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CASE REPORT

Nesiritide for the Treatment of Pulmonary Hypertension and Cor Pulmonale in an Infant

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Abstract Nesiritide is a synthetic form of B-type natriuretic peptide. It is approved for the treatment of acute exacerbations of congestive heart failure in hospitalized adult patients. It is currently under investigation for use in other settings and other patient populations. This article describes administration of nesiritide to an infant patient with severe pulmonary hypertension and cor pulmonale. No adverse reactions occurred during administration of the drug. Specifically, there was no hypertension, vomiting, arrhythmia, or changes in renal function. No changes in renal function occurred in the months subsequent to treatment. This case report illustrates that nesiritide can be safely administered to critically ill infants with pulmonary hypertension and cor pulmonale. Our patient experienced a decrease in pulmonary pressure and improved clinical condition during and after the infusion. However, further study is required to fully evaluate the safety and efficacy of nesiritide for these patients.

Keywords Cor pulmonale · Pulmonary hypertension · Nesiritide · B-type natriuretic peptide

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Despite advances in the care of newborn infants with respiratory distress syndrome, some former preterm infants still develop very severe bronchopulmonary dysplasia. Many go on to develop pulmonary artery hypertension. Rarely, the most severely affected infants progress to life-threatening right heart failure, or cor pulmonale. Treatment options for such severely affected infants are limited. Diuretics, inhaled or systemic bronchodilators, and inhaled or systemic corticosteroids tend to be the first-line therapies for such infants. Efficacy of these treatments is unknown. There is mounting evidence that the safety of these treatments, particularly systemic steroids, is in doubt. Some physicians, in an effort to help these patients, have started using sildenafil, with little scientific support for dose or duration of treatment. Systematic investigations of these treatments and newer medications are needed. We administered nesiritide (brand name Natrecor; Scios, Inc.) to a patient who was unresponsive to medical therapy for pulmonary hypertension and cor pulmonale, including those common medications listed previously, as well as inhaled nitric oxide.

Case Report

The patient was a 23 6/7 week preterm male with a birth weight of 635 g and Apgars of 1 and 5 at 1 and 5 minutes, respectively. He was a product of assisted reproductive technology and a twin gestation. His mother was a 32 year-old gravida 1, para 2 female with unremarkable maternal labs. His neonatal course was complicated by surfactant deficiency with RDS, hyperbilirubinemia, grade I intraventricular hemorrhage, a

patent ductus arteriosus that required surgical ligation on day of life (DOL) 72, apnea and bradycardia, necrotizing enterocolitis, retinopathy of prematurity, nephrocalcinosis, hypertension, and bronchopulmonary dysplasia (BPD) that eventually led to pulmonary hypertension and cor pulmonale. He had a complicated gastrointestinal history with prolonged feeding difficulty that was addressed with a combination of medical and nonmedical therapies. Due to his prolonged respiratory course, the patient was ventilator dependent and required tracheostomy.

He required mechanical ventilation for the first 84 days of life, including 8 days on high-frequency oscillatory ventilation when he was 14 days old. He successfully extubated on DOL 85. He remained on nasal continuous positive airway pressure, Oxyhood, and nasal canula for more than 60 days. Eventually, his respiratory condition worsened. He required intubation and mechanical ventilation. When it became clear that he was ventilator dependent, he underwent tracheostomy. He remained on mechanical ventilation for an additional 65 days in the neonatal intensive care unit (NICU) and after discharge.

During his NICU stay, at 2 months of life, the patient had a normal echocardiogram. However, at 4 months of life, while still in the NICU, his respiratory condition progressively worsened. Sepsis workup was negative and chest x-rays showed only chronic changes consistent with his diagnosis of BPD. An echocardiogram showed tricuspid regurgitation with a peak velocity of 4.3 m/sec corresponding to a right ventricular (RV) systolic pressure of 80 mmHg. There was enlargement of both the right ventricle and the atrium. One week later, the right ventricle showed worsening function with pulmonary artery dilation and mild pulmonary insufficiency. The echocardiographic findings and clinical condition (amount of respiratory support) seemed to stabilize for a few weeks. However, approximately 4 weeks after the diagnosis of pulmonary artery hypertension, the patient again developed increasing respiratory requirements. Echocardiogram now showed severely depressed RV function with severe dilatation of the right ventricle, atrium, and pulmonary artery. The TR jet peak velocity was 4.88 m/sec and RV systolic pressure was 100 mmHg.

