THE ABSORPTION OF CHLORAMPHENICOL IN THE NEWBORN

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The increasing prevalence of penicillin-resistant organisms, particularly staphylococci, in neonatal infections has led to the wider use of the more recent antibiotics. The absorption of one of these, chloramphenicol, has been studied in adults (Ley, Smadel and Crocker, 1948) and in children (Kelly, Hunt and Tashman, 1951; Ross, Burke and Rice, 1952). There is, however, no adequate published information on this subject in the newborn. At this age antibiotics are often given more or less prophylactically for quite minor infections, so that the problem of the correct dosage cannot be resolved by clinical results. The alternative is to give an amount which maintains a plasma level in excess of the *in vitro* sensitivity of the organisms. As there are good reasons for supposing that the absorption of the drug may be different in the first 10 days of life, the previous studies on children and older infants have been repeated for this age group. The investigation is based on 173 observations on 68 infants. Reports of cases of aplastic anaemia following the use of chloramphenicol (Gill, 1950; Wilson, Harris, Hensell, Witherbee and Kahn, 1952) have accentuated the need for a more cautious and informed administration of the drug.

Materials and Method

A microbiological assay was used employing a strain of *El Tor* vibrio which was completely inhibited by a concentration of 0.5 µg. per ml. The method is essentially that of Gray (1952), which is in turn a simplification and improvement of the original technique of Doorenbos and Kop (1951). A stock culture was maintained on a plain agar slope incubated aerobically at 37° C., subcultures being made approximately weekly.

Administration. The palmitate suspension was given just before the feed either by spoon or in a bottle diluted with an equal amount of expressed breast milk or dried milk mixture. The crystalline preparation was individually dispensed and added to the feed as a powder. No difficulty was experienced in giving the drug in either

form, but a number of infants receiving the higher doses of both preparations vomited after 24 to 48 hours of the course and continued until the drug was stopped. No other suggestions of toxicity were encountered, but in two cases not included in the trial oral thrush developed after 48 hours on doses of approximately 25 mg. per kg. six-hourly. In one of these *Monilia* was also found on a buttock rash.

Sampling. All assays were performed upon 1 ml. venous samples taken into sterile tubes containing 200 I.U. of dried heparin. These were then centrifuged and the plasma withdrawn. Where possible the assay was completed forthwith, but specimens which had to be kept overnight were stored at -28° C.

Assay. For the actual estimation a convenient dilution (solution A) of the plasma was made. This was 1 in 10 where the anticipated levels were below 20 µg. per ml., and 1 in 15 or 1 in 20 when higher levels were expected. For this purpose a 0.04 ml. constant drop Dreyer pipette was used, held vertically, delivering at the rate of one drop per second. The diluent was Armour peptone water (pH 7.2) with 1% dextrose and 1% Andrade's indicator added. The diluted plasma was then heated in a water-bath for 20 minutes at 60° C., thus destroying the normal inhibitory action of plasma on the growth of the vibrio (Doorenbos and Kop, 1951). Serial dilutions of solution A were then made with Dreyer pipettes in sterile 3 in. by $\frac{5}{8}$ in. test tubes, using the same diluent. Ten tubes were used, the first containing 10 drops of A and none of peptone water, the second nine drops of A and one of peptone water, and so on until the tenth tube, which contained one drop of solution A and nine of peptone water. Two control tubes each containing 0.4 ml. of diluent were also set up with each batch. All tubes except one of the controls were inoculated with a 5 mm. diameter wire loopful of an overnight growth of the vibrio in plain peptone water. The cultures were incubated at 37° C. for 18 hours. Where growth occurred the culture became pink. The tube containing the lowest concentration of chloramphenicol which inhibited growth was taken to contain 0.5 µg. per ml.

The sensitivity of the organism was titrated against known concentrations of pure crystalline chloramphenicol in plain peptone water at intervals throughout the trial, although not with each batch of readings. In

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all cases the organism was completely inhibited at a concentration of 0.5 μ g. per ml. and grew at 0.4 μ g. per ml.

Results and Discussion

The blood levels recorded at intervals after different doses of both crystalline and palmitate chloramphenicol are shown in Tables 1 and 2. The number of venipunctures on any one infant were deliberately limited. Infants who regurgitated or vomited part of any dose have been excluded.

