ANAESTHETIC MANAGEMENT OF RENIN SECRETING NEPHROBLASTOMA

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SUMMARY

We report the successful preoperative control and anaesthetic management of severe hypertension in a 7-month-old baby with nephroblastoma and increased renin activity. The strategy for selection of appropriate antihypertensive pharmacological agents and the anaesthetic implications and management of the condition are discussed.

KEY WORDS


Nephroblastoma (Wilms' tumour) is the commonest abdominal tumour of childhood [1]. It presents usually between the ages of 6 months and 5 yr and may be associated with severe hypertension secondary to increased renin secretion. Treatment is by surgical resection, followed by radiotherapy or chemotherapy. We describe the management of a child presenting with a large nephroblastoma and severe hypertension.

CASE REPORT

A 7-month-old female infant weighing 5.6 kg was referred to our hospital for investigation of an abdominal mass. Delivery at term had been uncomplicated and she experienced no problems until the age of 4 months, when her weight gain slowed, decreasing from the 50th to the 3rd percentile at presentation. She was receiving no medication. Examination revealed a cachectic, pale child who was otherwise normal except for an arterial pressure of 113/105 mm Hg and a firm mass in the left side of the abdomen. Abdominal ultrasound and i.v. pyelogram confirmed the presence of a large (10 x 6.4 x 8.2 cm), well defined, oval mass in the left abdomen which displaced the left kidney downwards. The mass extended to the right of the midline and deviated the aorta and inferior vena cava slightly. Liver and right kidney were normal. There was no evidence of metastases on the chest radiograph. Full blood count and serum electrolyte concentrations were normal and screens for tumour markers (hydroxymethyl-mandelic acid, vanillyl-mandelic acid, alphafetoprotein, beta human chorionic gonadotropin and neurone-specific endase) were negative. The tentative diagnosis of a renin secreting nephroblastoma was made and blood was sent for renin assay.

Accurate measurement of arterial pressure was difficult. Manual oscillometric methods, the use of a sonic-aid Doppler and non-invasive automatic pressure measurements (Dinamap) failed to produce repeatable readings unless the patient was sedated with triclofos. Pressures as great as 245/175 mm Hg were recorded, with fluctuations to 170/125 mm Hg. Preoperative control using oral propranolol 2 mg 8-hourly, increasing to 7 mg 8-hourly over the next 8 days, was attempted. During this time, an intrarterial catheter was inserted temporarily with great difficulty and continuous monitoring confirmed the markedly increased and labile arterial pressures. Echocardiography showed a thickened left ventricular wall with poor ventricular septal motion compatible with longstanding, severe hypertension. The patient remained restless and irritable with uncontrolled hypertension and it was decided that full sedation, airway control, invasive monitoring and appropriate hypotensive and fluid therapy in the intensive care unit (ICU) was the safest management of the child before surgery.

After placement of a peripheral i.v. line, anaesthesia was induced with halothane and nitrous oxide in oxygen. Arterial pressure was measured non-invasively every 1 min during the induction and revealed a decrease in systolic pressure from 180 to 140 mm Hg. With the gradual decrease in pressure, human albumin solution (HAS) 10 ml kg⁻¹ was administered. Vecuronium 0.2 μg kg⁻¹ and fentanyl 10 μg kg⁻¹ were given, after which nasal tracheal intubation was performed and the lungs were ventilated with air to normocapnia without further fluctuations in arterial pressure. Infusions of fentanyl, midazolam and vecuronium were started. A brachial arterial catheter was placed, again after much difficulty, and a central venous cannula via the right internal jugular vein. Propranolol administration was stopped and captopril 0.5 mg kg⁻¹ 8-hourly via a nasogastric tube was given, increasing over the next 48 h to 1 mg kg⁻¹ 8-hourly. Arterial pressure came under control with a maximum systolic pressure of 130 mm Hg. The anticipated vasodilatation was managed by infusing a further 35 ml kg⁻¹ of HAS and 20 ml kg⁻¹ of packed red cells during the
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48 h, and urine output was maintained throughout at 1–2 ml kg\(^{-1}\) h\(^{-1}\).

The patient underwent left nephrectomy 11 days after admission and 48 h after stabilization on the ICU, with the last dose of captopril given 4 h before surgery. Anaesthesia was maintained during the 2-h procedure with fentanyl 15 µg kg\(^{-1}\) and 0.4–0.6% isoflurane; neuromuscular block was produced with vecuronium. Systolic arterial pressure increased to 160 mm Hg after skin incision, but this was reduced to 125–130 mm Hg with an infusion of sodium nitroprusside. The resultant tachycardia of 170 beat min\(^{-1}\) was reduced to 120 beat min\(^{-1}\) with an infusion of esmolol 1.5–2.5 mg h\(^{-1}\). The vasodilator and beta-blocker infusions were stopped 5 min before clamping of the renal vein. Neither handling of the tumour nor clamping of the renal vein produced significant changes in arterial pressure. The measured blood loss of 100 ml was replaced with HAS and packed red cells. Urine output was maintained at 2 ml kg\(^{-1}\) h\(^{-1}\).

