Prostaglandin E_1 in suspected ductus dependent cardiac malformation

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SUMMARY   Fifty two sick neonates with major duct dependent cardiac defects were given short term intravenous infusions of prostaglandin E_1 (alprostadil) in doses varying between 0·005 and 0·1 µg/kg/minute. The object of the study was to try to achieve an effective but safe regimen that could be instituted as soon as such a diagnosis was suspected. Effective clinical improvement was achieved at each dosage but the incidence of side effects seemed to be dose related, and no serious side effects were noted at a dosage of 0·005 to 0·01 µg/kg/minute. It is recommended that a low dosage regimen be started before transfer to a paediatric cardiac centre.

The role of prostaglandins in maintaining ductus patency in the newborn infant is now well established and there are numerous reports of the successful use of prostaglandin E_1 and prostaglandin E_2 in sick newborn infants with both cyanotic[1-4] and acyanotic[4-6] ductus dependent cardiac malformations. These reports have mainly been concerned with the administration of prostaglandins once an exact cardiac diagnosis has been established. The object of this study was to establish a safe and effective regimen for prostaglandin E_1 that could be initiated on suspicion of a duct dependent cardiac defect in a sick neonate, either shortly after arrival at a paediatric cardiac centre or, perhaps more importantly, before transfer to such a centre. There would thus be the optimum chance of maintaining or improving such an infant's general status before urgent cardiac investigations and surgery, contributing to an improvement in morbidity and mortality in this group of critically ill neonates.

Our experience with prostaglandin E_1 dates from 1978 when we started to use it in individual clinical treatment for sick infants with proved major duct dependent cardiac malformations. The current series covers a three year period from 1980 and utilises a standard regimen of administration based on our earlier experience, the only variable factor being that of dosage.

Patients

The patients consisted of 52 consecutively admitted sick infants suspected of having major ductus dependent cardiac defects. Preterm infants, those requiring assisted ventilation, and any in whom clinical and arterial blood gas data were inadequate were excluded. Prostaglandin E_1 was started after clinical diagnosis of a major cardiac defect whose clinical course would be adversely affected by ductus closure. The cardiac diagnosis was subsequently confirmed by two dimensional echocardiography and by angiography (48 patients) or two dimensional echocardiography alone (four patients). The patients were divided into three groups. Group 1 consisted of 24 cyanotic infants with ductus dependent pulmonary blood flow (simple or complex pulmonary atresia (22 patients) and critical pulmonary stenosis (two patients)). Group 2 consisted of 18 patients with ductus dependent systemic blood flow (severe coarctation of the aorta (six), interrupted aortic arch (three), and hypoplastic left heart syndrome (nine)). Group 3 consisted of 10 infants with ductus dependent systemic-venous mixing (simple transposition of the great arteries). The initial inclusion of infants in the third group was because of unavoidable delay in access to the catheter laboratory and hence of balloon atrial septostomy.

The infants were assessed clinically, and upper and lower limb blood pressures were recorded. A chest radiograph and electrocardiogram were carried out on each infant. Observations of rectal temperature, apex, and respiratory rate were made; radial artery blood gases were estimated within an hour of starting prostaglandin E_1 and were repeated one to four hours after the start of treatment. Any side effects attributable to prostaglandin E_1 were recorded, and pyrexia was defined as a temperature of above 37^2°C occurring more than once in 24 hours.

The ages of the infants on beginning prostaglandin treatment ranged between 6 hours and 16 days. The older infants were in group 2. Twenty of the infants were less than 24 hours of age. The group 1 infants were all less than 8 days old and the group 3 infants less than 4 days old. The decision to give prostaglandin E_1 was based on the clinical diagnosis of a duct dependent cardiac defect. The group 1 and 3 infants had increasing cyanosis, with or without metabolic acidosis. The arterial Po_2 varied from 2·0 to 4·6 kPa (15·0 to 34·6 mmHg) in group 1 infants (Fig. 1) and 2·2 to 3·8 kPa (16·5 to 28·6 mmHg) in group 3 infants (Fig. 2). Arterial pH varied between 7·26 and 7·40 in group 1 and 7·18 and 7·37 in group 3. Prostaglandin E_1 was commenced for clinical deterioration in group 2 infants. Many of them were shocked and in low cardiac output with signs of severe cardiac failure and oliguria. Some were profoundly metabolically acidotic even after efforts at resuscitation and their arterial pH varied between 6·8 and 7·22 (Fig. 3) before they were given prostaglandin E_1.
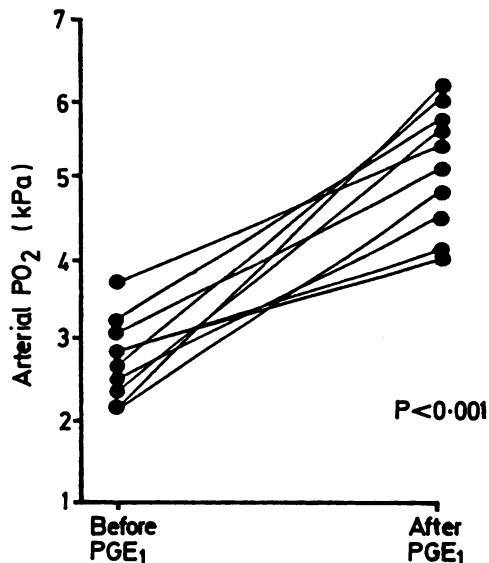

