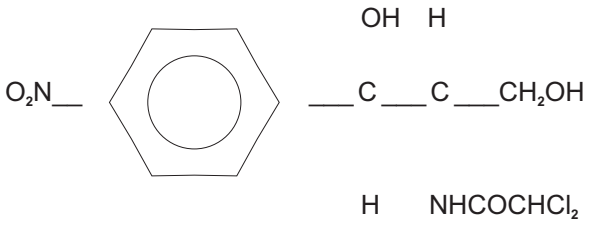
CHLOROMYCETIN CAPSULES (Chloramphenicol) & CHLOROMYCETIN PALMITATE SUSPENSION (Chloramphenicol Palmitate)

In line with CPL 99

PRESCRIBING INFORMATION

Description

Chloramphenicol/Chloramphenicol (palmitate) is an orally active antibiotic originally isolated from Streptomyces venezuelae. Chemical name of chloramphenicol is 2,2-Dichloro-N-{(2R,3R)-3- hydroxy-2-hydroxymethyl-4 nitrophenethyl)}acetamide, $C_{11}H_{12}Cl_2N_2O_5$ and its molecular weight (MW) is 323.1. Chemical name of chloramphenicol palmitate is (2R,3R) -2- (2,2-dichloroacetamido) -3- hydroxy -3- (4-nitrophenyl) propyl palmitate, $C_{27}H_{42}Cl_2N_20_6$ (MW = 561.5). The structure for chloramphenicol is:



Chloramphenicol occurs as fine, white to grayish or yellowish white, needle-like crystals, has a solubility of approximately, 2.5 mg/mL in water at 25° C, and is freely soluble in alcohol. The pK_a of the drug is 5.5. Chloramphenicol palmitate occurs as a fine, white, unctuous, crystalline powder having a faint odor and a bland mild taste and is insoluble in water and sparingly soluble in alcohol.

Each capsule contains 250 mg and 500 mg of chloramphenicol I.P. and each 5 ml of the suspension contains chloramphenicol palmitate I.P. equivalent to 125 mg chloramphenicol.

CLINICAL PHARMACOLOGY (1)

In vitro, chloramphenicol exerts mainly a bacteriostatic effect on a wide range of Gram-negative and Gram-positive bacteria and is active against rickettsiae, the lymphogranuloma-psittacosis group and Vibrio cholerae. It is particularly active against Salmonella typhi and Haemophilus influenzae. The mode of actions is through interference or inhibition of protein synthesis in intact cells and cell-free systems. Antagonism has been demonstrated in vitro between chloramphenicol, erythromycin, clindamycin and lincomycin.(2)

Chloramphenicol is rapidly absorbed from the GI tract. Chloramphenicol palmitate is hydrolyzed in the GI tract and is absorbed as free chloramphenicol.

Following oral administration of a single one gram dose of chloramphenicol base to healthy adults, average peak plasma chloramphenicol concentrations of about 11 mcg/ml were attained with 1-3 hours. Cumulative dosing gave a peak of 18 mcg/ml after the fifth dose of one gram, every 6 hours. Mean serum levels were 8-14 mcg/ml over a 48 hour period.

Most of the drug is excreted in the urine. Despite the small proportion of unchanged drug excreted in the urine, the concentration of free chloramphenicol in the urine is relatively high. From 8% to 12% of the antibiotic is excreted as free chloramphenicol. The remainder is excreted as inert metabolites, mainly glucuronate. Small amounts of active drug are found in bile and feces. Chloramphenicol diffuses rapidly, but its distribution is not uniform. Highest concentrations are found in liver and kidney, and lowest concentrations are found in brain and cerebrospinal fluid (CSF). Chloramphenicol enters CSF even in the absence of meningeal inflammation, appearing in concentrations about half of those found in the blood.

INDICATIONS AND USAGE (3)

Chloramphenicol is an antibiotic that is clinically useful for, and should be reserved for, serious infections caused by organisms susceptible to its antimicrobial effects when less potentially hazardous therapeutic agents are ineffective or contraindicated. However, chloramphenicol may be chosen to initiate antibiotic therapy on the clinical impression that one of the conditions below is believed to be present. In vitro sensitivity tests should be performed concurrently so that the drug may be discontinued as soon as possible if less potentially dangerous agents are indicated by such tests.

The decision to continue use of chloramphenicol, rather than another antibiotic when both are suggested by in vitro studies to be effective against a specific pathogen, should be based upon severity of the infection, susceptibility of the pathogen to the various antimicrobial drugs, and the efficacy of the various drugs in the infection (See WARNINGS and PRECAUTIONS.)

1. Acute infections caused by Salmonella typhi

Chloramphenicol is a drug of choice.** It is not, however, recommended for the routine treatment of the typhoid carrier state.

