Baby, birth weight 1,420 gm., was started on treatment of 50 mg/kg/48 hours of microcrystalline chloramphenicol at 4 days of age. Forty-eight hours later, the infant developed vomoting, followed by loose yellow stools, lethargy, ashen gray pallor, apnea, and death at 8 days of age. Blood levels reached a peak at 54μg/cc 24 hours following the start of the treatment, dropped to 40μg/cc at 48 hours when symptoms appeared, fellow to 25μg/cc at 72 hours, and rose again to 50μg/cc at 96 hours. Death occurred 14 hours after the last blood level noted. Blood culture drawn at death was sterile. No autopsy was permitted.

Baby, birth weight 1,990 gm., was started on treatment of 50 mg/kg/48 hours of microcrystalline chloramphenicol on the first day of life. Respiratory distress was present from birth. Tremors appeared on the third day, followed by distention of the abdomen, lethargy, ashen gray pallor, apnea, and death on the sixth day. Blood levels were 41μg/cc at 24 hours, and 38μg/cc at 48 hours. Blood culture drawn at death was sterile. No autopsy was permitted.

COMMENT

The normal metabolic pathway for chloramphenicol is absorption, conjugation with glucuronic acid in the liver, and excretion by the kidney tubules.(12) Some active chloramphenicol is removed from the circulation by glomerular filtration.(13) Accumulation of chloramphenicol in the premature infant must be due to differences in one or more of these factors.

Single-dose studies of the microcrystalline form of chloramphenicol clearly demonstrate its slow absorption, the peak level not being attained for 24 hours. Considering the low solubility of this form of the drug, a depot effect could be anticipated. Single-dose studies of chloramphenicol sodium succinate showed rapid absorption with a peak within 4 hours, but also gave prolonged levels with half-lives 2 to 3 times those of adults. Half-lives of the succinate ester given intravenously were much longer than those reported for adults, eliminating slow absorption as the explanation for the prolonged levels. Decreased kidney function in the premature is well established. (14–16). The glucuronide conjugated, or inactive, chloramphenicol is excreted by the renal tubules while the active form is filtered by the glomerules. Tubular excretion is quantitatively the most important excretory pathway, as 90% of the chloramphenicol in the urine is in the conjugated form in both the adult and premature. (12). However, the adult excretes 90% of a daily dose, in contrast to 1.4%–52% in the premature. Therefore, a decrease in tubular excretion in the premature must be one of the factors accounting for prolongation of blood levels.

A deficiency in conjugation by the liver must also be present to explain the prolonged levels of active chloramphenicol. If hepatic conjugation were normal with poor kidney function, only the inactive form would accumulate. This is seen clinically in anuric adults, where a renal defect only is present, the conjugated form alone accumulates to high levels and patients exhibit no toxicity.(17) In the premature, however, only 35% of the circulating chloramphenicol is in the inactive form.(5,10) A deficiency of the glucuronidase in the liver of the newborn has been documented. (18,19). The accumulation of active chloraphenicol in the premature can be explained by this deficiency. The finding that blood levels plateau on the third and fourth day, plus the correlation of levels with chronological age rather than birth weight, lend support to the idea that enzymatic deficiencies, which improve as the infant matures, are responsible for the prolonged blood levels.

As chloramphenicol and bilirubin apparently follow the same metabolic pathway, some correlation between blood levels of bilirubin and chloramphenicol could be expected. No correlation was demonstrated. In a previous study, there was no increase in the incidence of jaundice among premature infants receiving chloramphenicol compared with a similar group not receiving it.(3) In the same study, autopsies on infants who died with chloramphenicol toxicity did not reveal kernicterus.

There was no correlation between the levels of nitro compounds and a BUN of 53 mg% or less. One infant with a BUN of 89 mg% at the start of treatment accumulated nitro compounds, as did another infant with a low renal output for 24 hours. Infants with a BUN above 60 mg%, or other signs of defective renal function should be treated cautiously with a reduced dosage.

Premature infants were tested in all weight groups over 1,000 grams. No correlation between birth weight and blood levels was found. A definite correlation between age and blood levels was demonstrated. Tendency to accumulate nitro compounds in the blood stream was most marked during the first 4 days