

# Improvement in auditory and visual evoked potentials in jaundiced preterm infants after exchange transfusion

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**SUMMARY** Two preterm infants with peak serum bilirubin concentrations of 270  $\mu\text{mol/l}$  and 200  $\mu\text{mol/l}$ , respectively showed improvement in the wave peak latencies of the auditory and visual evoked potentials after exchange transfusion. The implications of this observation and the use of evoked potential recording in neonatal jaundice are discussed.

There is uncertainty among neonatologists of what a safe serum bilirubin concentration should be in a small preterm infant.<sup>1-3</sup> This uncertainty has resulted from the lack of an objective method to evaluate the acute cerebral effects of hyperbilirubinaemia. The measurement of auditory brain stem response is a useful clinical tool to monitor the effects, albeit transient, of acute hyperbilirubinaemia in full term infants.<sup>4</sup> Auditory brain stem responses of jaundiced preterm infants have not been studied and visual evoked potentials have not been reported in jaundiced neonates.

We report the changes in the auditory brain stem response and visual evoked potential in two preterm infants after exchange transfusion for hyperbilirubinaemia.

## Case 1

A girl, one of identical twins, weighing 1290 g and group O Rh negative, was born at 32 weeks' gestation by normal delivery to a group B Rh positive mother. There was no asphyxia at birth, but the infant had some facial bruising. On day 3 her serum bilirubin concentration rose to 270  $\mu\text{mol/l}$  and a two volume exchange transfusion was performed.

After the exchange the serum bilirubin concentration was 189  $\mu\text{mol/l}$ ; the auditory brain stem response wave I-III and I-V latency (Fig. 1); and the visual evoked potential negative peak latency shortened (Fig. 2). Serum biochemistry values before and after exchange were pH 7.43 and 7.40; calcium concentrations 1.98 and 2.01 mmol/l; sodium concentrations 145 and 145 mmol/l; potassium

concentrations 4.5 and 3.7 mmol/l; and chloride concentrations 110 and 108 mmol/l.

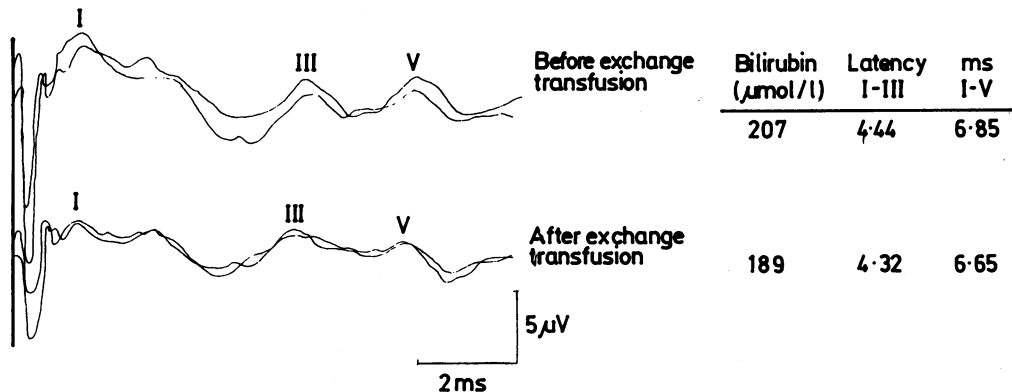
The jaundice resolved. Subsequently, however, the infant required a short period of continuous positive airway pressure for apnoea but eventually made a good recovery.

## Case 2

A 1700 g girl was born by elective caesarian section at 33 weeks' gestation to a gravida 4, para 2, rhesus isoimmunised mother. She underwent serial plasmapheresis antenatally as she had high and rising antibody titres. Apgar score was 8 at one minute. Examination showed a pale infant whose spleen was enlarged by 3 cm and liver by 4 cm. There was no oedema or ascites. The cord blood haemoglobin concentration was 65 g/l and bilirubin concentration 121  $\mu\text{mol/l}$ . Phototherapy was started and at 16 hours of age the serum bilirubin concentration had risen to 200  $\mu\text{mol/l}$ , and a two volume exchange transfusion was performed.