** In the treatment of typhoid fever, some authorities recommend that chloramphenicol be administered at therapeutic levels for 8 to 10 days after the patient has become afebrile to lessen the possibility of relapse.

2. Serious infections caused by susceptible strains in accordance with the concepts expressed above:

a. Salmonella species
b. H influenzae, specifically meningeal infections
c. Rickettsia
d. Lymphogranuloma-psittacosis group
e. Various gram-negative bacteria causing bacteremia, meningitis or other serious gram-negative infections
f. Other susceptible organisms which have been demonstrated to be resistant to all other appropriate antimicrobial agents.

CONTRAINDICATIONS (3,4)

Chloramphenicol is contraindicated in individuals with a history of hypersensitivity and/or toxic reaction to the product or its components. It must not be used in the treatment of trivial infections or where it is not indicated, as in colds, viral influenza, infections of the throat or as a prophylactic agent to prevent bacterial infections.

WARNINGS

Serious and fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia and bone marrow depression) are known to occur after the administration of chloramphenicol. In addition, there have been reports of aplastic anemia attributed to chloramphenicol which later resulted in leukemia. Blood dyscrasias have occurred after both short-term and prolonged therapy with this drug. Chloramphenicol must not be used when less potentially dangerous agents will be effective.

PRECAUTIONS

It is essential that adequate hematologic functions be closely monitored during treatment with the drug. While hematologic determinations may detect early peripheral hematologic changes, such as leukopenia, reticulocytopenia, or granulocytopenia, before they become irreversible, such determinations cannot be relied on to detect bone marrow depression prior to development of aplastic anemia.

Hospitalization may facilitate monitoring of appropriate laboratory determinations and clinical observations.

1. Baseline hematologic determinations should be made and determinations repeated approximately every two days during therapy. The drug should be discontinued upon appearance of reticulocytopenia, leukopenia, thrombocytopenia, anemia, or any other hematologic findings attributable to chloramphenicol. However, it should be noted that such determinations do not exclude the possible later appearance of the irreversible type of bone marrow depression.

2. Repeated courses of the drug should be avoided if at all possible. Treatment should not be continued longer than required to produce a cure with little or no risk of relapse of the disease.

3. Concurrent therapy with other drugs that may cause bone marrow depression should be avoided.

4. Excessive chloramphenicol serum levels may result from administration of the recommended dose to patients with impaired liver or kidney function, including that due to immature metabolic processes in the infant. The dosage should be adjusted accordingly or, preferably, the serum concentration should be determined at appropriate intervals.

5. There are no studies to establish the safety of this drug in pregnancy. Chloramphenicol is excreted in breast milk. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.

6. Since chloramphenicol readily crosses the placental barrier, caution in use of the drug is particularly important during pregnancy at term or during labor because of potential toxic effects on the fetus (Gray Syndrome). (5)

7. Precaution should be used in therapy of premature and full-term infants to avoid "Gray Syndrome" toxicity (see Adverse Reactions.) Serum drug levels should be carefully followed during therapy of the new born infant.

8. The use of this antibiotic, as with other antibiotics, may result in an overgrowth of nonsusceptible organisms, including fungi. If infections caused by nonsusceptible organisms appear during therapy, appropriate measures should be taken.

DRUG INTERACTIONS

Chloramphenicol has been shown to retard the biotransformation of tolbutamide, phenytoin, and dicoumarol in man (6). Chloramphenicol should be used with caution if administered concomitantly with lincomycin, clindamycin, or erythromycin. In vitro experiments have demonstrated that binding sites for erythromycin, lincomycin, clindamycin and chloramphenicol overlap and competitive inhibition may occur.(2) Rifampin therapy can reduce Chloramphenicol concentrations.(7)

ADVERSE REACTIONS

1. **Blood Dyscrasias**
   The most serious adverse effect of chloramphenicol 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. Peripherally, pancytopenia is most often observed, but in a small number of cases only one or two of the three major cell types (erythrocytes, leukocytes, platelets) may be depressed. A reversible type of bone marrow depression, which is dose related, may occur. This type of marrow depression is characterized by vacuolization of the erythroid cells, reduction of reticulocytes and leukopenia, and responds promptly to the withdrawal from chloramphenicol. Paroxysmal nocturnal hemoglobinuria also has been reported.

2. **Gastrointestinal Reactions**
   Nausea, vomiting, glossitis and stomatitis, diarrhea and enterocolitis may occur in low incidence.

3. **Neurotoxic Reactions**
   Headache, mild depression, mental confusion and delirium have been described in patients receiving chloramphenicol. Optic and peripheral neuritis have been reported, usually following long-term therapy. If this occurs, the drug should be promptly withdrawn.