After surgery, the patient was returned to the ICU and infusions of fentanyl, midazolam and vecuronium were continued. Her arterial pressure increased again and she was given an infusion of labetalol 2 mg kg\(^{-1}\) h\(^{-1}\). After initial success, control of arterial pressure deteriorated and infusion rates up to 10 mg kg\(^{-1}\) h\(^{-1}\) were inadequate. Captopril 4 mg twice daily was given in addition, with improvement, and the trachea was extubated on the third day after operation. Five days after surgery phenoxybenzamine 1–2 mg kg\(^{-1}\) day\(^{-1}\) in two divided doses was given instead of labetalol. The patient was returned to the ward the following day, but required phenoxybenzamine until day 15 and captopril until day 17, when her arterial pressure was 117/75 mm Hg.

Plasma renin assays obtained before surgery confirmed renin secretion by the tumour, 135 ng angiotensin I ml\(^{-1}\) h\(^{-1}\) (normal range 0.2–2.5 ng angiotensin I ml\(^{-1}\) h\(^{-1}\) supine; 1.5–8.0 ng angiotensin I ml\(^{-1}\) h\(^{-1}\) ambulant). The plasma concentrations 3 days after removal of the tumour had decreased to 3.1 ng angiotensin I ml\(^{-1}\) h\(^{-1}\). Histological examination showed a Stage I, well differentiated nephroblastoma (Wilms' tumour) with favourable histology and the patient was given a course of vincristine before discharge home on day 35 after admission.

**DISCUSSION**

Hypertension in association with nephroblastoma was first reported by Pincoffs and Bradley in 1937 [2], and is found in up to 60% of cases [3]. Increased serum concentrations of renin were demonstrated in 1969 [4], and immunohistochemical techniques have shown that both primary (from the tumour itself) and secondary renin secretion may occur [5]. Although many nephroblastomas are associated with increased concentrations of renin [6–9], not all patients are hypertensive [9, 10] as some renin is in the inactive prorenin form [11, 12].

Renin (half-life 80 min) is a protease enzyme, secreted normally by the juxtaglomerular apparatus, which acts specifically on circulating angiotensinogen to produce the decapeptide angiotensin I.

This in turn is cleaved to an octapeptide, angiotensin II (half-life 1–2 min), by converting enzymes present primarily in the lungs, although there is evidence for extrapulmonary conversion [13]. Angiotensin II is the major vasoactive component of the renin–angiotensin cascade and is involved in the homeostasis of extracellular fluid volume and electrolytes and maintenance of arterial pressure [14]. It is the most potent vasoconstrictor in the circulation, acting mainly on the arterial vascular bed, and to a lesser degree on the venous bed. While mild hypertension is a common feature of nephroblastomas, severe hypertension as in our patient is rare [8, 15]. Although the degree of hypertension does not affect the long-term outcome of the patient [3], severe forms need to be treated urgently to avoid the onset of central nervous system complications or cardiovascular decompen
dation [3, 16]. There is little information on a reliable method of controlling arterial pressure in these patients. There are similarities to cases of phaeochromocytoma, in which the hypertension is mediated by catecholamine-induced vasoconstriction. Pharmacological control before surgery ensures normal blood and extracellular fluid volumes and avoids sudden and dramatic variations in arterial pressure at the onset of anaesthesia [1]. As the mechanism of angiotensin II-induced hypertension can be intense vasoconstriction, it would seem prudent to attempt to control arterial pressure before surgery.

It appears logical to select pharmacological agents that counter the pathophysiological mechanisms responsible for the increased pressure. There are several sites along the renin–angiotensin cascade at which inhibition could occur. Sympatholytics, both centrally acting, such as methyldopa and clonidine, and some beta adrenoceptor antagonists such as propranolol, suppress the stimuli for renin release [14]. That the autonomous nature of renin production by nephroblastoma tumour cells is not affected is demonstrated by our patient and others [7, 17]. In addition, long-acting beta adrenergic block does not affect the underlying intense vasoconstriction, and can precipitate severe hypotension. The hypertension of nephroblastoma is typically labile and, in the event of a decrease in renin production, beta adrenergic block could prevent a compensatory increase in cardiac output. An analogous situation has been reported with the noradrenaline-mediated hypertension seen in severe autonomic tetanus [18].