After the exchange transfusion the serum bilirubin concentration fell to 108  $\mu\text{mol/l}$ ; and the auditory brain stem response wave I-III and I-V latencies shortened (Fig. 1). The visual evoked potential negative peak latency also shortened and a first positive peak became distinguishable (Fig. 2). Serum biochemistry values before and after exchange were pH 7.37 and 7.40; calcium concentrations 2.42 and 1.84 mmol/l; sodium concentrations 137 and 137 mmol/l; potassium concentrations 3.2 and 4.0 mmol/l; and chloride concentrations 104 and 100 mmol/l.

## Case 1



## Case 2

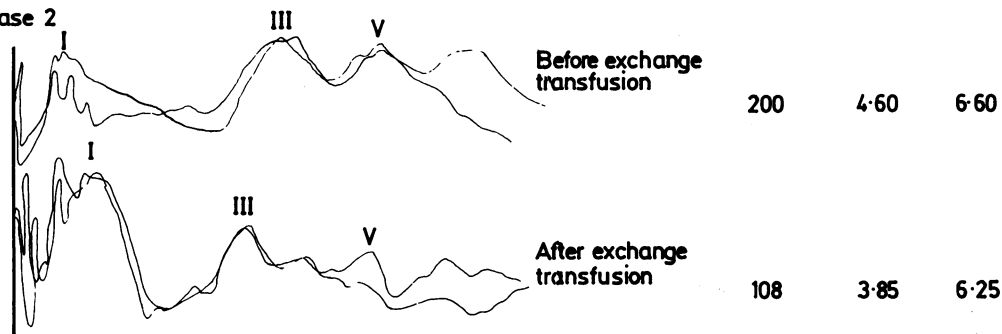


Fig. 1 Auditory brain stem responses in two infants before and after exchange transfusion. Tracings are from the same ear in each case.

No further exchange transfusion was required and the infant made an uneventful recovery.

In both cases, unfortunately, serial recordings were not obtained.

### Methods

This study was part of a larger project to evaluate the use of evoked potential in normal and high risk neonates. The project was approved by the hospital ethics committee.

Auditory brain stem responses and visual evoked potentials were measured with a Nicolet CA-1000 signal averager, and the tests were performed in a quiet side room in the neonatal intensive care unit. Recordings were taken one hour before and one hour after the exchange transfusion.

Auditory brain stem responses were recorded using three Grass gold-cup electrodes that were applied to each earlobe and referenced to the vertex of the infant's head. Impedance was below 2500 ohms. Click stimuli at 90 dbHL and a rate of

11.1/second were presented separately to each ear by handheld earphones with the non-test earpiece masked. A bandpass of 150–3000 Hz was used. The analysis time was 10 milliseconds and 1024 clicks were averaged. At least two trials were done for each ear, and excessive artefacts were automatically rejected.

Visual evoked potentials were recorded by an electrode placed at theinion that was referred to linked ears. The light stimulus was from the light emitting diode goggles (NIC-105) that were placed gently over and covering both eyes. The stimulus rate was 0.9/second, analysis time one second, and 64 flashes were averaged. At least two repeatable waveforms were obtained.

### Discussion

The auditory brain stem evoked response consists of a series of waves that represent the electrophysiological activity of the eighth nerve and the brain stem nuclei. In newborn infants wave I (eighth nerve), III

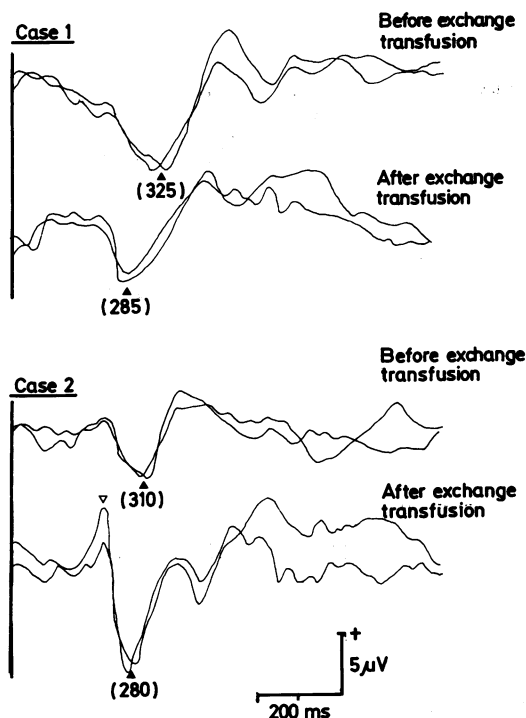


Fig. 2 Visual evoked potentials in two infants before and after exchange transfusion. ▲ = negative peak, ▽ = positive peak. Latency time is given in parentheses. In case 2 a distinct positive peak appears after exchange transfusion.

