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Acute Hypertension during Clonidine Taper in an Infant with Neonatal Abstinence Syndrome

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Authors' contributions

The authors equally designed, analyzed and interpreted and prepared the manuscript.

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Case Study

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ABSTRACT

A 2,600-gram infant treated with methadone and clonidine for Neonatal Abstinence Syndrome (NAS) developed acute hypertension following initiation of the clonidine taper, requiring treatment with a calcium channel blocker. While transient hypertension after discontinuing alpha-2 agonist treatment is common, prolonged elevation of blood pressure is uncommon. Thus, more gradual tapering and careful monitoring of blood pressure following discontinuation of clonidine in newborn patients could be warranted.

Keywords: Neonatal withdrawal syndrome; alpha-2 agonist; withdrawal; blood pressure.

1. INTRODUCTION

Neonatal Abstinence Syndrome [NAS] subsequent to in utero exposure to maternal medications is an increasing problem [1-3]. In some areas, Neonatal Intensive Care Units [NICUs] are often inundated with newborns suffering from prolonged withdrawal from opioids and other agents. Exposure to maternal opioids is the most common etiology leading to NAS. Treatment with a long-acting opioid such as methadone is the first line and most effective

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treatment for relieving the signs of withdrawal in the neonate [4-6]. Some infants have more difficult hospital courses and in addition to opioids, treatment often requires supplemental medications including; clonidine, phenobarbital and gabapentin [7]. Clonidine, an alpha-2 agonist, is an effective second-line drug for treating NAS [8-11]. It has minimal side effects in the neonate and is normally well tolerated. Hypertension following abrupt discontinuation of clonidine in newborns has been described, however, chronic hypertension has been described only in the adult literature [12,13]. We present the case of a newborn infant, who developed chronic hypertension following a slow clonidine taper. Implications for management of infants with hypertension in the setting of a clonidine taper as a treatment regimen for NAS, is discussed.

2. CASE REPORT

A 2,600-gram male infant was born via vaginal delivery at 37 weeks gestation to a 23-year-old Gravida 1 Para 0 female with a history of opioid and recreational marijuana use throughout pregnancy. Her past medical history was significant for opioid dependency, depression and anxiety. At the time of delivery, she was prescribed and taking 70 mg of methadone daily and admitted to smoking marijuana as frequently as several times per day. The baby was vigorous at birth with Apgar scores of 8 at one minute and 9 at five minutes. The baby was notably hypertonic and tremulous within 10 minutes of birth. Oral methadone, 0.1 mg/kg every 12 hours, was initiated on day of life one. Despite a gradual increase in total daily methadone dose, to as high as 0.5 mg/kg/day, Finnegan abstinence scores remained as high as 12. He was hyperphagic, tremulous, agitated and suffered from persistent insomnia. At 3 weeks of age, clonidine was added at 7.5 mcg/kg/day, given every 12 hours, secondary to continued signs of NAS. Due to persistent difficultly with adequate management of his withdrawal, the care team transferred the 29-day-old infant to a tertiary care center with a Level 3 NICU and neonatal pain specialist for a higher level of care. Following transfer, Finnegan abstinence scores remained elevated at 10 -15, and the neonate was very irritable. His total daily methadone dose was increased by 25% and the dosing frequency was increased to every 6 hours. The clonidine dose was increased to 20 mcg/kg/day and the frequency was changed to every 8 hours. Even with the increased clonidine and methadone, the baby remained irritable, so in addition phenobarbital was added and a level of 30 mg/dl was achieved. Following the above medication adjustments, signs of NAS in the infant resolved. Finnegan scores decreased to less than 5, and he was able to feed and sleep normally. The baby was maintained on these medications and symptom free for 48 hours prior to beginning the methadone taper. Methadone was the first medication to be weaned, allowing clonidine and phenobarbital to suppress the autonomic symptoms associated with NAS. The subsequent methadone taper was difficult due to intermittent symptoms, but was successfully completed over the following 2 months. Due to issues with parental compliance, at day of life 95 the medical team elected to start the oral clonidine taper in the hospital. Initially, the clonidine was to be weaned by 20% at each step of the taper, with a starting dose of 25 mcg every 8 hours. Following the second step of the taper (to 15 mcg every 8 hours), he developed hypertension, with systolic blood pressures as high as 125 mm Hg (Fig. 1). Previous blood pressure measurements ranged from 70-80 systolic. His heart rate remained at baseline, in the 120-140 range. A nephrology consultation was obtained, followed by a renal ultrasound, urinalysis, and 4-extremity blood pressures. The tests were all normal and the etiology of new-onset hypertension was determined to be secondary to clonidine withdrawal. Despite the team increasing the clonidine back to 25 mcg every 8 hours, the blood pressure remained elevated. The decision was made to start an alternate antihypertensive medication. Amlodipine 0.1 mg/kg /day, given once daily, was started two days after the clonidine was increased back to pre-taper dose. The amlodipine was titrated up to 0.2 mg/kg/day, given once daily, to achieve normal blood pressures for age. This goal was achieved within 5 days of beginning amlodipine. By 120 days of life, the clonidine taper was again initiated and he was easily tapered off the medication over the following 2 weeks, with the last week of the taper accomplished at home. He was also discharged home on phenobarbital and amlodipine with close follow up in the neonatal pain clinic. The phenobarbital was weaned over the next month, and the infant remained normotensive. At 6 months of age, amlodipine was discontinued and he had no further issues with hypertension.

