Chloramphenicol*

Class: Chloramphenicol

Overview

Chloramphenicol is a broad spectrum, effective and well-tolerated antibiotic - a simple neutral nitrobenzene derivative. However due to its propensity to cause blood dyscrasias in humans, the drug has been banned from use in food animals and is used with caution in companion animals. Chloramphenicol inhibits microbial protein synthesis by binding to the 50 S subunit of the 70 S ribosome and inhibiting the action of peptidyl transferase, thus preventing peptide bond formation. This mechanism also prevents the binding of aminoacyl transfer RNA to the peptidyl transferase active site. The drug is primarily bacteriostatic but can be bactericidal in high concentrations against some bacteria. Chloramphenicol can be used orally as a neutral tasting palmitate and parenterally as a water soluble sodium succinate. The drug is lipid soluble, heat stable and ninety percent of the chemical is excreted in the urine. In addition to hematological disturbances, the drug also can cause gastrointestinal and neurological effects and Gray syndrome, a life-threatening condition of newborns.

About half of plasma chloramphenicol is bound to albumin. The free portion, however, diffuses well into all tissues, including the central nervous system. The highest concentrations are found in the kidney, liver and bile. Significant levels are also found in body fluids such as cerebrospinal fluid and aqueous humor. Chloramphenicol does not reach effective concentrations in unaffected joints; however the drug does reach therapeutic levels in the presence of septic arthritis. Chloramphenicol never reaches effective levels in the prostate, even in the presence of significant infection or abscessation.

Chloramphenicol is metabolized in the liver and is biotransformed primarily by glucuronide conjugation. In cats, a genetic deficiency in glucuronyl transferase activity may lead to considerably extended plasma half lives, therefore dosage should be adjusted accordingly. The very young (less than four weeks of age) of many species lack microsomal enzyme capabilities and plasma half lives can be profoundly extended, although foals are not affected.

Two related antibiotics, thiamphenicol and its derivative, florfenicol, were developed by substituting a methyl sulfonyl group for the nitrophenol group that characterizes chloramphenicol. Thiamphenicol and florfenicol are both safer compounds; the former is less effective than chloramphenicol and the latter is more effective than chloramphenicol against some pathogens and is approved for use in cattle. Thiamphenicol and Florfenicol exhibit the same mechanism of action as the parent compound. Florfenicol penetrates the milk of lactating cows, but does not penetrate the CSF and aqueous humor to the same extent as chloramphenicol.

Chloramphenicol can produce two distinctive types of bone marrow suppression. Reversible, dose dependent suppression occurs in humans. At a daily dose of 50 mg/kg

for three weeks, this reversible condition is also demonstrated in cats. Dogs will experience only a milder suppression at even higher doses. Due to interference with mRNA and protein synthesis in rapidly multiplying cells, similar suppression is seen in neonatal animals receiving adult dosages of the drug.

In humans a second more serious irreversible, non-dose related aplastic anemia also occurs - often appearing after the drug is discontinued. This condition results in pancytopenia, bone marrow hypoplasia or aplasia, secondary infection and hemorrhagic diathesis. This non-reversible dyscrasia will occur in approximately one in 25,000 to one in 40,000 patients administered the drug. In order to eliminate the chance of such a condition resulting from food consumption, use of chloramphenicol is prohibited in food animals in the United States and several other countries. These blood dyscrasias seem to be related to the presence in chloramphenicol of the nitro group, therefore these conditions are not associated with the use of florfenicol or thiamphenicol.

Use of chloramphenicol has also been associated with additional undesirable physical effects. Hypersensitivity in dogs and cats may result in yet another manifestation of aplastic anemia. Gastrointestinal disturbances have occurred in non-ruminants, cats may exhibit anorexia and depression when duration of therapy exceeds one week and use in calves has resulted in malabsorptive disorders. Chloramphenicol has demonstrated adverse effect on structure and function of reproductive organs in rats. Due to interference with protein synthesis, excessive topical use may interfere with healing.