Over the course of the patient's cardiopulmonary illness, he was treated with diuretics, inhaled and systemic bronchodilators, inhaled steroids, and multiple courses of systemic steroids. The pulmonary hypertension was treated with inhaled nitric oxide and sildenafil. The patient continued to worsen despite aggressive maximal medical treatment. Institutional review board permission was sought, and received, to start the patient on nesiritide. Nesiritide therapy was delivered via a 1 μg/kg bolus followed by a continuous infusion of 0.005 μg/kg/min with repeat boluses and dose increases of 0.005 μg/kg/min every 3 hours to a maximum continuous dose of 0.03 μg/kg/min. He received 6 days of nesiritide therapy. Echocardiogram after 1 day of treatment showed mild RV dilatation with normal function and trivial TR (gradient not measurable). On the same day, the nitric oxide was discontinued with no worsening of clinical or echocardiographic findings. Two days later, a repeat echocardiogram showed mild ventricular hypertrophy with normal function. These findings were also present on multiple follow-up echocardiograms over the next 2 or 3 months. He eventually developed transient and trivial mitral, aortic, and pulmonary regurgitation that did not require intervention.

During the time of nesiritide treatment, his ventilator settings were weaned. His clinical improvement continued after the infusion. He was eventually discharged home with stable ventilator settings. Over the course of several months, he was weaned off his ventilator and most of his respiratory medications. He underwent tracheostomy take-down. Currently, he is doing well, with developmental issues consistent with his prematurity.

No adverse events, specifically no hypotension, arrhythmia, bradycardia, or vomiting, occurred during the study drug infusion. No changes in renal function were observed during the infusion or in the months after treatment.

Discussion

Cor pulmonale is a rare complication of severe bronchopulmonary dysplasia. The fibromuscular changes in pulmonary architecture associated with BPD can lead to increased pulmonary artery pressure. The most severely affected children may develop right ventricular dysfunction and failure, with sometimes fatal results. Current literature on the link between cor pulmonale and BPD is scarce. A 1992 study [17] found that of 23 BPD-affected infants, only 1 developed transient cor pulmonale over the course of 1 year.

B-type natriuretic peptide (BNP) is an endogenous peptide hormone released from the heart ventricles in response to stress. Elevated serum levels of BNP are associated with acute exacerbations of congestive heart failure in adults. BNP levels have been investigated in preterm infants with patent ductus arteriosus [3, 5, 14]. In term infants, elevated BNP levels are also associated with persistent pulmonary hypertension of the

newborn (persistent fetal circulation syndrome) but not neonates with respiratory distress due to other causes [11]. BNP levels in other cardiac conditions are under investigation. Because BNP is associated with acute changes in cardiac stress, it is not likely to be elevated in states of chronic ventricular stress (e.g., cor pulmonale), but BNP levels in these conditions are not known.

The BNP receptor is a membrane-bound G protein that catalyzes the conversion of GTP to cyclic GMP (cGMP). As a consequence, cGMP affects calcium homeostasis, leading to smooth muscle relaxation. This is particularly important in the pulmonary vasculature for the treatment of conditions such as persistent pulmonary hypertension of the newborn (PPHN). Indeed, this same pathway is modulated by inhaled nitric oxide, through a G protein in the cytosol, and prostaglandin inhibitors, such as sildenafil, by decreasing the catabolism of cGMP.

Nesiritide, recombinant human BNP, has been shown to be a safe and effective treatment for adults with acute exacerbations of congestive heart failure. It has also been suggested for the treatment of children with heart failure [9]. Its role in the treatment of chronic cardiac conditions in adults is under investigations. It may also have a role in other adult diseases and neonatal or pediatric conditions such as PPHN or cor pulmonale. Nesiritide's pulmonary vessel vasodilatory effects in a sheep model have been described [8]. It may also inhibit interstitial fibrosis, myocyte hypertrophy, and vascular smooth muscle hypertrophy [4]. These properties make it an attractive candidate for treating patients with cor pulmonale due to bronchopulmonary dysplasia because it may favor therapeutic remodeling of the pulmonary vascular bed.

Clinical experience with nesiritide in pediatric patients has been described in 56 published accounts. The patients varied in age from newborn to 19 years. Diagnoses included congestive heart failure, PPHN with renal failure, dilated cardiomyopathy, cardiac transplant, and congenital heart disease.

Moffett et al. [10] described the case of an infant who received nesiritide for PPHN and polycystic kidney disease. The infusion was given for 6 days and titrated through the dosing range used in this case (0.01–0.03 μg/kg/min). There were no adverse events during the infusion. Renal function and cardiac function improved. Creatinine decreased during the infusion. The patient eventually died 5 months later from sepsis, probably related to dialysis, but the authors did not discuss the specifics of the terminal events.

Marshall et al. [7] reviewed their experience with nesiritide in five critically ill pediatric patients. Patients ranged in age from 2 months to 13 years. Nesiritide infusions varied from 0.01 to 0.03 μg/kg/min and continued for 2–8 days. No adverse events were noted. All patients had improved cardiac output, peripheral perfusion, and renal function.

