Cardio-respiratory complications in patients receiving Chloramphenicol in Rwanda: A case series

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BACKGROUND:

In low-resource settings, antibiotic policy is complicated by the constraints of multiple drug resistance and by lack of affordability for patents [1]. Chloramphenicol remains widely used in these settings as an effective treatment for a range of serious infections [2], [3]. Important serious adverse effects of chloramphenicol include bone marrow suppression and 'grey baby' syndrome [4]. We report here three cases in which chloramphenicol treatment was associated with severe acute systemic cardio-respiratory complications within the space of 6 months of each other.

Key words (MeSH): Chloramphenicol; Anti-bacterial agents; Drug-Related Side Effects and Adverse Reactions; Developing Countries.

CASE REPORTS

Case 1

A 27-year-old male was admitted to hospital for hemodialysis for end-stage renal failure following failure of a kidney transplant. His treatment prior to admission was immunosuppression with tacrolimus 4 mg twice a day, mycophenolate mofetil (MMF) 750 mg twice a day and prednisolone 5 mg once a day; and treatment for hypertension with long-acting nifedipine 40 mg twice a day and furosemide 40 mg once a day. These medicines were continued during his admission.

Two weeks after his admission he developed fever. A chest radiograph was most consistent with a large abscess in the middle zone of the right lung field. Gram stain of sputum revealed no organisms and culture showed no growth. Glomerulo-filtration rate (GFR) was 9 ml/min/m2 on admission, serum creatinine 916 umol/L and urea 18.7 mmol/L. He received intravenous (IV) antibiotic treatment for 14 days with IV cefotaxime 1g twice a day, IV metronidazole 500 mg three times a day and oral cloxacillin 1g three times a day. He received chest physiotherapy but there was no improvement clinically or radiologically. His antibiotic treatment was therefore changed to IV chloramphenicol 500 mg three times a day. At the time of chloramphenicol administration, his GFR was 13 ml/min/m2, serum creatinine 651 umol/L and urea 20.4 mmol/L.

Within ten minutes of the start of the first IV infusion of chloramphenicol 500 gm, he developed whole body profuse sweating, excessive diaphoresis, shivering, hypotension, tachypnea, and oxygen desaturation. The chloramphenicol infusion was stopped immediately and the above features resolved over the following 45 minutes.

Chloramphenicol treatment was continued for a total of five doses as it was initially considered that these symptoms may be due to underlying sepsis. However, following further administrations of the chloramphenicol, similar features occurred, the patient noting on each occasion feeling malaise after the start of each chloramphenicol infusion, in the minutes prior to the above signs and other clinical abnormalities. After 2 days of chloramphenicol treatment, the features were considered drug-related. Chloramphenicol was stopped and treatment started with imipenem 500mg twice a day with no recurrence of the above episodes. The patient died two weeks later in the Intensive Care Unit from severe sepsis with an unidentified microbial cause.

Case 2:

A 59-year-old male with a history of hypertension was admitted to the Intensive Care Unit with GCS 12-13/15. A CT-scan examination of his brain revealed intraventricular and intracerebral hemorrhage.

During the admission, he developed symptoms consistent with meningoencephalitis in association with a urinary tract infection. The urine grew Enterobacter sensitive to chloramphenicol, which was subsequently prescribed IV at 1g three times daily. Immediately after the start of the first infusion, he developed spasms, profuse sweating, shivering, tachycardia and tachypnea. The chloramphenicol infusion was stopped immediately and the above features resolved over the following 2 hours. It was not clear whether this was drug related. Following each of the two further administrations of chloramphenicol, similar features occurred and so the chloramphenicol was discontinued, with no recurrence of the above symptoms. The patient remained in a coma and died a week later.

