8. Precaution should be used in therapy during lactation because of the possibility of toxic effects on the nursing infant.
9. 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.

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 of chloramphenicol.

An exact determination of the risk of serious and fatal blood dyscrasias is not possible because of lack of accurate information regarding 1) the size of the population at risk, 2) the total number of drug-associated dyscrasias, and 3) the total number of non-drug associated dyscrasias.

In a report to the California State Assembly by the California Medical Association and the State Department of Public Health in January 1967, the risk of fatal aplastic anemia was estimated at 1:24,200 to 1:40,500 based on two dosage levels.

There are reports of aplastic anemia terminating in leukemia attributed to chloramphenicol.

Paroxysmal nocturnal hemoglobinuria has also 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 If this occurs, the drug should be promptly withdrawn.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 the premature and newborn; the signs and symptoms associated with these reactions have been referred to as the "gray syndrome". One case of "gray syndrome" has been reported in an infant born to a mother having received chloramphenicol during labor. One case has been reported in a 3-month infant. The following summarizes the clinical and laboratory studies that have been made on these patients:

(1) In most cases therapy with chloramphenicol had been instituted within the first 48 hours of life.
(2) Symptoms first appeared after 3 to 4 days of continued treatment with high doses of chloramphenicol.
(3) The symptoms appeared in the following order:
  (a) abdominal distension with or without emesis;
  (b) progressive pallid cyanosis;
  (c) vasomotor collapse, frequently accompanied by irregular respiration;
  (d) death within a few hours of onset of these symptoms.
(4) The progression of symptoms from onset to exitus was accelerated with higher dose schedules.
(5) Preliminary blood serum level studies revealed unusually high concentrations of chloramphenicol (over 90 mcg./ml. after repeated doses).
(6) Termination of therapy upon early evidence of the associated symptomatology frequently reversed the process with complete recovery.

DOSAGE AND ADMINISTRATION

DOSAGE RECOMMENDATIONS FOR ORAL CHLORAMPHENICOL PREPARATIONS

The majority of micro-organisms susceptible to chloramphenicol will respond to a concentration between 5 and 20 mcg./ml. The desired concentration of active drug in blood 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 magnitude.

Except in certain circumstances (e.g., premature and newborn infants and individuals with impairment of hepatic or renal function) lower doses may not achieve these concentrations. Chloramphenicol, like other potent drugs, should be prescribed at recommended doses known to have therapeutic activity. 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 (approximately one 250 mg. capsule per each 10 lbs. 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 blood 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.") Precise control of concentration of the drug in the blood should be carefully followed in patients with impaired metabolic processes by the available microtechniques (information available on request).

Children—Dosage of 50 mg./kg./day divided into 4 doses at 6-hour intervals yields blood levels in the range effective against most susceptible organisms. Severe infections (e.g., 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 liver or kidney function may retain excessive amounts of the drug.

Newborn Infants—(See section titled "Gray Syndrome" under "Adverse Reactions.") A total of 25 mg./kg./day in 4 equal doses at 6-hour intervals usually produces and maintains concentrations in blood 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 blood 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 blood 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.

Infants and Children with Immature Metabolic Processes—In young infants and other 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 blood. In this group particularly, the concentration of the drug in the blood should be carefully followed by microtechniques. (Information available on request.)