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CASE REPORT

Chloramphenicol Toxicity Revisited: A 12-Year-Old Patient With a Brain Abscess

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Chloramphenicol, a broad-spectrum antibiotic, is rarely used in the United States due to its well-described adverse effects. Because of its limited use, many clinicians are unfamiliar with its indications, spectrum of activity, and potential adverse drug effects. We describe a 12-year-old patient who presented after two craniotomies for a persistent brain abscess complicated by long-term chloramphenicol administration. Findings for this patient were consistent with many of the adverse drug effects associated with chloramphenicol, including elevated chloramphenicol serum concentrations, anemia, thrombocytopenia, reticulocytopenia, and severe metabolic acidosis. Rare manifestations of chloramphenicol toxicity that developed in this patient included neutropenia, visual field changes, and peripheral neuropathy. Chloramphenicol administration was discontinued, and hemodialysis was initiated for severe metabolic acidosis. The patient recovered with severe visual field deficits. Although chloramphenicol is rarely indicated, it remains an effective antibiotic. Healthcare providers should become familiar with the pharmacology, toxicology, and monitoring parameters for appropriate use of this antibiotic.

INDEX TERMS adverse drug effect, brain abscess, chloramphenicol, drug toxicity

J Pediatr Pharmacol Ther 2012;17(2):182–188

INTRODUCTION

In 1947, chloramphenicol was discovered as a natural product secreted by the bacterium *Streptomyces venezuelae* found in soil and compost.[1] The antibiotic's efficacy was demonstrated with dramatic results in two typhus outbreaks in Bolivia and Malaysia in 1948.[2] In 1949, chloramphenicol was approved for use by the US Food and Drug Administration as the first broad-spectrum antibiotic. It was easily synthesized, inexpensive to produce, and could be administered orally, parenterally, or topically. Chloramphenicol's excellent tissue and fluid penetration coupled with its broad antimicrobial spectrum led to its rapid worldwide acceptance. In the 1950s, chloramphenicol was used extensively in the treatment of infectious conditions ranging from the common cold, acne, and bronchitis to severe infections such as bacterial meningitis.[3] In the 1960s, after several years of extensive use, chloramphenicol's popularity began to diminish when toxicity was linked to two distinct effects on the bone marrow: a) a predictable dose-dependent toxicity resulting in anemia that was reversible upon drug withdrawal, and b) an idiosyncratic reaction resulting in aplastic anemia that was unpredictable, irreversible, and frequently fatal, occurring with an incidence of 1 case in 24,000 to 40,000 courses of therapy.[4–9] Another form of chloramphenicol toxicity was the "gray syndrome" initially described in neonates.[10–14] This was a nonhematopoietic toxicity of chloramphenicol that, if left unrecognized and untreated, often resulted in cardiovascular collapse and death. This syndrome has also been recognized in infants[15] and adults,[16,17] generally following an accidental overdose. Apart from chloramphenicol's hematologic toxicity, less common adverse drug effects reported include metabolic acidosis,[18,19] encephalopathy,[20] neurotoxicity,[21,22] optic neuritis,[23–25] villous atrophy of small intestinal epithelium,[18] and cardiotoxicity.[26,27]

Chloramphenicol inhibits bacterial protein synthesis in susceptible organisms by binding reversibly to the 50S subunit of the 70S ribosome. This binding inhibits the mitochondrial enzyme peptidyl

transferase, which is necessary for peptide bond formation.[18] Chloramphenicol has broad-spectrum bacteriostatic activity against most Gram-negative, Gram-positive, aerobic, and anaerobic organisms including *Bacteroides* and *Fusobacterium* spp, as well as spirochetes, rickettsial, chlamydial, and mycoplasmal bacteria. The drug possesses marked bactericidal activity against common meningeal pathogens in children, for example, *Haemophilus influenzae, Streptococcus pneumoniae*, and *Neisseria meningitidis*.[28,29]

Chloramphenicol is an antibiotic that is rarely used in the United States due to its well-described toxicity profile and the wide availability of effective, alternate antibiotics. We describe the case of a 12-year-old boy who presented to our hospital with severe metabolic acidosis and bone marrow suppression after receiving a prolonged course of chloramphenicol for a brain abscess. Institutional Review Board approval was not indicated for this case report because it does not meet the Department of Health and Human Services definition of research.