4. **Hypersensitivity Reactions**
   Fever, macular and vesicular rashes, angioedema, urticaria and anaphylaxis may occur. Herxheimer reactions have occurred during therapy for typhoid fever.

5. **"Gray Syndrome"**
   Toxic reactions, including fatalities have occurred in premature infants and neonates. The signs and symptoms associated with these reactions have been referred to as Gray Syndrome. Although a single case of "Gray Syndrome" has been reported in a neonate born to a mother after having received chloramphenicol during labor, in most cases therapy with chloramphenicol has been instituted within the first 48 hours of life. The following summarizes the clinical and laboratory determinations that have been made on these patients.

Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol. The symptoms appeared in the following order: abdominal distension with or without emesis, progressive pallid cyanosis, vasomotor collapse, frequently accompanied by irregular respiration, death within a few hours of onset of these symptoms.

The progression of symptoms from onset to death was accelerated with higher dose schedules. Serum level determinations revealed unusually high concentrations of chloramphenicol (over 90 mcg/ml after repeated doses).

Termination of therapy upon early evidence of the associated symptomatology frequently revised the process with complete recovery.

OVERDOSAGE (3,8,9)

Levels exceeding 25 mcg/mL are frequently considered toxic. Chloramphenicol toxicity can be evidenced by serious hemopoietic effects such as aplastic anemia, thrombocytopenia, leukopenia, as well as increasing serum iron levels, nausea, vomiting and diarrhea. In the case of serious overdosage, charcoal hemoperfusion may be effective in removing chloramphenicol from plasma. Exchange transfusion is of questionable value following massive overdosage, especially in neonates and infants.

DOSAGE AND ADMINISTRATION

Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. Inhibition of the majority of sensitive organisms may be expected at concentrations of 5 to 20 mcg/ml. The desired concentration of active drug in serum should fall within this range over most of the treatment period. Dosage of 50 mg/kg/day divided into 4 doses at intervals of 6 hours will usually achieve and sustain levels of this order.

Except in certain circumstances (e.g. premature infants and neonates and individuals with hepatic or renal

impairment) lower doses may not achieve these concentrations. Close observation of the patient should be maintained and in the event of any adverse reactions, dosage should be reduced or the drug discontinued, if other factors in the clinical situation permit.

Adults

Adults should receive 50 mg/kg/day in divided doses [approximately one 250 mg capsule per each 4.5 kg (10 lbs) of body weight or one 500mg capsule per each 9 kg (20 lbs) of body weight] in divided doses at 6 hour intervals. In exceptional cases, patients with infections due to moderately resistant organisms may require increased dosage up to 100 mg/kg/day to achieve serum levels inhibiting the pathogen, but these high doses should be decreased as soon as possible.

Adults with impairment of hepatic or renal function, or both, may have reduced ability to metabolize and excrete the drug. In instances of impaired metabolic processes, dosages should be adjusted accordingly. (See discussion under Newborn Infants).

Pediatric patients

Dosage of 50 mg/kg/day divided at 6 hour intervals is effective against most susceptible organisms. Severe infections (eg., bacteremia or meningitis), especially when adequate cerebrospinal fluid concentrations are desired, may require dosage up to 100 mg/kg/day; however, it is recommended that dosage be reduced to 50 mg/kg/day as soon as possible. Children with impaired hepatic or renal function may retain excessive amounts of the drug.

Newborn infants

A total of 25 mg/kg/day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in serum and tissues adequate to control most infections for which the drug is indicated.

Increased dosage in these individuals, demanded by severe infections, should be given only to maintain the serum concentration within a therapeutically effective range. After the first two weeks of life, full-term infants ordinarily may receive up to a total of 50 mg/kg/day equally divided into 4 doses at 6-hour intervals. These dosage recommendations are extremely important because serum concentration in all premature infants and full-term infants under two weeks of age differs from that of other infants. This difference is due to variations in the maturity of the metabolic functions of the liver and the kidneys.

When these functions are immature (or seriously impaired in adults), high concentrations of the drug are found which tend to increase with succeeding doses.
(See section titled "Gray Syndrome" under Adverse Reactions)

Pediatric patients with Immature Metabolic Processes

In young infants and other pediatric children in whom immature metabolic functions are suspected, a dose of 25 mg/kg/day will usually produce therapeutic concentrations of the drug in the serum. In this group particularly, the concentration of the drug in the serum should be carefully followed by microbiological techniques where possible.

STORAGE CONDITIONS

Chloramphenicol capsules :	Store in a cool dry place
Chloramphenicol Palmitate Suspension :	Keep bottle securely closed. Protect from light.

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