Interactions with vaccines and other drugs are additional concerns. Chloramphenicol interferes with the anamnestic immune response; therefore vaccines should never be administered to people or animals while chloramphenicol is being administered. Chloramphenicol may prolong the duration of action of several drugs, including pentobarbital, codeine, phenobarbital, phenytoin, NSAIDs and coumarins. When used in combination with sulfamethoxypyridazine, hepatic damage may result. Chloramphenicol interferes with the actions of several bactericidal drugs, such as penicillins, cephalosporins and aminoglycosides and in most circumstances, concurrent use of these drugs should be avoided. Use of the drug with other antibacterials that target the 50 S ribosomal subunit, lincosamides and macrolides, should be avoided.

In veterinary medicine, safe use of the drug can be assured if chloramphenicol is not overdosed, if dosages are reduced in neonates and patients with impaired liver function or bone marrow suppression and if the duration of therapy is limited to a maximum of one week.

Resistance

Resistance to chloramphenicol is usually slow to develop and often occurs together with resistance to tetracycline, erythromycin, streptomycin and ampicillin. The most common mode of resistance to chloramphenicol is through the action of chloramphenicol acetyltransferases, enzymes that inactivate the drug. This mode of resistance can be chromosomally or plasmid mediated and other inactivating enzymes may be involved. These chloramphenicol acetyltransferases are constitutive in Gram-

negative bacteria but are inducible in Gram-positive organisms. An additional mode of resistance employed by *Pseudomonas aeruginosa* and some species of Proteus and Klebsiella is an induced permeability block that also can be mediated chromasomally or on plasmids. In *P. aeruginosa* an efflux pump often works in conjunction with this induced permeability to render the organism resistant to multiple antimicrobials, including chloramphenicol. Three proteins make up the structure of this efflux pump and function together to produce the effect. An efflux pump can also be encoded in the genome of *Campylobacter jejuni*, rendering the organism resistant to several antibiotics, including chloramphenicol.

Over the past fifteen years, resistance to chloramphenicol in enterobacteria has decreased, likely due to restricted use. Concern exists internationally with development of multi-drug resistant strains of *Salmonella typhi*, non-typhoidal Salmonella and Shigella species that include resistance to chloramphenicol. Due to development of resistance to chloramphenicol, third generation cephalosporins are now the drugs of choice for treatment of childhood bacterial meningitis, penicillin resistant pneumococcal and meningococcal meningitis and meningitis caused by *Haemophilus influenzae* type B.

Effectiveness

Chloramphenicol is used as therapy in systemic and local infections. Many Gram-positive and Gram-negative bacterial genera are susceptible to chloramphenicol, but most strains of *Pseudomonas aeruginosa* are not. The drug is used in veterinary medicine to treat chronic respiratory infections, bacterial meningoencephalitis, brain abscesses, ophthalmitis, intraocular infections, pododermatitis, skin infections and otitis externa. Urinary infections can be successfully treated with chloramphenicol despite the low concentration of active antibiotic present in the urine. It is notable that chloramphenicol is very effective against several species of Salmonella. Group B streptococci are uniformly susceptible and Rickettsia and Chlamydia species are also effectively treated by the drug. Chloramphenicol is used in human medicine as oral therapy for infections due to vancomycin resistant enterococci (VRE), vancomycin sensitive enterococci, methicillin sensitive *Staphylococcus aureus*, aerobic gram negative bacteria, and anaerobes such as Bacteroides species. The drug is used for therapy and prophylaxis of plague. Chloramphenicol is also an option for oral therapy of urinary tract infections caused by *E. coli*, Proteus, Klebsiella and Pseudomonas organisms as well as *E. coli* enteritis. In developing nations, chloramphenicol is often used intravenously in therapy for acute bacterial meningitis.

***References available by request. Call the Infectious Disease Epidemiology Section, Office of Public Health, Louisiana Department of Health and Hospitals (504-219-4563)**