Chloramphenicol

Document History
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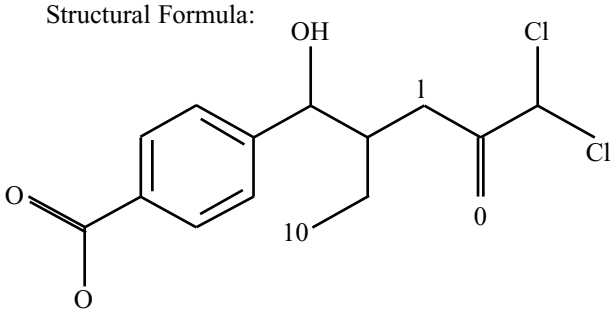
I. IDENTIFICATION[1,2]

Chemical Name: [R-(R*,R*)]-2,2dichloro-N-[2-hydroxy-1-(hydroxymethyl)-2-(4-nitrophenyl)ethyl]acetamide
Synonyms: Chloramphenicol; Chloromycetin, Levomycetin, D-threo-N-dichloroacetyl- 1 -p-nitrophenyl-2-amino- 1,3-propanediol; D-*threo*-N-(1,1'-dihydroxy-1-p-nitrophenyl-isopropyl) dichloroacetamide
Common Name: Chloramphenicol
CAS Number: 56-75-7
Molecular Formula: $C_{10}H_{12}Cl_2N_20_5$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1,2]

Physical State and Appearance: Solid-white to grayish-white or light yellow needles
Odor Description: Odorless, bitter taste
Odor Threshold: Unknown
Molecular Weight: 323.15
Conversion Factors: Not applicable
Boiling Point: No data available
Melting Point: 149°C–153°C (300°F–307°F)
Vapor Density and Pressure: No data available
Saturated Vapor Concentration: No data available
Flash Point/Flammability Limits: No data available
Autoignition Temperature: No data available
Solubility in Water: 0.25%–1% by weight at 25°C (77°F) Neutral and acid solutions are stable when heated
Stability: Decomposes if exposed to light.
Reactivity: The nitro group is readily converted to the amine by reduction.

III. USES

Chloramphenicol is a broad spectrum antibiotic that is used when less hazardous antibiotics are ineffective or contraindicated.[3] Chloramphenicol may be administered as a capsule, 1% ophthalmic ointment, 0.5% ophthalmic solution, oral suspension, or intravenous injection. It is used most widely in developing countries and in veterinary medicine. Chloramphenicol is handled in the free form, as a palmitate ester, or as a sodium succinate salt. This OEL applies to all forms of the compound when adjusted for molecular weight (e.g., 1.7 g of the palmitate is equivalent to 1 g chloramphenicol).

IV. ANIMAL TOXICOLOGY DATA

A. Acute Toxicity

1. *Oral Toxicity*[4,5]

Rats: LD_{50} = 2500–3400 mg/kg

Mice: LD_{50}= 2300–2640 mg/kg

2. *Eye Toxicity*[6]

Slightly irritating

3. *Skin Toxicity*[6]

Absorption: Not likely to be absorbed

Irritation: Nonirritating

Sensitization: Not a sensitizer in guinea pigs

4. *Inhalation Toxicity*

No data available

5. *Other Toxicity*

a. Intravenous[5]

Mice: LD_{50} = 110–203 mg/kg

Rats: LD_{50} = 171–279 mg/kg

Rabbits: LD_{50} = 117 mg/kg

b. Subcutaneous[4,7]

Rats: LD_{50} = 5447 mg/kg

Mice: LD_{50} = 1675 mg/kg

c. Intraperitoneal[5]

Mice LD_{50} = 1320 mg/kg

B. Subacute Toxicity

In studies in cats and dogs, dose-dependent and reversible bone-marrow depression were often accompanied by changes in peripheral blood, reduced food intake, body weight loss, and marked central nervous system depression. NOAELs were reported as follows for the various dosing regimens:

Cats (oral): 120 mg/kg/day after 14 days and 60 mg/kg-day after 21 days[8]

Cats (oral): 21 days — 25–40 mg/kg-day[9]

Dogs (oral): 14 days — 225–275 mg/kg-day[10]

Dogs (oral): 21 days — 100 mg/kg-day[11]

