SHORT REPORT

Ibuprofen and cerebral oxygenation and circulation

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The effect of prophylactic administration of ibuprofen on the cerebral circulation in preterm babies was measured with near infrared spectroscopy. No significant difference in the change in cerebral blood volume, change in cerebral blood flow, or tissue oxygenation index was found between administration of ibuprofen or placebo.

A multicentre prospective trial was performed to evaluate the effect of prophylactic ibuprofen on closure of the ductus before it becomes clinically evident and to prevent intraventricular haemorrhage.¹ In patients admitted to this trial in our hospital, we used near infrared spectroscopy to measure changes in cerebral blood volume (CBV), cerebral intravascular oxygenation (HbD (oxyhaemoglobin (HbO₂) – reduced haemoglobin (Hb))), and tissue oxygenation index (TOI) during the administration of ibuprofen or placebo.

Our hypothesis is that, in contrast with indomethacin, ibuprofen does not affect the peripheral circulation and oxygenation (as measured by changes in mean arterial blood pressure, heart rate, peripheral oxygen saturation, and Pao₂) or cerebral circulation and oxygenation (as measured by changes in CBV, HbD, and TOI).

PATIENTS AND METHODS

Patients with a gestational age of less than 31 weeks and a postnatal age of less than 6 hours were included. Exclusion criteria were major congenital malformations, severe congenital maternofetal infection, maternal use of nephrotoxic drugs, intraventricular haemorrhage or cystic leucomalacia before the first administration of the drug, apparent neurological dysfunction, and shock or life threatening infection. Ibuprofen was not started if there was a low platelet count, hyperbilirubinaemia, or a clinical bleeding tendency. The local hospital ethics committee approved the study protocol. Parental consent was obtained for all patients.

Changes in oxyhaemoglobin (ΔHbO_2), reduced haemoglobin (ΔHb), and total haemoglobin (ΔHbT) were measured by near infrared spectroscopy (NIRO300; Hamamatsu, Hamamatsu City, Japan). TOI was calculated using spatially resolved spectroscopy.² All measurements were performed on the right frontoparietal side with a 4 cm interoptode distance. The data were recorded in an analogous way with a sampling frequency of 100 Hz by the data acquisition system Cudas (Dataq Instruments, Akron, Ohio, USA). ΔHbD was calculated as a measure of cerebral blood flow. ΔCBV was calculated as a measure of cerebral blood volume as described by Wyatt *et al.*³ Electrocardiogram, pulse rate, peripheral oxygen saturation, and mean arterial blood pressure were recorded simultaneously by the Cudas system. Paco₂, Pao₂, pH, glycaemia, haemoglobin, and fetal haemoglobin were

measured in an arterial blood sample before and after the infusion.

Ibuprofen lysine or normal saline was given in a double blinded, prospective way. Ibuprofen lysine was made up as a 10 mg/ml solution. This resulted in 1 ml/kg ibuprofen lysine or normal saline on the first day and 0.5 ml/kg on days 2 and 3, given by intravenous infusion for 15 minutes with an interval of 24 hours between doses.

To compare ΔTOI , ΔCBV , and ΔHbD in the placebo and ibuprofen groups, a paired *t* test or a Wilcoxon matched pairs test was used. $p < 0.05$ was considered significant. We calculated that 19 patients were required in each treatment group to find a difference in CBV of 0.1 ml/100 g tissue and a difference in TOI of 5%, with a power of 80%.

RESULTS

Thirty seven babies were studied. The median postmenstrual age was 28 weeks, and the median birth weight was 1080 g. Nineteen babies received ibuprofen, and 18 received placebo. No adverse effects were seen during measurements. Table 1 gives the results.

No significant changes were found in HbD, peripheral oxygen saturation, heart rate, mean arterial blood pressure, Paco₂, or Pao₂. CBV increased significantly in both the ibuprofen and placebo group on day 2. HbT changed significantly for the ibuprofen group on day 1 and for both the ibuprofen and placebo group on day 2.

