Addendum

Since this paper was submitted recurrent gastroenteritis associated with different rotavirus serotypes has been reported by Fonteyne *et al.* (1978) and Rodriguez *et al.* (1978).

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Pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia

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SUMMARY 100 term (gestation at least 37 weeks), vertex presenting, vaginally delivered, and fetomaternal blood-group-compatible neonates were studied to evaluate the pathogenesis of neonatal hyperbilirubinaemia induced by oxytocin. 50 infants were born after oxytocin infusion for augmentation of labour and the other 50 were delivered spontaneously. The babies born after oxytocin induction of labour attained significantly higher serum bilirubin levels at age 72 ± 12 hours than the controls. Infants born after oxytocin showed significant hyponatraemia, hypo-osmolality, and enhanced osmotic fragility of erythrocytes at birth. These biochemical and physiological alterations can be explained by the antidiuretic effects of oxytocin and concomitant administration of large quantities of electrolyte-free dextrose solutions used to administer it. Our observations suggest that cord serum sodium and/or osmolality should be estimated and infants with serum sodium <125 mmol/l and/or osmolality <260 mmol/kg should be considered for prophylactic administration of phenobarbitone.

The role of oxytocin in causing neonatal hyperbilirubinaemia is now generally accepted (Osaki, 1975; Chew and Swann, 1977). However, the pathogenesis of such a hyperbilirubinaemia is still a matter of speculation. A relatively immature glucuronyl transferase system due to absence of the hormonal upsurge of normal labour (Sims and Neligan, 1975) and an enhanced placento-fetal transfusion due to oxytocin-induced uterine contractions, with resultant increase in red cell mass in neonates (Osaki, 1975), have been suggested. To explain the pathogenesis of oxytocin-induced neonatal hyperbilirubinaemia, we tested the antidiuretic effect of oxytocin.

Subjects and methods

From September to November 1977, 100 term (gestation at least 37 weeks), vertex presenting, vaginally delivered, fetomaternal blood-group-compatible neonates born at this hospital were studied. 50 of them were born after oxytocin infusion for induction or augmentation of labour (group 1), while the other 50 were delivered

spontaneously (group 2). Oxytocin infusion in 5% dextrose was started at a rate of 2 mU/min (infusate oxytocin concentration of 4 U/l), increasing by 2 mU/min every half-hour, until effective uterine contractions were achieved. The duration of oxytocin administration varied between 4 and 24 hours. Serum bilirubin (Michaelsson's modification of Jendrassik-Grof-Nosseline method), serum sodium (by flame photometer), and serum osmolality (by Fiske osmometer), were estimated in the cord blood samples of all the infants. Serum bilirubin and sodium estimation was again done at postnatal age of 72 ± 12 hours. Saline osmotic fragility of cord blood erythrocytes was determined in 30 infants from

each group. These infants did not differ significantly from the others. Phototherapy was withheld until the sample on day 3 was collected. None of the babies who developed early jaundice (<24 hours) or hyperbilirubinaemia (serum bilirubin $>200 \mu\text{mol/l}$; $>11.7 \text{ mg/100 ml}$) had cephalhaematoma, G-6-PD deficiency, or an intrauterine infection. Statistical significance of differences in serum bilirubin, sodium, osmolality, and red cell osmotic fragility in the two groups was determined by Student's *t* test. The correlation coefficient was calculated between serum sodium and serum osmolality at birth, and serum bilirubin at 72 ± 12 hours of age.

Results

Both groups were comparable as regards distribution of birthweights ($2.83 \pm \text{SD } 0.34$ and $2.79 \pm \text{SD } 0.41 \text{ kg}$ respectively), gestational age ($38.7 \pm \text{SD } 1.8$ and $39 \pm \text{SD } 1.5$ weeks respectively), asphyxia neonatorum, and maternal pre-eclamptic toxemia. Cord serum sodium level was $131.3 \pm \text{SD } 7.0 \text{ mmol/l}$ and osmolality $273.4 \pm 16.6 \text{ mmol/kg}$ in group 1. These values were significantly higher in group 2—namely, cord serum sodium level $137.4 \pm \text{SD } 5.3 \text{ mmol/l}$ and osmolality $288.0 \pm \text{SD } 8.4 \text{ mmol/kg}$ ($P < 0.01$ to < 0.001). Haemolysis started at a higher saline concentration and was completed earlier in group 1 (Fig. 1). Serum bilirubin at birth was $30 \pm 10 \mu\text{mol/l}$ ($1.73 \pm \text{SD } 0.6 \text{ mg/100 ml}$) in group 1, and $29 \pm 9 \mu\text{mol/l}$ ($1.69 \pm \text{SD } 0.5 \text{ mg/100 ml}$) in group 2. At age 72 ± 12 hours, babies in group 1 attained significantly higher mean serum bilirubin levels of $166 \pm 51 \mu\text{mol/l}$ ($9.7 \pm \text{SD } 3.0 \text{ mg/100 ml}$) compared with $113 \pm \text{SD } 44 \mu\text{mol/l}$ ($6.6 \pm 2.6 \text{ mg/100 ml}$) in group 2.

