Effective treatment of severe hypertensive crisis in 2-year-old child with neuroblastoma

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ABSTRACT

We describe a case of a 2-year-old boy with neuroblastoma and high catecholamine levels which developed a severe hypertensive crisis. An oral propranolol and oral angiotensin-converting enzyme inhibitor were used with a mild short transient benefit. However, an intravenous labetalol and oral doxazosin used for over 3 weeks resulted in successful blood pressure control. This report highlights the prolonged use of α and β-adrenergic antagonist therapy in children with neuroblastoma with refractory catecholamine-induced hypertension.

KEY WORDS: neuroblastoma, hypertensive crisis treatment, labetalol, doxazosin, children

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INTRODUCTION

An acute hypertension (HTN) is a relatively frequent complication in children and adolescents with cancer. However, if not recognized and treated promptly, it can lead to a hypertensive crisis with potentially significant morbidity and mortality. HTN is defined as systolic blood pressure (BP) and/or diastolic BP equal or greater than the 95th percentile for age, gender and height in at least three separate measurements. In contrast to adults, approximately two-thirds of children and adolescents have secondary hypertension. A hypertensive crisis is defined as a rapid increase of BP 5 mm above the 99th percentile for age, gender and height plus 5 mmHg [1–6]. Traditionally, a hypertensive crisis has been divided into two categories: hypertensive emergency and hypertensive urgency. Both require prompt pharmacologic intervention for BP reduction [1–3, 5]. The current recommendation is to reduce mean arterial pressure (MAP) by no more than 25% within the first 8 to 12 h and then gradually normalize it in the next 48 to 72 h. Treatment should not be too rapid to avoid inducing organ ischemia including cerebral hypoperfusion and death [1, 3]. Conscious patients initially treated with intravenous infusion should be transitioned slowly to oral medications after 24–48 h [2]. Many drugs are currently used to treat hospitalized children and adolescents with acute HTN and a hypertensive crisis. A number of hypertensive agents like many pediatric medications do not have pediatric FDA approval for use in acute HTN and a hypertensive crisis, and the treatment is based on adult indications and published reports.

A labetalol is an α and β-adrenergic blocker which reduces peripheral vascular resistance with little effect on cardiac output and which can be administered intravenously in children (bolus 0.2–1 mg/kg/dose, up to 40 mg/dose, infusion 0.25–3 mg/kg/h) [1, 7]. A doxazosin is a selective α-blocker which needs to be followed by β blockade in neuroendocrine causes of acute HTN such as pheochromocytoma caused by catecholamine excess. However, this agent is not registered for use in children [1].

In this paper we present a case of successful treatment of a hypertensive crisis due to catecholamine excess in a child with neuroblastoma with administration of intravenous labetalol and doxazosin for 4 weeks. Our case highlights the possible use of an unusual drug combination for the treatment of a hypertensive crisis which allowed for the continuation of anti-cancer treatment without organ damage.

CASE PRESENTATION

A 2-year-old boy (16 kg weight) was diagnosed with *N-MYC* amplified neuroblastoma after he was admitted to the hospital with a large abdominal mass extending into the chest. He had metastatic disease to the liver, bones and bone marrow. Treatment included a high-risk regimen with cisplatin, doxorubicin, cyclophosphamide, vincristine, carboplatin and etoposide.

