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

B Prendergast, D E Newby, L E Wilson, D J Webb, P S Mankad

Abstract
Objective—To assess the effect of endothelin type A (ET\textsubscript{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\textsubscript{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/m\textsuperscript{2}). 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\textsubscript{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.

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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.\textsuperscript{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 peptide\textsuperscript{2} which is released and cleared in the pulmonary circulation.\textsuperscript{3} Plasma concentrations of endothelin-1 are increased in subjects going to high altitude,\textsuperscript{4} in patients with chronic heart failure,\textsuperscript{5} and in patients with pulmonary hypertension.\textsuperscript{6} Moreover, in these conditions, the degree of pulmonary hypertension and pulmonary vascular resistance correlates closely with plasma endothelin-1 concentrations.\textsuperscript{4–6} Children with pulmonary hypertension and persistent pulmonary hypertension of the newborn\textsuperscript{7} also have raised plasma endothelin-1 concentrations that correlate with disease severity,\textsuperscript{7} and may play a role in its pathogenesis.\textsuperscript{8}

Studies in animal models of pulmonary hypertension have reported reversal of pulmonary hypertension with endothelin receptor antagonists\textsuperscript{10–12} and endothelin converting enzyme inhibition.\textsuperscript{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.\textsuperscript{14} Reddy and colleagues\textsuperscript{14} 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\textsubscript{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.
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 thermodilution 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
Endothelin antagonism in pulmonary hypertension after congenital heart surgery

507

vasculature. The balance of receptor expres-
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tension.
Anderson in postoperative pulmonary hyper-
eect in comparison with the systemic
pressure. It is therefore not surprising that
BQ-123 caused a reduction in systemic as well
as pulmonary arterial pressure and this is con-
istent with the haemodynamic effects seen with
the acute administration of BQ-123 in
patients with heart failure. However, in these
three infants, ET\textsubscript{A} receptor antagonism
appeared to be more selective for the pulmonary
circular bed, with a proportionately greater
effect in comparison with the systemic
circulation. This suggests that endothelin-1
provides a greater contribution to the mainte-
nance of vascular tone in the pulmonary
circulation in postoperative pulmonary hyper-
tension.

In animal models of pulmonary hyper-
tension induced by aortopulmonary shunting,
not only have raised plasma endothelin-1 con-
centrations been found, but also an increased
pulmonary vasoconstrictor response to
endothelin-1 infusion. 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\textsubscript{A} receptor within the pulmonary
vasculature. The balance of receptor expres-
sion is therefore largely shifted to the vasocon-
strictr ET\textsubscript{A} receptor and this may exacerbate
the pulmonary hypertension. Thus it would be
anticipated that selective ET\textsubscript{A} receptor antago-
nism would produce a greater reduction in
pulmonary vascular resistance than combined
ET\textsubscript{A} and ET\textsubscript{B} receptor antagonism.

A degree of systemic hypotension and
impaired oxygenation is the inevitable conse-
quence 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 vasodilata-
tion. 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\textsubscript{A}
receptor antagonism. This effect may be related
to the recently described improvement in pulmo-
nary vascular responsiveness to nitric oxide
following ET\textsubscript{A} receptor antagonism. The
mechanisms of this effect remain to be
established, but in an animal model of pulmo-
nary hypertension, ET\textsubscript{A} receptor antagonism
was associated with both an improvement in
endothelin dependent vasodilatation and an
increase in pulmonary vascular smooth muscle
sensitivity to nitric oxide. This
preliminary report of the use of ET\textsubscript{A}
receptor antagonism in infants with post-
operative 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 reduc-
tions in arterial oxygenation and systemic
blood pressure. These findings suggest that
endothelin antagonism, particularly in combi-
nation with inhaled nitric oxide, may represent
a valuable new approach to the treatment of
refractory postoperative pulmonary hyper-
tension which merits further but cautious
investigation.

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