A significantly negative correlation was found between cord serum sodium and osmolality, and serum bilirubin at 72 ± 12 hours of age (Fig. 2). Babies with cord serum sodium level up to 125

Fig. 1 Significantly increased osmotic fragility of cord blood erythrocytes in neonates born after oxytocin infusion during labour is compared with control group. Bars show standard deviation.

Fig. 2 Negative correlation between cord serum osmolality and sodium, and serum bilirubin level at postnatal age 72 ± 12 hours.

mmol/l had a mean serum bilirubin level of $195 \pm \text{SD } 41 \mu\text{mol/l}$ ($11.4 \pm \text{SD } 2.4 \text{ mg/100 ml}$). Those with cord serum sodium levels between 126 and 135 mmol/l, and above 135 mmol/l had a mean serum bilirubin level of $163 \pm \text{SD } 53 \mu\text{mol/l}$ ($9.53 \pm \text{SD } 3.08 \text{ mg/100 ml}$) and $131 \pm \text{SD } 41 \mu\text{mol/l}$ ($7.66 \pm \text{SD } 2.41 \text{ mg/100 ml}$) respectively. The difference is statistically significant ($P < 0.01$).

The hyponatraemia observed at birth in group 1 had disappeared by 72 ± 12 hours, when serum sodium levels were identical in the two groups ($136.53 \pm \text{SD } 6.07 \text{ mmol/l}$ in group 1 and $138.12 \pm \text{SD } 4.58 \text{ mmol/l}$ in group 2).

Discussion

The findings in this study show that oxytocin infusion during labour results in transplacental hyponatraemia and hypo-osmolality, increased osmotic fragility of cord blood erythrocytes, and a higher bilirubin level at postnatal age 72 ± 12 hours. The negative correlation between cord serum sodium and osmolality, and serum bilirubin at age 72 ± 12 hours, strengthens our previous observation that transplacental hyponatraemia and hypo-osmolality play a significant role in the pathogenesis of oxytocin-induced hyperbilirubinaemia (Singhi and Singh, 1977). It is well known that when administered by continuous IV infusion, oxytocin by virtue of its antidiuretic effect results in expansion of maternal extracellular fluid (ECF) with dilutional hyponatraemia and hypo-osmolality (Abdul-Karim and Assali, 1961; Morgan *et al.*, 1977; Schwartz and Jones, 1978). Large amounts of electrolyte-free solution—namely 5% dextrose used as a vehicle for oxytocin infusion—further aggravate these changes. Since maternal and fetal body fluids are in constant transplacental equilibrium, an expansion of fetal ECF, with resultant neonatal hyponatraemia and hypo-osmolality follows (Battaglia *et al.*, 1960; Schwartz and Jones, 1978). When blood is rendered hypo-osmolal, there is an inflow of water into erythrocytes (Blum and Forster, 1970). As a result erythrocytes swell and become osmotically more fragile. Significantly enhanced osmotic fragility of cord blood erythrocytes in the present study supports this hypothesis. These swollen and hyperfragile erythrocytes are easily trapped by the spleen, resulting in net higher bilirubin.

Our observations suggest that caution should be exercised while using oxytocin for induction or

augmentation of labour, especially when additional risk factors for hyperbilirubinaemia coexist. If oxytocin administration is unavoidable, maternal serum sodium and osmolality should be maintained within the normal range by using dextrose saline as a vehicle for oxytocin instead of plain dextrose solution. Cord serum sodium and, if possible, osmolality should be estimated in all babies born after oxytocin-induced or augmented labour. Infants with cord serum sodium level $< 125 \text{ mmol/l}$ and/or osmolality of $< 260 \text{ mmol/kg}$ are at risk of developing hyperbilirubinaemia and should be considered for prophylactic administration of phenobarbitone as an inducer of the hepatic microsomal enzyme system.

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