PEDIATRIC PHARMACOTHERAPY

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Nesiritide for Infants and Children with Heart Failure
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At the time of its introduction in 2001, nesiritide was the first agent approved for the treatment of adult acute decompensated heart failure in more than a decade.[1,2] Five years after its introduction, nesiritide remains a controversial therapy. While there is much more known about its potential benefits, there have also been concerns raised about its adverse effect profile and its overall impact on mortality. In the last three years, preliminary reports have shown nesiritide to be efficacious and well tolerated in infants and children with heart failure or low cardiac output syndrome that is unresponsive to traditional therapies. Its role in the routine management of heart failure in this population, however, remains undetermined. This issue of *Pediatric Pharmacotherapy* will review the pharmacology of nesiritide and the reports of its use in the management of pediatric heart failure.

Mechanism of Action
Endogenous B-type natriuretic peptide (BNP) is produced and excreted by the ventricular myocardium in response to increased myocardial stretch. Nesiritide is a recombinant form of BNP. Like the endogenous form, it is believed to produce its effects by binding to guanylate cyclase receptors in vascular smooth muscle and endothelial cells, leading to increased concentrations of guanosine 3'5'-cyclic monophosphate (cGMP) and dilation of veins and arteries. The venous effect is generally greater than the arterial effect. Nesiritide also possesses diuretic effects and decreases aldosterone, epinephrine, and endothelin-1.[1-4]

In clinical studies of adult heart failure patients, nesiritide has been shown to produce a dose-related reduction in pulmonary capillary wedge pressure (PCWP) and systemic arterial pressure. Studies conducted in adults have shown a significant improvement in clinical symptoms compared to placebo or nitroglyercin. In comparison studies with dobutamine, nesiritide was as effective and associated with a lower incidence of arrhythmias.[1-4]

Clinical Experience in Children
There are currently several papers in the medical literature describing the use of nesiritide in pediatric patients.[5-13] In 2004, Feingold and Law reported their experience in three children.[5] The first was a 19-year-old with Duchenne muscular dystrophy and dilated cardiomyopathy. After a 3 week history of worsening symptoms, he was admitted and treated with diuretics and nesiritide for 36 hours. The second case was a 17-year old-girl with congenital heart disease awaiting a heart transplant. Worsening fluid retention led to the decision to initiate diuretics and nesiritide. As in the first case, therapy was continued for 36 hours. The third patient was a 7-year-old boy who had undergone heart transplantation at 4 months of age. He was treated on two occasions for heart failure with poor urine output. The first treatment course lasted for 36 hours and the second for 117 hours. In all three cases, nesiritide was administered as a 1 mcg/kg IV bolus followed by an infusion ranging from 0.005 to 0.02 mcg/kg/min. The first and third cases responded well to treatment, with significant improvement in clinical symptoms and an increase in urine output. The second case did not respond to therapy. None of the patients exhibited hypotension or arrhythmias.

Simsic and colleagues from the Sibley Heart Center/Emory University published two more cases that year in *Pediatric Cardiology*.[6] They treated a 6-week-old infant with heart failure following surgery to repair coarctation of the aorta and close a ventricular septal defect and a 7-week-old with aortic valve stenosis. Both infants had increased intracardiac filling pressures postoperatively which failed to respond to diuretics and afterload reduction with milrinone. Nesiritide was initiated at a dose of 0.005 mcg/kg/min. The first patient was treated at that dose for 10 days. The second patient required an increase in dose to 0.01 mcg/kg/min; therapy was continued for 6 days. Both patients exhibited significant improvement in cardiac function and increased urine output without hypotension or arrhythmias.

Three additional papers have been published by clinicians at the University of Missouri.[7-9] Marshall and colleagues published a retrospective review of five children treated with nesiritide.[7] Two had undergone cardiac surgery, two had adult respiratory distress syndrome, and one had septic shock. In three of the patients, nesiritide was used as the primary agent to improve cardiac output. All of the children had clinical signs of improved perfusion. Urine output remained stable or increased. Nesiritide was also used in the treatment of hypertension in two infants receiving extracorporeal membrane oxygenation (ECMO)[8] and in a 17-year-old boy with acute myelogenous leukemia who developed renal insufficiency and cardiac dysfunction associated with septic shock.[9] As in previous papers, the authors of these reports concluded that nesiritide was an effective and well tolerated therapy for the management of pediatric patients with heart failure who fail to respond to standard therapies.

The largest retrospective review was published last year in *Pediatric Critical Care Medicine*.[10] Mahle and the group from the Sibley Heart Center reported their experience in 30 children (ages 5 days to 16 years) who were treated with nesiritide between July 2003 and August 2004. Eighteen of the patients had congenital heart defects, seven had dilated cardiomyopathy, and five had undergone cardiac transplantation. Twenty-four patients received a bolus dose. The dose of the continuous infusion ranged from 0.005 to 0.02 mcg/kg/min. The median duration of therapy was 4 days, with a range of 1 to 24 days. Overall, the patients exhibited a significant improvement in fluid balance (positive 0.8 ± 1.9 mL/kg/hr at baseline to negative 0.3 ± 1.8 mL/kg/hr after 24 hours of therapy; p=0.02). There was also a trend towards a reduction in right atrial pressure (9.2 ± 3.9 mm Hg prior to treatment compared to 11.2 ± 4.1 mm Hg on therapy; p=0.8). Therapy was discontinued in one patient for hypotension and one for an arrhythmia.

