Evaluation of oral and low dose intravenous prostaglandin E₂ in management of ductus dependent congenital heart disease

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SUMMARY Prostaglandin E₂ was given orally to 59 infants with ductus dependent congenital heart disease, and intravenous infusions were substituted for varying periods in 27 of them. An additional three neonates received intravenous treatment alone. Mean oral maintenance dose was 27 µg/kg per hour and the mean intravenous dose was 0.005 µg/kg per minute. Mean duration of treatment was 49 days (range 16 hours to 272 days). Oral treatment was almost always effective and was especially suitable for long term use. Low dose intravenous treatment was readily substituted when indicated. Complications were usually 'minor'. Growth of the infants and of their pulmonary arteries facilitated later surgical management.

The E type prostaglandins are widely used to maintain the patency of the ductus arteriosus¹⁻³ and thus improve the metabolic condition of neonates with reduced pulmonary blood flow or the coarctation syndrome. The use of prostaglandin E₁ (PGE₁) has been particularly well documented, and as a result of a multicentre study in the United States, comprehensive reports of its effectiveness² and side effects⁴ have been produced. Previous reports from this hospital described our earlier experience using prostaglandin E₂ (PGE₂) and highlighted the advantages of the oral preparation for both emergency and long term use.^{3 5 6} We showed that oral PGE₂ was easily administered and was rapidly and consistently effective. Its side effects seemed to have been less severe than those of intravenous PGE₁ or PGE₂ treatment. We showed that when it was necessary to give PGE₂ intravenously, a dose one tenth of that usually suggested would suffice.⁶ Recently, the effectiveness of intravenous PGE₁ in a similar dosage has been confirmed.⁷

We have established a policy of beginning treatment with the oral preparation of PGE₂ and of using low dose intravenous treatment only when vomiting, diarrhoea, or severe acidosis lessen the likelihood of reliable gastrointestinal absorption. In most cases treatment continues for several weeks to try to reduce the risks of palliative or corrective surgery and to encourage growth of the infants. Although the oral preparation of PGE₂ is not available in many countries, it has been used by centres besides

our own in the United Kingdom.^{8 9} There has not previously been a comprehensive report of the use of oral and low dose intravenous PGE₂ in a large series of patients, and it is our purpose to offer a critical evaluation of the advantages and side effects.

Patients and methods

The study began in 1979, having been approved by the research ethical committees of the hospital and the district health authority. Some of the data on the first 12 patients have been reported previously⁶ and are included in the present report in order to present our overall experience. We have reviewed the case notes of the 62 infants (30 boys and 32 girls) treated during a four year period. In most of the patients, treatment with PGE₂ was begun after a diagnosis had been made by cross sectional echocardiography. Cardiac catheterisation was undertaken subsequently. In four severely cyanosed and acidotic infants, treatment was begun before the diagnosis had been made. The diagnoses of the infants treated are listed in Table 1. Fifty three infants (85%) had a ductus dependent pulmonary circulation, seven had a ductus dependent systemic circulation, and two had transposition of the great arteries. The one infant with hypoplastic left ventricle who was treated had been thought initially to have the coarctation syndrome; treatment was stopped after diagnosis by cardiac catheterisation. Treatment was started during the

Table 1 Infants treated with PGE₂

Diagnosis	No	Mean age treatment started (days)	Mean wt treatment started (kg)	Duration of treatment Mean (range)	No alive	Postoperative hospital mortality	Hospital mortality for those without operation	Late mortality
PA, IVS	21	8.4	2.9	48 (1-167)	10	10	—	1
PA, VSD	14	4.1	2.7	92 (1-272)	8	1	2	3
PA, comp	10	3.0	3.0	27 (3-112)	3	1	3	3
TA	6	1.5	3.0	37 (6-125)	1	—	3	2
TGA	2	1.0	3.4	4.3 (0.5-8)	—	—	1	1
PVS	2	7.0	2.8	2.8 (0.5-5)	1	1	—	—
Coarct	3	6.0	3.6	0.8 (0.5-1)	3	—	—	—
IAA	3	5.3	2.7	69 (37-91)	—	2	1	—
HLH	1	1.0	2.7	0.3	—	—	1	—

PA, IVS=pulmonary atresia with intact ventricular septum; PA, VSD=pulmonary atresia, ventricular septal defect, PA, comp=pulmonary atresia with complicated anatomy; TA=tricuspid atresia; TGA=transposition of the great arteries; PVS=critical pulmonary valve stenosis; Coarct=coarctation of the aorta; IAA=interrupted aortic arch; HLH=hypoplastic left heart.

first week of life in 53 infants (85%) and on the first day in 28 (45%).

