RAPID COMMUNICATION

Plasma brain natriuretic peptide as a predictor of haemodynamically significant patent ductus arteriosus in preterm infants

V. F. PUDDY*, C. AMIRMANSOUR†, A. F. WILLIAMS* and D. R. J. SINGER†‡
*Regional Neonatal Unit, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE, U.K., †Heart Science Centre, Imperial College at the NHLI, Harefield UB9 6JH, U.K., and ‡Department of Pharmacology and Clinical Pharmacology, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE, U.K.

ABSTRACT

Patent ductus arteriosus (PDA) is an important cause of morbidity in extremely preterm infants. As increased plasma brain natriuretic peptide (BNP) is a common feature of adult cardiac disease, we investigated the value of plasma BNP concentration as a predictor of haemodynamically significant PDA in very preterm infants. We studied 18 preterm infants (12 male) of median gestational age 30 weeks (range 24–34), median birth weight 1.46 kg (0.54–2.13) and 11 healthy term controls. Plasma BNP levels were measured by double-antibody radioimmunoassay on days 3, 5 and 7 of life, and an echocardiogram was performed on day 7. Six infants of median gestation 26 weeks (26–30), median birth weight 0.92 kg (0.54–1.04) had PDA proven by echocardiography on day 7. BNP concentrations (pg/ml) on day 3 were significantly higher in these infants than in the remaining twelve [median 2012 (786–2759) versus 42 (7–704), P < 0.001]. In four infants PDA was treated successfully (one surgically, three with non-steroidal anti-inflammatory drugs). Two had haemodynamically insignificant closing ducts. In these infants with therapeutic or spontaneous resolution of a PDA, plasma BNP fell to normal values [median after treatment 9 pg/ml (8–27)]. Early measurement of plasma BNP in the first few days of life is a useful method for predicting those preterm infants who may require intervention for PDA.

INTRODUCTION

In preterm infants, a patent duct is normal on day 3 of life and may remain open in up to 50% of infants until the end of the first week of life. The presence of a haemodynamically significant patent ductus arteriosus (PDA) with a large left-to-right shunt is a common and important cause of morbidity in extremely preterm infants; risk of intraventricular haemorrhage, necrotizing enterocolitis, bronchopulmonary dysplasia and death is increased. Early closure of a haemodynamically significant PDA reduces morbidity [1]. Many parameters have been used to assess the haemodynamic significance of a PDA. Elevated left atrial/aortic root (LA/Ao) ratio > 1.5:1 and a ductal diameter of > 1.4 mm on an echocardiogram are believed to indicate a large left-to-right shunt [2]. However, echocardiographic assessment requires expensive equipment and operator experience which may not be available in all neonatal units. A raised atrial natriuretic peptide level has been reported to be a possible indication for therapeutic closure of a persistent PDA [3]. In this study we assessed the value...

Key words: natriuretic peptides, neonates, patent ductus arteriosus, BNP screening.
Abbreviations: PDA, patent ductus arteriosus; BNP, brain natriuretic peptide; LA, left atrial; Ao, aortic root; ND, not detectable.
Correspondence: Dr D. R. J. Singer, Department of Pharmacology and Clinical Pharmacology, St George’s Hospital Medical School, Cranmer Terrace, London SW17 0RE, U.K. (e-mail d.singer@sghms.ac.uk).
of plasma brain natriuretic peptide (BNP), a recognized indicator of congestive heart failure in adults [4], as an early predictor of haemodynamically significant PDA.

METHODS

Between November 2000 and April 2001 at St George’s Hospital we recruited 18 preterm infants of median gestational age 30 weeks (range 24–34), median weight 1.46 kg (0.54–2.13) and 11 healthy term controls. The St George’s Hospital local research ethics committee approved the study and written parental informed consent was obtained. Preterm infants with a major congenital anomaly (including a cardiac abnormality) were excluded.

<table>
<thead>
<tr>
<th>Table 1 LA/Ao ratio assessed by echocardiography on day 7, and plasma BNP on days 3, 5 and 7 after delivery in very preterm infants with or without persisting PDA by day 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<em>Values are median (interquartile range), <em>P &lt; 0.001 versus no PDA, ŽP = 0.04 versus no PDA.</em></em></td>
</tr>
<tr>
<td><strong>BNP pg/ml</strong></td>
</tr>
<tr>
<td>Day 7: no PDA (n = 12)</td>
</tr>
<tr>
<td>Day 7: PDA (n = 6)</td>
</tr>
</tbody>
</table>