Dogs (oral): 21 days — 300 mg/kg-day[12]

Dogs (oral): 3–5 weeks — 200 mg/kg-day.[5]

Cats (oral and ophthalmic): treated 5 days/week for 30 days (22 treatment days) — 50 mg and 100 mg dosages orally and 4.5 mg and 9 mg dosages of ophthalmic ointment (animals ranged from 2–4 kg in body weight). No effects were found in either the peripheral blood or bone marrow.[13]

Groups of five to 15 inbred strains of mice (C3H/Hc, CBA/Ca, BALB/c and C57BL/6) and one outbred stock (CD-1) were treated with 500 – 2500 mg/kg of chloramphenicol succinate (CAPS) in water by gavage for 7 days. CAPS caused anemia and reticulocytopenia in all strains and leucopenia in the inbred strains at all dose levels. The four inbred strains exhibited significant responses to CAPS at lower dose levels than in CD-1 mice, which were phenotypically more variable.[14]

C. Subchronic Toxicity

Dogs (oral): 4 months — 100 and 200 mg/kg/day caused no cumulative toxic effect on hematopoiesis, liver or kidney function, or effects on other visceral tissues (specific organs not mentioned).[5]

Dogs (oral): 16 weeks — 250 mg/kg/day decreased body weight and appetite, but there were no significant changes in peripheral blood. Liver, spleen, kidneys, and ribs were examined at study termination and no pathological changes were noted.[15]

The NOAEL of chloramphenicol given daily for 24 weeks was tested in mice and guinea pigs by various routes of exposure with the following results:[5]

Mice (oral): 385–425 mg/kg-day

Guinea pigs (oral): 250 mg/kg-day

D. Chronic Toxicity

Dogs (oral): 2 years, 5 or 6 days/week – 10 mg/kg/day (1 animal); 200 mg/kg-day (2 animals). [Animals were initiated in the study at 6 months of age.] Appetite and weight gain were suppressed at times, but no changes in the peripheral blood, bone marrow, or other organs were noted. Although the study is limited by number of animals, the data support a NOAEL of 200 mg/kg-day for hematological effects.[15]

E. Reproductive/Developmental Toxicity

Rats fed 220–300 mg/day (approximately 550 to 750 mg/kg-day calculated based on a body weight of 0.4 kg for a pregnant rat) chloramphenicol in their diets on Days 0–20 of gestation showed a significant increase in fetal resorptions, decreased fetal weight, and malformed ribs in the high dose group. Maternal effects were not described.[16]

In rats, rabbits, and mice, chloramphenicol showed clear embryotoxicity and inhibition of fetal growth (1000 mg/kg and 2000 mg/kg per day, by oral gavage, on Days 8-11 of gestation). At the high dose, fused sternebrae and umbilical hernias were observed. It should be noted, however, that this dose level approaches the LD_{50}. Decreased fetal weights in all species and incomplete ossification in the rabbit were noted at a 500 mg/day dosage. The only maternal effects observed at any dose were decreased weight gain in the mice. No observations of other maternal toxicity were reported in any of the species in this study. This study is limited however, since no concurrent untreated control group was used for comparison.[17]

Female Wistar rats given chloramphenicol 50 mg/kg-day subcutaneously during gestation (Days 7–21), were then randomly grouped into four groups of 15 rats per group. Dam weight gain during pregnancy, litter size, fetal weight, gross malformations of the fetuses, and weight gain of the offspring were not affected; however, the acquisition of a conditioned avoidance response in the offspring was impaired. This effect was also observed in newborns administered doses of 50 or 100 mg/kg-day on Postnatal Days 1–3.[18] Similar neurobehavioral deficits, including effects on conditioned avoidance response, open field behavior,

and seizure thresholds were observed beginning at the lowest dose tested in the offspring of five groups of eight pregnant albino mice, at the third stage of pregnancy given 25, 50, 100, or 200 mg/kg-day chloramphenicol (or distilled water (10 ml/kg per day) orally for 5–7 consecutive days during the third trimester of pregnancy.[19] These studies suggest a LOAEL of 25 mg/kg-day for neurodevelopmental toxicity.