Fig. 2 *Arterial Po_2 (kPa) before and four hours or less after prostaglandin E_1 (PGE_1) in 10 group 2 infants with transposition of the great arteries.*
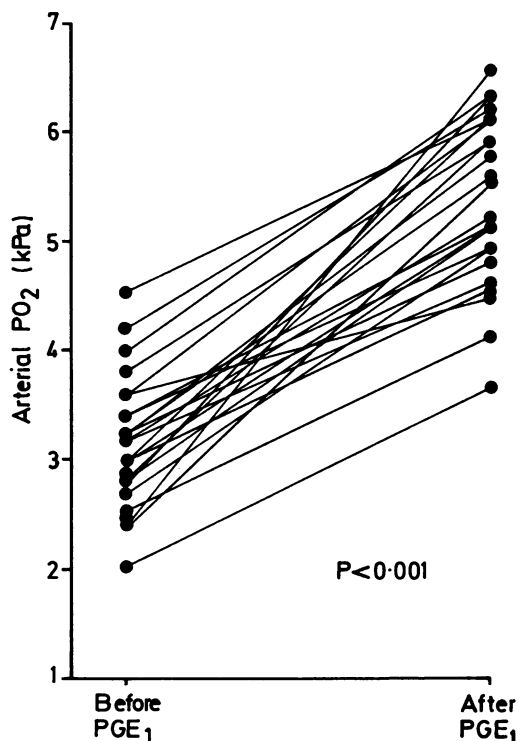

Fig. 1 *Arterial Po_2 (kPa) before and four hours or less after prostaglandin E_1 (PGE_1) in 24 group 1 cyanotic infants with duct dependent pulmonary blood flow.*

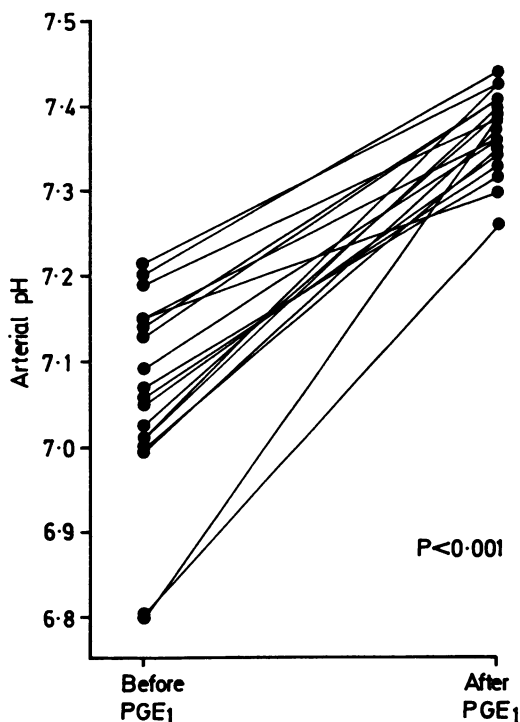*Conversion—SI to traditional units:* Po_2 1 kPa ≈ 7·5 mmHg.

Fig. 3 *Arterial pH before and four hours or less after prostaglandin E_1 (PGE_1) in 18 group 2 infants with ductus dependent systemic blood flow.*

The duration of treatment varied between five and 280 hours. (Group 1 mean 47 hours; group 2, mean 63 hours; group 3, mean 10 hours.) Prostaglandin E_1 was stopped after palliative or corrective surgery, balloon atrial septostomy, or the diagnosis of an inoperable cardiac defect.

