Chloramphenicol

Chemical name: D-(-)-threo-2-dichloroacetamido-1-(4-nitrophenyl)-1,3-propanediol
Synonym: Chloromycetin
CAS: 56-75-7
MF: $C_{11}H_{12}Cl_2N_2O_5$
MW: 323.15
pKa=5.5
Solubility: 1g in 400 ml of water; 1 g in 2.5 ml of ethanol; freely soluble in acetone and ethyl acetate.

Major uses
Chloramphenicol is a broad-spectrum antibiotic that was first isolated from *Streptomyces venezuelae* in 1947. The drug was subsequently chemically synthesized. It has both a bacteriostatic and bactericidal effect; in the usual therapeutic concentrations it is bacteriostatic. Chloramphenicol is used for the treatment of serious gram-negative, gram-positive, and anaerobic infections. It is especially useful in the treatment of meningitis, typhoid fever, and cystic fibrosis [1]. It should be reserved for infections for which other drugs are ineffective or contraindicated.

Human toxicity
Chloramphenicol can be toxic and even fatal at acute overdose. Symptoms of poisoning have been associated with nausea and vomiting (especially with oral exposure), metabolic acidosis (an early sign, more common with chronic toxicity), hypotension, hypothermia, abdominal distention, heart failure, cardiovascular collapse, and coma. Signs of toxicity may be delayed 5 to 12 h after overdose.

In neonates and toddlers, who develop excessive serum concentrations of the drug, chloramphenicol can cause "gray baby syndrome" consisting e.g. of progressive cyanosis, metabolic acidosis, vasomotor collapse, respiratory difficulty, and death [1].

Both oral and intravenous therapeutic doses of chloramphenicol range from 25 to 100 mg/kg/day in an adult. Doses should be adjusted to result in serum levels of 10 to 30 mg/l (31 to 93 μM) to avoid toxicity, especially in newborns, premature infants, and patients with hepatic disease.

Dose-related effects indicating toxicity of chloramphenicol are generally observed with plasma/serum levels greater than 25 to 30 mg/l [2]. Critical values causing serious toxicity exceed 60 mg/l [3]. The minimum lethal serum concentration, based on the data from several handbooks, was 70 mg/l [4]. The mean lethal concentration, based on two acute poisoning cases, was 190 mg/l [1].

Carcinogenicity: rating group 2A (IARC, 2004) [2]; probably carcinogenic to humans; a limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals.

Kinetic data
Absorption: after oral administration, chloramphenicol is readily absorbed from gastrointestinal tract [1, 4].

Kinetics is first-order [4].

Distribution: chloramphenicol is well distributed in body fluids and tissues. It readily penetrates into cerebrospinal fluid, pleural and ascitic fluids, and also across the placenta [2]. It is accumulated in the liver and kidney [4]. Chloramphenicol is highly lipophilic. Activity is unaffected over a pH of 2 to 9 [5].

Volume of distribution: 0.57 l/kg [1]; 1.2 l/kg [4].

Plasma half-life: 1.6-3.3 h [1]; 2.5 h [4].

Time to peak blood concentration: 2-3 h [4].

Plasma protein binding: 55% [4].

Elimination half-life: 1.6 to 4 h [2].

Passage of blood-brain barrier: free [4].

Metabolism and excretion

Chloramphenicol is extensively metabolized in the liver, primarily by the glucuronide conjugation, and, to a lesser extent, by hydrolysis of the amide linkage. Main metabolites found in the urine 8 hours after a single 500 mg oral dose were 48% as chloramphenicol glucuronide and 4.3% as p-nitrophenyl-2-amino-1,3-propanediol. Another minor metabolite, p-nitrophenyl-2-hydroxyacetamido-1,3-propanediol, was found in the urine of newborns in an unstated amount [1].

Excretion: a total of 93% of a dose is excreted in the 24 h urine; largely as inactive metabolites.. Five to 10% is excreted in unchanged form. About 3% of chloramphenicol and 5% of its glucuronide metabolite are excreted in the bile [1, 2].

Pharmacological mechanisms

Only the D-stereo isomer of chloramphenicol is biologically active. Chloramphenicol interferes with bacterial mitochondrial protein synthesis by binding to the 50S subunit of bacterial ribosomes. It blocks protein synthesis in bacteria and in mitochondria by interfering with the peptidyl transferase function (peptidyl transferase is a function of the 50S or 60S subunit; synthesis of the peptide bond is catalyzed by a peptidyl transferase activity). Also other mitochondrial enzymes, such as cytochrome oxidase and ATPase are inhibited. Consequently, oxidative phosphorylation is inhibited, and cellular energy is depleted [2].

Toxicological mechanisms

Much of the toxicity observed with this drug can be attributed to the effects described above (see Pharmacologic mechanisms). Some of the known effects of chloramphenicol include interference of attachment of messenger RNA to the ribosomes, which leads to inhibition of protein synthesis.

Chloramphenicol binds to mitochondrial ribosomes and inhibits enzyme synthesis, for example, enzymes necessary for oxidative phosphorylation. Among the enzymes that are affected by chloramphenicol are cytochrome oxidase and ATPase, mentioned above, as well as an enzyme ferrochelatase which is also localized in the mitochondria and is a final enzyme in heme biosynthesis (catalyzing the incorporation of iron in hemoglobin) [2, 4].

Chloramphenicol has weak negative inotropic effect [3]. Inotropic effects are ones that change the strength of contraction of the heart muscle.

High serum concentrations (> 25 mg/l) of chloramphenicol at chronic exposure are associated with a reversible bone marrow suppression expressed as a reticulocytopenia, anemia, leucopenia, thrombocytopenia, or any combination of these abnormalities. Most serious hematological toxicity, which is irreversible complication and often fatal, is associated with aplastic anemia (failure of bone marrow to produce blood cells) [6].

Target organs: heart, vascular system, CNS, liver, kidney [4].

References

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