

Early therapeutic experience with the endothelin antagonist BQ-123 in pulmonary hypertension after congenital heart surgery

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Abstract

Objective—To assess the effect of endothelin type A (ET_A) receptor antagonism in infants with pulmonary hypertension following corrective surgery for congenital heart disease.

Design—Open label, preliminary study.

Setting—Tertiary paediatric cardiothoracic surgical centre.

Patients—Three infants (aged 3 weeks, 7 weeks, and 8 months) with postoperative pulmonary hypertension unresponsive to conventional treatment, including inhaled nitric oxide.

Interventions—Patients received incremental intravenous infusions (0.1 to 0.3 mg/kg/h) of the ET_A receptor antagonist BQ-123.

Main outcome measures—The response to BQ-123 administration was determined using continuous invasive monitoring of cardiorespiratory variables.

Results—BQ-123 infusion caused a reduction in the ratio of pulmonary to systemic pressures (0.62 (0.01) to 0.52 (0.03), mean (SEM)) with an accompanying decrease in right ventricular stroke work index (4.6 (0.4) to 2.5 (0.3) g/m) and a tendency for the cardiac index to rise (2.1 (0.2) to 2.7 (0.6) l/min/kg/m²). This was associated with a well tolerated fall in the arterial partial pressure of oxygen (16.5 (4.1) to 12.4 (3.3) kPa) and mean systemic arterial pressure (57 (3) to 39 (3) mm Hg).

Conclusions—ET_A receptor antagonism in infants with postoperative pulmonary hypertension after corrective surgery for congenital heart disease led to significant improvement in pulmonary haemodynamic indices. However, these benefits were associated with reductions in systemic blood pressure and arterial oxygen saturation, the latter consistent with a ventilation-perfusion mismatch. On the basis of these results, studies in pulmonary hypertension will need to proceed with caution.

(Heart 1999;82:505-508)

Keywords: endothelin-1; pulmonary hypertension; receptor antagonism; congenital heart disease

Postoperative pulmonary hypertension is a common clinical problem following successful surgical correction of congenital heart defects and may lead to significant morbidity and mortality.¹ Its occurrence relates both to

pre-existing pulmonary hypertension and the acute effects of surgery and cardiopulmonary bypass. Dysfunction of the pulmonary vascular endothelium appears to be a major contributing factor for the development of pulmonary hypertension in this group of patients.

Endothelin-1 is an extremely potent endothelium derived vasoconstrictor peptide² which is released and cleared in the pulmonary circulation.³ Plasma concentrations of endothelin-1 are increased in subjects going to high altitude,⁴ in patients with chronic heart failure,⁵ and in patients with pulmonary hypertension.⁶ Moreover, in these conditions, the degree of pulmonary hypertension and pulmonary vascular resistance correlates closely with plasma endothelin-1 concentrations.⁴⁻⁶ Children with pulmonary hypertension⁷ and persistent pulmonary hypertension of the newborn⁸ also have raised plasma endothelin-1 concentrations that correlate with disease severity,⁸ are particularly marked after cardiopulmonary bypass,⁹ and may play a role in its pathogenesis.¹⁰

Studies in animal models of pulmonary hypertension have reported reversal of pulmonary hypertension with endothelin receptor antagonists^{11,12} and endothelin converting enzyme inhibition.¹³ Indeed, in a sheep model of pulmonary hypertension induced by aortopulmonary shunting in utero, endothelin antagonism eliminated the postoperative increase in pulmonary vascular resistance following cardiopulmonary bypass.¹⁴ Reddy and colleagues¹⁴ concluded that endothelin antagonism warrants further study in children at risk of pulmonary hypertension after surgical repair with cardiopulmonary bypass. There have been no published clinical studies to date assessing the therapeutic benefits of endothelin antagonism in postoperative pulmonary hypertension.

We report our preliminary experience with the therapeutic use of the endothelin type A (ET_A) receptor antagonist, BQ-123, in three infants with postoperative pulmonary hypertension following corrective surgery for congenital heart disease.

Methods

Written informed parental consent was obtained for each child and the study was approved by the local research ethics committee.

BQ-123 (American Peptide Company, Sunnyvale, California, USA) was given under a Department of Health (UK) Doctors and Dentists Exemption Certificate.

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Accepted for publication
19 April 1999

Table 1 Patient characteristics

Patient	Age (weeks)	Sex	Weight (g)	Diagnosis	Procedure	Inotropes and vasodilators
1	3	Female	3100	Anomalous aortic origin of left pulmonary artery, patent foramen ovale, persistent arterial duct	Mobilisation of left pulmonary artery with formation of pulmonary artery bifurcation, closure of patent foramen ovale, division of persistent arterial duct	Dopamine 3 µg/kg/min
2	7	Male	3500	Obstructed partial anomalous pulmonary venous drainage, left pulmonary artery stenosis, atrial septal defect	Right pulmonary vein to right atrium anastomosis, atrial diverting patch, left pulmonary artery patch	Dobutamine 20 µg/kg/min Glyceryl trinitrate 2 mg/kg/min
3	25	Female	6100	Ventricular septal defect, persistent arterial duct (Aicardi and Poland syndromes)	Patch closure of ventricular septal defect, closure of persistent arterial duct	Dobutamine 20 µg/kg/min Dopamine 3 µg/kg/min

The three infants (aged 3 weeks, 7 weeks, and 8 months) were anaesthetised according to our standard protocol. Phenoxybenzamine (1 mg/kg) was given before establishing cardiopulmonary bypass. Corrective surgery was performed after inducing systemic hypothermia and cold crystalloid cardioplegic arrest. A thermolilution pulmonary artery flow catheter (3 F; Baxter Health Care, Thetford, UK) and a left atrial line were inserted before discontinuing cardiopulmonary bypass.