Blood samples (0.5 ml) were taken into K$_2$-EDTA with 1000 units of trasylol (Aprotinin, Bayer, Leverkusen, Germany) on day 3, 5 and 7 of life in preterm infants and collected at delivery in healthy controls. Samples were centrifuged immediately for 15 min at 1500 rpm, at 4 °C, and the plasma was stored at −70 °C until analysis of plasma BNP levels by a double antibody radioimmunoassay (Shionoria, Osaka, Japan). The intra-assay coefficient of variation was 11% for plasma BNP > 20 pg/ml. An echocardiogram was performed on day 7 of life by a single investigator (V.F.P.) blinded to BNP concentration. A 7 MHz probe (Hewlett Packard, Palo Alto, CA, U.S.A.) was used to measure the LA/Ao ratio and PDA diameter (mm). Congenital structural cardiac abnormalities were excluded by completing a standard echocardiogram. The

![Figure 1](image)

**Figure 1** Plasma BNP levels in six very preterm infants with PDA on day 7, in twelve very preterm infants without PDA by day 7 and in eleven healthy infants at term

Results are also shown for the five infants where BNP results were obtained following duct closure. ***P < 0.001 for preterm infants with PDA at day 7 versus those without PDA by day 7. †P = 0.023 for BNP on day 7 for preterm infants without PDA by day 7 versus BNP in healthy infants at term.
decision to treat a PDA was taken by the attending clinician, in accordance with current clinical practice. After echocardiographic confirmation of duct closure, plasma BNP concentration was measured again. Results are expressed as the median and range, interquartile ranges are provided in Table 1, and the data were compared using the Mann–Whitney U test.

**RESULTS**

In the 18 preterm infants, BNP concentrations (pg/ml) on day 3 were median 265 (7–2759), day 5 median 20 [not detectable (ND)–3731] and day 7 median 18 (ND–2522). In the healthy term controls, on delivery median BNP level was 29 (9–190) pg/ml. On day 7, twelve preterm infants had a normal echocardiogram [median gestation 32 weeks (24–34), median birth weight 1.62 kg (0.92–2.12)] and six had a PDA proven by echocardiography without other cardiac disease [median gestation 26 weeks (26–30), median birth weight 0.92 kg (0.54–1.04)]. Four of these six were treated successfully (one by surgical ligation and three using non-steroidal anti-inflammatory drugs); two of the six had haemodynamically insignificant closing ducts. BNP concentrations on days 3, 5 and 7 (P < 0.001) and LA/Ao ratio on day 7 (P = 0.04) were higher in infants with persisting PDA (Table 1). In the absence of PDA, plasma BNP levels by day 3 were similar to values in the healthy term neonatal range (Figure 1). Pharmacological or surgical closure of PDA reduced plasma BNP concentrations to similar levels [median 9 pg/ml (8–27); n = 4].

**DISCUSSION**

Measurement of plasma BNP as early as the third day of life predicts those preterm infants who will have a haemodynamically significant PDA at the end of the first week. We suggest this test may complement or even replace echocardiography as an early indicator of the need to treat the PDA because it is simple and needs only 100 μl of plasma.

The plasma concentration of BNP is raised after birth at term, but falls rapidly to the normal adult range [5] suggesting that it has a role in perinatal circulatory adaptation. Levels correlate with changes in mean pulmonary arterial pressure during the first week of life in preterm infants [6]. Holmstrom and colleagues have suggested that the magnitude of shunting through a PDA is a major determinant of plasma BNP in premature infants, based on clinical and echocardiographic assessment of shunt severity [7]. Our data support this contention; we have observed that the normal fall in plasma BNP, when a PDA has closed by day 7, does not occur when a persistent ductus arteriosus is present. Under these circumstances levels are typically 10-fold greater than in controls on day 3, remaining high until the duct closes. The small number of patients in this study precludes multivariate modelling to evaluate the extent to which BNP provides diagnostic information beyond that obtained from gestational age and birth weight.

A recent placebo-controlled trial of indomethacin, administered prophylactically during the first 3 days of life to 1143 extremely low-birth weight infants, reported a reduced incidence of need for later therapeutic closure but no improvement in neurological outcome or mortality at 18 months [8]. Although prophylactic treatment may seem unjustified by such data, we suggest that the use of BNP screening might improve clinical management. By allowing early identification of infants at risk, BNP screening would offer an opportunity to target therapy and thus to expose only those likely to benefit from early closure to the risk of side-effects associated with treatment.

**ACKNOWLEDGMENTS**

The study was supported by a National Health Service Executive (London Regional Office) Responsive Funding grant (RFG 467). The views and opinions expressed do not necessarily reflect those of NHSE (LRO) or the Department of Health. D.R.J.S. is a member of the St George’s Cardiovascular Research Group.

**REFERENCES**