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Jaundice in preterm infants with hypoxia of various severity*

By

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Maximum serum bilirubin concentration and the possible influencing factors were studied in three groups of preterm infants suffering from hyaline membrane disease. The groups were selected according to the severity of hypoxia, estimated on clinical grounds. It was found that the severity of hypoxia per se did not influence the peak bilirubin level. From among the parameters studied, only caloric intake correlated significantly and negatively with maximum bilirubin concentration in the total patient material, and more strongly in the surviving infants.

The role of hypoxia in lowering toxic bilirubin concentration has well been established [4, 7, 9]. Much more debated is, however, whether hypoxaemia, hypercarbia and acidosis by themselves increase the hyperbilirubinaemia. Difficulties in answering the question are due to the fact that serum bilirubin level depends on the balance of production and excretion, both determined by many mechanisms. In a previous study (2) it was concluded that jaundice may have varied widely in preterm and full term infants with perinatal hypoxia, which probably did not influence the hyperbilirubinaemia.

The severity of perinatal hypoxia can be variable and no satisfactory method to quantify it could so far been found. Consequently, the patient material studied by us previously must have been inhomogeneous from this point of view. For this reason an attempt has been made to study and compare the jaundice of preterm infants with perinatal hypoxia of various severity, as reflected by their postnatal history and final outcome.

Patients and Methods

Sixty preterm infants (gestational age $\leq$ 36 weeks) with postnatal hypoxia were studied. Hypoxia was assumed to have occurred if hyaline membrane disease could be diagnosed on admission, on the basis of physical examination, X-rays and blood pH status. Serum bilirubin estimations were done by the Jendrassik–Gróf method daily, until the concentration of bilirubin had begun to fall. Babies with haemolytic disease due to blood group incompatibility

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and those with perinatal infection or extravasated haematoma were excluded. All infants were treated with phenonarbital and received phototherapy for icterus prevention. Fluid and caloric requirements were covered by parenteral infusion of 5—10% glucose in water and/or human milk. Oral or tube feeding was initiated as soon as possible. For treatment of respiratory distress, accepted methods of oxygen and ventilation therapy, acidosis correction with bicarbonate and transfusions were applied according to need.

To separate groups of infants with hypoxia and oxygen dependency of various severity, patients were selected and evaluated in three groups of twenty each, according to the final outcome, such as survivors, those who died with hyaline membrane disease (HMD), and those who died of hyaline membrane disease complicated by intraventricular haemorrhage (HMD + IVH). At postmortem examination, pulmonary histology was studied in every case.

In each group of newborn infants the following parameters were determined: (1) birthweight; (2) gestational age; (3) maximum bilirubin concentration; (4) postnatal age when maximum bilirubin concentration was detected; (5) haemoglobin level and haematocrit, determined in peripheral venous blood within six hours of birth; (6) maximum postnatal decrease in haemoglobin and haematocrit; (7) the lowest arterial pH, the highest negative base excess and pCO_2, measured in peripheral arterial blood postnatally; (8) average caloric intake in kcal/kg/day; (9) average fluid intake in ml/kg/day. The latter two parameters were calculated for the first postnatal week.

In each group of infants correlation analysis was performed between maximum bilirubin concentration and all the other parameters studied and detailed above. The significance of correlation between maximum bilirubin level and gestational age, birthweight, caloric and fluid intake was also tested in the total population of babies studied.

In most cases no reliable data were available concerning prenatal or sub partu drug treatment of the mothers.

Results

Birthweight and gestational age of infants in the three study groups is shown in Table I. It can be seen that survivors were more mature as they

Table I

Birthweight and gestational age of the infants studied

	No.	Mean	SD	SE	Range	p<
Birthweight (g)						
S	20	2059	349	78	1380—2630	0.01 0.001
HMD + IVH	20	1606	550	123	900—3100	ns
HMD	20	1598	414	92	900—2250	
Gestational age (weeks)						
S	18	33.3	1.7	0.4	30—36	0.05 ns
HMD + IVH	16	31.4	2.7	0.6	27—36	ns
HMD	13	31.9	2.2	0.6	28—35	

Abbrevations: S = survivors; HMD + IVH = infants who died of hyaline membrane disease associated with intraventricular haemorrhage; HMD = infants who died of hyaline membrane disease.