3. DISCUSSION

Clonidine has been used successfully as an adjunct for opioid withdrawal in newborn infants,

children and in adults. It can be administered via oral, transdermal, intrathecal, epidural or intravenous routes [14,15]. It is commonly used as a second-line therapy in the pharmacologic treatment of neonatal abstinence syndrome [16]. Clonidine is an alpha-2 agonist, acting at the presynaptic terminals to inhibit sympathetic outflow and autonomic symptoms of withdrawal such as tachycardia, hypertension, agitation and sweating. In a randomized, controlled trial of 80 infants, clonidine plus opium was more effective at decreasing the symptoms associated with NAS, compared with dilute tincture of opium and placebo. The study reported no new-onset hypertension following discontinuation of the drug, although the follow-up provided lasted only 48 hours and the dose of clonidine was relatively small [6 mcg/kg/day] [9]. While hypertension was not detected, one patient in the clonidine arm of the study, developed supraventricular tachycardia requiring adenosine, on day of life 5, three days after discontinuing clonidine.

Abrupt cessation of clonidine can result in signs of withdrawal, including tachycardia, hypertension and sweating [17]. The cardiovascular effects resulting from clonidine withdrawal are thought to be due to sympathetic hyperactivity [18]. An extreme case of acute withdrawal syndrome has been reported in a newborn, with inadvertent dislodgement of a clonidine patch, leading to profound symptoms of sympathetic hyperactivity [19]. In addition, signs of clonidine withdrawal (including agitation and tachycardia) have also been reported in a premature infant, following too rapid a taper, with cessation of symptoms following reintroduction of the drug [20].

In the case presented here, clonidine was slowly tapered and the neonate did not experience any signs of withdrawal aside from new-onset hypertension. In a term, newborn infant, a systolic blood pressure consistently over 100 mm Hg, is considered hypertensive [21,22]. In this infant, the systolic blood pressures were greater than 100 mm Hg on multiple successive readings and on all four extremities. Despite the team increasing the clonidine back to pre-taper baseline he remained hypertensive, requiring an anti-hypertensive agent, amlodipine. Amlodipine, an oral calcium channel blocker, was chosen for its ease of administration and familiarity in this patient population. As the infant was otherwise asymptomatic, evaluation for alternative etiologies of hypertension was performed. These studies did not find any physiologic or anatomic abnormalities that would explain the isolated hypertension. It is possible to have increased the clonidine to a higher level to obtain normotension, but the team was worried about the hypertension returning upon restarting the taper. Once the amlodipine was initiated and titrated to an effective blood level, the clonidine was tapered without complication and the infant remained normotensive [Fig. 1].

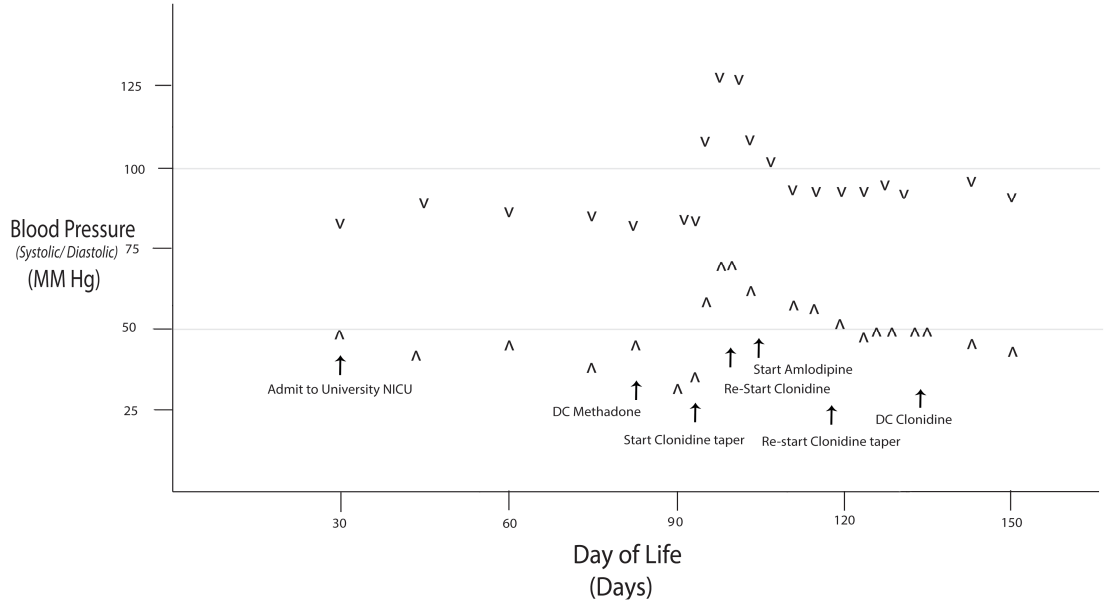

Fig. 1. Chart of average blood pressures during the first 5 months of life. Methadone and clondine treatments are note on the graph

Given the lack of evidence of organic pathology as a primary etiology for hypertension in this infant, it remains likely that the hypertension was due to his falling clonidine blood levels. It is not uncommon for the pain management team to see, mild cases of hypertension during clonidine tapers, which typically resolve spontaneously, without therapy. This case is unique in that the hypertension was severe and sustained. While possible, it is less likely that a medication error is responsible for the acute hypertension seen in the above case, as the clonidine suspension is compounded (100 microgram/mL oral suspension) by pharmacy technicians and double-checked by the NICU staff prior to patient administration [23].

4. CONCLUSION

In conclusion, we present the case of an infant with NAS on clonidine, in which new-onset hypertension developed following a gradual dose decrease. While rebound hypertension is a known risk of clonidine discontinuation, it has been previously thought that gradual taper of the medication would prevent this side effect. We recommend close blood pressure follow up upon initiation of a clonidine taper in neonates, as well as effectively slowing the taper, or adding an antihypertensive agent should new-onset hypertension occur.

CONSENT

All authors declare that written informed consent was obtained from the patient (or other approved parties) for publication of this paper and accompanying images.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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