F. Genotoxicity

Contradictory results were obtained with respect to the ability of chloramphenicol to induce dominant-lethal mutations in mice. It induced chromosomal aberrations in bone-marrow cells of mice, but not rats, treated *in vivo* (dosage not specified). It induced chromosomal aberrations, but not sister-chromatid exchanges (SCEs) in cultured human lymphocytes and chromosomal aberrations in one study using cultured pig lymphocytes. Chloramphenicol induced neither dominant-lethal nor sex-linked recessive lethal mutations in *Drosophila*. It induced chromosomal aberrations but no mutations in plants. Chloramphenicol was not mutagenic and did not cause DNA damage in bacteria.[20] Chloramphenicol was positive in the mouse lymphoma assay with and without activation.[21]

Leukocytes from normal human subjects exposed to chloramphenicol *in vitro* contained a significant increase in chromosomal aberrations. Chloramphenicol was added to the cultures 6 hours before harvesting in amounts to produce final concentrations of 10, 25, or 40 µgm/ml culture medium (controls exposed only to drug diluent). The types of changes were similar to those found in patients receiving large doses of chloramphenicol.[22]

G. Metabolism/Pharmacokinetics

Chloramphenicol was administered in 0.1 mL of Krebs-Ringer phosphate solution (pH 7.4) to anesthetized rats by tracheal cannula. Absorption half-time in the rat lung (time for 50% of the drug to be absorbed) was measured at 1.9 minutes.[23] Orally administered chloramphenicol is absorbed rapidly from the intestinal tract.[3]

The bioavailability of orally administered chloramphenicol ranges from 76% to 93%. It is distributed primarily to the liver and kidneys but also to the cerebrospinal fluid, breast milk, and fetal circulation.[24]

In humans, about 90% of the drug administered orally is recovered in the urine in 24 hours, principally in the form of inactive metabolic products that retain the aryl-nitro group intact. Less than 10% of the dose is excreted as unchanged chloramphenicol. The drug is partially excreted in the bile of lower animals, formed into nitro compounds and aryl amines that may be recovered by the intestinal tract.[25]

Plasma clearance half-life has been reported as between 2.3 hours and 6 hours.[3,24,25] Half-life values determined in other species ranged from 0.9 hours to 5.1 hours.[26,27]

V. HUMAN USE AND EXPERIENCE

1. Clinical

Chloramphenicol can be administered orally, parenterally, or topically. The human therapeutic dose by oral or parenteral administration is 50 mg/kg daily, although up to 100 mg/kg may be used in exceptional circumstances. The most serious adverse reaction associated with chloramphenicol use is bone-marrow depression. Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, and granulocytopenia) are known to occur after the administration of chloramphenicol. An irreversible type of marrow depression leading to aplastic anemia with a high rate of mortality is characterized by the appearance — weeks or months after therapy — of bone marrow aplasia or hypoplasia. The aplastic anemia associated with chloramphenicol use is not dose-related.[3] There have been reports of aplastic anemia attributed to chloramphenicol, which later terminated in leukemia.[28] Other cases of blood dyscrasias, some leading to death, have been reported after ophthalmic administration of chloramphenicol.[29–32]

A reversible type of bone-marrow depression, which is dose-related, can also occur.[3] Reversible toxic bone-marrow depression, predominately affecting erythropoiesis, developed in two of 20 patients given 2000 mg/day for 3 weeks and in 18 of 21 patients given 6000 mg/day for 3 weeks. The lowest reported dose leading to reversible bone marrow depression is 2000 mg/day for 21 days.[33]

A study of a population of male patients, most of them with chronic infections, showed that chloramphenicol-induced bone-marrow depression is frequently associated with total plasma antibiotic levels sustained at 25 micrograms per milliliter or higher. This suggests that toxic bone-marrow depression is a dose-related pharmacologic property of chloramphenicol. Although the correlation between plasma levels and dosage is inexact, toxic plasma concentrations were regularly attained with total daily doses of greater than 50 mg/kg of body weight.[27]

The incidence of aplastic anemia induced by chloramphenicol has been estimated as 1 in 58,000 or 1 in 75,000. Lethality in this condition is reported as 1 in 76,000. The rarity of the reaction indicates that it is most likely an idiosyncrasy due to a genetic predisposition. The effect was not seen in phases 1, 2 and 3 clinical trials or the animal toxicity studies for chloramphenicol.[34]

