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Change in blood pressure after treatment of patent ductus arteriosus with indomethacin

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Abstract

The effect of indomethacin treatment of patent ductus arteriosus (PDA) on blood pressure was studied in 24 preterm infants. PDA was diagnosed clinically and confirmed by echocardiography; the effect of treatment was monitored echocardiographically. Hourly intra-arterial recordings of systolic, diastolic, and mean blood pressure were averaged for the 48 hours before the first dose of indomethacin and for each of the three 24 hour periods after the first dose.

In the 16 infants in whom treatment was successful, the average mean blood pressure increased significantly over the three days after the first dose. On the third day after beginning treatment with indomethacin the average increase in mean blood pressure was 10·4 mm Hg. Fourteen of 16 infants showed an increase of 4 mm Hg or more. Systolic and diastolic blood pressure increased significantly by similar amounts, so the pulse pressure did not change. In the eight infants treated unsuccessfully, there was no consistent change in any of the blood pressure parameters. The maximum increase in mean blood pressure was 3 mm Hg.

These findings confirm that PDA is one of the determinants of blood pressure in preterm infants. The effect is general and there is no consistent change in pulse pressure when a PDA is closed. A general increase in blood pressure is a useful additional indicator of successful medical ductal closure.

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The conventional view of the effect of a patent ductus arteriosus (PDA) on systemic blood pressure has been that shunting in diastole causes a decrease in diastolic pressure and hence a widening of the pulse pressure.[1] This view has not stood up to close examination in preterm infants. In a cross sectional study we showed that haemodynamically significant PDA was associated with similar reductions in systolic and diastolic blood pressure and that as a result pulse pressure was not affected.[2] In a cross sectional study it is difficult to control completely for confounding variables. For example, in our study there was a statistically insignificant trend to infants with PDA needing higher mean maximum ventilatory pressures.[2] Another method by which to examine the effect of PDA on blood pressure is to study the changes in blood pressure longitudinally around the time of PDA closure. Increases of similar degrees in systolic and diastolic blood pressure have been documented at the time of surgical ligation of the PDA.[3–5] The effect of ductal closure induced by indomethacin on each of the parameters of blood pressure has not to our knowledge been documented. If changes consistently occurred, they might provide a further clinical pointer to the success of indomethacin treatment in an area where clinical signs can be unreliable.[6]

The aims of this study were twofold. Firstly, to confirm our cross sectional findings with a study of the change in the parameters of blood pressure which occur around successful and unsuccessful medical closure of PDA; and, secondly, to see if changes in blood pressure could be used as a reliable clinical indicator of successful medical closure.

Subjects and methods

Twenty four preterm infants were studied before and during indomethacin treatment for a PDA. Their mean gestational age was 27 weeks (24–30 weeks) and the mean birth weight 913 g (519–1610 g). The infants were recruited during three six month periods, ending February 1989 and July 1991 at the John Radcliffe Maternity Hospital in Oxford, and ending July 1992 at the King George V Hospital in Sydney, Australia. Criteria for inclusion in the study were firstly that there was intra-arterial blood pressure monitoring for at least 24 hours before and 48 hours after the first dose of indomethacin, and secondly that there was echocardiographic confirmation of ductal patency before treatment and echocardiographic monitoring of the effect of that treatment.

At the John Radcliffe Maternity Hospital echocardiography was performed with an ATL Ultramark 4 scanner with 7·5 MHz probe incorporating 5 MHz range gated pulsed Doppler crystal. At the King George V Hospital echocardiography was performed with an Accuson 128XP/10 scanner with a 7·5 MHz probe incorporating pulsed and colour flow Doppler. Ductal patency was established by direct imaging of the duct with colour flow or pulsed Doppler confirmation of a shunt through the PDA, or both. Left atrial aortic root ratio was measured, according to previously reported criteria,[7] as a semiquantitative assessment of the degree of left to right shunt. A duct was defined as closed when it could not be imaged as patent and no shunt could be recorded on colour flow Doppler imaging or a pulsed Doppler search of the pulmonary end of the duct. The diagnosis of PDA and the decision to treat were made on clinical criteria with echocardiographic confirmation. The effect of treatment was monitored

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Table 1 Comparison of infants with and without PDA closure. Results are mean (range) values

	With closure (n=16)	*Without closure (n=8)*
Gestation (weeks)	28 (25–30)	25 (24–28)
Birth weight (g)	1019 (577–1610)	700 (519–1344)
Postnatal age (days)	5 (2–10)	8 (4–12)

where possible with daily echocardiography; all infants had at least one echocardiogram in the three days after the first dose of indomethacin.

