

# Clonidine Withdrawal in a 3 Month old Premature Male Infant

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## Abstract

Acute clonidine withdrawal is widely reported in adults. Little evidence and no guidelines are available for managing clonidine therapy and withdrawal in neonates and young infants. We report a case of clonidine withdrawal in a 3 month-old premature infant receiving clonidine therapy for Neonatal Abstinence Syndrome due to antenatal and iatrogenic opiate exposure. During clonidine dose reduction, the baby developed hypertension, tachycardia and extreme agitation. Symptoms abated with prompt increase in clonidine dose and initiation of a more gradual discontinuation schedule. We recommend slowly tapering the clonidine dose by no more than 20-25% per week to prevent withdrawal symptoms.

## INTRODUCTION

Clonidine is a centrally acting alpha 2 adrenergic receptor agonist,<sup>1</sup> approved and marketed in the U.S. for hypertension treatment,<sup>2,3</sup> and epidural analgesia.<sup>4</sup> The alpha 2 agonists have sedative and anxiolytic properties which allow them to be useful in a variety of pediatric clinical domains including psychiatry,<sup>5,6</sup> anesthesia,<sup>7</sup> and critical care medicine.<sup>8,9</sup> Clonidine is also a treatment option for opioid withdrawal in the neonatal abstinence syndrome (NAS).<sup>10,11,12</sup> Clonidine and other alpha 2 agonists attenuate the symptoms of opioid withdrawal by inhibiting central nervous system noradrenergic hyperactivity.<sup>13,14</sup> Abrupt cessation of clonidine can cause withdrawal symptoms including hypertension, tachycardia and agitation.<sup>15,16</sup> We report the first known case of clonidine withdrawal in a premature infant being treated for opioid withdrawal.

## CASE REPORT

The patient was a 3 month old male infant born at 24 weeks gestation. He had multiple complications of prematurity including RDS, ROP and NEC requiring bowel resection. After a routine surgery for ROP at approximately 2 months of age, the baby developed pneumonia requiring prolonged mechanical ventilation. He was treated with parenteral opioids and benzodiazepines for just over 1 month. After the baby recovered from the respiratory disease, he required treatment for iatrogenic neonatal abstinence syndrome. He was treated with oral methadone 0.25 mg every 8 hours (0.3 mg/kg/day) and clonidine transdermal patch 50

microgram/day (20 microgram/kg/day). The baby was successfully weaned off methadone after 4 weeks. After the discontinuation of methadone, the clonidine patch was removed and the infant was switched to oral clonidine at a dose of 15 mcg twice daily. After 4 days the baby developed increasing irritability, tremor, tachycardia and hypertension consistent with clonidine withdrawal. The baby was treated by increasing the clonidine to 15 mcg orally 3 times a day. The infant was asymptomatic by the 2<sup>nd</sup> day of treatment. He was then slowly tapered off clonidine over the next 2 weeks without the return of symptoms.

## DISCUSSION

Clonidine has been used successfully as an adjunct for opioid withdrawal in newborn infants and adults.<sup>10,12</sup> It can be administered via the oral, transdermal, intrathecal, epidural or intravenous route. We routinely use oral or transdermal clonidine as an adjunct to methadone for treatment of neonatal abstinence syndrome (NAS). Our regimen initiates clonidine in babies with persistent Finnegan,<sup>16</sup> scores greater than 8 while on methadone or during methadone weaning. We use a clonidine compounded 100 microgram/mL oral solution,<sup>17</sup> at a dose of 10 micrograms/kg/day divided every 8 hours. The baby is re-evaluated daily for response to therapy. The clonidine dose is titrated up to 20 microgram/kg/day in 2.5 microgram/kg/day increments as needed to maintain Finnegan abstinence scores <8. If the dose is  $\geq 50$  micrograms/day we may switch a baby to the once-weekly transdermal clonidine patch. The patch allows

for more consistent delivery of drug and one less oral medication for nursing service to administer. The lowest dose clonidine transdermal patch commercially available delivers 100 microgram/day via a membrane-controlled transdermal delivery system.<sup>3</sup> When initiating clonidine patch therapy, we usually overlap with continue oral clonidine dosing for 12-36 hours until therapeutic effects from the patch are adequate.

In order to deliver 50 mcg/day (1/2 patch), we occlude one-half of the patch adhesive surface using one-half of the product's polyester protective peel-away slit liner. Likewise, we use one-fourth of the liner when attempting to deliver 75 mcg/day. The patch can be held in place with an appropriate clear adhesive dressing (e.g. Tegaderm®) applied over the patch backing. The patch is changed once-weekly but should be checked each shift by the baby's nurse to confirm continued placement.

We do not cut the patch. Cutting the clonidine patch will damage the integrity of the semipermeable patch membrane, possibly resulting in leakage of the patch's drug reservoir contents and imprecise drug delivery.<sup>18</sup>

Abrupt cessation of clonidine can result in a withdrawal symptoms including sympathetic hyperactivity with tachycardia, hypertension and sweating.<sup>19,20</sup> To prevent this we routinely taper the oral dose down slowly, with a decrease of about 20-25% per week, one week at a time. We do not routinely decrease the dose by 3-4% per day from each of the three daily doses in rotation, although such a clonidine weaning algorithm has been recommended by adolescent psychiatry providers.<sup>21</sup> In our case infant, the dose was decreased from 50 mcg/day to 30 mcg/day, a 40% decrease, which resulted in the baby becoming symptomatic. Although we looked for different sources of etiology of the symptoms, all tests, including a septic screen and ECG, were negative. We added back the clonidine resulting in resolution of the symptoms confirming the diagnoses of clonidine withdrawal.

In summary, we conclude that clonidine, although an excellent drug for assisting in treating NAS, it should be tapered slowly to prevent withdrawal symptoms in neonates and young infants.

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