

CHLOROMYCETIN[®] SUCCINATE AND CHLOROMYCETIN FOR PARENTERAL ADMINISTRATION

(Chloramphenicol Succinate, Parke, Davis & Company)
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WARNING

Serious and even fatal blood dyscrasias (aplastic anemia, hypoplastic anemia, thrombocytopenia, granulocytopenia) are known to occur after the administration of chloramphenicol. Blood dyscrasias have occurred after short term and with prolonged therapy with this drug. Bearing in mind the possibility that such reactions may occur, chloramphenicol should be used only for serious infections caused by organisms which are susceptible to its antibacterial effects. Chloramphenicol should not be used when other less potentially dangerous agents will be effective, or in the treatment of trivial infections such as colds, influenza, viral infections of the throat, or as a prophylactic agent.

Precautions: It is essential that adequate blood studies be made during treatment with the drug. While blood studies may detect early peripheral blood changes such as leukopenia or granulocytopenia, before they become irreversible, such studies cannot be relied upon to detect bone marrow depression prior to development of aplastic anemia.

Chloramphenicol is a broad-spectrum antibiotic which clinical experience has shown to have specific therapeutic activity against a wide variety of organisms. Its activity was demonstrated initially in culture filtrates from a species of soil organism collected in Venezuela, later designated as *Streptomyces venezuelae*. The antibiotic was subsequently isolated from culture filtrates, identified chemically, and later synthesized.

Experimental development of bacterial resistance to chloramphenicol by staphylococci *in vitro* occurs comparatively slowly and only to a moderate degree. Strains of decreased susceptibility to chloramphenicol are relatively short-lived both *in vitro* and in man. In a survey of experimental and clinical experiences on susceptibility of staphylococci to chloramphenicol, it was found that the incidence of chloramphenicol-resistant staphylococci appears unrelated to frequency or to intensity of use of this antibiotic. Development of resistance to chloramphenicol can be regarded as minimal for staphylococci and many other species of bacteria.

ANTIMICROBIAL AND PHARMACOLOGICAL PROPERTIES OF CHLORAMPHENICOL

Chloramphenicol injected intravenously is readily distributed throughout the circulating blood. Peak blood concentrations

will be dependent upon the rapidity of injection. After conditions of equilibrium with body fluids and tissues obtain, approximately 50 per cent reduction in blood concentrations will occur in the ensuing 3 to 4 hour period.

Chloromycetin Intramuscular (Steril-Vial 65) injected intramuscularly behaves as a repository material. Peak blood levels will occur much later, will not be as high, and persist for a longer period than those seen after intravenous injection or oral administration. Older children and adults, i.e. those patients who have mature enzyme systems, conjugate and eliminate chloramphenicol rapidly and attain lower peak blood levels than with other forms of administration. Premature and newborn infants show reduced ability to conjugate and eliminate chloramphenicol and in general will achieve blood levels much higher and of considerably longer duration than will older children or adults.

Chloromycetin Succinate (the sodium salt of the succinic acid ester of chloramphenicol) requires conversion to free chloramphenicol before exhibiting marked antimicrobial activity. When given intravenously its distribution is approximately the same as that of intravenous chloramphenicol (Ampoules 258); however, it requires some time before conversion to the effective free form. Intramuscular injection is followed by rapid conversion, and peak blood levels occur approximately 2 hours following injection.

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. Chloramphenicol enters cerebrospinal fluid even in the absence of meningeal inflammation, appearing in concentrations about half that found in the blood. This antibiotic has also been reported to occur in pleural and in ascitic fluids, saliva, and in milk, and it diffuses readily into all parts of the eye. Transport across the placental barrier occurs, with somewhat lower concentration in cord blood of newborn infants than in maternal blood.

Seventy to ninety per cent of a single oral dose of 50 mg. of chloramphenicol is excreted in 24 hours in the urine of human subjects, with 5 to 10 per cent as free chloramphenicol and the remainder as microbiologically inactive metabolites, principally the conjugate with glucuronic acid. Since the glucuronide is excreted rapidly, most nitro compounds in the blood are in the form of free chloramphenicol. Despite the small proportion of unchanged drug excreted in the urine, concentrations therein are relatively high, amounting to several hundred mcg./ml./24 hours in patients receiving 50 mg./kg./day. Small amounts of active drug are also found in bile and in feces. The disposition of the drug given by parenteral routes is similar.