}\cdot\text{min}^{-1}$ intraoperatively, and there were no arrhythmias. Neuromuscular block reversed spontaneously and no weakness was observed. It was subsequently found that her serum Mg level prior to induction of anaesthesia was $0.5 \text{ mmol}\cdot\text{L}^{-1}$ and despite the fairly large doses of MgSO_4 the maximum serum Mg level achieved was $1.4 \text{ mmol}\cdot\text{L}^{-1}$.

Prazosin and atenolol were recommenced postoperatively in the same dosages as previously, with good cardiovascular control. The phaeochromocytoma was localised to the right adrenal gland by CT and ^{131}I meta-iodobenzylguanidine (MIBG) scans.

On the morning prior to surgery for tumour excision, the patient received 5 mg prazosin and 100 mg atenolol orally, and 15 mg papavarenum IM. The placement of central venous and radial arterial lines under local anaesthesia produced a moderate pressor response with the BP rising to 160/100 mmHg. Anaesthesia was induced with 150 μg fentanyl and 250 mg thiopentone followed by a bolus of 4 g MgSO_4 given over five minutes. Muscle relaxation was achieved with 20 mg alcuronium and lidocaine 80 mg was given prior to intubation. A continuous infusion of 1 g/hour MgSO_4 was started and 2 g boluses given on incision and on three occasions during tumour handling. Anaesthesia was maintained with 50 per cent nitrous oxide in oxygen and 1–1.5 per cent enflurane. No other antihypertensive medication was required and intraoperative BP was controlled in the range 100/70 to 140/80 mmHg. Heart rate was stable between 80–100 $\text{beats}\cdot\text{min}^{-1}$, and no arrhythmias occurred. MgSO_4 was withdrawn after tumour excision and at the end of the procedure muscular relaxation was easily reversed. There were no postoperative complications. A total of 16 g of MgSO_4 had been administered over two hours and the intraoperative serum Mg levels were in the range of $2.6\text{--}3.9 \text{ mmol}\cdot\text{L}^{-1}$, with the peak level just prior to tumour devascularisation. At

the time of reversal of the neuromuscular block, one hour later, the serum Mg level was $2.5 \text{ mmol}\cdot\text{L}^{-1}$.

Case 2

This patient was a 24 year old pregnant woman who had a history of having had a malignant phaeochromocytoma removed in 1979 and three subsequent incomplete resections of recurrent tumours. She had been well controlled medically until her pregnancy. She now complained of headache, visual disturbances and feeling flushed. On admission her arterial blood pressure was 170/110 mmHg and her heart rate 116 $\text{beats}\cdot\text{min}^{-1}$. Fetal maturity was estimated at 32 weeks on ultrasound examination. Significant laboratory findings included a VMA excretion of 205 $\mu\text{mol}/24 \text{ hours}$ and metepinephrine 42.5 $\mu\text{mol}/24 \text{ hours}$ (normal $<5.5 \mu\text{mol}/24 \text{ hours}$).

Blood pressure was satisfactorily controlled with use of oral phenoxylbenzamine 20 mg eight hourly and atenolol 50 mg daily. The patient's progress was uneventful for the next four weeks, with an arterial blood pressure in the range 170/90–140/80 mmHg and no postural hypotension. It is of interest that her serum Mg level which was initially $0.83 \text{ mmol}\cdot\text{L}^{-1}$ fell to $0.57 \text{ mmol}\cdot\text{L}^{-1}$ during this period. On oral supplementation it improved but remained below normal at $0.71 \text{ mmol}\cdot\text{L}^{-1}$. Haematocrit and other electrolytes were unchanged during preoperative preparation. At 36 weeks gestation, adequate fetal maturity was established and it was decided to proceed with delivery by elective Caesarean section under general anaesthesia.