After chest closure, the infants were returned to the intensive care unit and maintained on a standard regimen of vecuronium (0.1 mg/kg/

h), fentanyl (5.0 µg/kg/h), and midazolam (0.1 mg/kg/h). Following rewarming, the ratio of pulmonary to systemic arterial pressure (P/S ratio) was determined using invasive monitoring. Infants were entered into the study if they did not have a residual left to right shunt on echocardiography and had a P/S ratio greater than 0.5 which did not respond to standard treatment, including inhaled nitric oxide (10 ppm increasing to 20, 30, and 40 ppm for 30 minutes at each dose). During the study period, the amount of sedation and inotropic support was maintained constant and atrial pressures kept stable using packed red blood cells or human albumin solution. Following stabilisation for three hours, BQ-123 was dissolved in 0.9% saline and given intravenously at 0.1, 0.2, and 0.3 mg/kg/h, for 30 minutes at each dose.

Data are presented as mean (SEM). Haemodynamic variables were measured in triplicate at each time point and the mean taken. Recognising the small sample size and inherent variation between haemodynamic variables, non-parametric analyses (Wilcoxon rank sum) were used to compare variables before, during, and after BQ-123 infusion. Statistical significance was assumed at the 5% level.

Results

Characteristics of the patients are shown in table 1.

Baseline left and right atrial pressures were 9.6 (1.2) and 7.3 (0.3) mm Hg, respectively, and did not change during or after BQ-123 infusion. However, the P/S ratio fell in all patients during BQ-123 administration ($p < 0.001$; fig 1) and returned to baseline about 90 minutes after discontinuation of the infusion. Concomitant with the changes in the P/S ratio, the systemic arterial pressure fell (fig 1), although the fall was proportionately less than for the pulmonary arterial pressure and was well tolerated. Right ventricular stroke work index mirrored the changes in P/S ratio and fell significantly in response to BQ-123 infusion, from 4.56 (0.31) to 2.90 (1.90) g.m/m² ($p < 0.001$). The cardiac index tended to increase and left ventricular stroke work index fell from 8.0 (0.9) to 6.2 (0.9) g.m/m² ($p < 0.001$) but there were no changes in heart rate, acid-base balance, or urine output.

Despite haemodynamic improvements, the arterial partial pressure of oxygen fell in all three infants during BQ-123 infusion, from 16.5 (4.1) to 12.4 (3.3) kPa. Because of the