CASE REPORT

A 12-year-old (weighing ~45.5 kg) African-American male presented to his local emergency department with a 5-day history of rhinorrhea, fever, headaches, left eye swelling, nausea, and vomiting. He also complained of left neck pain, difficulty swallowing, and bilateral lower extremity weakness. His medical history was significant for asthma and febrile seizures as a young child. He had known drug allergies, described as hives, to penicillin and ceftriaxone. His family history was significant for hypertension. His medications prior to admission consisted of albuterol, diphenhydramine, and acetaminophen.

Upon admission, a computed tomography (CT) scan revealed sinusitis and an intracerebral abscess. During the CT scan, the patient had a tonic-clonic seizure that was acutely managed with intravenous (IV) lorazepam and then with IV valproic acid for maintenance therapy. The patient underwent a bifrontal craniotomy to irrigate the frontal sinus and evacuation of a left frontal epidural abscess, subdural empyema, and intracerebral abscess. Cultures from the brain abscess and sinus drainage were positive for *Bacteroides* and *Fusobacterium* spp. Due to drug allergies, he began a 6- to 8-week course of IV metronidazole, 500 mg every 8 hours (33 mg/kg/day), and chloramphenicol, 1 gram every 6 hours (88 mg/kg/day). The patient stabilized and was subsequently discharged home on IV metronidazole, 500 mg every 8 hours, IV chloramphenicol, 1 gram every 6 hours, and divalproex extended release, 2 grams orally at bedtime.

Five weeks after the initial craniotomy (day 36 of chloramphenicol therapy), the patient presented with left periorbital edema, lethargy, and, on repeat CT scan, continued evidence of brain abscess. He was admitted to an outside hospital where a second craniotomy was performed for drainage of the abscess. Repeat cultures were sterile, and the patient's previous regimen of IV chloramphenicol, metronidazole, and oral divalproex was continued. Neither chloramphenicol nor valproic acid (VPA) serum concentrations were monitored. Over the next 2 weeks, the patient required multiple infusions of fresh frozen plasma secondary to coagulopathy. The patient also developed thrombocytopenia, acidosis, abdominal pain, diarrhea, and mental status changes. The cause of these problems was attributed to VPA, which was discontinued and replaced with oxcarbazepine 11 days prior to transfer. Upon parental request the patient was transferred to our institution after receiving approximately 50 days of IV chloramphenicol and metronidazole. On admission, the patient's vital signs were 98.4° F, heart rate of 150 beats per minute, respiratory rate of 20 breaths per minute, blood pressure of 109/76 mm Hg, and body weight of 45 kg. His admission laboratory values were notable for hyperammonemia, severe lactic acidosis, hyperkalemia, and thrombocytopenia (Table). Urine and blood culture results were negative. Test results were negative for *Clostridium difficile* toxin A and B, rotavirus-specific antigen, and enterovirus. The patient's serology results were negative for hepatitis A, B, and C antibody and for human immunodeficiency virus and Epstein-Barr virus antibodies. On physical examination, he was lethargic but able to follow commands with vigorous stimulation. Cardiopulmonary examination findings were normal. The abdomen had diffuse tenderness with distension in all quadrants. Abdominal radiographs showed nonspecific gaseous distension of bowel loops and a distended urinary bladder. His neurological examination was normal, other than extreme somnolence. Neuroradiological imaging showed a resolving abscess without any mass effect or acute changes. His medications on transfer were IV chloramphenicol, 1 gm every 6 hours, IV metronidazole, 500 mg every 8 hours, itraconazole, 200 mg orally every 12 hours, IV ranitidine, 50 mg every 8 hours, IV dexamethasone, 4 mg every 8 hours, and oxcarbazepine, 450 mg orally every 12 hours. All admission medications were continued except for itraconazole.

Based on the patient's history and diagnostic evaluation, a presumptive diagnosis of chloramphenicol toxicity was considered, based on the

