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Clonidine for neonatal abstinence syndrome: a single neonatology department's experience

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ABSTRACT

Clonidine has been shown effective in reducing sympathetic hyperactivity in neonatal abstinence syndrome (NAS). The aim of this study was to analyze clinical and laboratory characteristics of a group of newborns treated with clonidine for NAS due to maternal drug addiction and due to withdrawal from opioid analgesic therapy. Only one full–term newborn presented with metabolic acidosis and hyperkalemia; in others no clinical or laboratory adverse effects were detected. This report emphasizes the importance of alertness to potential adverse effects of clonidine therapy, and discusses possible pathophysiological aspects of hyperkalemia and metabolic acidosis during treatment for NAS.

Key words: newborn, sympathetic hyperactivity, metabolic acidosis, hyperkalemia

INTRODUCTION

Although clonidine is generally approved only as an adjunctive treatment for opioid withdrawal, it has been shown as an effective medicine in reducing sympathetic hyperactivity in neonatal abstinence syndrome (NAS). (1) Many autonomic symptoms of opioid withdrawal like nausea, vomiting, cramps, sweating, tachycardia and hypertension, result from the loss of opioid suppression of locus coeruleus during NAS. By activating presynaptic alpha2-receptors, clonidine reduces increased sympathetic tone via a negative feedback mechanism. The opioid NAS patients treated with clonidine in addition to reduced withdrawal symptoms benefit also from shorter duration of treatment and hospitalisation and are free of cardiovascular or sedation adverse effects. (2)

CASE SERIES

We analyzed clinical and laboratory findings of seven patients who were treated with clonidine because of NAS at the Department of Neonatology, Division of Pediatrics, University Medical Centre Ljubljana, Slovenia, from April 2013 to March 2014. Two patients were treated for NAS because of maternal drug addiction and five because of withdrawal from opioid analgesic therapy during intensive care (table 1). Routine daily controls of blood gases and ionogram revealed no abnormalities in six children, while in one- treated with clonidine for NAS due to maternal substitution therapy with methadone- hyperkalemia and metabolic acidosis was noticed. He was a full–term infant who developed NAS 48 hours after birth. The Finnegan score was 15 in three consecutive assessments and therapy with clonidine 1.1 μg/kg/6h was started orally on the third day of life (PD3). (3) Before treatment with clonidine urine output was 3–4 mL/kg/h; blood pressure and laboratory values were within normal limits. On the third day after introduction of clonidine (PD6), diuresis rose to 8 mL/kg/h; blood urea and sodium concentrations were found to be in the high normal values, but creatinine, potassium and blood gas analysis were still normal. The boy was fed with formula milk, received additional hydration but no potassium supplementation. Blood urea and sodium concentrations normalized but after nine days of clonidine therapy (PD12) metabolic acidosis with hyperkalemia (pH 7.35, pCO2 4.04 kPa, HCO3 16.7 mmol/L, BE -9 mEq/L, anion gap 14.5 mEq/L, K 6.6 mmol/L, venous blood) was found; ECG showed peaked T waves. Glucose by intravenous infusion was introduced but as the potassium level reached 7.2 mmol/L the fast acting insulin was started and clonidine stopped (PD12). Potassium levels normalized three days after abrupt clonidine withdrawal (PD15). The Finnegan score after clonidine withdrawal was under 8 so additional therapies were not introduced. The boy was discharged home at the age of 18 days in a stable condition.

DISCUSSION

Hyperkalemia with metabolic acidosis, which we observed in one of our patients treated with clonidine, is a potentially lethal condition since it can provoke life–threatening arrhythmias. In the broad differential diagnosis of acid–base and electrolyte imbalance, the plausible etiology could be probable or possible adverse reaction to clonidine, according to Naranjo's algorithm. (4) In a larger cohort, in a randomized, double–blind, controlled trial, where clonidine was added to opioid replacement therapy for opioid NAS, no hypertension, hypotension, bradycardia, or haemoglobin desaturation were observed; one infant developed supraven-

tricular tachycardia and three children died in the first two months of life. The reported causes of death were myocarditis, sudden infant death syndrome, and homicide and it is not known whether clonidine contributed to the deaths. (5) Contrary to our study, the authors did not report any laboratory findings in the patient group studied.

Clonidine acts as an 2–adrenoceptor agonist at central and peripheral 2–adrenoceptors. In addition to its central effect, it also acts via postsynaptic alpha2A-C–adrenoreceptor subtypes located in the distal tubules of the human kidney. Therefore, the kidney is subjected to a decreased sympathetic tone that causes an increase in renal blood flow, which possibly presented with polyuria in our patient. Clonidine–mediated diminished sympathetic tone also causes decreased plasma renin activity and consequently reduces aldosterone secretion, which prevents the excretion of K+. This effect could be potentiated by aldosterone–resistance, which often occurs in newborns. (6) In addition, the lack of sympathetic tone also decreases extrarenal disposal of potassium, which additionally could lead to hyperkalemia. In our patient, hyperkalemia did not reappear after discontinuation of clonidine, so we suppose that laboratory findings after 9 days of therapy with clonidine indicated the presence of type 4 renal tubular acidosis where hyperkalemia is the cardinal feature, and acidosis is mild when present. (7) Metabolic acidosis, which has been previously described as an adverse effect of clonidine, resolved spontaneously in all cases. (8)

In conclusion, we assume that metabolic acidosis type 4 with hyperkalemia in one of our patients was due to 1) decreased aldosterone secretion induced by clonidine, and 2) physiological resistance to aldosterone in human newborns, so we recommend regular controls of potassium blood levels after introducing clonidine for NAS.

Table 1. A case series of newborns treated with clonidine for neonatal abstinence syndrome.

Gender, Gestational age (weeks), Birth measures	Apgar score 1/5/10 min after birth	Additional diagnosis	Therapy of the mother/ newborn	Finnegan score before clonidine introduction	Time between drug withdrawal and clonidine introduction (days)	Duration of therapy with clonidine (days)	Maximal dose of clonidine (µg/kg)	Blood gas analysis	Ionogram	Blood pressure	Neurological assessment at discharge, postnatal age at discharge (days)
Female, 40 LGA	9/9/9	early onset sepsis with pneumonia (S. pneumonia)	midazolam fentanyl	14	2	3	2µg/12h	normal	normal	normal	axial hypotonia, 27
Female, 41 SGA	9/9/10	/	buprenorphine	16	3	7	3µg/8h	normal	normal	normal	irritable, 11
Male, 38 AGA	7/7/9	/	methadone	15	3	11	1,1µg/6h	metabolic acidosis	hyperK	normal	hypertonia, 16
Male, 39 LGA	4/7/8	meconium aspiration syndrome	midazolam fentanyl	15	2	5	2 µg/6h	normal	normal	normal	axial hypotonia, irritable, 20
Female, 37 SGA	3/7/7	perinatal asphyxia	midazolam morphine	16	2	7	2,7 µg/8h	normal	normal	normal	axial hypotonia, 21
Male, 35 AGA	8/9/9	apneic attacks (RSV bronchiolitis)	midazolam fentanyl	15	1	7	5,5µg/12h	normal	normal	normal	axial hypotonia, 38
Male, 39 AGA	9/10/10	arteriovenous malformation of cerebral vein, pulmonary hypertension	midazolam fentanyl	16	1	7	2,2µg/6 h	normal	normal	normal	optimal, 44

AGA, appropriate for gestational age; hyperK, hyperkalemia; LGA, large for gestational age; SGA, small for gestational age.

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