LACTIC ACIDOSIS WITH CHLORAMPHENICOL TREATMENT IN A CHILD WITH CYSTIC FIBROSIS

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ABSTRACT

Children with cystic fibrosis are commonly colonized with multi-resistant bacteria. In such patients, infectious exacerbation may require salvage therapy with uncommonly used antimicrobials, including chloramphenicol. Chloramphenicol is rarely used nowadays because of the associated severe adverse events. We describe the case of a 15-year-old female with terminal cystic fibrosis who required intravenous (IV) chloramphenicol treatment for a *Burkholderia cepacia* (*B. cepacia*) exacerbation. The child subsequently developed lactic acidosis and secondary respiratory compensation adding to her baseline respiratory distress. Based on the Naranjo scale, the probability of chloramphenicol being the cause of the hyperlactatemia and associated respiratory distress was rated as probable, as the adverse effects resolved upon discontinuation of the drug. Subsequent genotyping for mitochondrial polymorphism (G3010A) confirmed a possible susceptibility to lactic acidosis from mitochondrial RNA-inhibiting agents such as chloramphenicol. Hyperlactatemia is a rare but life threatening adverse effect that has been previously reported with chloramphenicol exposure, but is not generally thought of.

Clinicians should be aware of this potentially life threatening, but reversible adverse event. Lactate should be monitored under chloramphenicol and it should be discontinued as soon as this complication is suspected, especially in patients with low respiratory reserve.

Key Words: *cystic fibrosis, multi-resistant bacterial infection, lactic acidosis, mitochondria, chloramphenicol*

BACKGROUND

Cystic fibrosis is a chronic and progressively deteriorating disease affecting multiple organ systems with high morbidity. Most commonly, the lungs are very affected and patients experience repeated lung infections. As patients age and are exposed to multiple antibiotic therapies, their lower respiratory tract becomes colonized with multi-resistant pathogens. Treatment of infectious exacerbations can therefore require regimens that include multiple antimicrobials and the use of older drugs with a high burden of toxicity –such as chloramphenicol– may be necessary.

Chloramphenicol is a bacteriostatic agent that inhibits bacterial protein synthesis.[1] Associated toxicities include grey baby syndrome and medullary aplasia.[1–3]

This toxicity profile likely results from the inhibition of mitochondrial protein synthesis, which leads to respiratory chain protein insufficiency and eventual oxidative phosphorylation dysfunction.[2–6] This toxic phenomenon can result in hyperlactatemia and associated metabolic acidosis.[2–6] Inhibition of mitochondrial protein synthesis with lactic acidosis, medullar toxicity and peripheral neuropathy has been previously reported with linezolid, which shares pharmacological properties with chloramphenicol.[7–10]

We report the case of a cystic fibrosis patient awaiting lung transplant who developed abrupt and severe respiratory distress as compensation for a

new-onset lactic acidosis associated with chloramphenicol treatment.

CASE

A 15-year-old Caucasian girl, with cystic fibrosis, weighing 40 kg, was admitted to the pediatric intensive care unit (PICU) for acute respiratory distress thought to be caused by a deteriorating *B. cepacia* exacerbation. The child had no known drug allergy and she had never experienced a drug adverse reaction before. Treatments prior to hospital admission included dornase-alfa, inhaled tobramycin, cycles of IV antimicrobials (including tigecycline and meropenem, cycled with ceftazidime and aztreonam) due to chronic respiratory tract colonization with multi-resistant pathogens (*Acinetobacter,* methicillin-sensitive *S. aureus, P. aeruginosa* and *B. cepacia*) as well as nocturnal non-invasive ventilation (BiPAP). Other medication included pancreatic enzymes (pancrelipase), vitamin supplements (A, D, E, K, and a multivitamin), oral metoclopramide and probiotics (*Saccharomyces bourlardii*). Prior to PICU admission, the child had been on the lung transplant waiting list for 2 years. Concomitantly, she suffered from failure to thrive linked to her hypermetabolic state due to cystic fibrosis. Her history was also marked by multiple (6) hospital admissions for respiratory exacerbations in the 6 months leading up to her PICU admission.