Table. Patient's Laboratory Data During Hospitalization

Laboratory Test (normal range)	Laboratory Values on Admission	Laboratory Values on Hospital Day				
		1	2	3	5	13
WBC ([5–11] × 10^3 cells/mm^3)	5.71	2.25	1.95	1.25	5.30	7.34
Hgb (11–15 mg/dL)	11.7	9.1	7.9	7.2	8.9	7.8
Reticulocyte (0.5%–2.8%)	ND	0.14	ND	0.04	0.12	5.2
Platelets ([140–440] × 10^3/mm^3)	45	29	56	17	64	315
INR	1.88	1.56	1.44	1.33	1.04	ND
Prothrombin time (12.6–15.2 sec)	23	19.9	18.5	16.9	14.4	ND
ALT (10–45 IU/L)	96	150	258	542	641	101
Ammonia (7–35 μmol/L)	101	125	75	57	55	ND
Bilirubin, total (0.2–1.3 mg/dL)	1.5	2.1	1.8	2.2	1.4	0.6
Lactic acid (0.5–2.2 mmol/L)	21.6	32	8.1	2.9	2.5	ND
Potassium (3.5–5 meq/L)	6.3	5	3.7	3.8	5	4.0
Serum creatinine (0.7–1.3 mg/dL)	1.1	1	0.5	0.5	0.3	0.3
Chloramphenicol (10–20 mg/L)	61	35	3	<2.5	<2.5	ND
MHD-oxcarbazepine (15–35 mg/L)	22	ND	ND	ND	ND	ND

ALT, aspartate aminotransferase; Hgb, hemoglobin; INR, international normalized ratio; MHD, monohydroxy derivative; ND, not done; WBC, white blood cell count

findings of metabolic acidosis, bone marrow suppression, coagulopathy, and abdominal distention. Chloramphenicol was discontinued and replaced with meropenem approximately 24 hours after admission. A peak chloramphenicol serum concentration was obtained 1 hour after his last dose and then daily for 5 days (Table). Aggressive fluid resuscitation and sodium bicarbonate administration were initiated in response to the patient's profound lactic acidosis. Despite normal circulatory perfusion on physical examination, with good urine output and echocardiagraphic evidence of normal cardiac contractility, the lactic acidosis progressed to 32 mmol/L. With increasing acidosis and worsening mental status, two 4-hour cycles of hemodialysis followed by continuous venovenous hemodialysis (CVVHD) was initiated on hospital day two. After two days of CVVHD the lactic acidosis resolved (Table). The patient's mental status began to improve by day 3, at which point he complained of total vision loss. Neuroopthalmology consultation and magnetic resonance imaging (MRI) failed to demonstrate optic neuritis or cortical correlates with vision loss. At the time of discharge (13 days after admission), the patient could only differentiate light from dark and identify shapes at a close distance. The patient's neurological examination was also notable for a transient peripheral neuropathy, manifested by "pins and needles" sensation in both feet, which resolved during the hospital course. The bone marrow suppression evident on admission showed improvement and continued to improve by discharge and subsequent follow-up (Table). He was discharged home 13 days after admission to our institution.

DISCUSSION

In the United States, chloramphenicol is rarely used and generally not considered first-line therapy for any infection. In developing countries, it is widely used because of its low cost and oral, topical, and parenteral routes of administration and over-the-counter availability.[30–32] Due to its limited use in the United States, many clinicians are unfamiliar with its indications, spectrum of activity, and potential adverse effects. To our knowledge, the most recent report of chloramphenicol toxicity, published in 1992, described the cardiovascular

complications associated with elevated chloramphenicol serum concentrations in an infant.[27]

Our case report describes a patient who presented to our institution following two craniotomies for a persistent frontal lobe brain abscess complicated by long-term chloramphenicol administration. The patients' clinical course was consistent with the multiple adverse effects associated with prolonged chloramphenicol therapy. Laboratory findings highly suggestive of this diagnosis included prolonged and elevated chloramphenicol serum concentrations, anemia, thrombocytopenia, reticulocytopenia, and metabolic acidosis unresponsive to bicarbonate administration.[6,18,19] Rare manifestations of chloramphenicol toxicity that developed in this patient included neutropenia, visual changes, and peripheral neuropathy. Prior to being transferred to our institution, the patient had received 8 weeks of chloramphenicol therapy, at a dose of 90 mg/kg/day (75–100 mg/kg/day is recommended for meningitis), for a total dose exposure of 220 grams. His initial chloramphenicol serum concentration of 61 mg/L (desired average concentrations are 10–20 mg/L)[29,33–35] has been associated with the gray syndrome, consisting of cardiovascular collapse, respiratory distress, abdominal distension, metabolic acidosis, and coma. This syndrome has been reported to occur with chloramphenicol serum concentrations persistently >50 mg/L.[14–17,33,36] Our patient was possibly at the beginning stages of the gray syndrome, exhibiting severe metabolic acidosis, abdominal distension, and lethargy. Additionally, drug-drug interactions were considered as a possible explanation for the toxic chloramphenicol concentrations. No reported interactions in the literature were found between chloramphenicol and metronidazole, itraconazole, dexamethasone, and oxcarbazepine.

