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Echocardiography predicts closure of patent ductus arteriosus in response to ibuprofen in infants less than 28 week gestational age

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ABSTRACT

Background: Patent ductus arteriosus (PDA) is a frequent problem in preterm infants, and its incidence is inversely correlated with gestational age. The efficacy of medical treatment decreases with decreasing gestational age (GA), and failure rates as well as ductus ligation rates of 40% have been reported in <28 week GA newborns. The aim of this study was to determine whether echocardiographic parameters can predict response to ibuprofen treatment of PDA.
Study design: In a longitudinal study, 29 infants born <28 week GA were screened for a significant PDA (left atrial to aortic root ratio>1.4, anterior cerebral artery resistance index>0.8, and oxygen requirement>35%) at 24–72 h of life and, if a PDA was found, treated with 10–5–5 mg/kg ibuprofen intravenously every 24 h. Ductal parameters were monitored by serial echocardiography. Infant neurodevelopmental outcomes were assessed at 24 month corrected age.
Results: All 15 infants with significant PDA responded to the ibuprofen loading dose indicated by reduced PDA diameters or increased PDA maximum flow velocities (PDA V_{max}), and 7 patients showed an ongoing response resulting in a closed PDA after the 1st cycle (47%). Of the 8 non-responders, 7 received a 2nd cycle with 2 further responders (29%). All non-responders to the 2nd course had a PDA $V_{max} \leq 180$ cm/s and increasing ductal diameters after the 3rd ibuprofen dose of the 1st course.
Conclusion: Maximum flow velocity and diameter of the PDA at the end of the 1st cycle discriminate between responders and non-responders to further ibuprofen treatment.

1. Introduction

PDA is a frequent problem in preterm infants with respiratory distress (RDS) [1–3] and its incidence is inversely correlated with gestational age (GA) [3]. Up to two-thirds of these infants are judged to require pharmacological or surgical treatment for a hemodynamically significant PDA (hsPDA), because the left-to-right shunt is associated with various complications of prematurity [4–6]. Previously prophylactic application of indomethacin was favoured. Now early targeted treatment of the significant PDA, judged by clinical and echocardiographic findings [6] is preferred as a balance between the uncertainties of its benefit and the known side effects of both available COX inhibitors. Indomethacin, which has been widely used for PDA treatment, has more consequences for renal, mesenteric and cerebral perfusion [7,8] than ibuprofen, which is now used frequently. Its higher affinity to albumin and therefore competitive binding with bilirubin may, however, limit its therapeutic range [9]. Meta-analysis reported similar PDA closure rates of between 60 and 80% for both cyclooxygenase-inhibitors [10]. However, the efficacy of the two drugs decreases with decreasing GA, and failure rates as well as ductus ligation rates of 40% have been reported in <28 week GA newborns [11].

Several studies have addressed application and dosage for indomethacin treatment. In fact a shortened treatment course directed by echocardiography was recently published [12], but the ibuprofen dosing regimen (10–5–5 mg/kg for 3 days) is currently based on sparse pharmacokinetic data, and its efficacy in extremely immature infants has not been adequately addressed so far [13–15].

The aims of the present study were to observe the closing patterns of the hsPDA echocardiographically in <28 week GA infants during the first ibuprofen cycle and to explore if permanent closure of the ductus arteriosus can be predicted using data on initial ibuprofen response.

Abbreviations: Ao VTI, flow velocity time integral of the aortic flow; BPD, bronchopulmonary dysplasia; CA, corrected age; CI, cardiac index; CO, cardiac output; CP, cerebral palsy; CRIB, clinical risk index for babies; GA, gestational age; IVH, intraventricular hemorrhage; LA/Ao, left atrial to aortic root ratio; (hs) PDA, (hemodynamically significant) patent ductus arteriosus; PDA V_{max}, maximum flow velocity of the PDA shunt; PDA V_{mean}, mean flow velocity of the PDA shunt; PPHN, persistent pulmonary hypertension of the neonate; PVL, periventricular leukomalacia; RI, resistance index; RDS, respiratory distress syndrome; ROP, retinopathy of prematurity.

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2. Methods

2.1. Patient population

This observational longitudinal study was conducted in a tertiary referral neonatal intensive care unit at the Charité University Hospital, Campus Virchow, Berlin, Germany between July and November 2003. The study was approved by the medical ethics committee of the hospital. The termination of the study coincided with mounting concerns of increasing hyperbilirubinaemia and possible risk of bilirubin encephalopathy due to the interference of ibuprofen with bilirubin–albumin binding [9]. This led to a return to indomethacin treatment in our department.

Inborn infants below 28 week GA were eligible for the study after parental consent if they did not fulfill the following exclusion criteria: major congenital malformations including heart defects or hydrops fetalis. Until 72 h of life, infants were screened daily for hsPDA by echocardiography, where hsPDA was defined as: evidence of a left-to-right shunt through the PDA or retrograde blood flow in the pulmonary artery by color Doppler and at least one of the following parameters (1.) ratio of left atrial to aortic root diameter (LA/Ao ratio) >1.4; (2.) resistance index (RI) in the anterior cerebral artery >0.8; (3.) respiratory setback with a fraction of inspired oxygen of >0.35. Infants not fulfilling these hsPDA criteria served as the control group. All infants with an hsPDA were considered for early therapeutic ibuprofen administration if they did not present persistent pulmonary hypertension of the neonate (PPHN), intraventricular hemorrhage (IVH) grade III or more (Papile classification [16]), neurological disorders with seizures or coma, platelets below 50,000/mm^3 or urine output below 1 ml/kg/h. Pulmonary hypertension was ruled out echocardiographically by measuring the right ventricular systolic pressure in the presence of tricuspid regurgitation and by visualization of the shunt flow direction of the persistent foramen ovale and the PDA. The estimated right ventricular pressure was correlated with the systemic systolic blood pressure.

