Chloramphenicol: What We Have Learned in the Last Decade

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ABSTRACT: Chloramphenicol is a unique antibiotic. The kinetics and efficacy of the oral and intravenous preparations are comparable. Chloramphenicol is usually bacteriostatic but is bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis, and chloramphenicol's clinical efficacy against these meningeal pathogens is well established. Chloramphenicol can be used to treat serious pediatric infections when Haemophilus influenzae is a likely pathogen, as well as typhoid fever, anaerobic infections, bacterial meningitis in patients allergic to penicillin, brain abscesses, and rickettsial infections. The use of chloramphenicol is limited because of its toxicity. Aplastic anemia is very rare but can occur after either oral or intravenous administration. The gray syndrome can be eliminated and marrow suppression minimized by using chloramphenicol at the recommended doses and monitoring levels. During the last decade the increased use of chloramphenicol has not resulted in increased resistance or in frequent reports of toxicity. Thus, chloramphenicol remains an important inpatient antibiotic that can be invaluable for treating certain life-threatening infections.

During the last decade chloramphenicol has enjoyed a resurgence of use and new data have been generated. Chloramphenicol became available in 1949 and for the next ten years was a popular outpatient and inpatient antibiotic. By 1960, after chloramphenicol's three important toxicities—dose-related bone marrow suppression,1 aplastic anemia,2 and the gray syndrome3—had been defined, its use declined. In the 1970s the use of chloramphenicol increased because ampicillin-resistant Haemophilus influenzae and Bacteroides fragilis were susceptible to chloramphenicol and now in the 1980s chloramphenicol is being replaced by new cephalosporins and less toxic antibiotics for anaerobes. The purpose of this report is to discuss what has been learned about chloramphenicol during the last decade of clinical use.

SPECTRUM

Although resistance has developed in countries where chloramphenicol has been used indiscriminantly,4 bacterial susceptibilities to chloramphenicol in the United States have changed very little over the past decade. Lorian5 reviewed the 1973 to 1977 susceptibilities of bacteria isolated from hospitalized patients in the United States and found no increases in chloramphenicol resistance. Most nonenterococcal streptococci, Neisseria, Haemophilus influenzae, and anaerobes are susceptible to chloramphenicol. Treponema pallidum, Borrelia, Leptospira, Actinomycetes, Pseudomonas pseudomallei, Legionella, Rickettsia, Chlamydia, and Mycoplasma are also susceptible to chloramphenicol. It must be noted that in vitro susceptibility does not always correlate with in vivo efficacy (eg, clinical efficacy of chloramphenicol has not been studied against Legionella and Mycoplasma). Also, staphylococci are usually susceptible to chloramphenicol, but clinical studies are lacking. Pseudomonas aeruginosa, Acinetobacter, mycobacteria, fungi, and parasites are usually resistant to chloramphenicol. A Centers for Disease Control (CDC) study6 showed that of 5,474 Haemophilus influenzae cerebrospinal fluid and blood isolates done from 1977 to 1981, 21.2% were resistant to ampicillin, while no isolate was resistant to chloramphenicol. It is important to point out that Haemophilus influenzae organisms resistant to chloramphenicol have been reported,7 and thus susceptibilities must always be determined. Moreover, meningitis due to H influenzae resistant to both chloramphenicol and ampicillin...
has been reported. In the United States Salmonella and Shigella are usually susceptible to chloramphenicol. Infrequently, during therapy, Salmonella can develop R-factor-mediated chloramphenicol resistance.

Standard susceptibility determinations are usually done by inhibitory tests. To determine whether an antibiotic is bactericidal, specific cidal testing (eg, minimal bactericidal concentration [MBC]) must be requested. In the last decade studies have emphasized that chloramphenicol can be either bacteriostatic or bactericidal. Chloramphenicol is usually bactericidal against Haemophilus influenzae, Streptococcus pneumoniae, and Neisseria meningitidis, and bacteriostatic against staphylococci, Enterobacteriaceae, and anaerobes.

ANTAGONISM/SYNERGISM

There are conflicting reports regarding antagonism and synergism between chloramphenicol and other antibiotics. In vitro synergism, antagonism, and indifference have been demonstrated between chloramphenicol and ampicillin for Haemophilus influenzae. In vitro antagonism has been demonstrated between chloramphenicol and penicillin or ampicillin for Streptococcus pneumoniae, Neisseria meningitidis, or group B streptococci. Also, antagonism has been shown between chloramphenicol and gentamicin. In a study of 21 enteric organisms, chloramphenicol and ampicillin were usually synergistic when chloramphenicol was bactericidal, and antagonistic when chloramphenicol was bacteriostatic. The clinical significance of the antagonism or synergism between chloramphenicol and penicillins or aminoglycosides is unknown.