Two additional case reports were published earlier this year by Moffett and colleagues.[11,12] In the first paper, a 3-year-old girl with dilated cardiomyopathy and acute decompensated cardiac failure was treated with nesiritide (0.01 mcg/kg/min with no bolus) after failing to improve on standard vasoactive therapies.[11] The dose was titrated to a maximum of 0.4 mcg/kg/min and continued for a total of 45 days. During her treatment, urine output increased significantly and serum creatinine declined. On day 45, the patient received an inadvertent bolus of the entire contents of the syringe meant for a 24 hour infusion (a dose of 360 mcg or 36 mcg/kg). Despite the large overdose, the patient did not develop hypotension. There were also no significant changes in urine output or renal function associated with the overdose. The patient subsequently underwent a successful heart transplant.

In their second case report, the authors described the use of nesiritide in a term neonate with polycystic kidney disease, pulmonary hypertension, and heart failure.[12] The patient was treated with diuretics, milrinone, and nesiritide (0.01 mcg/kg/min initially, titrated to a maximum of 0.03 mcg/kg/min). Urine output increased significantly at the start of treatment and cardiac output improved. Nesiritide was continued for 6 days, until the patient developed anuria which no longer responded to dose titration.

Earlier this month, the results of a prospective evaluation of nesiritide were published in *Pediatric Cardiology*. Jefferies and colleagues at Texas Children's Hospital studied the safety and efficacy of 55 nesiritide courses in 32 children (age range 1 month-20 years). The underlying etiologies of the patients' heart failure was mixed, with the majority of patients having a congenital heart disease (26%) or dilated cardiomyopathy (38%). All patients received an initial infusion rate of 0.01 mcg/kg/min, with titration up to 0.03 mcg/kg/min if needed. The minimum duration of therapy was 72 hours. All of the children received furosemide during nesiritide use. Dopamine and milrinone were also widely used. The authors reported no cases of hypotension or arrhythmias in 478 cumulative days of therapy. Mean urine output increased from 2.35 ± 1.61 mL/kg/hr at baseline to 3.10 ± 1.94 mL/kg/hr on day 4 (p<0.01). Mean central venous pressure decreased from 13 to 7 mmHg (p=0.018), as well as patient weight (30.4 kg vs 29.7 kg, p<0.001). Serum creatinine and potassium values decreased slightly. Subjective responses from the older children revealed decreased thirst and improved appetite.

Pharmacokinetics and Pharmacodynamics
Nesiritide is administered IV as a bolus or a continuous infusion. In adults, it has a biphasic disposition, with an initial elimination phase of 2 minutes and a terminal elimination half-life of approximately 18 minutes. The mean volume of distribution at steady state has been estimated to be 0.19 L/kg, with a mean clearance of 9.2 mL/min/kg. Nesiritide is cleared through three mechanisms: lysosomal proteolysis within cells, cleavage by endopeptidases on vascular lumenal surfaces, and renal filtration. Dosage adjustment

is not required in patients with renal dysfunction.[3,4]

In adults, the maximum pharmacodynamic effects of nesiritide occur approximately 3 hours after initiation of therapy. Significant reduction of PCWP (60% of the maximum effect) is typically seen within the first 15 minutes of treatment. The duration of effect after discontinuation varies among patients. Blood pressure values typically return to baseline within 1 to 3 hours. The pharmacokinetic and pharmacodynamic characteristics of nesiritide in children have not been evaluated.[3,4]

Drug Interactions
At this time, there have been no specific drug interactions reported with nesiritide. Patients receiving nesiritide in conjunction with other afterload reducing agents, including oral angiotensin converting enzyme (ACE) inhibitors, should be closely monitored for the development of symptomatic hypotension. The manufacturer recommends that nesiritide not be mixed or co-infused with other drugs. It is known to be incompatible with bumetanide, enalaprilat, furosemide, heparin, hydralazine, and insulin.[2-4]

Adverse Effects
In clinical trials in adults, the most common adverse effect has been hypotension, occurring in 11-35% of patients. As a result, nesiritide is considered contraindicated in patients with cardiogenic shock or hypotension at baseline. Other common adverse effects with nesiritide include: ventricular arrhythmias (3-10%), angina (2-6%), bradycardia (1-5%), headache (7-9%), abdominal pain (1-3%), back pain (1-4%), insomnia (2-6%), dizziness (3-6%), anxiety (2-3%), nausea (4-13%), and vomiting (1-4%).[3,4]

Adverse renal effects have also been associated with nesiritide use. In patients with severe heart failure whose renal function is dependent on the renin-angiotensin-aldosterone system, the anti-aldosterone effects of nesiritide may lead to renal impairment. The manufacturer reports that 17-28% of patients in their clinical trials experienced an increase in serum creatinine more than 0.5 mg/dL above baseline.[4] In 2005, Sackner-Bernstein and colleagues performed an assessment of five randomized clinical trials conducted in 1,269 adults.[14] The relative risk of worsening renal function in the patients treated with the standard dose of nesiritide compared to those given other therapies was 1.54 (95% CI 1.19 to 1.98; p=0.001). The need for dialysis, however, was not different in the nesiritide-treated patients compared to those receiving other therapies.