Hourly measurements of systolic, diastolic, and mean blood pressure were recorded for 48 hours before and 72 hours after the first dose of indomethacin. Blood pressure was monitored for at least 24 hours before and 48 hours after. All measurements were taken from direct intra-arterial monitoring via a size 3·5FG umbilical catheter or a 24G peripheral arterial cannula. In all except three infants the catheters were in a postductal position (left radial, umbilical, or posterior tibial); the other three were in the right radial artery. In Oxford, the catheters were connected to Viggo-Spectramed (R) transducer located at the mid thoracic level, in turn connected to a Hewlett-Packard 78834A multichannel monitor. At the King George V Hospital, they were connected to a Lifemed (R) transducer, in turn connected to a Neotrak 515A multichannel monitor. The systems were recalibrated at least once every 24 hours according to the manufacturers' recommendations. A 'damped signal' was defined as one where the pulse pressure was less than 12 mm Hg; only the mean blood pressure from these recordings was used in the analysis. The standard reference point for assessment of the change in blood pressure was the time of the first dose of indomethacin.

The fractional inspired oxygen concentration (F_{IO_2}) and the mean airway pressure were averaged for each of the 24 hour periods as an index of respiratory status. The policy on the two neonatal units was to adjust F_{IO_2} and ventilation to maintain the arterial and transcutaneous oxygen tension between 6·5 and 10·5 kPa and the arterial carbon dioxide tension between 4·5 and 6 kPa.

All infants were treated with one of two indomethacin regimens, either 0·2 mg/kg intravenously 12 hourly for three doses or 0·1 mg/kg intravenously daily for six doses. If not already fluid restricted, fluid intake was reduced by 20–30 ml/kg/day; urine output and blood electrolytes were monitored at least every 24 hours.

Table 2 Change in ventilation and oxygen requirements after treatment with indomethacin

	48–24 hours before	*24–0 hours before*	*0–24 hours after*	*24–48 hours after*	*48–72 hours after*
PDA closed (n=16)					
Mean (SD) F_{IO_2}	0·44 (0·22)	0·44 (0·19)	0·39 (0·18)	0·38 (0·18)	0·32 (0·05)
Mean (SD) mean airway pressure (cmH_2O)	8·3 (1·9)	8·4 (2·2)	7·8 (2·7)	6·8 (3·0)	4·8 (3·2)
PDA not closed (n=8)					
Mean (SD) F_{IO_2}	0·29 (0·07)	0·28 (0·07)	0·36 (0·12)	0·43 (0·18)	0·46 (0·18)
Mean (SD) mean airway pressure (cmH_2O)	7·1 (2·2)	6·7 (1·6)	7·6 (2·0)	7·1 (1·2)	7·5 (1·0)

Statistical analysis was by paired and unpaired Student's *t* test with statistical significance accepted at p values of less than 0·05.

Results

Complete PDA closure was achieved in 16 of the 24 infants. In the other eight the duct was not closed by medical treatment; two of these infants had later surgical ligation and the other six closed spontaneously at a later date. Those in whom the duct did not close were of lower gestational and higher postnatal age at the time of treatment (table 1).

Fourteen of the 16 infants with successful duct closure had daily echocardiography. The other two were scanned on day 3 and confirmed to have a closed duct. On day 1 after the first dose, six of 14 had closed; on day 2, 11 of 14 had closed; and all were closed by day 3. The mean ratio of the diameter of the left atrium to that of the aortic root (LA:Ao) decreased from 1·79 the day before indomethacin treatment to 1·26 the day after. In those where the duct was still patent on day 1, marked constriction of the duct and a decrease in the LA:Ao was seen in all subjects, the mean LA:Ao decreasing from 1·64 to 1·34. In the eight infants where treatment was unsuccessful the duct remained patent in all echocardiographic studies. Some were seen to constrict in response to indomethacin but none were seen to close completely and then reopen.

All infants were mechanically ventilated at the time of treatment. In the successfully treated infants, the mean F_{IO_2} and mean airway pressure decreased in the three days after the first dose of indomethacin, whereas they increased in those where treatment was not successful (table 2).

The hourly recordings of blood pressure were averaged for the 48 hours before the first dose of indomethacin and then for each of the three subsequent 24 hour periods. The mean of each parameter in the pretreatment 48 hours was taken as the baseline for each infant and the change in blood pressure for each of the days after indomethacin treatment was expressed as the change for that infant from this individual baseline.

