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Letter to the Editor

Before Lactic Acidosis is Attributed to the Joint Administration of Caffeine and Clarithromycin, all other Causes must be Carefully Excluded

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We read with interest the article by Volpon *et al.* about a 2-month-23-day-old girl with a history of prematurity who was admitted for refusal to feed, nasal obstruction, dyspnea and multiple apnea episodes and treated with caffeine without lactic acidosis^[1]. After exclusion of a viral and bacterial infection, the patient was treated with non-invasive ventilation, caffeine and clarithromycin^[1]. This treatment led to an improvement in respiratory insufficiency, but serum lactate gradually increased^[1]. Lactic acidosis recovered only after caffeine and clarithromycin were discontinued^[1]. The study is noteworthy, but several points should be discussed.

The first point is that serum lactate can increase not only due to caffeine administration, but also due to various other causes^[2]. In general, lactic acidosis can be caused by shock (cardiogenic, hypovolemic, distributive, obstructive), cardiac arrest, regional tissue ischemia (mesenteric ischemia, limb ischemia), trauma, burns, compartment syndrome, necrotizing tissue infections), diabetic ketoacidosis, drugs (alcohol, cocaine, carbon monoxide, cyanide), anaerobic muscle activity (seizure, heavy physical exertion, excessive breathing), thiamine deficiency, malignant diseases, liver disease, medication (metformin, linezolid, propofol, paracetamol, beta2-agonists, theophylline, reverse transcriptase inhibitors, epinephrine) or mitochondrial disorders (MID)^[2]. Psychological stress can also increase serum lactate. The main cause of lactic acidosis is impaired oxygenation of the tissue, either due to reduced oxygen supply or impaired mitochondrial oxygen utilization^[2]. Falsely elevated lactate levels may be due to pre-analytical rather than analytical problems, e.g. difficult blood sampling with prolonged phlebotomy or prolonged transportation times to the laboratory^[2]. Have all these alternative causes of lactic acidosis been thoroughly ruled out in the index patient? What medications other than caffeine and clarithromycin did the patient receive in the ICU?

The second point is that serum lactic acidosis is often accompanied by an increase in cerebrospinal fluid (CSF) lactate^[3]. Elevated CSF lactate can result either from elevated serum lactate or from isolated elevated CSF lactate in the presence of normal serum lactate. Causes of elevated serum lactate include central nervous system (CNS) infections, accidental or neurosurgical head trauma, subarachnoid hemorrhage, alcohol-induced seizures, and MID with CNS involvement^[3]. Was the index patient examined for CSF lactate and was it elevated or not?

The third point is that no cerebral imaging was performed^[1]. The index patient had numerous episodes of apnea with subsequent oxygen desaturation^[1]. However, the patient only underwent polysomnography, which revealed CNS immaturity, but no CNS imaging^[1]. Why was the suspected immaturity of the brain not confirmed by cerebral MRI? It would also have been interesting to know if the patient underwent magnetic resonance spectroscopy (MRS) to determine if there was a double lactate peak or a decreased NAA peak, as is often the case with MIDs. Cerebral imaging would have been necessary not only to determine a possible CNS cause for the recurrent apneic episodes, but also to determine whether these episodes, which occurred prior to admission without lactic acidosis, had resulted in hypoxic brain injury.

The fourth point is that no long-term outcome was reported. Did the apnea episodes recur? Did the lactic acidosis recur?

To summarize, this interesting study has limitations that affect the results and their interpretation. Addressing these limitations could strengthen the conclusions and support the message of the study. Before attributing lactic acidosis in a neonate to the combined administration of caffeine and clarithromycin, all other factors must be considered.

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