Effect of infusion rate of indomethacin on cerebrovascular responses in preterm neonates

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SUMMARY Cerebrovascular responses were studied in preterm infants by Doppler ultrasound and cerebral electrical impedance for one hour after intravenous indomethacin infusion for patent ductus arteriosus. Indomethacin in a dose of 0.2 mg/kg body weight was infused over five minutes in one group of infants (20 doses) and over 20 minutes in a second group of infants (16 doses). There were no significant differences between the two groups in birth weight (mean=1068 g, range 569–1950), gestational age (mean 28.4 weeks, range 25–31), or postnatal age (mean 18.1 days, range 6–42).

There was a significant reduction in both the Doppler mean flow velocity in the anterior cerebral artery (mean (SE) –20 (4.2)%) and peak amplitude of cerebral electrical impedance (–26 (3.9)%) within two minutes of starting the indomethacin infusion over five minutes. There was no significant change after the infusion over 20 minutes. There were no significant changes in blood pressure or carbon dioxide tensions after infusion at either rate. The results suggest that infusion of indomethacin over five minutes caused a potentially deleterious reduction in cerebral blood flow. No such reduction occurred when it was infused over 20 minutes.

Indomethacin is widely used to close haemodynamically important patent ductus arteriosus in neonates.^{1,2} Its pharmacokinetics have been studied^{3–6} and its comparative safety established in a collaborative study with a one year follow up.⁷ Various dose regimens have been studied to maximise the clinical efficacy.^{8,9}

Concern arose recently after the observation that therapeutic doses of indomethacin given to preterm neonates may cause a reduction in Doppler blood flow velocity in intracranial arteries.^{10,11} Cowan¹⁰ found a reduction of up to 75% in mean Doppler flow velocity in the intracranial arteries after four doses of 0.2 mg/kg body weight had been given in less than three minutes. Evans *et al*¹¹ found a mean reduction of 39% after 15 doses of 0.2 mg/kg body weight had been given within 15 seconds. Cerebral blood flow measured by the ¹³³xenon clearance technique has been reported to fall by a mean of 22% after six doses of 0.2 mg/kg body weight were given over one minute.¹²

Reduction in cerebral blood flow has also been reported in the fetuses and newborns of several animal species.^{13–16} This may be caused by constriction of the microvasculature^{17–19} in response to

inhibition of prostaglandin synthesis within the endothelium.²⁰ Extrapolating from the result that the largest reduction in cerebral blood flow velocity occurred after the fastest infusion, Cowan¹⁰ recommended that indomethacin be given slowly over at least five minutes.

This study was designed to investigate whether cerebrovascular responses measured by both Doppler ultrasound and cerebral electrical impedance were different when indomethacin was infused over five minutes from when it was infused over 20 minutes.

Patients and methods

The study was performed in two stages. The effect of indomethacin sodium trihydrate (Indocid PDA) infused over five minutes was studied after 20 doses in seven patients. In a further five patients the infusion period was changed to 20 minutes and the response after 16 doses was studied.

Each infant had clinical evidence of a haemodynamically important patent ductus arteriosus and they were all either receiving artificial ventilation or oxygen by headbox. All had received medical

treatment consisting of fluid restriction and (in most cases) diuretics for at least 48 hours before the indomethacin was given. In 11 patients cross sectional echocardiography was done, and the presence of an important patent ductus arteriosus confirmed by a left atrial to aortic root diameter ratio of greater than 1.4:1. Clinical details of the infants are shown in the table.

Indomethacin was given intravenously in a dose of 0.2 mg/kg on three occasions 12 hours apart. Arterial or capillary carbon dioxide tensions were measured before the indomethacin was given. During 10 doses, transcutaneous carbon dioxide tensions were monitored continuously, as were heart rate and peripheral or umbilical arterial blood pressure during 20 doses.

Cerebral electrical impedance was measured as previously described.²¹ The cardiac-synchronous pulsatile impedance change was digitised and 16 cardiac-synchronous wave forms averaged by a dedicated microprocessor. This signal reflected the changes in cranial blood volume during the cardiac cycle. The signal was recorded continuously by chart recorder, and the peak amplitude of cerebral electrical impedance measured. This measurement correlates in infants with the direction of change in cerebral blood flow estimated by ¹³³xenon clearance.²²

Doppler ultrasound examination of blood flow velocity in the anterior cerebral artery was carried out through the anterior fontanelle with a continuous wave system using fast Fourier analysis of the Doppler frequency shift spectrum (Angioscan III). A 4 MHz probe was used in larger babies and an 8 MHz probe in smaller babies. The maximum signal was sought using sound and visual display of the spectrum from the region of the anterior cerebral artery. The Angioscan automatically calculated a mean frequency shift from the spectral information averaged over a memory block that varied from four to six heart beats, depending on the heart rate. The percentage change from the average

of the three baseline measurements of the mean frequency shift was calculated. Doppler examinations were made intermittently, with the probe removed between examinations.