PHARMACOKINETICS

During the last decade, the pharmacokinetics of chloramphenicol have been reexamined using precise assays. The chloramphenicol package insert and the 1985 Physicians' Desk Reference state in bold print:

As soon as feasible, an oral dosage form of chloramphenicol should be substituted for the intravenous form because adequate blood levels are achieved with chloramphenicol by mouth.

Oral forms are completely absorbed and give levels comparable to those of intravenous chloramphenicol succinate. The oral forms include chloramphenicol palmitate, a tasteless ester available as a suspension, and chloramphenicol base, available in capsules. Chloramphenicol palmitate, which has no antimicrobial activity, is hydrolyzed in the duodenum to active chloramphenicol and is then completely absorbed.

Chloramphenicol succinate, a soluble ester without antimicrobial activity, is hydrolyzed in the liver, lungs, and kidneys after intravenous administration. In infants and children, 6% to 80% of the drug is not hydrolyzed and is excreted unchanged in the urine. Chloramphenicol succinate should not be given by the intramuscular route. This recommendation is based on clinical relapse of typhoid fever in four of four patients treated with intramuscular chloramphenicol succinate, versus relapse in one of four patients treated with oral chloramphenicol. In a 1985 study, Shann et al demonstrated reliable absorption of intramuscular chloramphenicol succinate, but clinical studies are needed before the intramuscular route can be recommended.

The therapeutic range for chloramphenicol serum levels is 10 to 20 μg/ml. The half-life of chloramphenicol can vary from patient to patient and can vary with time in a single patient. The half-life of chloramphenicol is usually prolonged in premature and term neonates, in patients with liver disease, in patients with portal hypertension, and, in my experience, in patients with septic shock.

Chloramphenicol has excellent tissue penetration and excellent penetration into body fluids, including synovial fluid, pleural fluid, ascites fluid, aqueous humor, sputum, breast milk, and cerebrospinal fluid with either inflamed or uninflamed meninges. About 5% to 10% of active chloramphenicol is excreted unchanged in the urine resulting in urine levels of 150 to 200 μg/ml; in renal failure, however, urine levels are greatly decreased.

Simultaneous administration of chloramphenicol and phenobarbital can decrease the half-life of chloramphenicol. Simultaneous administration of chloramphenicol and phenytoin can increase or decrease the half-life of chloramphenicol and can also increase the half-life of phenytoin. Thus, use of chloramphenicol with phenobarbital or phenytoin or both necessitates monitoring the levels of these drugs.

The current dosage recommendations for chloramphenicol are 25 mg/kg/day for premature infants and neonates less than 2 weeks of age, 50 mg/kg/day for neonates 2 to 4 weeks of age, 50 to 100 mg/kg/day for older infants and children, and 50 mg/kg/day for adults given in four divided doses. In infants and children, I initiate therapy with 50 to 75 mg/kg/day because 100 mg/kg/day frequently results in high levels. Ideally, chloramphenicol peak (one hour after infusion) and trough (just before next dose) levels should be obtained 24 to 48 hours after starting therapy, then repeated every three to five days. It is important that chloramphenicol levels are monitored more closely.
in premature infants and neonates, in patients with liver disease, and in patients receiving phenobarbital or phenytoin. Ideally, in these patients, levels should be measured 18 to 24 hours after starting therapy, then repeated every two to three days. Dosage should be adjusted to keep levels between 10 and 20 μg/ml.

TOXICITY

Chloramphenicol has three well established toxicities—aplastic anemia,2 the gray syndrome,3 and bone marrow suppression.1 Although in the last decade the gray syndrome and bone marrow suppression have been better defined, the risk factors for aplastic anemia remain controversial.

The incidence of fatal aplastic anemia associated with oral chloramphenicol has been estimated to be one case for every 24,500 to 40,800 courses.25 There are more than 700 case reports of aplastic anemia following oral chloramphenicol. The incidence of aplastic anemia after intravenous chloramphenicol is not known;6 however, there are now ten case reports of aplastic anemia associated with intravenous chloramphenicol.6,26-29