Effect on Mortality
In addition to evaluating adverse reactions, the effect of nesiritide on overall patient mortality has also been assessed in adults. When data from seven manufacturer-sponsored clinical trials were combined, mortality through 30 days was 5.3% in the nesiritide-treated patients compared to 4.3% in patients treated with traditional therapies. Mortality at 180 days, evaluated in four trials, was 21.7% in patients given nesiritide compared to 21.5% in the patients treated with other agents.[4] The impact of nesiritide on mortality in children with heart failure has not been evaluated.

Dosing Recommendations
Based on guidelines for adults and the cases reported in the pediatric population, the recommended dose of nesiritide for infants and children with heart failure is an IV bolus of 1-2 mcg/kg followed by a continuous infusion initiated at 0.005 to 0.01 mcg/kg/min.[1-13] Although no clear maximum dose has been established for children, the maximum rate of infusion during clinical trials in adults was 0.03 mcg/kg/min.[4] Pediatric case reports have cited doses as high as 0.09 mcg/kg/min.[8] If hypotension occurs, the dose should be reduced or discontinued.

Availability and Cost
Nesiritide (Natrecor®; Scios) is available in 1.5 mg single-use vials. The average wholesale price (AWP) for nesiritide is $529.93 per vial. For comparison, the AWP for dobutamine is $4.38 per 250 mg vial and for nitroglycerin is $7.00 per 50 mg vial.[15] Numerous cost-benefit analyses have been conducted comparing nesiritide to traditional agents in adults, with mixed results. While the acquisition cost is substantially higher, in some analyses, this has been offset by a reduction in hospital admissions and need for intensive care.[1,2]

Summary
Nesiritide is a useful therapy in the management of patients with acute decompensated heart failure who have failed to respond to traditional agents. Preliminary reports in infants and children have been positive, particularly in patients who fail to respond to diuretics. However, nesiritide has the potential to produce serious adverse effects, including hypotension and renal dysfunction. In addition, the overall impact of nesiritide on mortality is not yet clear. More research is needed to determine the benefits and risks of this therapy in children.

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Pharmacology Literature Review

Dosing cards for bioterrorism emergencies

In response to the call to prepare for a variety of potential bioterrorism, chemical, and radiation emergencies, members of the Department of Health and Human Services have prepared dosing cards to streamline the treatment of children in these events. In this article, the authors describe the process of developing the resource and provide a website, www.hhs.gov/pharmacy/cccrf.html, where the cards may be downloaded. Montello MJ, Tarosky M, Pincock L, et al. Dosing cards for treatment of children exposed to weapons of mass destruction. **Am J Health-Syst Pharm 2006;63:944-9.**

Montelukast pharmacokinetics

The pharmacokinetic profile of montelukast was evaluated in this study of 14 children between 3 and 6 months of age. Each patient received a single 4 mg oral dose. The average area under the concentration-time curve (AUC) was 3644.3+481.5 ng·hr/mL, with an average half-life of 0.94+0.38 hrs), similar to values observed in older infants (ages 6-24 months). Subsequent treatment with a 4 mg or 8 mg dose was used for evaluating tolerability. The most frequent adverse effect observed during the study was diarrhea. The authors suggest that this dosing range may be appropriate for further testing of montelukast in the treatment of postviral bronchiolitis. Knorr B, Maganti L, Ramakrishnan R, et al. Pharmacokinetics and safety of montelukast in children aged 3 to 6 months. **J Clin Pharmacol 2006;46:620-7.**

Transdermal methylphenidate review

A transdermal methylphenidate delivery system was recently approved by the Food and Drug Administration for use in children with attention deficit/hyperactivity disorder (ADHD). The authors of this paper provide a concise review of this new formulation, including information from the studies conducted to date in children with ADHD. Anderson VR, Scott LJ. Methylphenidate transdermal system: in attention-deficit hyperactivity disorder in children. **Drugs 2006;66:1117-26.**

Transfer of anesthetics into breastmilk

There is little information about the safety of breastfeeding in the first days after maternal surgery. To address this issue, the milk and blood concentrations of midazolam, propofol, and fentanyl were evaluated in five lactating women undergoing general anesthesia. The average percentage of the maternal dose present in the milk samples was 0.005% for midazolam, 0.027% for propofol, and 0.033% for fentanyl. Based on these results, the authors concluded that the minor amount of drug found in breastmilk does not justify interrupting breastfeeding. Nitsun M, Szokol JW, Saleh HJ, et al. Pharmacokinetics of midazolam, propofol, and fentanyl transfer to human breast milk. **Clin Pharmacol Ther 2006;79:549-57.**