Blood Sugar Changes in Neonatal Hyperbilirubinaemia and Phenobarbitone Therapy

C. Y. YEUNG

From the Department of Paediatrics, University of Hong Kong, Hong Kong

Yeung, C. Y. (1972). *Archives of Disease in Childhood*, **47**, 246. **Blood sugar changes in neonatal hyperbilirubinaemia and phenobarbitone therapy.**

A controlled study was carried out to show the effect of bilirubinaemia and phenobarbitone therapy on the blood sugar metabolism in newborn infants. In the control infants, a significant inverse correlation existed between the serum bilirubin and the blood sugar levels in the first 4 days. The liver seemed to be a factor in producing such a relation. Glucose may be a useful adjunct to the treatment of neonatal hyperbilirubinaemia. Phenobarbitone therapy had significantly raised the blood sugar levels and lowered the serum bilirubin levels in these infants. It is suggested that enhancement of liver function or induction of hepatic enzymes may be the cause.

The blood sugar level of the newborn infant may fluctuate over a wide range in the neonatal period. In a group of healthy Chinese infants, the author (Yeung, 1971) has noted that the blood sugar levels in the first week were lower than those reported in other series (Cornblath and Schwartz, 1966a; Neligan, 1965). Conditions predisposing to hypoglycaemia such as cold injury (Blattner, 1968), brain damage (Shelley and Neligan, 1966), islet cell tumour (François *et al.*, 1962), and inherited metabolic disorders (Cornblath and Schwartz, 1966b), or infants who were small-for-dates (Cornblath *et al.*, 1966) or whose mothers were diabetic (Farquhar, 1970) were not present in the groups studied. Neither was sepsis, which could result in hypoglycaemia (Yeung, 1970), a contributory cause. An important feature, however, was the prevalence of 'idiopathic hyperbilirubinaemia'. 86% of the infants had a serum bilirubin level over 10 mg/100 ml and in a third of them it was over 15 mg/100 ml. Such a marked incidence of hyperbilirubinaemia is not encountered in most Western centres. An attempt was made in this study to find out if there was any correlation between the blood sugar and the serum bilirubin levels in the early neonatal period.

The effect of phenobarbitone therapy in lowering the serum bilirubin levels has been well documented (Lancet, 1971). Such effect has been attributed to

the enhancement of liver function resulting in increased excretion of bilirubin. The liver plays an important role in the maintenance of the blood sugar level. A compound such as phenobarbitone which affects the liver functions through stimulation of the various enzyme systems (Lancet, 1971; Burns, 1964) and protein fractions (Levi, Gatmaitan, and Arias, 1969) may possibly be able to affect the sugar metabolism through a similar mechanism. As yet such information is lacking. A controlled study was designed here to show the effect of phenobarbitone therapy on the blood sugar level in the early neonatal period.

Materials and Methods

Group O infants (38–42 weeks) born of primigravida mothers with blood group O, Rh + and with no complications of pregnancy were allocated alternatively to a control and a treatment group. The latter received syrup phenobarbitone 5 mg 8 hourly for 3 days starting 6 to 8 hours after birth, and the former were given no medication. Infants with birthweights below 2.5 kg and those with erythrocyte glucose-6-phosphate dehydrogenase (G6PD) or pyruvate kinase (PK) deficiencies were not included, because of their known association with neonatal hyperbilirubinaemia. Infants who developed infections during the study period were also excluded because of the frequent association with hypoglycaemia (Yeung, 1970).

Daily serial blood sugar and serum bilirubin estimations were done in the morning after fasting for 3 to 4 hours with heel-pricked capillary samples for 6 days.

The serum bilirubin was estimated by direct spectrophotometry and the true sugar by the semi-microtechnique with Varley's modified method of Asatoor and King (1964). The erythrocyte G6PD and PK activities were detected with the fluorescent spot test (Beutler, 1966).

Results

Twenty-eight term infants were allocated to each of the 2 study groups (Table I). 10 infants were excluded from the study; 8 of them developed sepsis and 2 had erythrocyte G6PD deficiency.

TABLE I
56 Infants Selected for Blood Sugar Study

Clinical Group	No. Included	Number of Infants Excluded		Total
		Infected*	G6PD Deficient	
Control	24	4	0	28
Treated	22	4	2	28

*One had *Esch. coli* septicaemia, 5 had umbilical sepsis, and 2 had gastroenteritis.

In the control infants, an inverse correlation was found between the blood sugar and the serum bilirubin levels. Such relation was found to be statistically significant ($P < 0.05$) on each day for the first 4 days of life (Fig.). Similar correlation was also observed in the first 5 days among the

FIG.—Correlation between serum bilirubin and blood sugar in newborn infants.

infants treated with phenobarbitone ($r = -0.175$ to -0.298), though such correlation did not reach statistical significance.