Treatment was usually begun using the oral preparation of PGE₂ but in 10 infants there was reason to believe that gastrointestinal absorption would be poor, and a low dosage, intravenous infusion was used instead. Intravenous treatment was also substituted when oral treatment was ineffective, or if the infant developed gastrointestinal complications. Oral treatment was then reintroduced at the earliest opportunity. Prostaglandin E₂ was given orally to 59 infants, of whom 27 also received intravenous treatment, for periods ranging from a few hours to 38 days. Three patients were given intravenous treatment only. The duration of treatment was determined both by the response to treatment and by the clinical assessment of the optimal time for surgery. The response was assessed by the clinical condition of the infant, and, where indicated, by arterial blood gas analysis. The initial oral dose ranged from 15 to 60 µg/kg per hour, and the dosage interval was gradually increased after the first week while carefully monitoring the response. The initial intravenous dose was 0.003 to 0.006 µg/kg per minute, and was increased if necessary to a maximum of 0.02 µg/kg per minute.

In the longer term, growth of the infant was monitored and in those in whom more than one cardiac catheterisation was performed, the diameter of the right pulmonary artery was measured.⁶ Eight patients had skeletal surveys, and plasma alkaline phosphatase activity was measured in 18.

Results

In 60 infants there was initial clinical and biochemical improvement during PGE₂ treatment. Two infants did not improve: in one there was an anatomical explanation—at necropsy the ductus

arteriosus, main pulmonary artery, and left branch were absent, the right pulmonary artery arising from the ascending aorta. Eight infants had an unsatisfactory overall response to orally administered PGE₂; five were successfully treated instead with intravenous PGE₂ and three had operations. In one other infant who had been treated for 46 days, an operation was not considered to be possible and treatment was stopped.

Duration and method of treatment. The mean duration of treatment was 49 days, the range being 6 hours to 272 days. Sixteen infants were treated for less than 1 week, 19 for 1 to 4 weeks, 15 for 4 to 12 weeks, and 12 for more than 12 weeks. Ten patients who had vomiting or diarrhoea or severe acidosis at presentation were treated initially with intravenous prostaglandins because it was considered that absorption of the oral preparation would be unreliable. Seven of them subsequently received oral treatment. Another five received intravenous treatment after they had responded poorly to oral treatment; two of these responded again to oral treatment later. Fourteen patients, after an initial period of oral treatment, were treated intravenously because of diarrhoea (10 patients), necrotising enterocolitis (three patients), or pneumonia (one patient).

Dosage. The oral starting dose was mean (SD) 28 (14) µg/kg per hour, the maximum dose was mean (SD) 45 (22) µg/kg per hour, and the maintenance dose was mean (SD) 27 (19) µg/kg per hour. The mean intravenous dose was 0.005 µg/kg per minute. Six patients were eventually treated at home using oral PGE₂ in a dose of 62.5 to 250 µg at 6 to 8 hourly intervals.

Growth. Forty two infants were treated for more than 14 days; 29 gained weight along their expected

Table 2 Right pulmonary artery (RPA) size at angiography in 10 infants who had two catheterisations

Case no*	Diagnosis	Duration of PGE ₂ treatment before 2nd angiogram	RPA diameter (mm)	
			1st angiogram	2nd angiogram
1	PA, IVS	29	2.0	2.5
2	PA, VSD	75	3.0	6.0
3	PA, VSD	137	2.5	3.5
4	PA, IVS	68	2.5	4.0
5	PA, TA	69	2.5	3.0
6	PA, IVS	53	4.5	6.0
7	PA, IVS	49	4.0	6.0
8	TA	44	2.0	2.0
9	PA, VSD	43	3.0	4.0
10	PA, IVS	131	3.5	6.5
Mean		70	3.0	4.4

*Patients 1-5 previously reported.⁶

PA=pulmonary atresia; IVS=intact ventricular septum; VSD=ventricular septal defect; TA=tricuspid atresia.

centiles, 9 more slowly than expected, and 4 not at all. Of 17 infants treated for more than 10 weeks, only two, both with aortic arch interruption, had a weight velocity below the 3rd centile.

Pulmonary arterial growth. (Table 2). Ten infants each had two angiograms, the second after a mean period of PGE₂ treatment of 70 days. Five have been previously reported.⁶ The right pulmonary artery increased in diameter in nine of the 10 infants.

Complications. (Table 3). Twenty six infants (44%) had complications possibly caused by PGE₂ treatment. In all, 35 infants had one or more complications in their clinical course. Seven had more than one PGE₂-related complication. Apart from apnoea, none of the PGE₂-related complications could be regarded as 'major'. 'Minor' complications (fever, diarrhoea, transient 'jitteriness') occurred in 23 patients—in 17 during oral and in six during intravenous treatment. Three babies were 'jittery' for a brief period during the early phase of treatment; one had had birth asphyxia and another had an episode of focal seizures. Four others had seizures

in association with severe hypoxia and acidosis. Cardiovascular complications⁴ such as arrhythmia, hypotension, or vasodilatation were not seen.