The repeatability of the two methods was calculated to ascertain whether any observed changes might be accounted for by poor repeatability of the techniques. The repeatability coefficient (defined as the limits within which 95% of the differences between two measurements of the same process lay)²³ was calculated from baseline measurements made one and three minutes before indomethacin was given, making certain that the clinical state of the baby was stable during this period.

Doppler examinations were carried out and peak amplitude of cerebral impedance noted at one, two, four, six, eight, and 10 minutes, and then at five minute intervals to one hour from the time indomethacin infusion was started.

Results are shown as mean (SE). Differences between the impedance and Doppler measurements before and after indomethacin were sought by two way analysis of variance, and if a significant difference existed the paired *t* test was used to establish the significance of differences between individual measurements. A *p* value of <0.05 was accepted as significant. The influence of gestational and post-natal age on responses was assessed by multiple linear regression analysis.

Results

The responses of Doppler mean flow velocity and cerebral electrical impedance after infusion of indomethacin over five minutes are shown in figs 1 and 2. The maximum reduction in Doppler mean flow velocity (−20(4.2)%) occurred four minutes after starting the infusion, and the maximum reduction of cerebral electrical impedance (−26(3.9)%) occurred by one minute; these values were significantly different from the baseline values (*p*<0.01 in both cases). The responses after indomethacin

Table Comparability of the groups

Five minute infusion			20 Minute infusion		
Birth weight (g)	Gestational age (weeks)	Postnatal age (days)	Birth weight (g)	Gestational age (weeks)	Postnatal age (days)
1340	29	6	1005	27	42
642	26	7	569	25	8
601	26	11	1123	27	8
1950	32	7	891	28	10
1100	31	21	1414	31	11
883	28	7, 26	1109	30	11
1259	29	8

Fig 1 Percentage change of Doppler mean flow velocity in the anterior cerebral artery after indomethacin infusion over five minutes. Figures are mean (SE).

Fig 2 Percentage change of cerebral electrical impedance peak amplitude after indomethacin infusion over five minutes. Figures are mean (SE).

Fig 3 Percentage change of Doppler mean flow velocity in the anterior cerebral artery after indomethacin infusion over 20 minutes. Figures are mean (SE).

Fig 4 Percentage change in cerebral electrical impedance peak amplitude after indomethacin infusion over 20 minutes. Figures are mean (SE).

infusion over 20 minutes are shown in figs 3 and 4. There was a slight reduction ($-4.2(2.3)\%$) in Doppler flow velocity and an increase ($7.4(4.0)\%$) in cerebral electrical impedance, but these were not significantly different from the baseline values.

Responses to the first, second, and third doses of indomethacin infused over five minutes were not significantly different. The maximum changes in Doppler mean flow velocity for the three doses was $-18(2.1)\%$, $-22(4.1)\%$, and $-20(5.4)\%$; for cerebral electrical impedance they were $-20(6)\%$, $-26(3.2)\%$, and $-30(7.8)\%$, respectively.

There was no obvious trend in the continuous blood pressure recording after indomethacin given over either five or 20 minutes. Transcutaneous carbon dioxide tensions changed inconsistently and apparently independently of the dose of indomethacin. Of the 33 measurements made before the indomethacin was given, only two were more than 6 kPa (1 kPa=7.5 mm Hg). At these times, when

carbon dioxide tensions were 7.1 and 7.8 kPa, the changes in Doppler mean flow velocity and cerebral electrical impedance were similar to the response in the same patient when carbon dioxide tension was <6 kPa. Multiple linear regression analysis of gestational age and postnatal age, with the mean maximum response of Doppler mean flow velocity and cerebral electrical impedance used sequentially as the dependent variable, showed no significant effect of either of these variables on response after indomethacin infused over five minutes.

The repeatability coefficient of Doppler mean flow velocity was 0.59 cm/s (mean 7.19 cm/s) and of cerebral electrical impedance was 2.4 mOhm (mean 22.2 mOhm). In 95% of cases therefore, assuming that the variable had not changed, repeated measurements could be expected to be within 16% of one another for Doppler mean flow velocity and within 22% for cerebral electrical impedance.