Case 3:

A 19-year-old female was admitted to hospital with a 3-day history of headaches and fever, having been unwell for the previous two weeks. On examination she had meningism. Falciparum malaria was confirmed on blood smears. In view of the cerebral features, she was treated both for malaria with quinine and for meningitis with IV chloramphenicol. Chloramphenicol 1g was given first by slow infusion in normal saline, and was immediately followed by malaise and pain in the arm proximal to the site of her intravenous access cannula. She also developed a localized erythematous plaque around the cannula site. One hour after the start of the infusion, she developed rapid palpitations and diffuse abdominal pain.

The chloramphenicol infusion was then stopped. Her symptoms resolved over the next 45 minutes.

She was also prescribed quinine by IV infusion, with a loading dose of 1200 mg in dextrose 5% over 4 hours. The quinine infusion, started in the opposite arm 1 hour after starting chloramphenicol, was continued without associated adverse effects either during the loading dose or maintenance dose infusions (600mg 3 times daily as IV infusion). She made a full recovery without further symptoms and was discharged home after 3 days.

All patients described above had different diseases in the hospital but all had comparable and dramatic symptoms immediately or less than 45 minutes after infusion of chloramphenicol which subsided in less than an hour after stopping the infusion.

In such cases the question arises as to whether this is the consequence of the primary agent (chloramphenicol), a consequence of the effect of the agent on, for example the microorganism or issues surrounding the manufacturing including the possibility of contamination. The clinical presentations of these patients were suspected to be related to chloramphenicol as chemical side effects or contaminated samples or coincidence of the clinical pattern of the diseases.

The absence of clinical presentation prior to chloramphenicol, rapid onset and rapid resolution after stopping chloramphenicol were factors to support adverse drug reaction of chloramphenicol. Chloramphenicol therapy has been associated with Jarisch–Herxheimer (JHR) reactions (sudden fever, rigors, and persistent hypotension) [5]. J-H reactions are typically delayed in onset [6], early symptoms were described as being after two hours or more. The outcome is different but most recover the clinical presentation in 24 hours. However, in our patients the recovery of clinical presentation was in less than 45 minutes.

Vaughan at.al [7] reported three cases where symptoms started within four hours of initiation of antibiotics with different outcomes. A systematic review [6] suggests that symptoms of JHR start the earliest two hours after the drug is administered and these appeared with different antibiotics. The symptoms include fever, rigors, severe headache, tachycardia, tachypnea, hypertension, severe rigors, pulmonary deterioration, chills, hypotension, nuchal rigidity, photophobia, respiratory distress, abdominal pain, profuse vomiting, sharp rise in temperature, oligoanuric and weakness. Our patients had many of these symptoms but the early presentation and quick resolution after stopping the infusion are not consistent with these descriptions.

The pathogenesis of the reactions in our patients includes the drug itself or a manufacturing issue. To detect the faulty drug requires bringing the sample out of the country for analysis which is not feasible in our setting, part of this may influence limited adverse drug reaction reported by Lense at. al [8] due to lack of awareness and knowledge on what, when, and to whom to report ADRs. ADR reporting is not in health professionals' routine and this should be improved through awareness of their existence. The reaction is typically a brisk "all-or-nothing" event that follows the first dose of an anti-bacterial agent in a variety of infectious diseases. The severity and frequency of the reaction depends, however, on the nature of the underlying infectious process. It is particularly marked in those with underlying syphilis or louse-borne relapsing fever, a disease in which this reaction has been particularly well studied. The Jarisch-Herxheimer reaction is characterized by a number of pathophysiological events: by alteration in body temperature, typically an initial rise of 1-2°C sometimes followed by a subsequent fall in temperature. There is associated hyperventilation and vasoconstriction, often followed by a period of intense vasodilatation leading to hypotension [3].

