

Sutherland and his co-workers (19,20) recently reported 5 cases of fatal circulatory collapse in newborn and premature infants that they believed to be due to chloramphenicol toxicity. (19,20) Their findings clinically and at autopsy were similar to our findings. They postulated that the high blood levels demonstrated were due to poor absorption, poor excretion or failure of conjugation. Dorn and Smith (21) reported prolonged blood levels in the newborn and the premature infant after a single dose of chloramphenicol.

SUMMARY AND CONCLUSIONS

Premature babies delivered after rupture of the fetal membranes for twenty-four hours or longer were assigned to one of four treatment groups. Group 1 received no antibiotic, Group 2 received chloramphenicol alone, Group 3 received penicillin and streptomycin, and Group 4 received all three. The mortality of the group treated with penicillin and streptomycin was the same as that of the untreated group, but a higher number of the treated babies had gastrointestinal symptoms.

The mortality rates of the two groups given chloramphenicol were significantly higher than those of the other two groups.

The babies receiving chloramphenicol followed a typical clinical course. Gastrointestinal symptoms appeared first, followed by circulatory collapse and death. Blood levels of chloramphenicol showed a continuous rise. Removal of the drug stopped the progression of symptoms. Recovery left no sequelae.

Since the administration of chloramphenicol was the only factor common to the two groups having the high mortality, and the absence of chloramphenicol the only factor common to the two groups with the low mortality, chloramphenicol in the dosage used must have been responsible for the increase in mortality observed. Poor liver function, especially in the glucuronide conjugation system, as well as decreased kidney function, allowed normally safe doses to accumulate to toxic levels. This toxicity manifested itself by a characteristic picture of circulatory collapse.

If toxicity is partially due to failure of glucuronide conjugation, other drugs using this pathway of metabolism should be evaluated for use in the premature infant.

No benefit to the infants from administration of penicillin or streptomycin could be demonstrated. Since there were more symptoms in the group treated with penicillin and streptomycin than in the non-treated group, these drugs may not be harmless. Therefore, the use of prophylactic antibiotics has been discontinued in this nursery.

We are indebted to the Pediatric Attending and House Staff of the Los Angeles County Hospital for help with this study, to Dr. Frederick Moore, who prepared the statistical analysis, to Drs. Charles F. Weiss and A. J. Glazko, Parke, Davis and Company, who did the assays on blood levels, and to Mary Finley, R.N., and the nursing personnel of the Premature Center.

REFERENCES

1. Glazko, A. J., Wolf, L. M., and Dill, W. A. Biochemical studies on chloramphenicol (Chloromycetin) I Colorimetric methods for determination of chloramphenicol and related nitro compounds *Arch. Biochem.* 23:411-418, 1949.
2. Glazko, A. J. Personal communication.
3. Potter, E. L., and Thierstein, S. Glomerular development in kidney, as index of fetal maturity *J. Pediat.* 22:695-706, 1943.
4. McCance, R. A. Renal physiology in infancy. *Am. J. Med.* 9:229-241, 1950.
5. Barnett, H. L. Kidney function in young infants *Pediatrics* 5:171-179, 1950.
6. Barnett, H. L., and Vesterdal, I. Physiologic and clinical significance of immaturity of kidney function in young infants. *J. Pediat.* 42:99-119, 1953.
7. Lathe, G. H., and Walker, M. Synthesis of bilirubin glucuronide in animal and human liver *Biochem. J.* 70:705-712, 1958.
8. Billing, B. H., Cole, P. C., and Lathe, G. H. Excretion of bilirubin as diglucuronide giving direct van den Bergh reactions *Biochem. J.* 65:774-784, 1957.
9. Schmid, R. Direct-reacting bilirubin, bilirubin glucuronide, in serum, bile, and urine. *Science* 124:76 1956.
10. Driscoll, S. G., and Hsia, D. Y.-Y. Development of enzyme systems during early infancy *Pediatrics* 22 (4):785-845, 1958.
11. Glazko, A. J., Dill, W. A., and Rebstock M. C. Biochemical studies on chloramphenicol (Chloromycetin). III. Isolation and identification of metabolic products in urine *J. Biol. Chem.* 183:679-691, 1950.