TABLE II

Biochemical and some clinical data of the three groups of newborn infants studied

	No.	Mean	SD	SE	Range	p<
Max. bilirubin conc. (mg/dl)						
S	20	14.0	4.9	1.1	4.1—22.3	ns
HMD + IVH	20	15.3	3.9	0.8	7.6—24.0	0.01 > ns
HMD	20	12.4	2.4	0.5	8.5—17.4	
Postnatal age (days)						
S	20	4.5	0.9	0.2	3—6	ns
HMD + IVH	20	4.0	1.0	0.2	3—6	> 0.01
HMD	20	3.6	0.7	0.1	2—5	ns
Haemoglobin (g/dl)						
S	20	18.4	2.7	0.6	15.0—25.0	ns
HMD + IVH	20	17.2	2.8	0.6	12.9—25.0	> ns
HMD	20	18.1	1.9	0.4	14.0—22.2	ns
Haematocrit per cent						
S	20	57.7	6.5	1.4	48—75	0.05
HMD + IVH	20	53.0	6.7	1.5	40—64	> ns
HMD	20	55.8	6.2	1.4	40—67	ns
△ *Haemoglobin (g/dl)*						
S	20	3.1	1.9	0.4	0.8—7.9	ns
HMD + IVH	20	4.8	3.2	0.7	0.5—9.3	> ns
HMD	20	3.0	1.7	0.3	0.9—6.5	ns
△ *Haematocrit, per cent*						
S	20	12.0	4.2	0.9	3—21	0.01
HMD + IVH	20	18.0	8.9	2.0	4—28	> ns
HMD	20	11.6	5.5	1.2	5—23	0.01
Actual pH						
S	20	7.27	0.06	0.01	7.19—7.27	0.01
HMD + IVH	20	7.20	0.07	0.01	7.07—7.30	> 0.001
HMD	20	7.12	0.12	0.02	6.71—7.27	0.02
Base excess						
S	20	— 9.2	—4.4	—0.9	(—2)—(—15)	ns
HMD + IVH	20	—10.6	—4.6	—1.0	0.0—(—20)	> ns
HMD	20	—10.2	—3.7	—0.8	(—3)—(—17)	ns
pCO_2						
S	20	54.6	17.9	4.0	25—92	ns
HMD + IVH	20	63.0	13.8	3.0	38—96	> ns
HMD	20	70.0	14.0	3.1	46—95	ns
Fluid intake (ml/kg/day)						
S	20	101	13.2	2.9	76—123	0.001
HMD + IVH	20	70	18.8	4.2	37—111	> 0.001
HMD	20	69	9.4	2.1	55— 92	ns
Caloric intake (kcal/kg/day)						
S	20	74.2	45.1	10.0	28.7—198.0	0.01
HMD + IVH	20	28.7	10.8	2.4	17.4— 52.1	> 0.001
HMD	20	25.6	3.8	0.8	22.9— 33.2	ns

Abbrevations: S = survivors; HMD + IVH = infants who died of hyaline membrane disease associated with intraventricular haemorrhage; HMD = infants who died of hyaline membrane disease.

were significantly heavier ($p < 0.01$ and $p < 0.001$) and of longer gestational age than those who died. All the other parameters determined or calculated are detailed in Table II. Peak bilirubin concentration was detected in all groups on the 4—5th postnatal day. It was significantly ($p < 0.01$) higher in infants with hyaline membrane disease associated with intraventricular haemorrhage than in those who died but in whom no intraventricular haemorrhage was found at autopsy. Maximum bilirubin concentration of the survivors was slightly but not significantly higher than that of HMD infants (14.0 vs 12.4 mg/dl and lower than the peak bilirubin level of HMD + IVH babies (14.0 vs 15.3 mg/dl). A wide range of individual maximum bilirubin values characterized all groups of infants.

The mean haemoglobin level measured in peripheral venous blood within six hours of birth was similar in the three study groups, and they displayed no significant difference in the fall of haemoglobin concentration. As for the haematocrit and its decrease, the initial haematocrit was the lowest in IVH babies and the fall of haematocrit was significantly ($p < < 0.01$) greater in IVH than in survivors or HMD babies.