Phenoxylbenzamine 20 mg and atenolol 25 mg were given orally on the morning of surgery. Diazepam 10 mg, 10 mg metoclopramide and 30 ml sodium citrate were given orally 30 minutes preoperatively. On arrival in the operating room, arterial blood pressure was 170/100 mmHg, and this increased during the insertion of arterial and central venous lines under local anaesthesia to 200/120 mmHg. Four grams of MgSO_4 were administered by slow IV injection and this reduced the arterial blood pressure to 150/90 mmHg, but produced an unpleasant burning sensation. Following pre-oxygenation, anaesthesia was induced with thiopentone $4 \text{ mg}\cdot\text{kg}^{-1}$, and the trachea intubated after 100 mg succinylcholine, while cricoid pressure was applied. Intubation produced an increase in arterial blood pressure to 180/100 mmHg which responded well to a further bolus of 2 g MgSO_4 and a continuous infusion of MgSO_4 was maintained at 2 g/hour throughout the procedure. Anaesthesia was maintained with 50 per cent oxygen in nitrous oxide with 0.75 per cent enflurane, and intermittent succinylcholine. Two further boluses of 2 g MgSO_4 were given intraoperatively to control small increases in arterial blood pressure and throughout surgery the blood pressure remained in the

range 130/80–170/90 mmHg. Heart rate was well controlled and no arrhythmias occurred. A healthy female infant weighing 1540 g (Apgar scores 7/10) was delivered. Following surgery, the patient awakened and resumed spontaneous ventilation readily and the MgSO_4 infusion was discontinued after extubation. One hour later she required a continuous infusion of phenoxybenzamine in order to control her arterial blood pressure which had increased to 230/120 mmHg. The following day, oral therapy was restarted and she made a satisfactory recovery. Intraoperative Mg levels were in the range 2.4–3.3 $\text{mmol}\cdot\text{L}^{-1}$.

Discussion

The problem of the management of phaeochromocytoma in pregnancy is a complex one, and various approaches have been suggested. These include vaginal delivery with subsequent elective tumour excision,⁶ Caesarean section with simultaneous tumour excision^{7–10} and Caesarean section with delayed tumour excision.¹¹

Whichever approach is used, anaesthesia for operative delivery of the pregnant patient with a phaeochromocytoma is complicated by the restraints imposed by considerations of fetal welfare. The normal technique of heavy sedation prior to surgery, and deep anaesthesia with large doses of opiates to minimize input stimuli is not appropriate at the time of operative delivery. Alpha-adrenergic blockade has been the mainstay of perioperative blood pressure control,¹² but is often inadequate on its own during the stresses of surgery¹³ and may be accompanied by severe hypotension at the time of delivery.^{10,14} The use of sodium nitroprusside in pregnant patients is controversial¹⁵ as acidosis and cyanide accumulation occurs to a greater degree in fetal lambs than in the mother; the fetus may also have immature mechanisms for cyanide metabolism.¹⁶ In addition the drug may reduce uterine blood flow.¹⁷ Regional blockade has been said to be contra-indicated,¹⁸ although there have been reports of successful management with epidural anaesthesia.^{6,19} In our first case epidural analgesia was totally ineffective in controlling cardiovascular instability during labour.

The rationale for the use of MgSO_4 infusions in the anaesthetic management of phaeochromocytoma is based on the ability of Mg to inhibit the release of catecholamines from the adrenal medulla,^{1–3,20} to reduce the sensitivity of alpha-adrenergic receptors to catecholamines,²¹ and to exert a direct vasodilator effect.⁴ The levels of Mg required to exert these effects appear to be in the range of 2.5–4.0 $\text{mmol}\cdot\text{L}^{-1}$.^{21,22} The successful use of MgSO_4 in the management of a case of phaeochromocytoma has been reported recently⁵ and we have personal

experience of the value of this agent in several other cases of uncomplicated phaeochromocytoma. Similar benefits from Mg infusion in controlling catecholamine-induced crises associated with severe tetanus also lend support to the use of this agent,²³ and the ability of MgSO_4 to block catecholamine release in humans has recently been demonstrated.²⁴ The appeal of MgSO_4 in the management of the pregnant patient with phaeochromocytoma is enhanced by the well established role for this agent in the management of pregnancy-induced hypertension^{25,26} and its apparent lack of effects on the fetus.²⁷