The prostaglandin E_1 was dissolved in 4·5% dextrose saline or 5% dextrose infused into a peripheral vein using an IVAC or constant infusion pump. Each infant was initially given the maximum volume of fluid calculated for age and weight. The concentration of prostaglandin E_1 was electively decreased during this study to see whether side effects could be avoided while maintaining ductus patency (Table 1). The first six infants were given a concentration of prostaglandin E_1 of 0·1 ug/kg/minute whereas the last six infants received 0·005 ug/kg/minute. If major complications occurred the prostaglandin E_1 was temporarily stopped and subsequently restarted at a lower dosage.

Table 1 *Dosage of prostaglandin E_1 (PGE₁) related to numbers of infants in each clinical group*

Dose PGE₁ (µg/kg/min)	Total	Group 1	Group 2	Group 3
0·1	6	3	3	0
0·05	15	6	4	5
0·03	9	4	5	0
0·02	6	3	2	1
0·01	10	4	3	3
0·005	6	4	1	1

Results

There were no failures of response to prostaglandin E_1 in the 52 infants studied. The group 1 and 3 infants became obviously less cyanosed within 30 to 60 minutes of starting prostaglandin E_1 and the arterial Po_2 increased significantly within four hours of starting treatment (Figs. 1 and 2), regardless of dosage. There was an improvement in arterial pH in

Fig. 4 *Right ventricular angio (lateral) of infant with simple transposition of the great arteries illustrating posterior pulmonary artery filling through widely patent ductus arteriosus (infant receiving prostaglandin E_1 0·01 ug/kg minute).*

those infants in whom it had already been reduced. A widely patent ductus arteriosus was shown by right ventricular angiography or arteriography in the group 3 infants (Fig. 4) but it subsequently closed spontaneously in all these infants. The 10 infants continued to do well after balloon atrial septostomy and nine of them have already had successful Mustard procedures. There was a gradual but striking improvement in the group 2 infants as judged by muscle tone, clinical increase in cardiac output, and improvement in leg pulses in the infants with coarctation of the aorta. Once a satisfactory cardiac output had been achieved renal flow could usually be re-established with diuretics, though one infant required a short period of peritoneal dialysis. Clinical improvement was usually noticed in this group one to two hours after starting prostaglandin E_1 and continued over many hours. Arterial pH, which responded significantly to prostaglandin E_1 (Fig. 3), was unrelated to the concentration used and continued after the four hour assessment. The numbers, however, are too small in the lower dosages to be sure that the results would be consistently satisfactory. After stopping prostaglandin E_1 in infants found to have the hypoplastic left heart syndrome, some 36 to 48 hours elapsed before there was clinical evidence of reclosure of the ductus.

Side effects

The side effects ascribed directly to prostaglandin E_1 are described in Table 2. Forty one episodes were recorded in 19 infants, 12 of whom had more than one side effect. The most serious side effect was of sudden apnoea which occurred in four cyanotic infants in group 1 within four hours of starting prostaglandin E_1. Hypoventilation and abnormal breathing patterns were noted in six additional infants in whom respiration had been rapid but regular before starting the treatment. Nine infants became 'jittery' within four hours of starting treatment and two developed generalised convulsions. Frequent loose stools were documented in at least

Table 2 *Side effects of prostaglandin E_1 (PGE₁) related to dosage (52 infants)*

Side effect	Total occurrences	Dose PGE_1 (μg/kg/min)
Apnoea	4	0·05–0·1
Hypoventilation	6	0·03–0·1
Convulsions	2	0·05–0·1
'Jitteriness'	9	0·02–0·1
Diarrhoea	9	0·02–0·1
Pyrexia	11	0·02–0·1

nine infants. Two infants in group 2 developed necrotising enterocolitis but they were so sick that this complication could not be definitely ascribed to prostaglandin E_1. Pyrexia occurred in 11 infants but was not a worrying problem. The fever was usually low grade and sometimes resolved spontaneously, though in other infants it subsided after stopping treatment. There were no problems of hypotension, flushing, tachycardia, or arrhythmias in this series. Bradycardia occurred only in conjunction with respiratory insufficiency.

Relating side effects to the dosage of prostaglandin E_1 we found that apnoea and convulsions occurred in the dose range 0·05 to 0·1 ug/kg/minute; hypoventilation in the range 0·02 to 0·1 ug/kg/minute; and 'jitteriness', diarrhoea, and pyrexia in the range 0·02 to 0·1 ug/kg/minute. No side effects were recorded in the 16 infants given a prostaglandin E_1 dosage of 0·005 to 0·01 ug/kg/minute.