In the United States, chloramphenicol is available only as chloramphenicol succinate for intravenous administration. Chloramphenicol succinate is a prodrug, having no antibacterial activity, which must be hydrolyzed by the liver to chloramphenicol base. Chloramphenicol base is metabolized primarily in the liver through glucuronide conjugation (phase II reaction). Approximately 85% to 90% of chloramphenicol glucuronide conjugate is eliminated through the liver with 10% to 15% being renally eliminated as chloramphenicol base. There is a threefold variation in metabolism in children and even greater variability in the neonate, who has limited glucuronidation capability.[18,35] Appreciation of the developmental changes in hepatic maturation and renal function in the neonate explains the potential toxicity (i.e., gray syndrome) observed in this population when receiving excessive chloramphenicol dosing.[11,34,35,39] The initial pharmacokinetic studies describing the altered metabolism of chloramphenicol in the newborn[12] can be explained by the delayed maturation of glucuronidation pathways. The specific uridine 5′-diphospho-glucuronosyltransferase (UGT) isoform responsible for glucuronidation of chloramphenicol has now been identified as UGT 2B7.[40] The ontogeny of UGT 2B7 is understood largely from the number of studies of the ontogeny of morphine, a CYP 2B7 substrate in newborns, infants, and children.[41] Delayed development of chloramphenicol glucuronidation is consistent with the ontogeny of UGT 2B7 as implicated from these studies.[42] However, genetic variation in UGT 2B7 activity may account for the apparent dose-dependent toxicity of chloramphenicol reported in adults and may possibly be associated with the toxicity observed in our patient. These findings illustrate the importance of understanding the age-dependent developmental differences in drug metabolizing enzyme activity and how the pharmacokinetics can be markedly altered in newborns compared with adults.[39]

The pharmacokinetic parameter estimates of chloramphenicol show the expected variability with an apparent volume of distribution ranging from 0.6 to 1.4 L/kg and an elimination half-life of 4 to 8 hours in children and adults.[18,34] The desired serum concentrations of chloramphenicol are defined by the susceptibility of the organism and the dose-related toxicity. The minimal inhibitory concentration for the majority of organisms susceptible to chloramphenicol is from <4.0 to 12.5 mg/L. The risk of dose-related toxicity increases when peak chloramphenicol base serum concentrations persistently exceed 25 mg/L.[35] These criteria help establish the desired peak serum concentrations for chloramphenicol base between 15 to 25 mg/L (not to persistently exceed 25 mg/L) and trough concentrations of 5 to 10 mg/L. Due to this narrow "therapeutic" range and the variability in pharmacokinetic disposition, the ability to predict serum concentrations from a standard dose and dosing interval is limited. This requires frequent chloramphenicol serum concentration monitoring in all patients.[18,33–35] A peak chloramphenicol succinate and chloramphenicol base serum concentration should be obtained 60 to 90 minutes after a 30-minute infusion and a trough just prior to the next 6-hour dose during the first 24 to 36 hours of therapy and weekly or more often as necessary.[18,35] Both forms of chloramphenicol should be monitored, if possible, because the bioavailability of active chloramphenicol (i.e., the base) is patient dependent and is a function of metabolism and renal excretion (~30%) of chloramphenicol as the inactive succinate salt.[34]

The toxicity of chloramphenicol can be explained mostly by its effects on mitochondria. Chloramphenicol dose-related bone marrow suppression is observed in virtually all patients who receive the drug. This expected effect of chloramphenicol is due to its ability to reversibly inhibit mitochondrial protein synthesis and ferrochelatase found on the inner membrane of mitochondria.[25,27,30,43] The hematologic effects occur in sequence. Initially, increased serum iron concentrations and vacuolation of the marrow erythroblasts occur. Then reticulocytopenia occurs between days 3 and 5. A decrease in hemoglobin is seen between days 5 and 10. Finally, thrombocytopenia appears after 10 to 14 days of treatment. Neutropenia is rare but may occur after 10 to 21 days of therapy. More pronounced effects are seen with higher doses and in patients who have hepatic impairment. A complete blood count, reticulocyte count, and platelet count should be obtained at the start of treatment and then every 3 to 4 days during treatment. Hematologic effects may be minimized by maintaining peak chloramphenicol base concentrations between 15 and 25 mg/L. Recovery from dose-related bone marrow suppression takes approximately 7 to 10 days after therapy has been discontinued.[6–9] On admission, our patient had reticulocytopenia, anemia, thrombocytopenia, and leukopenia (Table). By day 13, cell line recovery was evident except that anemia was still present.