The failure of MgSO_4 to exert any beneficial effect during the operative delivery of the first case was initially disappointing. However, the subsequently obtained serum Mg levels made it clear that the most likely reason for this failure was the fact that therapeutic levels of Mg were never approached despite a large dose of MgSO_4 , probably due to a gross Mg deficit prior to the intervention. The excellent cardiovascular control obtained on the second occasion in this patient could be attributed to a number of factors including the longer period of stabilization and the fact that the patient was no longer pregnant. In addition, the use of intravenous opiates prior to intubation was limited on the first occasion by concern for fetal well-being, and there were no such considerations at the second procedure. However, despite these factors, similar changes in BP occurred during the insertion of monitoring lines, demonstrating that the patient could still mount a significant pressor response. In view of this, the total absence of a pressor response to intubation, after the marked hypertension at the time of Caesarean section, was impressive. It seems reasonable to conclude that Mg-enhanced blood pressure control during tumour excision, and that the failure of this agent to control cardiovascular disturbances during delivery was due to inadequate serum levels being obtained. This argument is strengthened by the entirely satisfactory control obtained in the second case in which therapeutic levels of Mg were maintained throughout. It should be noted that no other anti-adrenergic agent was employed, and a standard Caesarean section anaesthetic technique was used in this patient, and yet cardiovascular control was excellent. Withdrawal of the MgSO_4 at the end of surgery led to a rapid increase in blood pressure which necessitated the use of an infusion of phenoxybenzamine. This abrupt withdrawal was prompted by concerns of adequate neuromuscular function in the postoperative period, but as no non-depolarizing relaxants had been used, it might have been more advisable either to withdraw the agent slowly, or to continue the infusion until oral drugs could be resumed. There is no precedent to serve as a guide.

Both patients demonstrated severe Mg deficiency prior

to delivery, and the reasons for this are not hard to find. Pregnancy itself has been shown to increase demand for Mg, and may frequently produce Mg deficits.²⁸ In addition, catecholamines mobilize Mg from the intracellular compartment, and increase renal excretion of the ion. Thus, after an initial increase in serum Mg, prolonged catecholamine excess will produce Mg depletion. Hypomagnesaemia will increase the sensitivity of blood vessels to the vasospastic effects of catecholamines,⁴ thus increasing the problems of cardiovascular control whatever agent is used. In addition this deficit will result in poor response to Mg therapy as exemplified in the first patient.

Several useful lessons can be drawn from these cases. Firstly, it has been shown that Mg can provide satisfactory control of the cardiovascular system during delivery in a patient whose pregnancy is complicated by a phaeochromocytoma, provided that adequate blood levels can be attained. Secondly, they highlight the fact that hypomagnesaemia is likely to be present in such cases. This will not only worsen cardiovascular disturbances, but also will make the determination of the correct dose of Mg to achieve therapeutic levels almost impossible. Hypomagnesaemia should always be looked for and corrected. Finally, in view of its well-established role in pregnancy-induced hypertension, and of the possible problems with other agents, Mg may well be regarded as an ideal adjunct to the anaesthetic management of the pregnant patient with a phaeochromocytoma.