Discussion

All infants in this series responded to prostaglandin E_1, emphasising the potentially predictable response of the newborn ductus.[7] Twelve per cent, however, of a larger series of 301 infants with cyanotic congenital heart disease failed to make a significant response,[4] and non-responders have been reported by others.[2 3 5 6] It has been suggested that favourable determinants of responsiveness are an initially low arterial Pao₂ and an age of less than 96 hours,[4] while unfavourable determinants of responsiveness in retrospect are an irreversibly closed ductus[3 4 6] and severe acidaemia and collapse.[5] There is no clear evidence that interarterial treatment is more effective than central or peripheral venous treatment and, indeed, oral administration of prostaglandin E_2 may be equally effective.[8] Environmental oxygen concentration was at one time thought to be relevant but more recent work has shown that prostaglandin E_1 is effective in relieving the ductus in both high and low oxygen concentrations.[9]

In the normal term infant functional closure of the ductus occurs within a few hours of birth and anatomical closure in 21 days,[10] when irreversible degenerative changes in the medical musculature have occurred. From this time prostaglandins would clearly cease to dilate the ductus and it seems likely that their effectiveness must decline in the preceding period. It has been suggested that increased flow through the ducts may delay anatomical closure[11] and it seems clear that the best chance of a good response to prostaglandins lies in their early administration while the circulatory and metabolic status of the infant is relatively satisfactory. Most published reports refer to infants given prostaglandins

after establishing a diagnosis but the infants in the present series were given prostaglandin E_1 when a duct dependent cardiac defect was suspected, and this approach would seem to have justifiable arguments in its favour. If the infant should subsequently be proved to have an unfavourable defect such as the hypoplastic left heart syndrome, prostaglandins can subsequently be stopped by agreement, as in this series, though recent advances in palliative surgical techniques have improved the potential prognosis for some of these infants. If prostaglandin E_1 is given early, before definitive diagnosis, it must sometimes be given outside its usual therapeutic indications. In the cyanotic group, persistence of the fetal circulation could be an important diagnostic error. Prostaglandin E_1, however, may be helpful in these infants because of its pulmonary vasodilator effect[7] even though it will be stopped after a firm diagnosis is made in order to encourage ductus closure. An infant with obstructed total anomalous pulmonary venous drainage may deteriorate further if given prostaglandin E_1 as a direct result of increasing ductal flow[12] but it is an uncommon anomaly[13] with a characteristic clinical presentation. The precise diagnosis of an acyanotic collapsed infant in gross cardiac failure may be extremely difficult but if, for instance, an infant with myocarditis were given prostaglandin E_1 based on the incorrect diagnosis of a duct dependent cardiac defect, the infant should be helped by improvement of left ventricular myocardial oxygenation and function.[14]

Although there are numerous reports of the role of prostaglandin in neonates with cardiac malformation, as were those designated to our groups 1 and 2, there are few references to their use in group 3 infants with simple transposition of the great arteries before balloon atrial septostomy. Both prostaglandin E_1 and E_2, however, seem to raise successfully the arterial Pao_2 in this group of cyanosed infants.[15] Presumably the mechanism of the improved arterial Pao_2 is due to increased ductus flow resulting in increased blood flow to pulmonary artery and left atrium, increased left atrial pressure, and hence increased arterial venous mixing through a stretched foramen ovale. A decrease in pulmonary vascular resistance may also be a favourable factor. The infants we have reported and those of Beitzke and Suppan[15] responded to prostaglandin treatment but this response implies the capability of adequate arterial-venous mixing at atrial level. We have recently had experience of an infant with simple transposition of the great arteries who failed to respond to prostaglandin E_1 infusion and, indeed, developed pulmonary oedema. Subsequent catheterisation confirmed the diagnosis but the

catheter could not be passed to the left atrium so it was supposed that the infant had premature closure of the foramen ovale and emergency surgical septectomy was carried out. Despite the possibility of this problem, our policy is to utilise prostaglandin E_1 for sick infants suspected of having transposition of the great arteries, particularly if there is a predicted delay in access to laboratory facilities for balloon atrial septostomy. It is also our current practice to arrange for prostaglandin E_1 treatment to be started before transfer in any infant judged to have a major duct dependent cardiac defect after telephone discussion with the referring paediatrician.

Despite awareness of the possibility of side effects, it may be difficult to decide whether a particular complication results directly from prostaglandin treatment or whether it could have been coincidental in the clinical course of a sick neonate,[1 16] and reports on the incidence of known side effects are few. In a large multicentre study of 481 infants, however, 21·5% had one or more documented side effect,[16] compared with 36·5% in our own series.