The first report of gray syndrome was described in 1959 after high-dose chloramphenicol use in three newborn infants.[10] In the same year, results of chemoprophylaxis in premature infants showed that 19 (63%) of 30 babies died who received intramuscular doses of 100 to 165 mg/kg/day of chloramphenicol compared to 6 (18%) of 32 babies who received no antibiotic. Typically, the patient is an infant who has received $\geq$100 mg/kg/day of chloramphenicol for 3 to 5 days and then develops symptoms that progressively worsen until death. The syndrome begins with abdominal distention with or without emesis, followed by progressive pallid cyanosis and then vasomotor collapse frequently accompanied by irregular respirations, coma, and death.[11] The gray syndrome is generally associated with chloramphenicol concentrations $>$50 mg/L and can occur at any age if drug excretion is impaired or if excessive doses are administered.[14–17,33,36] The syndrome is presumably caused by the inhibition of mitochondrial electron transport in liver and myocardial and skeletal muscle.[18,29,34]

Metabolic acidosis is an early sign of chloramphenicol toxicity and is often refractory to sodium bicarbonate administration. The mechanism involves the inhibition of mitochondrial NADH oxidase and cytochrome enzymes, which favor anaerobic metabolism and lactic acid accumulation, as seen in our patient.[18,19] If chloramphenicol is required for management in any patient with unexplained metabolic acidosis or impaired liver function, serum concentrations should monitored closely and dosage adjusted accordingly.

Chloramphenicol neurotoxicity is a rare adverse effect generally associated with prolonged use. Optic neuritis is the most common neurotoxicity and can often be accompanied by peripheral neuropathy.[22–25] Peripheral neuropathy is characterized by symptoms of burning, tingling, or numbness of the extremities. The onset of visual symptoms is generally acute and occurs during therapy. Initial symptoms are blurred vision followed by a decrease in visual acuity, visual field defects, impaired color (red-green) discrimination, and fundus changes. Central or pericentral scotomata are demonstrated consistently in all patients. Of the 54 patients reported in the English-language literature, the mean duration of chloramphenicol therapy at the time of neurologic findings was 229 days (range, 10–1513 days), with a mean total exposure dose of 255 grams (range, 10–1600 grams).[21] Our patient received 56 days of chloramphenicol and a total exposure dose of 220 grams. The mechanism(s) of neurotoxicity is unknown. Direct neurotoxicity, hypersensitivity, and vitamin B deficiency have been speculated. Treatment involves discontinuing chloramphenicol and the consideration of large doses of vitamin B_{12} and B_6.[21–24] Most patients will have subjective improvement in visual acuity within 2 weeks. Complete recovery ranges from a few days to months with a few patients having minimal to no improvement in vision.[20–24] Our patient received hydroxocobalamin, 1 mg intramuscularly daily for 5 days, and intravenous pyridoxine, 100 mg daily, beginning on day 4 of admission. At discharge, a daily B-complex vitamin was started. Unfortunately, at his 3-month outpatient neurology visit, this therapy was not successful in improving his vision, requiring him to enter a school for the deaf and blind.

In patients with chloramphenicol toxicity and adequate liver function, intensive supportive care is necessary to allow time for the patient to eliminate chloramphenicol metabolically. In patients with impaired liver function, charcoal-hemoperfusion has been reported as an effective method of removal.[44]

Chloramphenicol should only be used in life-threatening infections when no other suitable, safer antibiotic is available. Initial dosage should be based on the patients' age and body weight. In patients who are severely ill in association with liver dysfunction, the dose should be reduced. Chloram-

phenicol base serum concentrations should be closely monitored and adjusted to maintain peak serum concentrations between 15 and 25 mg/L and trough concentrations between 5 to 10 mg/L. Hematologic monitoring should occur before therapy and every 3 to 5 days during therapy. Chloramphenicol should be discontinued, if possible, in the case of neutropenia, unresponsive metabolic acidosis, and evidence of neurotoxicity.

Despite its availability and use for over a half a century, chloramphenicol remains an effective antibiotic when used appropriately. The continued increase in antimicrobial resistance to currently available antibiotics may necessitate the increased use of chloramphenicol in the future.

DISCLOSURE The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ABBREVIATIONS CT, computed tomography; CVVHD, continuous veno-venous hemodialysis; MRI, magnetic resonance imaging; VPA, valproic acid

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