The worst negative base excess and the highest pCO_2 values measured during the patients' postnatal course were similar ($p > 0.05$) in the three study groups. The lowest mean actual pH, 7.12, occurred in the HMD pa-

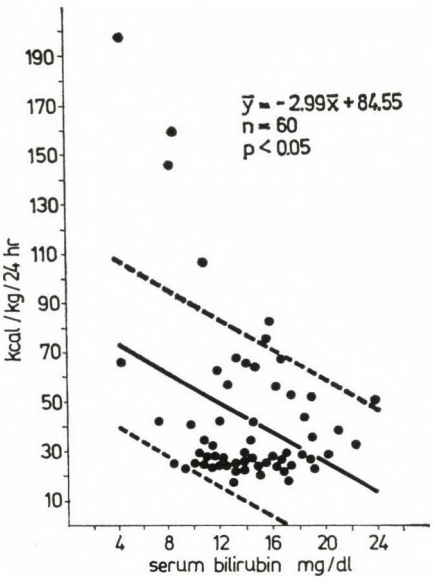

FIG. 1. Correlation between caloric intake and peak bilirubin concentration in sixty preterm infants suffering from perinatal hypoxia of various severity

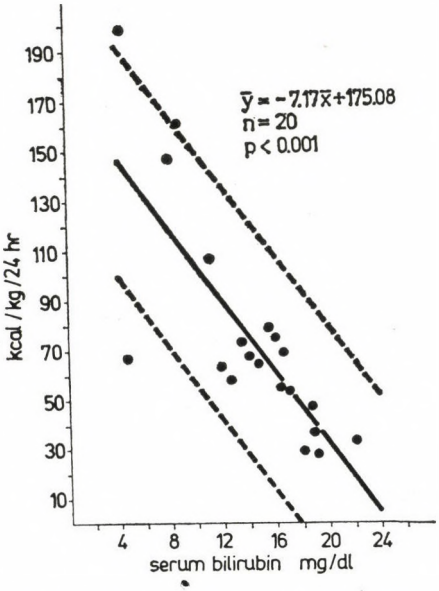

FIG. 2. Correlation between caloric intake and maximum serum bilirubin concentration in twenty preterm infants who survived hyaline membrane disease

tients, while the highest one, 7.27, in the group of survivors.

Table II shows that the survivors received significantly ($p < 0.001$) more fluid (101 ml/kg/day) and calories (74.2 kcal/kg/day) than either the HMD patients (69 ml/kg/day and 25.6 kcal/kg/day) or the HMD + IVH infants (70 ml/kg/day and 28.7 kcal/kg/day).

Birthweight, gestational age, initial haemoglobin level and haematocrit, furthermore the fall in the latter two parameters did not correlate significantly with the maximum bilirubin concentration in any of the groups. Neither was there a relation between peak bilirubin concentration and the pH status. In the total population of infants and also in the group of survivors, the maximum bilirubin level correlated significantly and inversely with caloric intake ($r = -0.3086$, $p < 0.05$ and $r = -0.7828$, $p < < 0.001$, respectively) but not with fluid intake (Figs 1 and 2). No statistically significant correlation was found in any of the other parameter-pairs tested.

Discussion

Serum bilirubin concentration depends on the balance of production and excretion of bilirubin. All factors increasing the former and/or decreasing the latter may cause a rise of the level. Consequently, with an inverse change of the balance a fall in bilirubin concentration will result.

It has generally been accepted that neonatal hypoxia increases the risk of kernicterus. This might be due either to a rise of the free bilirubin fraction of of the total indirectly reacting bilirubin concentration, but the role of altered permeability of the blood-brain barrier should also be taken into account.

The present study was undertaken to investigate the possible relationship between the severity of hypoxia and hyperbilirubinaemia, on the one hand, and an attempt was made to find perinatal parameters correlated with the peak bilirubin concentration of preterm infants with postnatal hypoxia, on the other hand.

Since the development of neonatal indirect hyperbilirubinaemia is hardly predictable, and its severity depends on too many determinants, selection of an optimum control group would have been difficult, if not impossible. For this reason, we grouped newborn infants partly with common characteristics like prematurity, hyaline membrane disease, intraventricular haemorrhage, and partly with different ones, such as the severity of hypoxia and oxygen dependency, haemoglobin and haematocrit level, fluid and caloric intake, birthweight and gestational age. The severity of hypoxia was classified on clinical grounds, i.e. according to the postnatal course of the patients. We assumed that treatment being principally similar in the three study groups, it was correct to suppose that survivors experienced the least, and those who died of hyaline membrane disease associated with intraventricular haemorrhage the most, severe hypoxic insult.