The effect of phenobarbitone therapy on the blood sugar and serum bilirubin comparing with the controls is shown in Tables II and III. It will be noted that the drug resulted in significant lowering of the serum bilirubin (Table II) and raising of the blood sugar levels (Table III).

TABLE II
Effect of Phenobarbitone Therapy on Serum Bilirubin Level in Newborn Infants

Clinical Group	Age (dy)					
	1	2	3	4	5	6
Control	6.0 ± 2.1*	8.4 ± 2.1	11.0 ± 2.7	12.8 ± 2.7	12.9 ± 3.8	12.3 ± 5.1
Treated	5.5 ± 1.7*	7.4 ± 2.6	8.4 ± 3.2	8.6 ± 3.5	7.6 ± 3.4	6.8 ± 3.2
P value	<0.40	<0.20	<0.005	<0.001	<0.001	<0.001

*Mean serum bilirubin levels ± SD in mg/100 ml.

TABLE III
Effect of Phenobarbitone Therapy on Blood Sugar Level in Newborn Infants

Clinical Group	Age (dy)					
	1	2	3	4	5	6
Control	41.4 ± 15.8*	50.0 ± 17.1	49.5 ± 12.5	52.5 ± 12.4	58.3 ± 15.0	64.6 ± 14.2
Treated	49.8 ± 16.5*	52.5 ± 18.0	60.4 ± 14.0	68.5 ± 12.1	61.3 ± 14.7	63.3 ± 12.5
P value	<0.10	<0.40	<0.001	<0.005	—	—

*Mean blood sugar levels ± SD in mg/100 ml.

Discussion

Hypoglycaemia is common in infants with severe haemolytic disease of the newborn (Raivio and Österlund, 1969; Price, 1969). Hypertrophy of the β -cells of the islets of the pancreas (Brahler and Dallenbach-Hellweg, 1963) and an increased content of extractable insulin (Driscoll and Steinke, 1967) suggested that the hypoglycaemia is mediated through hyperinsulinism. The present study showed that in infants who do not exhibit any features of haemolysis, a significant inverse correlation exists between the serum bilirubin and the blood sugar levels in the first 4 days of life (Fig.). Higher serum bilirubin levels were significantly associated with lower blood sugars. It is not known, however, whether significant hyperinsulinism was present in these infants. The fact that they were selected from normal and otherwise healthy population (except for a degree of hyperbilirubinaemia) makes a postulation of hyperinsulinism unlikely.

Impairment of the liver function is thought to be the cause of unconjugated hyperbilirubinaemia in the majority of jaundiced newborn infants in Hong Kong (Yeung and Field, 1969). The significant lowering of serum bilirubin levels by phenobarbitone in these infants (Yeung and Field, 1969; Yeung *et al.*, 1971) with confirmed evidence of enhancement of liver functions (Catz and Yaffe, 1968; Stern *et al.*, 1970; Yeung and Yu, 1971) offers support for this hypothesis. Such impairment of hepatic function could have resulted in lowering the blood sugar as well. The liver seems to be an important factor in the inverse correlation between the serum bilirubin and the blood sugar levels. Glucose administration to jaundiced infants may therefore serve a dual purpose of providing the necessary ingredient for glucuronidation of bilirubin (Billing and Lathe, 1958) and raising the blood sugar level which is depressed by the hyperbilirubinaemia.

This study also showed that the blood sugar levels were significantly raised on the third and the fourth day by phenobarbitone therapy (Table III). A return of the blood sugar to control levels was observed on cessation of treatment. The serum bilirubin levels were also significantly lowered (Table II). The inverse correlation between the serum bilirubin and the blood sugar levels persisted in the first five days in the treated infants, though the relation has not reached a statistical significant value. The rise in blood sugar in these infants was probably the result of enhancement of liver function or enzymatic induction by phenobarbitone.

The therapeutic value of phenobarbitone in the

treatment of neonatal hypoglycaemia will be rather limited because it takes 2 days before a significant rise of blood sugar could be effected. In jaundiced infants, however, phenobarbitone therapy may be useful not only in preventing further rise of the bilirubin level but also in raising the blood sugar, thus preventing brain damage by the combined effect of hyperbilirubinaemia and hypoglycaemia.

I am grateful to Professor C. Elaine Field for encouragement in this work; to Professor Daphne Chun for access to study the patients at Tsan Yuk Hospital; to Dr. A. Chan for clinical assistance; and to the Director of Medical and Health Services of Hong Kong for permission to publish.