References

- 1 Douglas WW, Rubin RP. The mechanism of catecholamine release from the adrenal medulla and the role of calcium in stimulus-secretion coupling. *J Physiol* 1963; 167: 288–310.
- 2 Lishajko F. Releasing effect of calcium and phosphate on catecholamines, ATP, and protein from chromaffin cell granules. *Acta Physiol Scand* 1976; 79: 575–85.
- 3 Von Euler VS, Lishajko F. Effects of Mg^{++} and Ca^{++} on noradrenaline release and uptake in adrenergic nerve granules in different media. *Acta Physiol Scand* 1973; 89: 415–522.
- 4 Altura BM, Altura BT. Role of magnesium ions in contractility of blood vessels and skeletal muscles. *Mg Bulletin* 1982; 1a: 102–14.
- 5 James MFM. Magnesium sulfate in phaeochromocytoma. *Anesthesiology*, 1985; 62: 188–9.
- 6 Davies AE, Navaratnarajah M. Vaginal delivery in a patient with a phaeochromocytoma. *Br J Anaesth* 1984; 56: 913–6.
- 7 Dean RE. Phaeochromocytoma and pregnancy. *Obstet Gynecol* 1958; 11: 35–9.
- 8 Barzel US, Barilan Z, Rumney G, Lazebnik Y, Eckerling B, De Vries A. Phaeochromocytoma and pregnancy. *Am J Obstet Gynecol* 1964; 89: 519–22.
- 9 Schenker JG, Chowers I. Phaeochromocytoma and pregnancy. *Obstet Gynecol Survey* 1971; 26: 739–47.
- 10 Galletly DC, Yee P, Muling TJB. Anaesthetic management of combined caesarean section and phaeochromocytoma removal. *Anaesth Intensive Care* 1983; 11: 249–53.
- 11 Venuto R, Burstein P, Schneider R. Phaeochromocytoma: antepartum diagnosis and management with tumour resection in the puerperum. *Am J Obstet Gynecol* 1984; 148: 431–2.
- 12 Burgess GE. Alpha blockade and surgical intervention of pheochromocytoma on pregnancy. *Obstet Gynecol* 1978; 53: 266–9.
- 13 Griffith MI, Felts JH, James FM, Meyers RT, Shealy GM, Woodruff LF. Successful control of pheochromocytoma in pregnancy. *JAMA* 1974; 229: 437–9.
- 14 Burgess GE, Cooper JR, Marino RJ, Peuler MJ. Anesthetic management of combined cesarean section and excision of pheochromocytoma. *Anesth Analg* 1978; 57: 276–9.
- 15 Willoughby JS. Sodium nitroprusside, pregnancy and multiple intracranial aneurysms. *Anaesth Intensive Care* 1984; 12: 351–7.
- 16 Naulty J, Cefalo RC, Lewis PE. Fetal toxicity of nitroprusside in the pregnant ewe. *J Pediatr* 1977; 91: 808–13.
- 17 Lieb SM, Zugaib M, Nuwayhid B *et al.* Nitroprusside-induced hemodynamic alterations in normotensive and hypertensive pregnant sheep. *Am J Obstet Gynecol* 1981; 139: 925–31.
- 18 Schenker JG, Granai M. Phaeochromocytoma and pregnancy – an updated appraisal. *Aust N.Z. J Obstet Gynaecol* 1982; 22: 1–10.
- 19 Stoneham J, Wakefield C. Phaeochromocytoma in pregnancy. *Anaesthesia*, 1983; 38: 654–8.
- 20 Kirpekar SM, Misu Y. Release of noradrenaline by splenic nerve stimulation and its dependence on calcium. *J Physiol* 1967; 188: 219–34.
- 21 Altura BM, Altura BT. General anaesthetics and magnesium ions as calcium antagonists on vascular smooth muscle. In: *New Perspectives on Calcium Antagonists*. Weiss GB (ed) Maryland: American Physiological Society. 1981. pp. 131–45.
- 22 James MFM, Cork RC, Dennet J. Cardiovascular effects of magnesium in the baboon. *Magnesium* 1987 (in press).
- 23 James MFM, Manson EDM. The use of magnesium sulphate infusions in the management of very severe tetanus. *Intensive Care Med*. 1985; 11: 5–12.
- 24 Lipman J, James MFM, Erskine J, Plitt ML, Eidelman J, Esser JD. Autonomic dysfunction in severe tetanus: Magnesium sulfate as an adjunct to deep sedation. *Crit Care Med* 1987; (in press).

- 25 Pritchard JA, Pritchard SA. Standardized treatment of 154 consecutive cases of eclampsia. *Am J Obstet Gynecol* 1975; 123: 543-52.
- 26 Pritchard JA, Cunningham G, Pritchard SA. The Parkland Memorial Hospital protocol for treatment of eclampsia: Evaluation of 245 cases. *Am J Obstet Gynecol* 1978; 148: 951-63.
- 27 Stone SR, Pritchard JA. The effects of maternally administered magnesium sulphate on the neonate. *Obstet Gynecol* 1970; 35: 574-8.
- 28 Seelig MS. Magnesium deficiency in the pathogenesis of disease. p. 29. New York: Plenum Medical Book Company, 1980.

Résumé

La conduite anesthésique de deux patientes atteintes de phéochromocytome compliquant la grossesse est présentée. Chez une patiente l'accouchement fut suivi plus tard par la résection électorale de la tumeur. Le sulfate de magnésium fut utilisé lors des trois anesthésies avec un succès notoire à deux occasions. Lors d'un des ces accouchements il a été impossible d'acquiescer un niveau sanguin adéquat de magnésium à cause d'une déficience de magnésium sévère pré-existante. L'hypomagnésémie est probablement présente dans de tels cas et doit être corrigée dans la période pré-opératoire. Le sulfate de magnésium est un additif utile pour la conduite anesthésique des patientes gravides atteintes de phéochromocytome lorsqu'un taux sérique adéquat de magnésium peut être acquis.