The remaining infants with an hsPDA received the first dose of 10 mg/kg ibuprofen (Pedea®, Orphan Europe, Paris, France) at a postnatal age between 24 and 72 h and were enrolled in the advanced echocardiographic study protocol while completing the ibuprofen course of two maintenance doses of 5 mg/kg each at 24 hour intervals as a continuous intravenous infusion over 15 min. Infants received a second course of ibuprofen with the same dosing regimen if echocardiography revealed a persistent or re-opened duct after the initial course of ibuprofen and our criteria for an hsPDA were still fulfilled. Surgical ligation was initiated in non-responders to the second course.

2.2. Echocardiography

Comprehensive echocardiographic evaluation to ascertain normality of cardiac anatomy and to rule out PPHN was performed as an initial examination within the first 24 h of life (baseline). Direct visualization of the PDA with pulsed Doppler echocardiography and color flow mapping to diagnose an hsPDA were done repetitively in the parasternal short axis as well as in the high suprasternal axis. The minimal internal ductal diameter was averaged from 3 to 5 measurements in the parasternal short axis with visualization of the ductus in color Doppler mode. The maximum and mean velocities (PDA V_{max}, PDA V_{mean}) of the PDA shunt measured by pulsed Doppler in the parasternal short axis and the LA/Ao ratio in M-mode (parasternal long axis) were recorded. To estimate the cardiac output (CO), the flow velocity time integral of the aortic flow (Ao VTI) and the aortic valve diameter (dAo) were registered and heart rate (HR) recorded by continuous ECG during echocardiography was averaged. The CO was then calculated using the following equation: $CO\ (ml/min) = (\pi \times (dAo/2)^2) \times AoVTI \times HR$. Dividing CO by the infant's birth weight gave the cardiac index (CI). Screening for a new onset of pulmonary hypertension was done in every echocardiographic examination.

Infants of the treatment group underwent echocardiographic assessment 24 h after the first and third doses of ibuprofen. Further echocardiographic investigations were performed depending on outcome after completion of the first ibuprofen cycle. Successful response to ibuprofen treatment was defined as absent ductal shunt flow after therapy. Examination was performed by two experienced echocardiographers using an HDI 3500 (ATL Philips Medical Systems®, Hamburg, Germany) with a curved array transducer of 7.5–10 MHz.

2.3. Concomitant treatment and clinical data

Daily clinical care was performed by the attending neonatologist according to common practices. Standard intravenous fluid administration started with 80–90 ml/kg/d and was augmented daily by 10 ml/kg depending on weight loss and urinary output. Additional medication was given by the attending neonatologist depending on the clinical status of the newborn: In intubated infants, surfactant was administered in doses of 100 mg/kg (Curosurf®, Nycomed Pharma GmbH, Ismaning, Germany). Surfactant administration was repeated in some patients during the first 24 h of life when clinically necessary. Cranial ultrasound scans were performed on days 1 to 3, thereafter on day 7, day 28, before discharge, and when clinically indicated. The RI was calculated as: RI = systolic peak velocity − end diastolic velocity / systolic peak velocity.

The neonates' date and time of birth, mode of delivery, GA, birth weight and gender were recorded and the following clinical parameters were prospectively documented until 24 h after the last ibuprofen dose: CRIB-score, daily weight, fluid intake, urine output, blood pressure, type of ventilatory support, need for supplemental oxygen, and concomitant medication including inotropic support. Data on maternal history and medical treatment including tocolytic drugs and betamethasone for acceleration of fetal lung maturation were gathered retrospectively from the medical records of the mothers.

2.4. Ibuprofen assay

To determine R(−) and S(+) ibuprofen stereoisomer plasma levels, 0.2 ml EDTA blood was drawn 5 min after the saline flush following the initial dose and 24 h after the third. Drug concentration was assessed by high-pressure liquid chromatography in plasma supernatants.

2.5. Outcome data and neurodevelopmental assessment

Bronchopulmonary dysplasia (BPD) was defined as the need for supplementary oxygen at a postmenstrual age of 36 weeks. IVH was graded according to Papile [16]. Cystic periventricular leukomalacia (PVL) was diagnosed by cranial ultrasound. ICROP criteria were used for retinopathy of prematurity (ROP). Cerebral palsy (CP) was diagnosed in keeping with the European consensus paper. Auditory tests were performed to determine hearing impairment with thresholds over 35 dB. Neurodevelopment was evaluated at 24 month corrected age (CA) using the Bayley Scales II of Infant Development for cognitive, social, speech, gross and fine motor skills. A result of less than 70 points (>2SD below the mean of 100 points) indicated severe impairment [17].

2.6. Statistical analysis

SPSS version 11.5 (SPSS Inc., Chicago, Illinois, USA) was used. Statistical calculations involved the Wilcox-test for two independent samples and the chi-square-test for more than two independent samples. A p-value below 0.05 was considered significant.

3. Results

Twenty-nine infants were screened during the study period, whereby 14 infants had to be excluded from early therapeutic ibuprofen treatment