DISCUSSION

We can conclude that TOI, HbD, and CBV did not change significantly during administration of ibuprofen in comparison with placebo in the first three days in very premature infants. This confirms the study of Patel *et al.*⁴ who compared ibuprofen with indomethacin and found no change in cerebral blood flow and CBV when ibuprofen was given, in contrast with indomethacin which caused a decrease in cerebral blood flow and CBV. Our study gives extra information because it was performed in a double blinded, randomised way in a placebo controlled design, and ibuprofen was given within the first six hours. Furthermore near infrared spectroscopy data were collected on changes in CBV, HbD, and TOI at the same time.

A second important observation was the effect of ibuprofen on peripheral circulation and oxygenation. No change in the continuous measurements of mean arterial blood pressure, heart rate, or peripheral oxygen saturation was found during the infusion of ibuprofen.

A third observation is the increase in HbD, HbT, and CBV in both groups. The infusion of 1 ml/kg and 0.5 ml/kg of fluid would already have caused a considerable and sometimes

Abbreviations: CBV, cerebral blood volume; Hb, reduced haemoglobin; HbO₂, oxyhaemoglobin; HbD, cerebral intravascular oxygenation (HbO₂ – Hb); HbT, total haemoglobin; TOI, tissue oxygenation index

Table 1 Change in cerebral blood volume (Δ CBV in ml/100 g), tissue oxygenation index (Δ TOI in %), cerebral intravascular oxygenation (Δ HbD = Δ HbO₂ - Δ Hb in μ mol/l), total haemoglobin (Δ HbT in μ mol/l), peripheral oxygen saturation (Δ SAT in %), heart rate (Δ HR in beats/min), and mean arterial blood pressure (MABP in mm Hg) after infusion of 10 mg/kg (1 ml/kg) ibuprofen or 1 ml/kg placebo on days 1, 2, and 3

	Day 1		Day 2		Day 3	
	Ibuprofen	Placebo	Ibuprofen	Placebo	Ibuprofen	Placebo
Δ CBV	0.19 (0–0.39)	0.12 (–0.14–0.38)	0.44 (0.23–0.66)*	0.44 (0.17–0.70)*	0.15 (–0.17–0.48)	0.11 (–0.20–0.40)
Δ TOI	2.0 (–0.4–4.2)	–0.7 (–2.9–1.4)	0.5 (0.2–0.7)*	1.2 (–1.2–3.6)	–1.2 (–3.5–1.0)	–4.8 (–12.0–2.5)
Δ HbD	2.9 (–1.4–7.3)	2.4 (–2.3–7.1)	3.7 (–1.6–8.9)	1.4 (–0.9–3.8)	2.7 (–2.1–7.6)	1.8 (–1.8–5.5)
Δ HbT	3.1 (0.1–6.1)*	1.9 (–2.5–6.4)	7.3 (3.6–11.1)*	5.7 (2.4–8.9)*	1.7 (–2.6–5.9)	2.0 (–1.5–5.5)
Δ SAT	–0.3 (–1.2–0.6)	–0.5 (–1.3–0.3)	–0.2 (–1.6–1.1)	–0.3 (–0.9–0.2)	–0.1 (–0.7–1.0)	0.4 (–1.0–1.8)
Δ HR	–0.3 (–3.5–2.9)	0.6 (–2.2–3.5)	1.1 (–2.5–4.8)	–1.0 (–4.7–2.6)	–2.5 (–6.5–1.5)	–1.5 (–1.7–4.7)
Δ MABP	0.9 (–0.5–2.1)	–0.3 (–2.5–1.7)	0.6 (–0.8–2.0)	–0.9 (–2.4–0.5)	2.5 (–2.5–7.6)	–0.8 (–3.1–1.1)

Values are mean (range). There were no significant changes between the groups. Significant changes within the groups—that is, individual changes between the starting and end point of the measurement—are indicated with an asterisk.

significant change in these variables. This confirms the work of Roll *et al*,⁵ who found that a blood sample taken from the umbilical arterial catheter showed a significant decrease in both CBV and HbD.⁵ This reflects the high sensitivity of NIRO300 to even very small changes in blood volume and blood flow. Therefore, if the effect of two drugs or a drug and placebo on cerebral circulation are being studied using near infrared spectroscopy, it is important that the same volumes are used.

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