References

Gardner, P. S., McQuillin J., and Court, S. D. M. (1970). Speculation on pathogenesis in death from respiratory syncytial virus infection. *British Medical Journal*, **1**, 317–330.

Glasgow, J. F. T., and Ferris, J. A. J. (1968). Encephalopathy and visceral fatty infiltration of probable toxic aetiology. *Lancet*, **1**, 451–453.

Hogan, G. R., Ryan, N. J., and Hayes, A. W. (1978). Letter: Aflatoxin B1 and Reye's syndrome. *Lancet*, **1**, 561.

Linneman, C. C., Jr, Shea, L., Partin, J. C., Schubert, W. K., and Schiff, G. M. (1975). Reye's syndrome: epidemiologic and viral studies, 1963–1974. *American Journal of Epidemiology*, **101**, 517–526.

McQuillin, J., and Gardner, P. S. (1968). Rapid diagnosis of respiratory syncytial virus infection by immunofluorescent antibody technique. *British Medical Journal*, **1**, 602–605.

Reye, R. D. K., Morgan, G., and Baral, J. (1963). Encephalopathy and fatty degeneration of the viscera: a disease entity in childhood. *Lancet*, **2**, 749–752.

Shield, L. K., Coleman, T. L., and Markesbery, W. R. (1977). Methyl bromide intoxication: neurologic features, including simulation of Reye's syndrome. *Neurology (Minneapolis)*, **27**, 959–962.

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Chloramphenicol and phenobarbitone—a drug interaction

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SUMMARY Two infants with meningitis who were treated with phenobarbitone and high-dose chloramphenicol showed progressive falls in the peak blood levels of chloramphenicol. A standard chloramphenicol dose of 50 mg/kg daily would have produced subtherapeutic blood levels after only a few days. The importance of measuring serial blood chloramphenicol concentrations is stressed.

Infants and young children with bacterial meningitis are often treated with phenobarbitone to prevent convulsions. Chloramphenicol is the antibiotic of choice for the treatment of *Haemophilus influenzae* meningitis. A possible interaction between these two drugs is recognised (Bella *et al.*, 1968) but has not been specifically reported in man. We therefore report two infants with *H. influenzae* meningitis treated with phenobarbitone and chloramphenicol, in whom peak blood levels of chloramphenicol decreased with time in spite of maximum recommended dosage. The first case alerted us to the problem, the second prompted a more detailed study.

Case reports

Case 1. This 7-month-old girl presented with a 4-day history of upper respiratory infection, followed on the day of admission by fever, lethargy, irritability, and refusal to feed. Cultures of blood and CSF gave a pure growth of *H. influenzae*, sensitive to chloramphenicol. She was treated with IV chloramphenicol succinate (100 mg/kg per 24 h) plus phenobarbitone (10 mg/kg per 24 h). Blood chloramphenicol concentration was measured by bioassay based on the method described by Louie *et al.* (1976). Peak blood chloramphenicol levels were 31 mg/l on days 2 and 3 but they fell to less than 5 mg/l on day 5. On day 6 oral treatment with pure chloramphenicol in the same dose was substituted. On day 8 the peak blood level was still < 5 mg/l and the dose of chloramphenicol was therefore doubled (200 mg/kg per 24 h). Subsequently, peak blood levels of between 7 and 11 mg/l were maintained until day 23, when treatment was stopped. Her subsequent progress was unremarkable and she remains in good health 12 months later.

Case 2. This 3-month-old boy presented with a one-day history of vomiting, fever, lethargy, and irritability culminating in a brief convulsion. Cultures of blood and CSF gave a pure growth of *H. influenzae*, sensitive to chloramphenicol. He was treated with IV chloramphenicol succinate (100 mg/kg per 24 h) for 8 days, before being changed to oral pure chloramphenicol in the same dosage. He was treated throughout his illness with phenobarbitone (10 mg/kg per 24 h). Chloramphenicol was given for a total of 19 days and he made a full recovery. Although chloramphenicol blood levels were initially satisfactory, they fell rapidly during the first few days of IV treatment (Figure). The biological half-life of chloramphenicol fell from 7 h 18 min on the 3rd day to 4 h 6 min on the 5th.