INFANTS TREATED SUCCESSFULLY

In these 16 infants there was no significant difference between the average mean blood pressure in the two 24 hour periods before the first dose. The average mean blood pressure for these periods was 35·6 and 36·7 mm Hg respectively (p=0·38). The change in mean blood pressure increased steadily over the next three days (fig 1). The increase was significant from day 1 onwards ($p<0·001$). In the 14 infants who had echocardiography on day 1, there was no significant difference in the increase in mean blood pressure between those with a closed or a restricting but patent duct; the mean increase was 5·3 and 4 mm Hg respectively (p=0·55). By the third day, the average increase in mean blood pressure was 10·4 mm Hg with a range of from 1 to 23

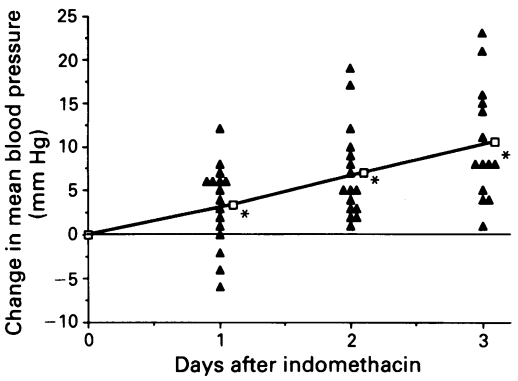

Figure 1 Change in mean blood pressure in successfully treated infants on each of the three days after beginning indomethacin treatment. The closed triangles indicate change for each infant and the open squares the average change for the group. A significant change ($p<0·001$) from the pretreatment levels is shown by the asterisk.

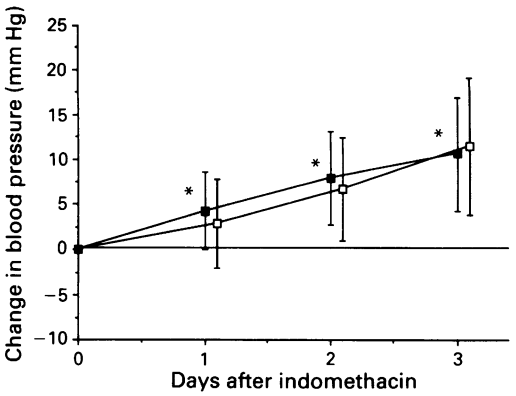

Figure 2 Mean and SD for change in systolic blood pressure (open squares) and diastolic blood pressure (closed squares) on each of the first three days after beginning indomethacin treatment. A significant change ($p<0·05$) in systolic and diastolic blood pressure from the pretreatment levels is shown by the asterisk.

mm Hg. Of the 14 infants studied to day 3, all except one showed an increase in mean blood pressure of at least 4 mm Hg. This infant had a ventricular septal defect as well as a PDA. Two other infants were only studied for 48 hours; in one blood pressure monitoring was discontinued and the other died. The former had shown an increase in mean blood pressure of 7 mm Hg on day 2; the latter had fulminating respiratory failure and had an increase in mean blood pressure of only 1 mm Hg.

Changes in systolic and diastolic blood pressure were studied in 15 of the 16 infants; the other infant had a damped trace. Systolic and diastolic blood pressure also increased progressively by similar amounts after indomethacin treatment (fig 2). The two parameters had shown a significant increase from day 1 onwards from their respective pretreatment values ($p<0·05$). There was a statistically insignificant trend to diastolic pressure increasing earlier than systolic; however, by day 3 the mean change in systolic blood pressure was 11·4 mm Hg and diastolic blood pressure was 10·6 mm Hg. As a result of this, there was no consistent change in pulse pressure with PDA closure (fig 3). The average change in pulse pressure on day 3 was an insignificant increase of 1·0 mm Hg with a range from −9 to +9 mm Hg. Arterial catheter site had no significant influence on the change in pulse pressure. In the 12 infants with a postductal arterial catheter site the mean pulse pressure increased by 1·5 mm Hg between the pretreatment period and day 3 after treatment (24 to 25·5 mm Hg). In the three infants with a preductal catheter site, the mean pulse pressure decreased by 1 mm Hg over the same time period (23 to 22 mm Hg) ($p=0·6$).

INFANTS TREATED UNSUCCESSFULLY

In these eight infants there was no significant difference between the average mean blood pressure in the two 24 hour periods before the first dose. The average mean blood pressures for these periods were 32·7 and 32·6 mm Hg respectively ($p=0·8$). After the first dose of indomethacin there was no significant change in average mean blood pressure on any of the subsequent three days (fig 4). On day 3 the average change on mean blood pressure was zero with a range from −3 to +3 mm Hg. Systolic and diastolic blood pressure and pulse pressure likewise showed no significant change over this three day period.

Discussion

An increase in systemic blood pressure at the time of surgical ductal ligation has been documented in several reports.[3–5] Marshall *et al*[3]

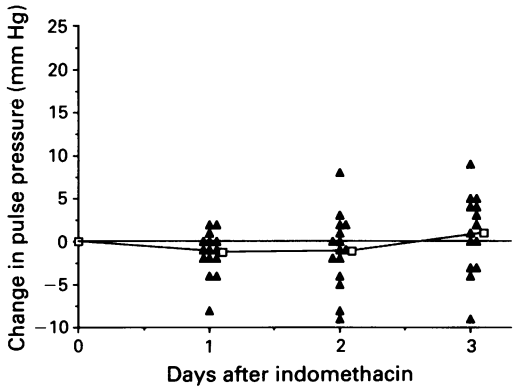

Figure 3 Change in pulse pressure in successfully treated infants on each of the three days after beginning indomethacin treatment. The closed triangles indicate change for each infant and the open squares the average change for the group.