Chloramphenicol is known to be associated with bone marrow toxicity, especially aplastic anemia and bone marrow suppression. The pathogenesis of aplastic anemia remains uncertain but the most common, dose-dependent, reversible bone marrow suppression is known as a consequence of mitochondrial injury [9]. Chloramphenicol binds to the 50S ribosomal subunit and inhibits the peptidyl transferase step in protein synthesis [10]. It works as a broad spectrum antibiotic against a variety of pathogens including Spirochaetes, Rickettsiae, Chlamydiae, Mycoplasmas, Tryponemapallidum, Borrelia, Leptospira, Pseudomonas pseudomallei and Actinomyces [11].

Alone or in combination with ampicillin, chloramphenicol has the same effect in community acquired acute bacterial meningitis in comparison to third generation cephalosporins (ceftriaxone or cefotaxime) [12]. Bacteria resistant to chloramphenicol either harbor plasmids bearing the structural gene for the enzyme, chloramphenicol acetyltransferase (CAT) like E. coli and other Gram-negative bacteria or synthesize CAT only in the presence of chloramphenicol and related compounds (eg. Gram-positive bacteria such as staphylococci and streptococci) [13], [14].

This initial evaluation of chloramphenicol safety was conducted to raise awareness of pharmacovigilance to clinicians and other health providers.

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REFERENCES:

[1] I. C. Gyssens, "Antibiotic policy by," no. 1997, pp. 2–4, 2017.

[2] M. Fukuda, H. Ohashi, C. Matsumoto, S. Mishima, and Y. Shimomura, "Methicillin-resistant Staphylococcus aureus and methicillin-resistant coagulase-negative Staphylococcus ocular surface infection efficacy of chloramphenicol eye drops.," Cornea, vol. 21, no. 7 Suppl, pp. S86-9, 2002.

[3] T. Butler et al., "Treatment of typhoid fever with azithromycin versus chloramphenicol in a randomized multicentre trial in India," J. Antimicrob. Chemother., vol. 44, no. 2, pp. 243–250, 1999.

[4] R. H. Mulhall, J de Louvois, "Chloramphenicol toxicity in neonates : its incidence and prevention . Sign up today - FREE," Br. Med. J. (Clinical Res. ed.) Vol., no. 1980, pp. 2–3, 2017.

[5] D. Fekade et al., "Prevention of Jarisch–Herxheimer Reactions by Treatment with Antibodies against Tumor Necrosis Factor α," N. Engl. J. Med., 1996.

[6] G. Guerrier and E. D'Ortenzio, "The Jarisch-Herxheimer Reaction in Leptospirosis: A Systematic Review," PLoS ONE. 2013.

[7] C. Vaughan, C. C. Cronin, and E. K. Walsh, "Jarisch -Herxheimer reaction," pp. 118–121, 1994.

[8] L. T. Gurmesa and M. G. Dedefo, "Factors affecting adverse drug reaction reporting of healthcare professionals and their knowledge, attitude, and practice towards ADR reporting in Nekemte Town, West Ethiopia," Biomed Res. Int., 2016.

[9] A. A. Yunis, "Chloramphenicol toxicity: 25 years of research.," Am. J. Med., 1989.

[10] B. Weisblum and J. Davies, "Antibiotic inhibitors of the bacterial ribosome.," Bacteriol. Rev., 1968.

[11] P. Shukla, F. W. Bansode, and R. K. Singh, "Chloramphenicol Toxicity : A Review," J. Med. Med. Sci., 2011.

[12] K. Prasad, A. Kumar, T. Singhal, and P. K. Gupta, "Third generation cephalosporins versus conventional antibiotics for treating acute bacterial meningitis," Cochrane Database of Systematic Reviews. 2007.

[13] P. Trieu-Cuot, G. De Cespedes, F. Bentorcha, F. Delbos, E. Gaspar, and T. Horaud, "Study of heterogeneity of chloramphenicol acetyltransferase (CAT) genes in streptococci and enterococci by polymerase chain reaction: Characterization of a new CAT determinant," Antimicrob. Agents Chemother., 1993.

[14] W. V. Shaw, "Chloramphenicol Acetyltransferase: Enzymology and Molecular Biology," Crit. Rev. Biochem., 1983.