The association of aplastic anemia with oral chloramphenicol may be misleading because chloramphenicol toxicity studies were done at a time when most patients received oral chloramphenicol. Two recent hospital audits of chloramphenicol revealed that 97% of chloramphenicol-treated patients received only intravenous therapy.30 According to incidence figures for meningitis31 and the pediatric use of chloramphenicol for other infections, approximately 500,000 pediatric patients have received initial therapy with intravenous chloramphenicol during the last decade. Yet the only case60 of aplastic anemia reported in the pediatric age group is that of a 17-year-old patient whose bone marrow aplasia may have not been from the chloramphenicol.32 The low number of case reports associating intravenous chloramphenicol with aplastic anemia has led us6 and others33 to speculate that intravenous chloramphenicol causes less aplastic anemia than oral chloramphenicol, but this speculation is not supported by all experts.34 It is doubtful that this controversy will be resolved because a prospective study comparing the use of oral and intravenous chloramphenicol would require many thousands of patients. If a patient has an intravenous line for fluids or other medication, I use intravenous chloramphenicol; if a patient does not need an intravenous line, I use oral chloramphenicol. The inherent morbidity and mortality of an intravenous line negates the potentially decreased toxicity of intravenous chloramphenicol.

There are four case reports of aplastic anemia after ocular chloramphenicol preparations.6,35 After passing through the nasolacrimal ducts, ocular chloramphenicol can be absorbed in the gastrointestinal tract. Ocular chloramphenicol should be used only for infections caused by organisms resistant to all other ocular antibiotics.

The gray syndrome, which is characterized by abdominal distention, pallid cyanosis, and circulatory collapse, was first reported in neonates who received more than 100 mg/kg/day of chloramphenicol for at least two days.3 As a result, the dosage recommendations for chloramphenicol were reduced, and now the gray syndrome occurs most frequently with accidental overdosage of chloramphenicol.6 With the present dosage recommendations the gray syndrome has not been reported in patients with normal liver function. Mulhall et al36 reported the gray syndrome in neonates given as little as 9 mg/kg/day over the recommended 25 mg/kg/day. The pathogenesis of the gray syndrome may be related to high concentrations of chloramphenicol interfering with tissue respiration by inhibiting mitochondrial electron transport.37 Decreased myocardial contractility has been shown by echocardiography in patients with the gray syndrome.38 Charcoal-column hemoperfusion appears to be the best therapy to reduce the high chloramphenicol levels39; otherwise, treatment of the gray syndrome is supportive.

Chloramphenicol-associated bone marrow suppression is dose-related and reversible. The common sequence of suppression is (1) delayed plasma iron clearance (early), (2) rise in serum iron level (early), (3) reticulocytopenia (three to five days), (4) increased marrow myeloid/erythroid ratio and vacuolization of marrow precursors (three to seven days), (5) hemoglobin decrease (five to ten days), and (6) thrombocytopenia (ten to 14 days). Neutropenia, which is rare, can also occur and is an indication for stopping therapy.32 Unfortunately, bone marrow suppression does not always follow this sequence. In a recent study40 comparing chloramphenicol plus gentamicin, clindamycin plus gentamicin, and ticarcillin plus gentamicin for abdominal or pelvic sepsis, similar rates of anemia and leukopenia were found among the three groups. In the chloramphenicol group reticulocytopenia (14% vs 2% in the other groups) and thrombocytopenia (9.5% vs 2.0% in the other groups) occurred more frequently. Complete blood counts and platelet estimates should be obtained twice weekly. If the absolute neutrophil count falls below 500/cu mm or the platelet count falls below 50,000/cu mm, an alternate antibiotic should be chosen.
Chloramphenicol has been shown to decrease the anamnestic response to tetanus toxoid, to inhibit neutrophil function, and to suppress in vitro cell-mediated immunity. The clinical significance of these observations is unknown. Chloramphenicol’s effectiveness in the treatment of chronic neutropenia may be related to its immunosuppressant activity.

Chloramphenicol has other toxicities, which include hemolytic anemia in patients with the Mediterranean variant of glucose-6-phosphate dehydrogenase deficiency and optic neuritis can occur with chronic use. Oral chloramphenicol can cause nausea, stomatitis, and diarrhea. Chloramphenicol has been implicated as a cause of a hepatitis-pancytopenia syndrome and pseudomembranous colitis, but these reports need to be confirmed.

**USE**

A 1973 Tennessee study of more than 350,000 Medicare patients showed that of the 992 patients who received oral chloramphenicol during the year of the study, the drug was indicated in only one.44 In a 1976 follow-up study the authors reported a fourfold decrease in the use of chloramphenicol for outpatients.45 In a 1981 Albany College study (verbal communication, November 1983) 14,219 outpatient drug prescriptions were randomly surveyed, and only one prescription was for chloramphenicol.

