Chloramphenicol

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Overview

- Chloramphenicol is a broad-spectrum, bacteriostatic antimicrobial agent that acts through the inhibition of protein synthesis via the 70S ribosome and its 50S ribosomal subunit.
- Due to high lipophilicity, it has good penetration into protected sites (eg, brain, aqueous humor, prostate).[1]
- Although adverse effects limit use of chloramphenicol as a first-choice treatment, methicillin-resistant *Staphylococcus pseudintermedius* is often susceptible.[2]

Adverse Effects & Risk Factors

- Common adverse effects in dogs include GI upset (eg, vomiting, diarrhea, anorexia, drooling, gagging), lethargy, restlessness, increased hepatocellular enzymes, and generalized trembling or shaking.[2]
- Anemia and other bone marrow suppression can occur secondary to mitochondrial damage at high doses or extended durations.
  - Dogs can experience effects at doses of 225 mg/kg for 14 days or 50 mg/kg for 50 days.[2,3]
  - Cats are at higher risk than dogs because of deficiencies in effective glucuronidation enzymes that can lead to prolonged plasma, tissue, and, subsequently, mitochondrial concentrations.[3]
- Peripheral neuropathy that manifests as pelvic limb weakness in larger dogs (>55 lb [25 kg]) has been reported.[2]
  - Signs resolved after the drug was discontinued.
- Risk factors include a history of hepatic disease, neoplastic disease, polypharmacy, and exposure durations over 10 days.
  - Baseline and midtreatment CBC and serum chemistry profiles are recommended in patients with any of these factors.[1,2,4]
- Humans are susceptible to developing anemia (dose-dependent and idiosyncratic aplastic forms) from inhibition of mitochondrial protein synthesis via the 70S ribosome.
  - Owners should be advised to handle the drug carefully and use appropriate protective equipment (eg, gloves, eye protection, facial shields) when needed.[1,2]

Drug Interactions

- Efficacy is decreased when chloramphenicol is used with bactericidal drugs such as fluoroquinolones or other inhibitors of the 50S ribosomal subunit (eg, macrolides).[1]

- Chloramphenicol specifically inhibits canine CYP2B11 and thus increases the half-life of methadone, barbiturates (eg, phenobarbital), digoxin, propofol, and primidone in dogs.[5-7]
  - Because of highly variable changes in drug pharmacokinetics, therapeutic drug monitoring of chronic medications (eg, phenobarbital) is recommended midway through and after treatment with chloramphenicol.
  - Patients should be monitored for such adverse effects as sedation, polyuria, and polydipsia during treatment.[7]
- Chloramphenicol is metabolized by both phase I and phase II enzymes in the liver.
  - Hepatic dysfunction can increase plasma concentrations and half-life, which can lead to an increased risk for adverse effects.
  - Conversely, induction of P450 enzymes from concurrent administration of medications such as phenobarbital can decrease plasma concentrations and half-life, which can lead to a decrease in overall efficacy.[1,5]

Antimicrobial Stewardship

- Selective pressure changes to normal flora can lead to resistance in fecal enterococci and a nosocomial source for multidrug-resistant bacteria with zoonotic potential.[8]
  - Cohabitation with dogs and cats has been associated with zoonotic transfer of multidrug-resistance (mdr) genes between enterococci.[8]
  - Resistance to chloramphenicol is associated with resistance to other antimicrobial agents.[8]
- Risk factors for fecal resistance include coprophagia and previous exposure to fluoroquinolone antimicrobial agents.[8]

Alternative administration routes may lower systemic exposure and decrease gut biome changes and should be considered when possible.[9]

- Alternative administration routes (eg, regional limb perfusion) may lower systemic exposure and decrease gut microbiome changes and should be considered when possible.[9]

Legal Considerations for Use

- The Animal Medicinal Drug Use Clarification Act of 1994 specifically prohibits extra-label use of chloramphenicol in food animals.[10]
  - Because of the increased popularity of pot-bellied pigs as pets, veterinarians must recognize that all porcine species are considered under federal law as food animals.
  - This federal law also applies to meat rabbits and backyard chickens, which occasionally may be presented to small animal practices.[10]

References

1. Dowling PM. Chloramphenicol, thiamphenicol, and florfenicol. In: Giguère S, Prescott JF, Baggot JD, Walker RD, Dowling PM, eds. *Antimicrobial Therapy in Veterinary Medicine*. 4th ed. Ames, IA: Blackwell Publishing; 2006:241-248.
2. Short J, Zabel S, Cook C, Schmeitzel L. Adverse events associated with chloramphenicol use in dogs: a retrospective study (2007-2013). *Vet Rec*. 2014;175(21):537.
3. Papich MG, Riviere JE. Chloramphenicol and derivatives, macrolides, lincosamides, and miscellaneous antimicrobials. In: Riviere JE, Papich MG, eds. *Veterinary Pharmacology and Therapeutics*. 9th ed. Ames, IA: Wiley-Blackwell; 2009:945-982.
4. Li CH, Cheng YW, Liao PL, Yang YT, Kang JJ. Chloramphenicol causes mitochondrial stress, decreases ATP biosynthesis, induces matrix metalloproteinase-13 expression, and solid-tumor cell invasion. *Toxicol Sci*. 2010;116(1):140-150.
5. KuKanich B, KuKanich K. Chloramphenicol significantly affects the pharmacokinetics of oral methadone in Greyhound dogs. *Vet Anaesth Analg*. 2015;42(6):597-607.
6. Ciaccio PJ, Duignan DB, Halpert JR. Selective inactivation by chloramphenicol of the major phenobarbital-inducible isozyme of dog liver cytochrome P-450. *Drug Metab Dispos*. 1987;15(6):852-856.
7. Houston DM, Cochrane SM, Conlon P. Phenobarbital toxicity in dogs concurrently treated with chloramphenicol. *Can Vet J*. 1989;30(7):598.
8. Leite-Martins L, Mahú MI, Costa AL, et al. Prevalence of antimicrobial resistance in faecal enterococci from vet-visiting pets and assessment of risk factors. *Vet Rec*. 2015;176(26):674.
9. Kelmer G, Tatz AJ, Famini S, Bdolah-Abram T, Soback S, Britzi M. Evaluation of regional limb perfusion with chloramphenicol using the saphenous or cephalic vein in standing horses. *J Vet Pharmacol Ther*. 2015;38(1):35-40.
10. Animal Medicinal Drug Use Clarification Act of 1994, 21 USC §530 (1994). U.S. Government Publishing Office. Accessed at https://www.ecfr.gov/cgi-bin/text-idx?SID=054808d261de27898e02fb175b7c9ff9&node=21:6.0.1.1.16&rgn=div5#21:6.0.1.1.16.5.1.2. Updated October 1, 2017. Accessed October 4, 2017.