These figures confirm the wide range in the rate and degree of absorption of the drug that has been a feature of previous studies on older infants and children. The levels two hours after administration of the crystalline preparation were of the same order as those found by Kelly *et al.* (1951); however, in the newborn, they appeared to be maintained for longer, and where the dose was repeated six-hourly maximum concentrations were attained in 24 hours. At this interval 25 mg. per kg. maintained levels substantially in excess of 10 μ g. per ml., which is the

TABLE 2
RESULTS WITH CHLORAMPHENICOL PALMITATE

Dose (mg. kg.)	Plasma Levels* (μ g./ml.)			
	2 Hours	6 Hours	10 Hours	24 Hours
50	< 5.0 < 5.0 < 5.0 < 5.0 < 10.0 5.0 8.3 16.6	7.1 8.3 12.5 5.5 5.0 5.0 10.0 12.5	< 5.0 7.1	
Six hourly	< 5.0	< 10.0	8.3	25.0
Six hourly	< 5.0	7.1	10.0	25.0
100	< 5.0 < 7.5 5.0 6.25 6.3 8.3 8.3 10.0 10.9 12.5 15.0 5.0	< 5.0 7.5 7.1 10.0 16.6 6.3 10.0 10.0 15.0 18.75 16.6 5.0	10.0 10.0 6.25 12.5 8.3 16.6 (12.5 at 48 hours)	7.1 5.0 5.0 16.6 (12.5 at 48 hours) 25.0 25.0 (50.0 at 48 hours)
Six hourly	16.6	12.5		
Six hourly	5.0	10.0		
150	< 10.0 10.0 10.0 10.0 12.5 20.0	< 10.0 12.5 14.3 16.6 16.6 33.3	< 10.0 14.3 12.5 16.6 16.6 16.6	
	24 Hours	48 Hours	72 Hours	
100 then 25 six hourly	5.0 6.26 7.5 7.5 12.5	5.6 16.6 15.0 15.0 10.0	10.0 8.3 15.0 16.6	

* Except where otherwise stated the levels are following a single dose.

minimal inhibitory concentration *in vitro* for the majority of susceptible organisms (Bliss and Todd, 1949). In most of the cases this level was attained in two hours.

Chloramphenicol palmitate was absorbed more slowly, less effectively, and over a longer period than the crystalline form. Plasma levels in general above 10 μ g. per ml. could be maintained by a dose of 25 mg. per kg. six-hourly. Such a dose would be incapable of effecting an adequate therapeutic level in the first few hours. This could be accomplished in most cases, however, by giving an initial dose of 100 mg. per kg.

Summary and Conclusions

Crystalline chloramphenicol was more quickly and completely absorbed in the newborn than the palmitate form, the use of the latter offering no particular advantages.

TABLE 1

RESULTS WITH CRYSTALLINE CHLORAMPHENICOL

Dose (mg. kg.)	Plasma Levels* (μ g./ml.)			
	2 Hours	6 Hours	10 Hours	24 Hours
25	< 5.0 < 5.0 < 5.0 * 5.5 * 8.3 * 10.0 12.5 * 15.0 16.6 16.6 * 16.6 * 25.0	< 5.0 < 5.0 < 5.0 6.3 8.3 6.3 8.3 16.6 7.1 8.3 10.0 16.6		
50	6.3 10.0 * 12.5 * 15.0 16.6 16.6 * 16.36 * 16.36 * 25.30 25.30 20.30 35.30	5.5 5.5 16.6 12.5 16.6 16.6 16.36 12.35 16.36 25.30 20.30 50.30	< 5.0 < 5.0 8.3 10.30 25.30 Contd. six hrly. ..	25.30 50.30
75	11.31 14.33 16.36 20.30 25.30	12.35 20.30 33.33 33.33 50.30		
	24 Hours	48 Hours	72 Hours	
25 every six hours ..	14.3 16.6 20.0 25.0 33.3	20.0 16.6 20.0 25.0 20.0	33.3 16.6	

* These samples are from premature infants, all of whom weighed over 31 lb. 8 oz.

+ Except where otherwise stated the levels are following a single dose.

A dosage of 25 mg. per kg. of the crystalline preparation six-hourly, and 100 mg. per kg. of the palmitate initially followed by 25 mg. per kg. six-hourly, is suggested.

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palmitate and the pure crystalline chloramphenicol for standardization.

REFERENCES

- Bliss, E. A. and Todd, G. P. (1949). *J. Bact.*, **58**, 61.
 Doorenbos, W. and Kop, J. (1951). *Lancet*, **1**, 691.
 Gill, P. F. (1950). *Med. J. Aust.*, **i**, 768.
 Gray, J. D. (1952). Personal communication.
 Kelly, R. S., Hunt, A. D. Jr. and Tashman, S. G. (1951). *Pediatrics*, **8**, 362.
 Ley, H. L., Smadel, J. E. and Crocker, T. T. (1948). *Proc. Soc. Exp. Biol.*, N. Y., **68**, 9.
 Ross, S., Burke, F. G. and Rice, E. C. (1952). *Antibiot. and Chemother.*, **2**, 199.
 Wilson, L. E., Harris, M. S., Henstell, H. H., Witherbee, O. O. and Kahn, J. (1952). *J. Amer. med. Ass.*, **149**, 231.