Other adverse reactions, such as gastrointestinal and central nervous system (CNS) disturbances have been reported with low incidence.[3] There are also indications of reversible optic nerve injury and optic atrophy associated with chloramphenicol treatment.[35–37] Hypersensitivity reactions have rarely been reported.[38,39]

2. Occupational

Contact sensitivities have been reported in ophthalmologists exposed daily to 5% chloramphenicol.[40] In a manufacturing facility where chloramphenicol was being produced, seven of 285 workers exposed to the drug had positive patch tests.[6]

One report linked long-term occupational exposure to chloramphenicol dust with hematologic changes and chromosomal damage in two pharmaceutical operators.[41] The operations were described as visibly dusty; however, chloramphenicol levels present in their work environment were not measured. The workers were not wearing respiratory protection.

In the former Soviet Union, workers were exposed to concentrations of chloramphenicol ranging from 2.5 mg/m^3 to 60 mg/m^3 in the dustier operations. No mention is made of respiratory protection. Health effects noted were decreased red blood cell count with no change in white blood cell count. Also, 4% to 7% of the workers had allergic occupational dermatitis, which was confirmed by a patch test.[42]

Contact dermatitis to chloramphenicol in veterinary topical medications was reported in a farmer. The farmer's clinical history included an episode of conjunctivitis treated with chloramphenicol eye drops. On two other occasions while farming, the patient had contact with chloramphenicol from animal medicants. In all these situations, swelling, itching, and redness of the contact area developed 1 to 2 days later. Patch tests showed no immediate reaction to the chloramphenicol and both the standard series and open patch tests were negative. Chloramphenicol 1% tested positive after 48–96 hours. Although contact dermatitis to chloramphenicol is rare, this case indicated that medications containing chloramphenicol can cause occupational dermatitis.[43]

3. Other

Chloramphenicol has been classified by the International Agency for Research on Cancer (IARC) as a 2A carcinogen (*probably carcinogenic to humans*).[2] The NTP classifies chloramphenicol as *reasonably anticipated to be a human carcinogen*, based on limited evidence of carcinogenicity from studies in humans. IARC cited that numerous case reports have shown leukemia to occur after medical treatment for chloramphenicol-induced aplastic anemia.[44]

VI. RATIONALE

The OEL for Chloramphenicol is based on protection from hematological and neurodevelopmental effects. Chloramphenicol has been shown to induce bone-marrow depression after human therapeutic use and in animal studies, including absorption of eye drops and ointments. The lowest (therapeutic) dose at which reversible bone-marrow suppression has been observed clinically is 2000 mg/day (approximately 36 mg/(kg-day) for a 55 kg patient) following treatment for 21 days. Longer-term animal studies in several species identified NOAELs for hematological effects following oral dosing in the range of 100 to 425 mg/kg-day. Aplastic anemia is a side effect induced by chloramphenicol, but the incidence is very low and is thought to be an idiosyncratic reaction due to a genetic predisposition. Human clinical experience suggests that chloramphenicol may induce leukemia in individuals who exhibit other serious hematological side effects. This finding is supported by the induction of chromosome aberrations in several assays. However, this cancer outcome was not seen in the phase 1, 2, and 3 clinical trials or the animal toxicity studies. The dose-response for these severe idiosyncratic hematological responses including aplastic anemia and leukemia is not adequate for use in deriving the OEL. Based on animal studies, relatively high doses of chloramphenicol in the range of 1000 mg/kg-day are embryo- and fetotoxic. In addition, exposure in- utero and during the early postnatal period in rats and mice has been shown to impair neurobehavioral performance in early adulthood at oral doses as low as 25 mg/kg-day. No evidence of significant skin absorption or systemic toxicity following dermal exposure was reported and no skin notation is assigned. Chloramphenicol was negative in a dermal sensitization test in guinea pigs, but a low incidence of sensitization in some worker populations has been reported. These data are inadequate to assign a sensitization notation. A OEL of 0.5 mg/m^3 is based on the lowest NOAEL for hematological effects at 100 mg/kg/day and should provide an adequate degree of protection from adverse hematological and neurodevelopmental effects.

VII. RECOMMENDED OEL

8-hr time-weighted average (TWA): 0.5 mg/m^3 for all forms of the compound, measured as chloramphenicol

VIII. REFERENCES

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