Discussion

The early reduction in Doppler mean flow velocity after the five minute infusion of indomethacin is similar to previously published results.^{10 11} Cerebral blood flow decreases within two minutes in newborn animals.¹⁷⁻¹⁹ This change is dose dependent, and in the newborn dog is about 20% with the dose used in this study,^{14 24} which may be just enough to affect the cerebral circulation when infused rapidly but may not have an effect after slower infusion where instantaneous brain blood concentrations are lower. No previous studies have addressed the effect of different infusion rates on cerebrovascular responses. Another possible explanation as to why there was a difference in response after infusion at the two rates is that there was a difference in the two study groups. There were, however, no differences between the groups in gestational age, postnatal age, birth weight, carbon dioxide tension at the start of the infusion, and clinical state.

Whether there are any potentially deleterious effects of a reduction in cerebral blood flow associated with treatment with indomethacin is unknown. In experiments in animals, decreases in cerebral blood flow associated with indomethacin have not been associated with a reduction in cerebral metabolic rates of oxygen or glucose.^{13 25 26}

The repeatability coefficients of both Doppler mean flow velocity and cerebral electrical impedance suggest that the reduction after the five minute infusion of indomethacin was not likely to have been accounted for by measurement variability. Results of both techniques suggest reductions in cerebral blood flow²⁷ of about the same magnitude as seen in newborn animals¹⁵ and humans.¹²

Hypercapnia, postnatal age, and gestational age may affect the magnitude of the cerebrovascular response after infusion of indomethacin. Cerebral blood flow is reduced more when there is hypercapnia^{26 28 29} but no similar effect of carbon dioxide tension was seen in this study on Doppler mean flow velocity or cerebral electrical impedance. In newborn dogs postnatal age is an important determinant of the magnitude of cerebrovascular response, but we saw no such effect. No studies have directly addressed the effect of gestational age on cerebrovascular responses but it seems likely that responses should be greater at lower gestational age down to an unknown lower limit.¹⁵ We did not observe an effect of gestational age.

Indomethacin has effects on blood pressure control mediated by the autonomic nervous and renin angiotensin systems.^{30 31} Evans *et al*¹¹ found a mean increase of 15% in blood pressure in the neonate after indomethacin had been given. In this study

there was no consistent change in blood pressure after infusion at either rate.

The efficacy of indomethacin in closing the patent ductus arteriosus was not examined in this study, but it seems to be associated with steady state serum concentration.³⁻⁶ Because the half life of indomethacin in the neonate is at least eight hours and usually about 20 hours^{3 6} there should be no difference in serum concentrations after infusion at the different rates used in this study, and hence efficacy would be expected to be the same.

We recommend that in clinical practice and in studies to determine optimal dosage schedules indomethacin be infused over 20 minutes or longer. Until further data are available there must be concern about the possible deleterious effects of the apparent reduction in cerebral blood flow observed with shorter infusion periods.

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References

- Silove ED. Pharmacological manipulation of the ductus arteriosus. *Arch Dis Child* 1986;**61**:827-9.
- Goldberg SJ. Response of the patent ductus arteriosus to indomethacin treatment. *Am J Dis Child* 1987;**141**:250.
- Yaffe SJ, Friedman WF, Rogers D, Lang P, Ragni M, Saccar C. The disposition of indomethacin in preterm babies. *J Pediatr* 1980;**97**:1001-6.
- Brash AR, Hickey DE, Graham TP, Stahlman MT, Oates JA, Cotton RB. Pharmacokinetics of indomethacin in the neonate. *N Engl J Med* 1981;**305**:67-72.
- Yeh TF, Luken J, Raval D, Thalji A, Carr I, Pildes RS. Indomethacin treatment in small versus large premature infants with ductus arteriosus. *Br Heart J* 1983;**50**:27-30.
- Seyberth HW, Knapp G, Wolf D, Ulmer HE. Introduction of plasma indomethacin level monitoring and evaluation of an effective threshold level in very low birth weight infants with symptomatic patent ductus arteriosus. *Eur J Pediatr* 1983;**141**:71-6.
- Peckham GJ, Miettinen OS, Ellison RC, *et al*. Clinical course to one year of age in premature infants with patent ductus arteriosus: results of a multicentre trial of indomethacin. *J Pediatr* 1984;**105**:285-91.
- Mahony L, Caldwell RL, Girod DA, *et al*. Indomethacin therapy on the first day of life in infants with very low birth weight. *J Pediatr* 1985;**106**:801-5.
- Rennie JM, Doyle J, Cooke RW. Early administration of indomethacin to preterm infants. *Arch Dis Child* 1986;**61**:233-8.
- Cowan F. Indomethacin, patent ductus arteriosus, and cerebral blood flow. *J Pediatr* 1986;**109**:341-4.
- Evans DH, Levene MI, Archer LNJ. The effect of indomethacin on cerebral blood flow velocity in premature infants. *Dev Med Child Neurol* 1987;**29**:776-82.
- Pryds O, Greisen G, Johansen KH. Indomethacin and cerebral blood flow in premature infants treated for patent ductus arteriosus. *Eur J Pediatr* 1988;**147**:315-6.
- Hohimer AR, Richardson BS, Bissonette JM, Machida CM. The effect of indomethacin on breathing movements and cerebral blood flow and metabolism in the fetal sheep. *J Dev Physiol* 1985;**7**:217-28.
- Leffler CW, Busija DW. Arachidonate metabolism on the cerebral surface of newborn pigs. *Prostaglandins* 1985;**30**:811-8.