Inpatient use of chloramphenicol was studied at the Medical Center of Vermont where 1.6% and 1.2% of inpatients, respectively, received chloramphenicol. Inpatient indications for chloramphenicol can include serious *Haemophilus influenzae* infections, meningitis, brain abscess, anaerobic infections, rickettsial diseases, and typhoid. During the last decade, chloramphenicol therapy for meningitis, for abdominal and pelvic sepsis, and for typhoid has been reevaluated.

The treatment of bacterial meningitis requires bactericidal antibiotics. Chloramphenicol failures can occur when chloramphenicol is bacteriostatic against the meningeval pathogen. Also, in a study of gram-negative bacilli meningitis in 19 patients treated with chloramphenicol, six patients developed resistant organisms during therapy. Chloramphenicol is bactericidal against *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, and its efficacy against these pathogens is well established. Chloramphenicol can be used in penicillin-allergic adults with suspected pneumococcal or meningococcal meningitis and can be used to treat meningitis caused by relatively penicillin-resistant pneumococci (MIC 0.12 to 1.0 μg/ml). Cefuroxime, a second generation cephalosporin, and ceftriaxone and moxalactam, third generation cephalosporins, all achieve higher *Haemophilus influenzae* bactericidal titers in the cerebrospinal fluid than chloramphenicol or ampicillin; however, in prospective studies of meningitis, clinical efficacy and time required to sterilize the cerebrospinal fluid was not different in patients treated with a cephalosporin or conventional therapy (chloramphenicol plus ampicillin initially, then continuing only one antibiotic when susceptibilities are available). In many institutions cephalosporins have replaced chloramphenicol for initial meningitis therapy because the new cephalosporins have less toxicity and levels do not have to be monitored.

The antibiotics of choice for the treatment of brain abscesses usually include a penicillin plus chloramphenicol or metronidazole. Chloramphenicol can be used because of its central nervous system penetration and its anaerobic spectrum, and because it has been effective even without surgery. Chloramphenicol, however, is only bacteriostatic against anaerobes and can be inactivated in abscesses. Some physicians prefer metronidazole over chloramphenicol because the former is bactericidal against anaerobes and when combined with penicillin has resulted in a mortality of less than 10%. Unfortunately, no prospective studies have compared different antibiotics in the treatment of brain abscesses.

For suspected abdominal or pelvic sepsis, antibiotic therapy should be directed against gram-positive cocci including enterococci, gram-negative enterics, and anaerobes including *Bacteroides fragilis*. Prospective controlled studies have shown several protocols to be effective for abdominal or pelvic sepsis: a penicillin, an aminoglycoside, and chloramphenicol; a penicillin, an aminoglycoside, and clindamycin; clindamycin, and an aminoglycoside; metronidazole and an aminoglycoside; cefotaxime and an aminoglycoside; and cefoperazone and cefotaxime. Of the protocols for treatment of abdominal or pelvic sepsis, the combination of ampicillin, clindamycin, and an aminoglycoside has the in vitro advantage of the best spectrum, and thus is the commonly recommended protocol though clinical data demonstrating superiority of this combination are lacking.

Pillay et al reported no difference in efficacy between oral chloramphenicol and oral amoxicillin in the treatment of typhoid fever. In another typhoid study, Snyder et al reported a fever
duration of 122 hours in patients treated with oral chloramphenicol, 150 hours with intramuscular ampicillin, and 166 hours with oral trimethoprim-sulphamethoxazole. Outcome was not different among the three treatment groups. Butler et al. compared intravenous trimethoprim-sulphamethoxazole to intravenous chloramphenicol for the treatment of typhoid fever and found no difference in clinical efficacy. Chloramphenicol as well as ampicillin, amoxicillin, and trimethoprim-sulphamethoxazole are all effective for typhoid fever. Salmonella typhi can be resistant to any of these antibiotics, and susceptibilities must always be determined.

Chloramphenicol or tetracycline is effective therapy for rickettsial infections. In children less than 9 years old and in pregnant women, for whom tetracycline is contraindicated, chloramphenicol should be used.

CONCLUSION

In the 1970s there was a renaissance in the use of chloramphenicol. During this last decade the clinical efficacy of chloramphenicol has been re-established and chloramphenicol’s pharmacokinetics have been better defined. With proper dosing and careful monitoring of serum levels, serious toxicity is infrequent; however, with improper dosing or with failure to follow levels, serious toxicity can result. Now with the availability of less toxic alternatives, the indications for chloramphenicol have again narrowed. Remembering chloramphenicol’s unique spectrum, pharmacokinetics, and clinical efficacy, it is possible that there will be a second chloramphenicol renaissance in the future.

References

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