The patient had hypertension (160/110) when admitted to hospital and had very high level of dopamine in urine test (2900 μg/24 h). Oral angiotensine-converting enzyme inhibitor (captopril 0.3 mg/kg four times a day) and hydrochlorothiazide (1 mg/kg/day) were administered with a very short transient benefit and because of that an oral beta-blocker was added (propranolol 0.5 mg/kg four times a day) with small improvement. The patient subsequently developed a full-blown hypertensive crisis (225/145) with brain disturbance (headache, nausea, vomiting, confusion, seizures) and oedema of the renal parenchyma with disturbed peripheral perfusion. The initial dose of intravenous labetalol was 0.3 mg/kg/h in continuous infusion and was escalated to 1 mg/kg/h without improvement in BP control. Doxazosin was then added (1 mg twice a day) and the dose of labetalol was escalated to 2.7 mg/kg/h. Hydrochlorothiazide and oral angiotensine-converting enzyme inhibitor were maintained. This allowed to hold BP within acceptable levels and to preserve organ function. Chemotherapy continued during this process with some modifications to adjust for the decrease in clearance of creatinine and after 2 weeks levels of dopamine (1200 μg/24 h) decreased. However, the patient required the same intensive hypertensive management for 2 weeks. At the time dopamine levels reached 500 μg/24 h, the patient tolerated a gradual reduction with discontinuation of intravenous labetalol infusion and oral doxazosin after 4 weeks of treatment. The patient continued to receive an oncological treatment which included chemotherapy, radiation therapy and surgery. The patient required administration of an oral beta-blocker until surgery. The patient is now 1.5 years after hypertensive crisis and does not have any signs of organ failure, and is in remission of neuroblastoma.

DISCUSSION

We report the case of a hypertensive crisis in a child with neuroblastoma who was successfully treated with an intravenous infusion of labetalol and oral doxazosin for over

3 weeks. To our knowledge this is the first case of effective and safe prolonged administration of intravenous labetalol and oral doxazosin in children.

Neuroblastoma is one of the most common solid tumors in children. Catecholamine release is a typical phenomenon in neural crest cell tumors like neuroblastoma. However, the development of a symptomatic catecholamine release syndrome with severe HTN is rare and these patients rarely require anti-hypertensive treatment before resection [8, 9]. Despite the rarity of this phenomenon, a hypertensive crisis should be identified quickly to avoid organ damage and minimize morbidity and mortality. In a hypertensive crisis, pediatric literature recommends the use of intravonous infusions of anti-hypertensive drugs [2–5, 7]. Several agents effectively control hypertension in patients with pheochromocytoma or neuroblastoma. The most commonly used agents are selective α antagonists (phenoxybenzamine, phentolamine, doxazosin, prazosin) which are followed with β blockers (labetalol, propranolol, atenolol) if necessary [3, 4, 6–8, 10, 11]. Additionally, fluid and salt repletion are important when α blockers are used to prevent hypotension, since rapid reductions in BP in children may result in acute neurological complications, visual loss and acute renal failure [3].

Labetalol is α and β-adrenergic blocker which reduces peripheral vascular resistance and has a relatively long half-life (3–5 h). Continuous intravenous infusion typically starts with dose of 0.25–1 mg/kg/h (with a maximum dose of 3 mg/kg/h) [1, 5, 7, 12]. Some authors documented that lower doses may also be effective [7, 10]. Labetalol should not be used in patients with bronchospastic disease like asthma or congestive cardiac failure as it has a negative inotropic effect and should also be used with caution in children with diabetes. However, according to the literature side effects of this drug are not significant [7, 10]. Long-acting oral medications should be introduced in a conscious child within 24–48 h of commencement of continuous infusion of the anti-hypertensive after the BP has been controlled. Effective continuous infusion dosages range from 0.25 to 1.5 mg/kg/h with mean infusion duration of 67.3 ± 57.1 h [7]. Prolonged use of intravenous infusion may result in sodium and water retention and tachyphylaxis [4].

In our patient, because of the size of the tumor, upfront surgery was not possible and therefore an aggressive anti-hypertensive regimen had to be instituted. Importantly, this treatment did not interfere with the overall oncological management and did not result in severe side effects.

CONCLUSION

In summary, this report highlights the safety and efficacy of prolonged use of α and β-adrenergic antagonist therapy in a child with neuroblastoma with refractory catecholamine -induced HTN. Our case offers a good rationale for the combined use of labetalol and doxazosin but more studies are necessary to investigate and define the best approach to the management of hypertensive emergencies in children.

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Conflict of interest: nothing to declare.

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A. idea & design of the article; B. clinical data collection; C. analysis of the data; D. interpretation; E. writing the manuscript; F. references