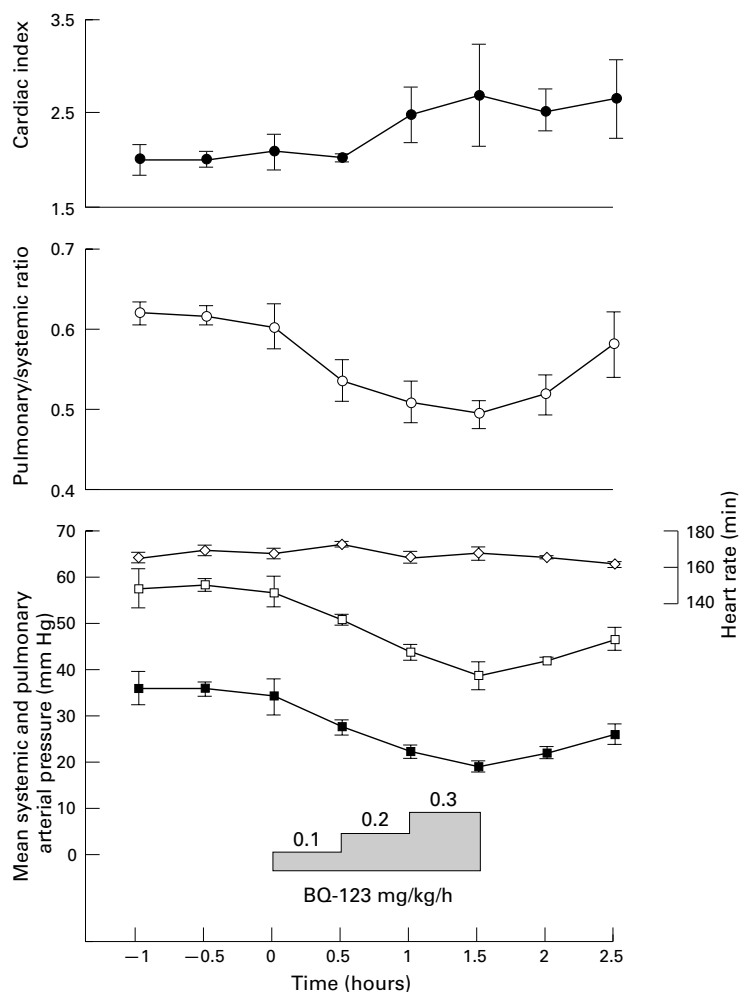


Figure 1 Effect of BQ-123 (0.1 to 0.3 mg/kg/min) on cardiac index (●), pulmonary/systemic ratio (○), heart rate (◇), and mean systemic (◻) and pulmonary (■) arterial pressure in infants with postoperative pulmonary hypertension following corrective surgery for congenital heart disease. (Error bars are SEM, $n = 3$.)

reduction in arterial oxygen partial pressures, nitric oxide (20 ppm) was reintroduced into the ventilatory circuit of two infants two hours after starting the BQ-123 infusion (patients 1 and 3). Both infants then responded promptly to nitric oxide administration, with the partial pressures rising from 7.4 to 8.2 kPa and from 8.4 to 10.5 kPa. The third infant (patient 2) did not receive inhaled nitric oxide because in that infant the partial pressure of oxygen was 18.6 kPa at its nadir. Qualitatively, this did not appear to correlate with cardiopulmonary bypass time.

No adverse effects were seen on withdrawal of BQ-123 and all three infants survived to the 30th postoperative day.

Discussion

Although potentially life threatening, postoperative pulmonary hypertension following corrective surgery for congenital heart disease is usually reversible. When conventional treatment, including inhaled nitric oxide, fails further measures such as extracorporeal circulatory support and membrane oxygenation may be required. We have conducted the first preliminary study to examine the therapeutic effects of ET_A receptor antagonism under such circumstances. Although we were able to show a significant improvement in pulmonary haemodynamic indices, this was associated with arterial hypoxaemia and systemic hypotension.

Endothelin-1 is continuously released by the endothelium and contributes to the maintenance of basal vascular tone^{15 16} and blood pressure.^{17 18} It is therefore not surprising that BQ-123 caused a reduction in systemic as well as pulmonary arterial pressure and this is consistent with the haemodynamic effects seen with the acute administration of BQ-123 in patients with heart failure.¹⁹ However, in these three infants, ET_A receptor antagonism appeared to be more selective for the pulmonary vascular bed, with a proportionately greater effect in comparison with the systemic circulation. This suggests that endothelin-1 provides a greater contribution to the maintenance of vascular tone in the pulmonary circulation in postoperative pulmonary hypertension.

In animal models of pulmonary hypertension induced by aortopulmonary shunting, not only have raised plasma endothelin-1 concentrations been found, but also an increased pulmonary vasoconstrictor response to endothelin-1 infusion.²⁰ These findings may, in part, relate to the upregulation of endothelin-1 and endothelin converting enzyme expression, as well as the 10-fold downregulation of the ET_B receptor within the pulmonary vasculature.²¹ The balance of receptor expression is therefore largely shifted to the vasoconstrictor ET_A receptor and this may exacerbate the pulmonary hypertension. Thus it would be anticipated that selective ET_A receptor antagonism would produce a greater reduction in pulmonary vascular resistance than combined ET_A and ET_B receptor antagonism.

A degree of systemic hypotension and impaired oxygenation is the inevitable consequence of effective systemic vasodilatation and these are the limiting factors in the clinical use of conventional agents. Intrapulmonary ventilation/perfusion matching is dependent upon local hypoxic vasoconstrictive reflexes and so is impaired by pulmonary vasodilatation. Although they were initially unresponsive to inhaled nitric oxide, improved oxygenation was seen in the two patients who received inhaled nitric oxide (20 ppm) after ET_A receptor antagonism. This effect may be related to the recently described improvement in pulmonary vascular responsiveness to nitric oxide following ET_A receptor antagonism.²² The mechanisms of this effect remain to be established, but in an animal model of pulmonary hypertension, ET_A receptor antagonism was associated with both an improvement in endothelium dependent vasodilatation and an increase in pulmonary vascular smooth muscle sensitivity to nitric oxide.²²

This first preliminary report of the use of ET_A receptor antagonism in infants with postoperative pulmonary hypertension following corrective surgery for congenital heart disease suggests an improvement in the pulmonary to systemic ratio and right ventricular stroke-work index. However, these benefits were counterbalanced by potentially adverse reductions in arterial oxygenation and systemic blood pressure. These findings suggest that endothelin antagonism, particularly in combination with inhaled nitric oxide, may represent a valuable new approach to the treatment of refractory postoperative pulmonary hypertension which merits further but cautious investigation.

We thank Dr M J Godman for funding the study through the Calderwood Research Endowment Fund. DEN was the recipient of a British Heart Foundation Junior Research Fellowship (FS/95009). DJW is supported by a Research Leave Fellowship from the Wellcome Trust (WT 0526330).

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