Peptides that structurally mimic endogenous angiotensinogen, and compete with it for binding to renin, and highly specific antibodies that complex with renin, limiting its ability to bind to angiotensinogen, are under development [14]. Angiotensin I has minimal vasoactive properties and captopril, an angiotensin-converting enzyme (ACE) inhibitor, has been used previously [8, 16, 17] and was useful in controlling hypertension in our patient. It is the most practical drug available for interrupting the cascade, and would appear to be the agent of choice for control of hypertension up to the time of surgery. Its plasma clearance half-life is 2 h, but the clinical half-life (50% recovery of initial response) is 4 h [19].
and the last dose should be given at least 4 h before removal of the tumour so that rebound hypotension does not occur.

Angiotensin II and aldosterone may be inhibited at their respective receptors [14]. Saralasin, a synthetic angiotensin II analogue, has been used to control severe hypertension in nephroblastoma [16], but it has limitations. Spironolactone has not been used in these patients and it is likely that the vasoactive effects of angiotensin II are greater than those of aldosterone.

Diuretics such as frusemide have little effect on arterial pressure and may worsen electrolyte abnormalities [15]. The combined alpha + beta adrenoceptor antagonist, labetalol, has been ineffective before surgery [8]. Pure alpha adrenoceptor antagonists may be used for acute intraoperative control (phentolamine [15]) and in the longer term (phenoxybenzamine in our patient), although this latter drug may be carcinogenic in rats and its use should be limited [20]. Hydralazine and diazoxide, both direct vasodilators, have been shown to be disappointing in their control of preoperative pressures [7, 8, 15-17]. Sodium nitroprusside was used with some success in controlling intraoperative peaks of arterial pressure in our patient. The resultant tachycardia was controlled by an infusion of esmolol, a short-acting cardioselective beta adrenoceptor antagonist [21].

The anaesthetist faces many problems when dealing with these patients. Electrolyte concentrations may be deranged, particularly if both kidneys are involved and excessive concentrations of aldosterone [4, 6, 17] or aggressive diuretic therapy [15] may result in unpredictable neuromuscular block and predispose to cardiac arrhythmias. Patients are frequently anaemic, although this may be masked by the relative hypovolaemia. It is difficult to measure arterial pressure accurately at the extremes encountered and the tendency to dismiss the results as “unlikely” must be avoided. Patients with severe hypertension may present with central nervous system complications or cardiovascular decompensation [3, 16] and it would seem advisable to attempt to control the pressure. However, the need for arterial pressure control before surgery is debatable, as most literature reports unsuccessful control with uneventful induction of anaesthesia [2-4, 7, 8, 15].

In severe cases it is important to measure central venous pressure so that intravascular volume may be controlled. Third space losses may be great and excessive bleeding during tumour dissection may occur, particularly if the patient remains hypertensive. Veins should be cannulated in the upper limbs in case the inferior vena cava is clamped. Direct arterial pressure must be monitored as large fluctuations in pressure should be anticipated [6]. It is frequently difficult to cannulate the arteries, as the severe hypertension, together with intense vasoconstriction, results in thick-walled arteries with narrowed lumens. In some cases the tumour may be sufficiently large to split the diaphragm and embarrass ventilation [16]. With large tumours gastric emptying may be delayed and a rapid sequence induction of anaesthesia may be necessary. Infusions of noradrenaline and sodium nitroprusside should be available to treat rapidly any excessive troughs or peaks in arterial pressure [15]. In patients with smaller tumours, a more gradual onset of anaesthesia using an inhalation induction with halothane seems appropriate. Although this technique is associated with vasodilatation, the onset is slower and allows time for adequate treatment.

After induction of anaesthesia, variations in arterial pressure may be caused by obstruction of the inferior vena cava during tumour manipulation or excessive blood loss. Tumour handling may cause hypertension, which should be controlled with short acting agents such as sodium nitroprusside and esmolol. Decreases in arterial pressure on ligation of the renal vein should be treated with intravascular volume replacement, supplemented by infusions of noradrenaline 0.5–2 μg min⁻¹ or angiotensin 0.01–0.2 μg kg⁻¹ min⁻¹ (Angiotensin (Hypertensin) is available only on a named-patient basis, from CIBA Laboratories).

Patients remain hypertensive for 1-3 weeks after tumour resection [3, 8]. As renin concentrations have been shown to return rapidly to normal values [8], this is most likely a result of residual hypertrophy of the left ventricular wall and the arterial wall media [4]. Delayed resetting of baroreceptors, as occurs in hypertension after repair of coarctation of the aorta, may also occur [22].

REFERENCES

13. Caldwell PRB, Seegal BC, Hsu KC. Angiotensin converting