The most important reported short term side effects of prostaglandin E_1 treatment in sick neonates are those affecting the cardiovascular system (hypotension, vasodilatation, flushing, rhythm and conduction disturbances); the respiratory system (apnoea and hypoventilation); the gastrointestinal system (frequent stools and diarrhoea); the central nervous system (twitching and convulsions); and generalised systemic (pyrexia).[2 3 7 16 17] The side effects of prostaglandin E_2 seem to be similar to those of E_1.[18] Pyrexia is thought to be due to a central effect of prostaglandins on the mid brain and the re-setting of the thermoregulation centres at higher body temperature.[19] Diarrhoea has been specifically reported in infants receiving prostaglandin E_1, and colicky pain and diarrhoea have been complained of by human volunteers given oral prostaglandins.[21] It is possible that abdominal discomfort may have accounted for the restlessness of some of our infants. 'Jitteriness', tremors, and convulsions, however, are probably due to the central action of prostaglandins.[22] Hypoventilation and apnoea are thought to be central in origin[19] but this well documented and serious side effect is of interest because studies in conscious adults[23] and anaesthetised dogs and cats[24 25] have shown that prostaglandin E_1 stimulates ventilation. Prostaglandins E_1 and E_2 have been shown to cause apnoea in newborn swine,[26] and, recently, institution of respiratory movements in fetal lambs, within an hour of starting prostaglandin E_2 has been reported.[27] It is possible that there may be a critical concentration of prostaglandin E_2 in the newborn infant above

which inhibition of respiration occurs, but this remains speculative.

Whereas Lewis et al[16] found cardiovascular complications to be their most common group side effect, we did not record any such complication other than bradycardia associated with hypoventilation or apnoea, while pyrexia, though not constituting a clinical problem, was our most frequent side effect. The most dramatic and worrying complication was that of apnoea which occurred in 7·7% of our 52 infants, in 16·5% of a series of 78 infants,[17] and in 12% of 481 infants.[16] Although these attacks may be terminated by stopping prostaglandin[17] the sudden and unsuspected onset of apnoea, often early in treatment, implies standby facilities for intubation and ventilation during prostaglandin E_1 treatment[16 28] and could add to the hazards of interhospital transfer. Cyanotic congenital heart disease and a birthweight of less than 2 kg have been shown to be predisposing features.[16] It has also been suggested that apnoea may occur more readily in infants receiving prostaglandin E_2 rather than E_1[3] and serious apnoeic attacks have been reported with both its short term use[28] and long term oral treatment.[29] This suggestion remains unsubstantiated; in our series, apnoea occurred only in cyanotic infants with duct dependent pulmonary blood flow but our patients were all term infants.

The site of prostaglandin infusion is not now thought to be related to side effects other than that interarterial administration may favour vasodilatation and oedema. In our own experience peripheral venous administration has proved entirely satisfactory, although a central line may be preferred. While oral prostaglandins have their protagonists both in the short and the long term,[8] nevertheless the intravenous route offers dosage confidence and some practical advantages in the early stages of treatment.

We strongly support the view that apnoeic attacks and other major side effects are dose related, whether using prostaglandin E_1 or E_2.[18] We did not record any serious side effects in infants given less than 0·02 ug/kg/minute and, conversely, our four infants who became apnoeic were receiving 0·05 to 0·1 ug/kg/minute. Review of the reports confirms dosage of prostaglandin E_1 varying between 0·02 ug/kg/minute and 0·5 ug/kg/minute, with 0·1 ug/kg/minute being the most frequently documented concentration. An initial dose of 0·1 ug/kg/minute is still recommended by the manufacturers (Upjohn) supplying alprostadil.

Side effects were not directly related to dosage in the report of the United States multicentre trial,[16] although it is clear that the infusion rate was reduced below 0·1 ug/kg/minute in some of the infants studied and was stopped in others because of side effects. Recently a review article has recommended 0·05 ug/kg/minute as initial dosage[30] with subsequent reduction in dosage. We feel, however, that even this regimen may be unsafe for transporting sick infants, particularly since apnoeic attacks may occur early in treatment, and would reiterate that dosages of 0·005 ug/kg/minute to 0·01 ug/kg/minute have so far been found effective and free from serious side effects, while recognising the potential fallacies of small numbers and individual tolerance. Although our lowest dose of 0·005 ug/kg/minute was therapeutically successful in the six infants we treated, we need further experience before unreservedly supporting this as a recommended dosage. We suggest, however, that a logical and safe approach to treatment would be to begin with a small concentration of prostaglandin E_1, of 0·001 to 0·01 ug/kg/minute, with the option of a later small increase in dosage in the unexpected event of there being an inadequate response in an infant known to have a duct dependent cardiac defect once that infant has been assessed at a paediatric cardiac centre.

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