The child was initially admitted to the pediatric infectious disease ward for febrile respiratory distress caused by *B. cepacia* exacerbation. Upon hospitalization, bacterial cultures showed at least 3 different strains of *B. cepacia* with varying antimicrobial resistance profiles. Despite broadening of the antimicrobial regimen upon hospital admission (i.e., addition of 20 mg/kg/day IV trimethoprim/sulfamethoxazole (TMP/SMX), 70 mg/kg/day IV chloramphenicol to tigecycline (50 mg IV twice daily) and meropenem (120 mg/kg/day)), an increase in the non-invasive ventilatory support, and a trial of diuretics, the patient's condition continued to deteriorate. She began to display signs of severe respiratory fatigue and confusion, eventually requiring PICU admission.

Initial laboratory tests done in the PICU (day 7 post-admission) showed hyperkalemia (6.5 mmol/L)

and hyperlactatemia (8 mmol/L) without acidemia (initial capillary blood gas: pH=7.42, pCO_2=39.9 mmHg, HCO3=25 mmol/L; Figure 1) or hyperglycemia (6.1 mmol/L). We therefore suspected hyperlactatemia with respiratory failure due to compensated metabolic acidosis. Other than transient tachycardia, the patient was hemodynamically stable and no clinical signs of tissue hypoperfusion were present, which was corroborated by a normal central venous oxygen saturation ($ScVO_2$=72%). The child did not require beta-adrenergic agents such as inotropes or vasopressors. Lactate continued to increase; peaking at 9.5 mmol/L approximately 8 days following hospital admission. Despite hyperlactatemia, no significant acidosis developed. Anion gap was estimated at 16. Given the absence of tissue hypoxia and hypoperfusion, other causes of hyperlactatemia were explored.

As stated previously, multiple antimicrobials were used concomitantly on the ward. Two of these, both initiated upon hospitalization, could have caused hyperlactatemia: chloramphenicol due to its effect on oxidative phosphorylation[1,2,4–6] and TMP/SMX due to propylene glycol in the injectable formulation.[11] Both drugs were discontinued simultaneously on day 9 of admission.

The high concentration of propylene glycol in the IV TMP-SMX formulation (45% w/v for an intake of 0.55 g/kg/24h during 8 days) could have explained the slightly elevated osmolar gap.[11,12] However, the absence of renal or hepatic dysfunction made iatrogenic propylene glycol intoxication a less plausible cause for the hyperlactatemia.

Serum lactate gradually returned to normal (Figure 1) following discontinuation of both antibiotics with the patient's respiratory status concomitantly improving clinically. Interestingly, serum bicarbonate and pCO_2 gradually returned to higher than normal values, as expected in a chronically compensated hypercarbia (venous blood gas: pH=7.43, pCO_2=53.8 mmHg, HCO3=35.2 mmol/L on day 14).

IV TMP/SMX treatment was resumed 36 hours after lactate normalization and no subsequent metabolic disturbances were noted.

Thus, according to the Adverse Drug Reaction Probability Scale by Naranjo et al., our patient suffered