Mahle et al. [6] administered nesiritide to 30 patients aged 5 days to 16.7 years. These were critically ill patients with heart failure related to dilated cardiomyopathy, heart transplant, or congenital heart disease who were already receiving diuretics and inotropic agents. Doses ranged from 0.005 to 0.02 μg/kg/min and continued from 1 to 27 days (median, 4). Infusion was discontinued in 2 patients due to possible complications. One was for a decrease in blood pressure that was not life threatening, and the other was for arrhythmia (premature ventricular complexes) that could have possibly been related to the infusion. There was no change in serum creatinine. Improved fluid balance and diuresis were the most common beneficial effects of nesiritide infusion. They also showed a decrease in right atrial pressure. They concluded that nesiritide is well tolerated in this critically ill population.

Feingold and Law [2] reported a series of four nesiritide infusions in three patients aged 19, 17, and 7 years. The doses ranged from 0.005 to 0.02 μg/kg/min and the duration was 36–117 hours. One patient had hypotension that required decreased nesiritide dose but no other intervention. No serious adverse events were encountered.

Experience with nesiritide in seven patients awaiting heart transplant was described by Sehra and Underwood [16]. Patients ranged from 3 to 121 months of age. Doses ranged from 0.005 to 0.02 μg/kg/min, and infusions ranged from 1 to 16 days (mean, 10.6 ± 4.1). No significant changes in blood pressure were noted. No change in electrolytes or arrhythmias occurred. Infusions were discontinued in two patients due to ''untoward effects; which were ultimately deemed unrelated to nesiritide.'' The authors provided a lengthy discussion with specific justification for why these events were not related to the infusion. The authors concluded that nesiritide is safe and effective for pediatric patients with heart failure.

The known clinical experience with nesiritide in pediatric patients was discussed in a 2004 editorial by Schamberger [15]. The conclusion of this review was that ''nesiritide appears reasonably safe in pediatric patients at similar maintenance doses as in adults (0.01–0.03 μg/kg/min).'' The author called for larger studies to learn more about the effects, optimal dosing, and appropriate applications of nesiritide in pediatrics.

Our case adds to the literature on nesiritide in pediatric patients in that it describes positive results

following a novel application of an already approved medicine. Our patient experienced improvement in his clinical condition in conjunction with nesiritide infusion. The therapeutic effects were sustained even after the infusion was discontinued. More important, no adverse events occurred during or after the infusion, even at the maximum dose administered for 6 days. BNP levels in this patient were not measured prior to study infusion. However, normal levels of BNP in term newborns have only been sporadically investigated [11]. In our limited experience with BNP levels in chronic neonatal conditions, our preliminary data suggest that BNP levels for these infants are not elevated (unpublished data). However, other authors have published data on chronic adult conditions. These authors have shown increased BNP levels in patients with primary pulmonary hypertension, pulmonary embolism, and both acute cor pulmonale and chronic cor pulmonale as a result of chronic obstructive pulmonary disease [1, 18–20]. Currently, we have no explanation for our contrary findings. It is possible that as more data are collected in our ongoing study, differences in BNP levels may be found.

Given that nesiritide is an acute smooth muscle relaxant and may have therapeutic effects on the remodeling of vascular beds, it is reasonable to assume that it may be beneficial for some patients affected by cor pulmonale as a consequence of BPD. However, the optimum dose and duration of treatment in infants are unknown. Likewise, potential adverse events remain a concern. The most common adverse event in adult patients receiving the medication is hypotension. Serious hypotension has not occurred in the published literature on pediatric patients treated with nesiritide.

There has been much discussion in the adult literature regarding the effect of nesiritide on renal function in adult patients. Two retrospective reviews, by the same author, have suggested increased mortality in adult patients treated with nesiritide [12, 13]. However, thorough investigation has found little evidence to support serious renal toxicity as a result of nesiritide infusion. In the pediatric literature, when information on urine output and serum creatinine levels is available, renal function is either unchanged or actually improves. This includes a patient with preexisting renal disease [10].

Conclusion

This case describes the administration of nesiritide to a pediatric patient with cor pulmonale. He had dramatic improvement in his echocardiographic findings, as well as his clinical condition, after starting the nesiritide infusion. He was weaned off inhaled nitric oxide 1 day after starting the infusion and his respiratory status stabilized and improved over the 6 days of nesiritide. Echocardiographic findings and clinical improvement were sustained, and the patient eventually was discharged home and weaned off respiratory support. No adverse events occurred either during or after the infusion.

There is increasing evidence that nesiritide can be safely administered to neonatal and pediatric patients and may be beneficial for some cardiorespiratory conditions. However, optimum dosing and duration of treatment is unknown. As with all reports of this nature, further investigation, specifically large, blinded, randomized, controlled trials, is required.

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