(superior olive), and V (inferior colliculus) are consistently recordable.<sup>5</sup> Our two preterm infants showed clearly a shortening of the wave I–III and I–V latencies (brain stem transmission time) after exchange transfusion. This indicates objectively improvement in brain stem function after a lowering of the serum bilirubin concentration by exchange transfusion. More dramatic effects of the recovery of the electrophysiological activity of brain stem function after exchange transfusion have been reported by Wennberg *et al*<sup>6</sup> and by us in a larger study.<sup>7</sup> Both studies, however, were of full term infants with haemolytic disease and much higher serum bilirubin concentrations (> 300 μmol/l). We have also shown that larger full term infants had abnormal, albeit transient, auditory brain stem responses even with serum bilirubin concentrations as low as 255 μmol/l.<sup>4</sup> In that study we found an improvement in auditory brain stem response changes, including the shortening of interpeak latency or increase in amplitude or appearance of waves, in nine of 13 jaundiced infants who were

studied sequentially. The findings suggest that the latency changes observed in our two preterm infants were related to the lowering of serum bilirubin concentration.

Visual evoked potentials have been studied in high risk infants with asphyxia at birth<sup>8</sup> and respiratory distress syndrome.<sup>9</sup> The effects of neonatal hyperbilirubinaemia on visual evoked potentials have not been reported. Our infants showed a shortening of the first negative peak latency. This is probably causally related to the lowering of serum bilirubin concentrations after exchange transfusion, as in our experience this negative peak latency varies little individually even on retesting and with maturation. Furthermore, in the second infant the first positive peak appeared only after exchange transfusion. Although this positive peak was inconsistently found in infants below 37 weeks' gestation, its appearance with the reduction in bilirubin concentration suggested a cause and effect relation. The toxic effect of bilirubin on the visual pathway has not been described neither has the visual cortex or pathway been specifically implicated in kernicterus. Studies of kernicterus in Gunn rats by Blanc and Johnson, however, did show some changes in the lateral geniculate bodies.<sup>10</sup> As the negative and positive peaks of the visual evoked potentials may originate from the basal and apical dendrites of the preterm visual cortex<sup>11</sup> hyperbilirubinaemia may effect their functional integrity, transiently at least. Further pathophysiological studies of a larger group of preterm infants are required to verify this observation.

Additional factors relating to the exchange transfusion apart from the reduction of serum bilirubin concentration could have had an influence on the auditory brain stem response and visual evoked potential latencies in our two infants. Asphyxia at birth and acidosis have been noted to alter auditory and visual evoked potential latencies.<sup>8, 12</sup> Both our infants, however, were not asphyxiated at birth and their blood pH was normal before and after the exchange transfusion. It could be conjectured that an increase in colloid osmotic pressure resulting from the exchange transfusion may cause a reduction in cerebral interstitial fluid, which might in turn influence brain stem function.

The findings of altered auditory brain stem responses and visual evoked potentials in two preterm infants with moderate hyperbilirubinaemia raise questions about the safety of the observed serum bilirubin concentrations. In full term infants transient and rapidly reversible alterations of auditory brain stem responses have been described with moderate hyperbilirubinaemia.<sup>4</sup> Analogous serum bilirubin concentrations found in full term infants

have not been associated with any convincing evidence of irreversible bilirubin toxicity at long term follow up.<sup>13 14</sup> Similarly, analogous serum bilirubin concentrations in preterm infants have not been associated with evidence of neurotoxicity at long term follow up.<sup>15 16</sup> Transient alterations of evoked responses may represent reversible neurotoxicity.

The implications of these findings for the management of hyperbilirubinaemia are not clear. The accumulating evidence of the entry of bilirubin to the brain at serum concentrations that were previously considered to be relatively safe and the evidence of the transient nature of the acute neurotoxicity suggest that there is no sharply defined threshold concentration above which bilirubin enters the brain and causes permanent damage.

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