FIG. 1 Serum lactate, serum bicarbonate and pCO2 values over time since Intensive Care Unit (ICU) admission.
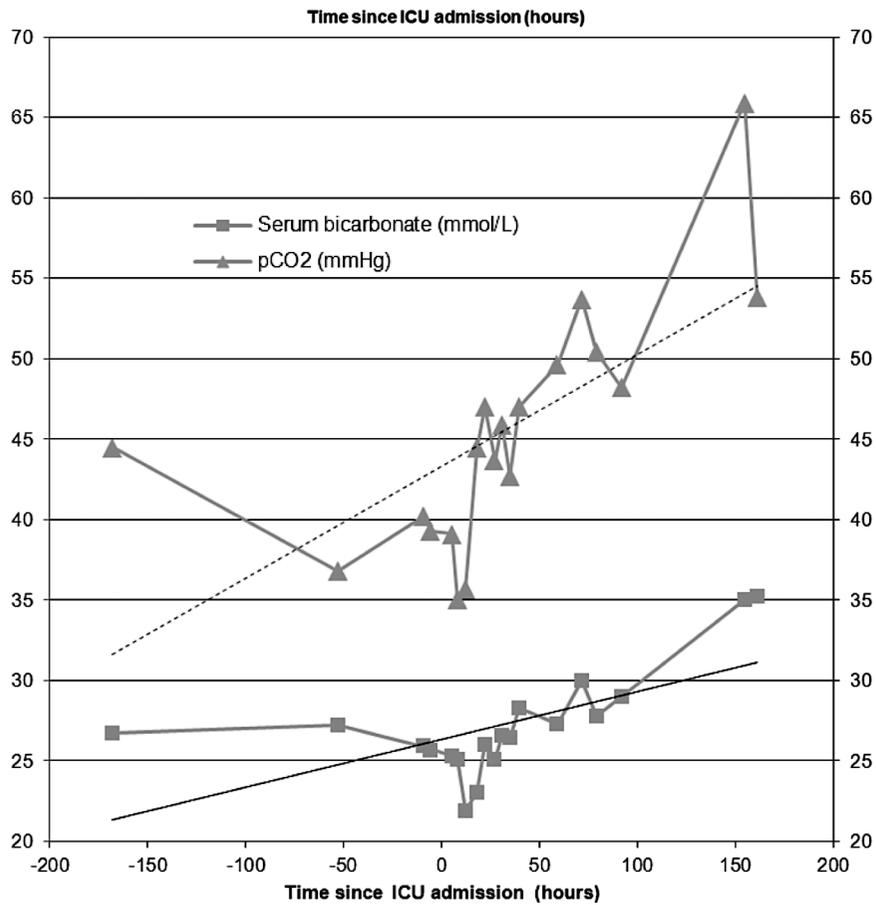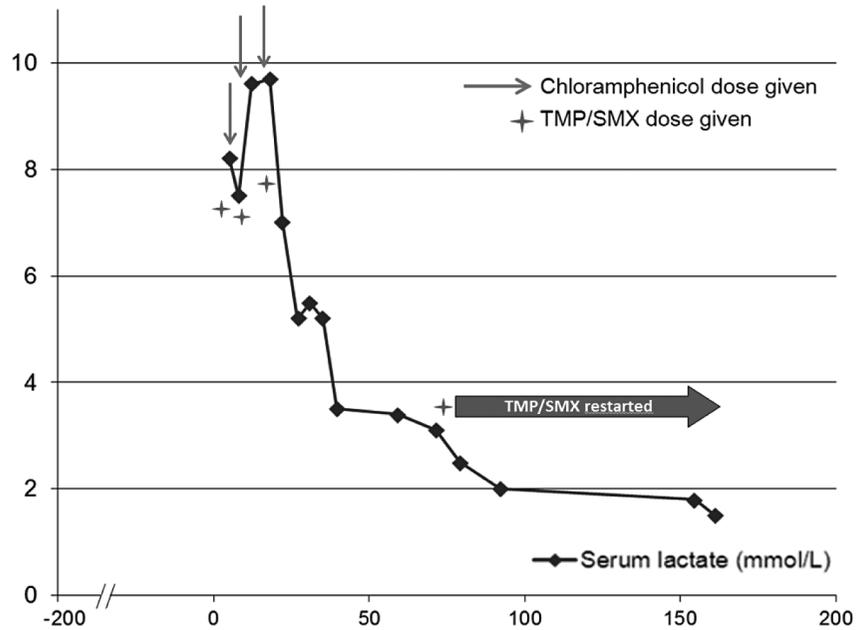
a "probable adverse drug reaction" from chloramphenicol exposure.[13]

Given this plausible association between chloramphenicol and hyperlactatemia, we explored mitochondrial gene polymorphisms known to be associated with drug-induced hyperlactatemia. Targeted genomic testing was done specifically screening for polymorphisms using restriction enzyme digestion of PCR fragments amplified from patient blood DNA.[7,8] The child presented G3010A polymorphism, which has been associated with an increased risk of lactic acidosis with another antimicrobial, linezolid.[7–10]

DICUSSION

This report describes a case of reversible lactic acidosis, probably caused by chloramphenicol in a genetically predisposed child with cystic fibrosis.

Chloramphenicol is an old antimicrobial that is now rarely used in North America. Its severe hematologic toxicity, the potential risk for grey baby syndrome, and the availability of safer alternatives have precluded its general use. Its one-dose regimen is, however, still considered as a first-line therapy for the treatment of meningococcal meningitis in developing countries where alternatives are not readily available.[14] Exposure to chloramphenicol is extremely rare today and there are limited published data supporting its role in aerobic metabolism toxicity and lactic acidosis. This toxicity mechanism was probably under recognized at the time, thus only the clinical manifestation of this mitochondrial toxicity are stated as adverse effects (grey baby syndrome, neuropathy, etc.). To our knowledge, only 1 case series (4 children 4 to 11 years of age)[2] and 1 case report (a 12-year-old child treated for a brain abscess)[3] described lactic acidosis associated with chloramphenicol exposure. Nevertheless, *in vitro* studies suggest that chloramphenicol has a potent adverse effect on respiratory chain protein synthesis.[4–6] Chloramphenicol acts by binding the bacteria's 50S ribosomal subunit, similarly to the more recently developed antibiotic linezolid, from the oxazolidinoneclass.[6,15] Reports of bacterial cross-resistance between oxazolidinones and

chloramphenicol confirm that these antimicrobials share a very similar pharmacologic target.[15]