Apnoea

Apnoea seemed to be related to PGE₂ treatment in three patients, two of whom were receiving oral and one intravenous treatment. Two infants had transient apnoea after the first dose of PGE₂, one oral the other intravenous, but the dose was then reduced and they were successfully treated for 16 and 19 days, respectively. In one of them, the serum calcium concentration was 1.4 mmol/l at the time of the apnoea. In another five infants, apnoea was seemingly not related to PGE₂ treatment. One had pneumonia and required mechanical ventilation. None of the other patients with apnoea required ventilation, and they included one preterm infant who had suffered apnoeic attacks before beginning PGE₂ treatment and three babies with necrotising enterocolitis.

Necrotising enterocolitis

All five infants who developed necrotising enterocolitis had had cardiac catheterisation via the femoral vein, three on the preceding day. At the time, three were receiving oral and two intravenous PGE₂ treatment. One required a laparotomy and colostomy and all recovered.

Common 'minor' problems

Four infants had documented infections. Two of three who developed pneumonia had Di George's syndrome; another had gastroenteritis. Fever (temperature at 38°C or greater for more than one day) occurred in 14 infants soon after the onset of treatment and did not influence management. Diarrhoea (more than eight stools per day or loose

Table 3 Complications possibly related to PGE₂ treatment

Complications	Treatment route	
	Oral	Intravenous
Apnoea	2	1
'Jitteriness', seizure	1	2
Fever	11	3
Diarrhoea	12	1
Total complications	26	7
Infants with complications	19	7
Total infants treated	59	30

stools containing blood in the absence of radiological evidence of necrotising enterocolitis) occurred in 13 patients, but vomiting was not seen in the absence of infection. Seven infants had both fever and diarrhoea. Lethargy and poor feeding were noted in some infants during the first few weeks of treatment and nursing staff commented on a characteristic oily and 'spotty' skin in some infants treated for more than four weeks.

Bone

One of eight patients (treated for a mean period of 105 days) who had skeletal surveys showed minor periosteal changes of the ulna but of no other bones. No patient had clinical signs of cortical hyperostosis. Three of 18 infants in whom alkaline phosphatase activity was measured had values above the upper limit of normal for our laboratory. One infant with normal radiographic appearances had histological evidence of increased cellularity and vascularity of the periosteum on a rib biopsy performed at thoracotomy.

Relation of dosage to complications

In those infants who developed complications the mean oral dose of PGE₂ at the time was 33 µg/kg per hour. Three patients who had each received more than 66 µg/kg per hour all had fever or diarrhoea. Early in the study, two infants had apnoeic attacks after the first dose of PGE₂, one having received 50 µg/kg orally, the other having received 0.05 µg/kg per minute intravenously. The two infants who developed necrotising enterocolitis while on intravenous treatment both presented with apnoea and were receiving 0.003 µg/kg per minute.

Outcome. (Table 1). Forty six infants had operations. Of these, 16 died in hospital, and six died unexpectedly at home. Of the 24 who survived surgery, six had had cardiopulmonary bypass for correction of pulmonary atresia with intact ventricular septum and one, with isolated pulmonary stenosis, had had pulmonary valvotomy under inflow occlusion. Two survivors had not had surgery, one with pulmonary atresia, ventricular septal defect and absent main pulmonary artery whose systemic-pulmonary collaterals provided adequate pulmonary blood flow and one with Down's syndrome whose ductus arteriosus was patent four months after stopping PGE₂ treatment. In all, there were 26 survivors (mean age 22.3 months, range 7 to 51 months) of whom 18 were well, two were not thriving, and six had severe handicap (one with hemiplegia, one microcephaly with hemiplegia, one severe cyanosis with motor

delay, one Down's syndrome, one global developmental delay, and one speech delay).

Deaths during PGE₂ treatment. Eight infants died during PGE₂ treatment. Two had congestive cardiac failure; one had cardiac tamponade complicating cardiac catheterisation; one, who had collapsed before beginning PGE₂ treatment, had disseminated intravascular coagulopathy; one died unexpectedly 29 days after an unsuccessful systemic-pulmonary shunt operation; one had a congenital absence of the ductus arteriosus; one failed to respond to either oral or intravenous treatment; and in one treatment was stopped after 46 days because of inoperability.

Discussion

The efficacy of intravenous and oral PGE₂ treatment in maintaining ductus arteriosus patency has been well documented.^{1 6 8 9} Whenever possible, we have used the oral preparation in preference to the intravenous because it is easier to administer and its absorption and beneficial effects are rapid. It is particularly suitable for long term use, and has enabled most infants so treated to grow satisfactorily.^{8 9} As a result of having been able to increase the interval between doses, a few infants were discharged from hospital and were given oral PGE₂ at home. We have also confirmed our earlier observation that intravenous doses as low as 0.003 µg/kg per minute are effective for both initial and long term use.