Mean peak bilirubin concentration in the three groups was practically similar. The highest bilirubin level was measured in patients with intraventricular haemorrhage, a slightly lower one in the survivors, and a similar ($p > 0.05$) level which, however, was significantly ($p < 0.01$) lower than that in the newborns with intraventricular haemorrhage, was observed in infants who died of hyaline membrane disease not associated with intraventricular haemorrhage. Considering the remarkably wide range of individual values found in all three groups of infants, it has been concluded that no direct relation exists between hypoxia and the severity of hyperbilirubinaemia.

The results of this study demonstrated in addition that birthweight, gestational age, initial erythrocyte mass have no predictive value as to the expectable peak bilirubin concentration. Similarly, no conclusive relation was found between the bilirubin level and the parameters reflecting the least compensated acid-base status of the patients, and the maximum fall in haemoglobin and haematocrit. The lack of a statistically significant correlation between the above parameters does not exclude the additional and most certainly combined effect of the factors in terms on changes in bilirubin concentration.

A positive finding was the significant ($p < 0.05$) inverse correlation between the peak bilirubin level and caloric intake in the total of newborn infants studied and also in the group of survivors ($p < 0.001$). The cause of this relationship remains obscure although several explanations can be offered [1, 3, 5]. Considering the low caloric content of fluids infused parenterally to the patients, it is obvious that a greater caloric intake could be achieved if more of the total fluid and caloric supply could be given orally. The beneficial effect of early feeding on neonatal jaundice has been suggested by several workers [6, 8, 10, 11]. In the present study the time of the first feeding was not evaluated from the point of view of hyperbilirubinaemia, but the greater mean caloric intake certainly represented an earlier oral feeding with rapidly increasing volume input. It seems therefore logical to conclude that oral feeding and/or a higher caloric intake, at least above the appropriate level, lessens hyperbilirubinaemia of newborn infants with hypoxia and oxygen dependency. The effect may be due to the reduced enterohepatic recirculation of deconjugated bilirubin or to an increased bilirubin clearance which is in some way related to the caloric supply.

The practical implication of the study is that caloric supply should be initiated as soon as possible; besides, a satisfactory caloric supply appears to be advantageous for the prevention of hyperbilirubinaemia.

Reference

1. Bevan, B. R., Holton, J. B.: Inhibition of bilirubin conjugation in rat liver slices by free fatty acids, with relevance to the problem of breast milk jaundice. Clin. chim. Acta, **41**, 101 (1972).

2. Fekete, M., Horváth, M., Vincellér, M.: Perinatal asphyxia and jaundice in newborn infants. Acta paediat. Acad. Sci. hung. **19**, 17 (1978).
3. Foliot, A., Ploussard, J. P., Housset, E., Christoforov, B., Luzean, R., Odièvre, M.: Breast milk jaundice: In vitro inhibition of rat liver bilirubin uridine diphosphate glucuronyl-transferase activity —and Z protein-bromosulfophthalein binding by human breast milk. Pediat. Res. **10**, 594 (1976).
4. Gartner, L. M., Snyder, R. N., Chabon, R. S., Bernstein, J.: Kernicterus. High incidence in premature infants with low serum bilirubin concentrations. Pediatrics **45**, 906 (1970).
5. Hargreaves, T.: Effect of fatty acids on bilirubin conjugation. Arch. Dis. Child. **48**, 446 (1973).
6. Laurance, B. M., Smith, B. H.: The premature baby's diet. Lancet **1**, 589 (1962).
7. Phibbs, R. H., Johnson, P., Kitterman, J. A., Gregor, G. A., Tooley, W. H.: Cardiorespiratory status of erythroblastotic infants. Relationship of gestational age, severity of hemolytic disease and birth asphyxia to idiopathic respiratory distress syndrome and survival. Pediatrics **49**, 5 (1972).
8. Smallpeice, V., Davies, P. A.: Immediate feeding of premature infants with undiluted breast milk. Lancet **2**, 1349 (1964).
9. Stern, L., Doray, B. H.: Hypothermia, acidosis and kernicterus in small premature infants. Proc. XII. Int. Congr. Pediatrics, Mexico City 1968. Vol. 3, p. 465.
10. Wharton, B. A., Bower, B. D.: Immediate or later feeding for premature babies. A controlled trial. Lancet **2**, 969 (1965).
11. Wu, P. Y. K., Talmann, P., Gabler, M., Vaughan, M., Metcoff, V.: Early versus late feeding of low birth weight neonates; effect on serum bilirubin, blood sugar and responses to glucagon and epinephrine tolerance tests. Pediatrics **39**, 733 (1967).

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