Antimicrobials targeting bacterial ribosomal subunits often show an affinity for the eukaryote mitochondrial ribosomes because their genomes share similarities[6]. The eucarytote mitochondrion is protected from potentially harmful antibiotics by the human cellular membrane. Antimicrobials penetrating this membrane can reach the mitochondria and thus impair its biogenetic activity. Mitochondrial protein synthesis is essential for oxidative phosphorylation, the metabolic process allowing production of adenosine triphosphate (ATP), the main energy source of intracellular synthetic activity.[6] Thus, mitochondrial toxicity can lead to lactic acidosis in subjects exposed to such antimicrobials.

This seems to be the case of linezolid, which has a high affinity for ribosomal 23S subunit of the 50S unit of bacteria.[9,16] Binding to this subunit prevents complex formation with subunit 70S, thus inhibiting protein synthesis.[9] This affinity for the bacterial ribosome is shared with mitochondrial ribosomal subunit 16S due to structural homology.[9,16] Impairment of the mitochondrial oxidative metabolism is a well-known adverse effect of linezolid.[9] Multiple case reports of severe life-threatening lactic acidosis associated with this drug have been published.[9,17,18]

In 2005, Soriano et al. showed that patients with linezolid-induced lactic acidosis had depressed mitochondrial complex-IV activity, lower mitochondrial mass and decreased cytochrome C-oxidase expression.[17] All of which resolved after linezolid discontinuation, supporting its inhibitory effect on mitochondrial RNA[17]. Inhibition of mitochondrial protein synthesis is also thought to be implicated in the myelosuppression and the ocular and peripheral neuropathies associated with linezolid.[18] These adverse events have also been linked to chloramphenicol.[1]

Our hypothesis is that chloramphenicol's toxicity profile might be related to its ability to inhibit mitochondrial protein synthesis.

Specific polymorphisms on mitochondrial DNA (A2706G and G3010A) coding for mitochondrial 16S rRNA gene are thought to place subjects at higher risk for lactic acidosis with linezolid exposure.[7–10]

These mutations could confer a higher linezolid affinity for human mitochondria. The presence of G3010A in our patient's genome further supports our hypothesis. Our patient had been previously exposed to chloramphenicol before but for shorter periods of time. No serum lactate value was obtained at that time.

Given linezolid's and chloramphenicol's shared mechanism of action and the documented *in-vitro* effect of chloramphenicol on human mitochondria, it is reasonable to believe that chloramphenicol exposure has led to mitochondrial toxicity and secondary lactic acidosis in our patient. The child was never exposed to linezolid, and considering her mitochondrial genome, we would recommend avoiding this agent, as well as chloramphenicol if possible.

Lactate is a product of anaerobic cellular metabolism which can be seen in states of tissue hypoxia (*type A*) but it is also observed in non-hypoxic contexts (*Type B*).[19] For example, toxins that impair oxidative phosphorylation, such as chloramphenicol, can result in potentially life threatening lactic acidosis.[4] Lactic acidosis in sepsis has been associated with a 3-fold increase in mortality, and its severity is related to unfavourable outcome.[20–22] The presence of a coexisting pathophysiological phenomenon, such as chronically compensated hypercarbia, can mislead serum pH and bicarbonate interpretation and delay diagnosis.[19] The respiratory compensation induced by lactic acidosis can be very detrimental in patients with low baseline respiratory reserve such as cystic fibrosis patients. The increased work of breathing, coupled with poor muscle mass and inadequate gas exchange can lead to rapidly evolving respiratory failure.

Clinicians should be aware of the potentially life-threatening but reversible adverse effect that is drug-induced lactic acidosis, especially in patients with low respiratory reserve. Agents that are suspected to be involved should be discontinued and genetic studies to confirm mitochondrial polymorphism should be considered.

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TRANSPARENCY DECLARATION

The authors (Goyer I, Iseppon M, Thibault C, Krajinovic M, Abaji R, Autmizguine J) have no financial or moral conflict of interest to declare.

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