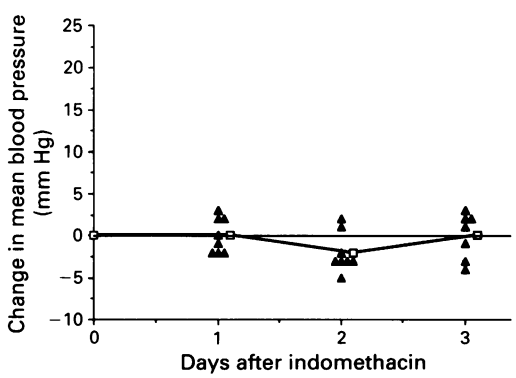

Figure 4 Change in mean blood pressure in unsuccessfully treated infants on each of the three days after beginning indomethacin treatment. The closed triangles indicate change for each infant and the open squares the average change for the group.

and Ratner *et al*[4] reported immediate increases in systolic, mean, and diastolic blood pressure at the time of surgical ligation. In contrast, Sonnesson *et al*,[5] reporting changes in five preterm infants at the time of surgery, showed a greater increase in diastolic pressure in line with the conventional thinking on the PDA. Blood pressure was monitored in Sonnesson's study with a Dinamap oscillometric monitor, a method since shown to be not consistently accurate in preterm infants.[8] We are not aware that changes in systolic, mean, and diastolic blood pressure have been previously documented at the time of medical PDA closure. In this study we have shown that where medical treatment is successful, there is a gradual and significant increase in all the parameters of blood pressure over the three days after the first dose of indomethacin. Increases in systolic and diastolic blood pressure are similar and as a result pulse pressure is not consistently affected by PDA closure. This seems to confirm our cross sectional findings[2] in preterm infants that the effect of a PDA on blood pressure is general, and that a change in pulse pressure cannot be seen as a reliable indicator of ductal patency or ductal closure.

Were there other factors which could explain the increases in blood pressure reported here? The mean age at treatment in the successful group was 5 days and it has been reported that blood pressure increases over the first week of life in term and preterm infants.[9] Although this may have contributed to the increase, the difference in average mean blood pressure in the two 24 hour periods before the first dose of indomethacin was not significant. As indomethacin has widespread vasoconstrictor activity[10 11] and also causes disturbance of fluid and electrolyte balance,[12] could these effects have increased blood pressure in isolation from the effect on the duct? Although this is again possible, the fact that the infants in whom the duct did not close showed no consistent change in blood pressure makes it unlikely.

Why should PDA closure increase blood pressure? Systemic blood pressure is a product of cardiac output and systemic vascular resistance. A PDA connects the relatively high resistance systemic circulation to the low resistance pulmonary circulation; a left to right shunt and a reduction in systemic vascular resistance results. The left ventricle responds by increasing cardiac output to cope with the volume load and to maintain systemic pressures.[13] The ductal shunt occurs throughout the cardiac cycle with maximum velocity and flow in systole,[14] and as a result systolic and diastolic pressures will tend to decrease. The extent to which they decrease will depend on the size of the shunt and the ability of the left ventricle to compensate.[13] When the duct is closed, the peripheral vascular resistance increases immediately, cardiac output decreases,[15] and blood pressure increases. Marshall *et al* showed that the rate of increase in blood pressure could be modified by performing a more gradual surgical ligation.[3] Thus the effect on peripheral vascular resistance is likely to be the main reason for the reported increase in blood pressure.

Clearly, echocardiography is the most accurate means of assessing the success of a course of indomethacin; however, many neonatal units do not have immediate access to echocardiographic skills and so rely on clinical criteria and physical signs. Fourteen of the 16 successfully treated infants studied here showed an increase in mean blood pressure of 4 mm Hg or more; none of the eight unsuccessfully treated infants showed an increase of more than 3 mm Hg. The two groups were not completely comparable in that the unsuccessful group was of lower gestational and higher postnatal age, documented risk factors for a lack of response to indomethacin.[16] It would seem, however, that an increase in arterial blood pressure is a useful additional clinical pointer to successful medical PDA closure.

In conclusion, this study has confirmed longitudinally that the PDA is one of the determinants of blood pressure in early preterm life. The effect on blood pressure is global and as a result arterial pulse pressure is not consistently affected by significant ductal shunting. Successful medical PDA closure is usually associated with a general increase in systemic blood pressure.

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