REFERENCES

- Beutler, E. (1966). A series of new screening procedures for pyruvate kinase deficiency, glucose-6-phosphate dehydrogenase deficiency, and glutathione reductase deficiency. *Blood*, **28**, 553.
- Billing, B. H., and Lathe, G. H. (1958). Bilirubin metabolism in jaundice. *American Journal of Medicine*, **24**, 111.
- Blattner, R. J. (1968). Central nervous system damage and hypoglycemia. *Journal of Pediatrics*, **72**, 904.
- Brahler, H. J., and Dallenbach-Hellweg, G. (1963). Die Langerhansschen Inseln bei fetaler Erythroblastose. *Virchows Archiv für Pathologische Anatomie und Physiologie und für klinische Medizin*, **336**, 544.
- Burns, J. J. (1964). Implications of enzyme induction for drug therapy. *American Journal of Medicine*, **37**, 327.
- Catz, C., and Yaffe, S. J. (1968). Barbiturate enhancement of bilirubin conjugation and excretion in young and adult animals. *Pediatric Research*, **2**, 361.
- Cornblath, M., Joassin, G., Weisskopf, B., and Swiatek, K. R. (1966). Hypoglycemia in the newborn. *Pediatric Clinics of North America*, **13**, 905.
- Cornblath, M., and Schwartz, R. (1966a). *Disorders of Carbohydrate Metabolism in Infancy*, p. 38. Saunders, Philadelphia and London.
- Cornblath, M., and Schwartz, R. (1966b). *Disorders of Carbohydrate Metabolism in Infancy*, p. 115. Saunders, Philadelphia and London.
- Driscoll, S. G., and Steinke, J. (1967). Pancreatic insulin content in severe erythroblastosis fetalis. *Pediatrics*, **38**, 448.
- Farquhar, J. W. (1970). The infant of the diabetic mother. *Postgraduate Medical Journal*, **45**, 806.
- François, R., Pradon, M., Sherrer, M., and Ugliengo, A. R. (1962). Hypoglycemia due to pancreatic islet cell adenoma. *Journal of Pediatrics*, **60**, 721.
- Lancet* (1971). Editorial. Jaundice of the newborn and phenobarbitone, **1**, 119.
- Levi, A. J., Gatmaitan, Z., and Arias, I. M. (1969). Deficiency of hepatic organic anion-binding protein as a possible cause of non-haemolytic unconjugated hyperbilirubinaemia in the newborn. *Lancet*, **2**, 139.
- Neligan, G. A. (1965). *Recent Advances in Paediatrics*, 3rd ed., p. 110. Ed. by D. Gairdner. Churchill, London.
- Price, H. V. (1969). Hypoglycaemia complicating haemolytic disease of the newborn. *Archives of Disease in Childhood*, **44**, 248.
- Raivio, K. O., and Österlund, K. (1969). Hypoglycemia and hyperinsulinemia associated with erythroblastosis fetalis. *Pediatrics*, **43**, 217.
- Shelley, H. J., and Neligan, G. A. (1966). Neonatal hypoglycaemia. *British Medical Bulletin*, **22**, 34.
- Stern, L., Khanna, N. N., Levy, G., and Yaffe, S. J. (1970). Effect of phenobarbital on hyperbilirubinemia and glucuronide formation in newborns. *American Journal of Diseases of Children*, **120**, 26.

- Varley, H. (1964). *Practical Clinical Biochemistry*, 3rd ed., p. 35. Heinemann, London; Interscience, New York.
- Yeung, C. Y. (1970). Hypoglycemia in neonatal sepsis. *Journal of Pediatrics*, **77**, 812.
- Yeung, C. Y. (1971). Some disorders of carbohydrate metabolism in newborn. *Bulletin of the Hong Kong Medical Association*, **23**, 53.
- Yeung, C. Y., and Field, C. E. (1969). Phenobarbitone therapy in neonatal hyperbilirubinaemia. *Lancet*, **2**, 135.
- Yeung, C. Y., Tam, L. S., Chan, A., and Lee, K. H. (1971). Phenobarbitone prophylaxis for neonatal hyperbilirubinemia. *Pediatrics*, **48**, 372.
- Yeung, C. Y., and Yu, V. Y. H. (1971). Phenobarbitone enhancement of bromsulphalein clearance in neonatal hyperbilirubinemia. *Pediatrics*, **48**, 556.

Correspondence to Dr. C. Y. Yeung, Paediatric 'B' Unit, Queen Elizabeth Hospital, Kowloon, Hong Kong.