Discussion

90% of chloramphenicol is inactivated in the liver either by conjugation with glucuronic acid or by reduction to aryl amines before being excreted in the urine. The remaining 10% is excreted unaltered in the urine. In these two infants there was a rapid

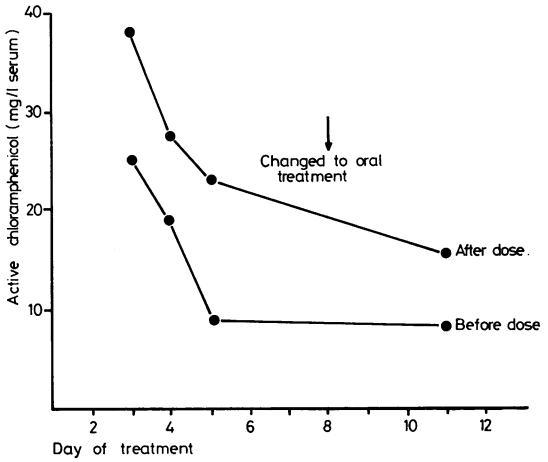

Figure *(Case 2) Blood levels of active chloramphenicol during treatment with chloramphenicol 100 mg/kg per 24 h plus phenobarbitone 10 mg/kg per 24 h. Blood levels were measured before and one hour after the 12 midday dose.*

decline in chloramphenicol blood levels despite sustained IV treatment in high dosage. This decrease is probably explained by the induction of hepatic microsomal enzymes by phenobarbitone. Increased glucuronidation of chloramphenicol and a consequent decrease in therapeutic activity have been demonstrated in rats pretreated with phenobarbitone (Bella *et al.*, 1968).

The conventional chloramphenicol dose for meningitis and septicaemia is 50–100 mg/kg per 24 h in infants and children. A lower dose is usually recommended for neonates whose renal and liver immaturity delays chloramphenicol excretion, but Black *et al.* (1978) showed that doses of up to 95 mg/kg per 24 h may be needed to maintain therapeutic blood levels in this age group also. Our two patients show that during treatment with phenobarbitone even the maximum recommended dose of chloramphenicol, 100 mg/kg per 24 h, may be insufficient to maintain peak blood levels within the therapeutic range 15–25 mg/l. We therefore recommend that in all patients who receive enzyme-inducing anticonvulsants (Conney, 1967), chloramphenicol blood levels should be measured every one or 2 days to avoid the hazards of excessive or inadequate dosage. It is possible that newer anticonvulsants with less enzyme-inducing activity, such as sodium valproate, will prove to have less effect on chloramphenicol metabolism than phenobarbitone.

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References

Bella, D. D., Ferrari, V., Marca, G., and Bonanomi, L. (1968). Chloramphenicol metabolism in the phenobarbital-induced rat. Comparison with thiamphenicol. *Biochemical Pharmacology*, **17**, 2381–2390.

Black, S. B., Levine, P., and Shinefield, H. R. (1978). The necessity for monitoring chloramphenicol levels when treating neonatal meningitis. *Journal of Pediatrics*, **92**, 235–236.

Conney, A. H. (1967). Pharmacological implications of microsomal enzyme induction. *Pharmacological Reviews*, **19**, 317–366.

Louie, T. J., Tally, F. P., Bartlett, J. G., and Gorbach, S. L. (1976). Rapid microbiological assay for chloramphenicol and tetracyclines. *Antimicrobial Agents and Chemotherapy*, **9**, 874–878.

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Food allergy

Response to treatment with sodium cromoglycate

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SUMMARY Two children with food allergy could not be successfully managed on dietary restriction alone. There was a good response to treatment with oral sodium cromoglycate but none to placebo treatment. The use of sodium cromoglycate in the management of food allergy should be studied further.

Allergy to cows' milk and other foodstuffs presents a difficult problem in diagnosis and management in children. Diagnostic criteria were discussed by Walker-Smith (1975). Reports by Freier and Berger (1973) and Kuzemko and Simpson (1975) suggested that treatment with oral sodium cromoglycate might relieve symptoms. Two children are reported who demonstrated specific food intolerance, and their response to treatment with oral sodium cromoglycate is described.

Case reports

Case 1. A baby girl was breast fed for the 1st month