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- ¹⁵ Leffler CW, Busija DW. Arachidonic acid metabolites and perinatal cerebral hemodynamics. *Semin Perinatol* 1987;**11**: 31–42.
- ¹⁶ Ment LR, Stewart WB, Duncan CC, Scott DT, Lambrecht R. Beagle puppy model of intraventricular hemorrhage: effect of indomethacin on cerebral blood flow. *J Neurosurg* 1983;**58**: 857–62.
- ¹⁷ Pickard JD, Tamura A, Stewart M, *et al.* Prostacyclin, indomethacin and the cerebral circulation. *Brain Res* 1980;**197**:425–31.
- ¹⁸ Dahlgren N, Siesjo BK. Effects of indomethacin on cerebral blood flow and oxygen consumption in barbiturate-anaesthetized normocapnic and hypercapnic rats. *J Cereb Blood Flow Metab* 1981;**1**:109–15.
- ¹⁹ Crockard HA, Iannotti F, Ladds G. Cerebrovascular effects of prostaglandin inhibitors in the gerbil. *J Cereb Blood Flow Metab* 1982;**2**:67–72.
- ²⁰ Hagen AA, White RP, Robertson JT. Synthesis of prostaglandins and thromboxane B₂ by cerebral arteries. *Stroke* 1979;**10**:306–9.
- ²¹ Colditz P, Pryds O, Greisen G, Murphy D, Rolfe P, Wilkinson AR. Cerebral electrical impedance: do indices derived from it provide information on cerebral blood flow in the neonate? *Scand J Clin Lab Invest* (in press).
- ²² Colditz P, Greisen G, Pryds O. Comparison of electrical impedance and ¹³³xenon clearance for the assessment of cerebral blood flow in the newborn infant. *Pediatr Res* (in press).
- ²³ Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. *Lancet* 1986;**i**:307–10.
- ²⁴ Leffler CW, Busija DW, Beasley DG. Effect of therapeutic dose of indomethacin on the cerebral circulation of newborn pigs. *Pediatr Res* 1987;**21**:188–92.
- ²⁵ McCulloch J, Kelly PAT, Grome JJ, Pickard JD. Local cerebral circulatory and metabolic effects of indomethacin. *Am J Physiol* 1982;**243**:H416–23.
- ²⁶ Eriksson S, Hagenfeldt L, Law D, Patrono C, Pinca E, Wennmalm A. Effect of prostaglandin synthesis inhibitors on basal and carbon dioxide stimulated cerebral blood flow in man. *Acta Physiol Scand* 1983;**117**:203–11.
- ²⁷ Greisen G, Johansen K, Ellison PH, Fredricksen PS, Mali J, Friis-Hansen B. Cerebral blood flow in the newborn infant: Comparison of Doppler ultrasound and 133-xenon clearance. *J Pediatr* 1984;**104**:411–7.
- ²⁸ Sakabe T, Siesjo BK. The effect of indomethacin on the blood flow-metabolism couple in the brain under normal, hypercapnic and hypoxic conditions. *Acta Physiol Scand* 1979;**107**:283–4.
- ²⁹ Busija DW, Heistad DD. Effects of indomethacin on cerebral blood flow during hypercapnia in cats. *Am J Physiol* 1983;**244**:H519–H524.
- ³⁰ Anderson RJ, Berl T, McDonald KM, Schrier RW. Prostaglandins: effects on blood pressure, renal blood flow, sodium and water excretion. *Kidney Int* 1976;**10**:205–15.
- ³¹ Dusting GJ, Moncada S, Vane JR. Prostaglandins, their intermediates and precursors: cardiovascular actions, and regulatory roles in normal and abnormal circulatory systems. *Prog Cardiovasc Dis* 1979;**21**:405–30.

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