Several infants considered to be inoperable at presentation because of small pulmonary arteries subsequently had successful shunt operations. McMahon *et al*⁸ found that the pulmonary artery size increased in only four of 11 patients treated for two to eight months with oral PGE₂. They compared pulmonary artery diameter at initial angiogram with that measured at operation. In our study, the pulmonary artery diameter increased in nine of the 10 patients who had angiography before and after treatment with PGE₂.

This group of infants has a high operative mortality in the neonatal period. In the Liverpool study,¹⁰ only three of nine infants with pulmonary atresia and 10 of 20 with other causes of pulmonary oligoemia survived. Bove *et al*¹¹ showed that 76% survived non-bypass surgery, and that 43% survived cardiopulmonary bypass. In their series, all infants with pulmonary atresia had shunt surgery. In our study, 23 of 53 infants (43%) with pulmonary oligoemia survived. They included six of the 14 who had corrective surgery under cardiopulmonary bypass for pulmonary atresia with intact ventricular septum and one for critical pulmonary stenosis

under inflow occlusion. In the group with pulmonary atresia and intact ventricular septum who had surgery, the mean age at operation of survivors was 33 days, while the mean age of those who died was 61 days. We suggest that this reflects our policy of using PGE₂ for the longest periods in those patients with the most difficult anatomy.

We have tried to indicate those complications that may have been caused by PGE₂. In many infants with major complications, other factors that were likely to have contributed were present. It is noteworthy that cardiovascular complications⁴ such as arrhythmia, hypotension, or cutaneous vasodilatation were not encountered.

Apnoea has been reported after administration of PGE₁ and PGE₂.⁴⁻⁶ In this series, apnoea occurred in the absence of other explanations in only three infants, two of whom had been treated with appreciably higher doses than is our current practice and one of whom had been initially treated uneventfully for 29 days. We suggest that the low plasma concentrations associated with the oral dosage and the low intravenous dosage we have employed contributed to this low incidence.

Necrotising enterocolitis was not necessarily related to PGE₂ treatment, and has been well documented in infants after cardiac catheterisation.¹²⁻¹³ Dickinson *et al*¹³ found an incidence of 14 out of 111 catheterisations. All the infants in our series who developed this complication had been catheterised.

Fever and diarrhoea were common but not serious problems, which bears out the experience of others.⁴ The four babies who had generalised seizures during PGE₂ treatment had all suffered periods of profound hypoxia and acidosis. One with transient focal seizures and two with 'jitteriness' had no obvious predisposing factor other than the PGE₂ treatment.

Histological disruption of the wall of the ductus arteriosus after infusion of PGE₁ has been reported by some¹⁴⁻¹⁵ but disputed by others;¹⁶⁻¹⁷ our surgical colleagues have not seen friability of the ductus, aorta, or pulmonary arteries in patients treated with PGE₂. As previously reported¹⁸ pulmonary vascular smooth muscle was not affected by long term oral PGE₂ in those infants studied.

Clinical cortical hyperostosis was not seen. Its radiological absence in those infants who received PGE₂ for the longer periods of time persuaded us not to continue with further seemingly unnecessary investigations. We suggest that the occurrence reported by others during long term PGE₁ infusion was probably dose related.¹⁷⁻¹⁹ If PGE₂ influences bone resorption in the same way as PGE₁, it would seem that our patients might have been

protected from this complication by the low dosage that they received.

Our results do not enable us to show whether the long term outlook of the group as a whole has been improved by delaying surgery, but our surgical colleagues prefer to operate on infants weighing 3.5 kg or more. The small group of patients with interrupted aortic arch, however, showed no long term benefit; although their acid base balance improved they remained in congestive cardiac failure and did not thrive.

The short term use of prostaglandins is well established and we suggest that in selected patients a longer period of treatment will allow growth. Long term treatment may be undertaken safely, effectively, and simply by using the oral route. We recommend the oral administration of PGE₂ in an initial dose of 20 to 25 µg/kg hourly, decreasing the frequency of doses after the first week. When gastrointestinal absorption is expected to be poor or when oral treatment is ineffective we begin an intravenous infusion at a dose of 0.003 µg/kg per minute, rarely needing to increase the dose for more than a few hours, and exceptionally using a dose as high as 0.01 to 0.02 µg/kg per minute. Our current practice is to treat this group of patients with oral PGE₂ for between one and four weeks initially, and then to decide, on an individual basis, whether to proceed with surgery or to plan a longer course of treatment to encourage further growth.

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