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Fenoldapam for Acute Kidney Injury in Children

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Abstract:

We report two cases of children with severe cardiomyopathy requiring treatment with ventricular assist devices who developed acute kidney injury and were treated with fenoldopam. Therapy with fenoldopam appeared successful in one case in that renal replacement therapy was avoided with improvement in urine output and renal function. These are the first reported cases of fenoldopam use in children with acute kidney injury receiving mechanical circulatory support.

Introduction

Ventricular assist devices (VADs) are utilized in children when longer-term circulatory support or bridge therapy to cardiac transplantation is warranted. Infants and children awaiting heart transplantation can be successfully bridged with VAD therapy [1, 2]. Acute kidney injury (AKI) associated with VAD therapy is a common complication, with a high mortality rate [3].

Fenoldopam is a selective dopamine (DA)-1 receptor agonist with systemic and renal vasodilating properties that may improve survival and decrease the need for renal replacement therapy (RRT) in critically ill adult patients with or at risk for AKI [4]. There is scant literature describing the use of fenoldopam in infants and children with AKI [5-9]. We describe two cases of fenoldopam use in pediatric patients with prerenal and/or ischemic/hypoxicinduced AKI who were receiving VAD therapy.

Case reports

Case 1

An 8-year-old girl with dilated cardiomyopathy and cardiogenic shock was placed on a Thoratec[R] left-ventricular assist device (Thoratec Corporation, Pleasanton, CA, USA) as a bridge toward heart transplantation. Her immediate postoperative course was complicated by hypertension and AKI. Prior to surgery to the first postoperative day (POD), her blood urea nitrogen (BUN) and serum creatinine (SCr) increased from 93 to 98 mg/dl and 0.8 to 1.4 mg/dl, respectively. Serum sodium (SNa), urine sodium (UNa), and urine creatinine (UCr) concentrations on POD 1 were 148 mmol/l, 27 mmol/l, and 56 mg/dl, respectively, and calculated fractional excretion of sodium (FENA) was 0.45%.

Table 1 Renal function before and after fenoldopam initiation

Case 1	Baseline prior to fenoldopam initiation	24 h after fenoldopam initiation	48 h after fenoldopam initiation
Urine output (ml/kg/hr)	1.4	2.4	6.0
BUN (mg/dl)	137	147	124s
SCr (mg/dl)	1.3	1.3	1.0
Weight (kg)	31	28.3	27.1
Case 2			
Urine output (ml/kg/hr)	1.0	1.4	3.6
BUN (mg/dl)	44	74	80
SCr (mg/dl)	0.6	1.0	1.1
Weight (kg)	5.1	5.2	5.3

BUN blood urea nitrogen, SCr serum creatinine

The patient was medically managed with continuous intravenous (IV) infusions of furosemide, milrinone, and nitroprusside; twice daily IV chlorothiazide; and as-needed IV hydralazine for the next 5 postoperative days. Urine output was adequate and stable, and a decrease in BUN from 127 to 115 mg/dl and SCr from 0.7 to 0.6 mg/dl were noted on POD 6 and 7, respectively. On POD 8, the patient's BUN and SCr increased to 137 mg/dl and 1.3 mg/dl, respectively, and urine output decreased from 3.9 to 1.4 ml/kg per hour. The patient was receiving IV furosemide at 0.16 mg/kg per hour and twice-daily IV chlorothiazide at 20 mg/kg per dose. Urinalysis demonstrated 30 mg/dl protein, 100 red blood cells per highpower field (RBC/HPF) (Foley catheter in place), and occasional hyaline casts. SNa, UNa, and UCr concentrations were 142 mmol/l, 95 mmol/l, and 29 mg/dl, respectively, and calculated FENA was 3.0%. As she was receiving diuretic therapy, the increased FENA could be due to the natriuretic effects of the diuretics or progression to ischemic/hypoxic AKI. It was anticipated that renal replacement therapy would need to be initiated if her BUN continued to rise and/or if her urine output did not increase. Continuous IV fenoldopam was initiated on POD 8 at 0.2 mcg/kg per minute and on POD 9 increased to 0.4 mcg/kg per minute. Urine output increased from 1.4 to 2.4 ml/kg per hour within 24 h after fenoldopam initiation and to 6 ml/kg per hour within 48 h after starting the fenoldopam infusion. A decreasing trend in BUN, SCr, and weight was also observed within 2 days of starting fenoldopam (Table 1). As shown in Fig. 1, fenoldopam did not decrease her mean arterial pressure (MAP) or heart rate (HR). As fenoldopam was increased to 0.4 mcg/kg per minute on POD 9, the continuous IV nitroprusside infusion was decreased but MAP remained unchanged. The nitroprusside dose was subsequently titrated upward for blood pressure control. Renal function continued to improve over the subsequent postoperative days, and the patient did not require renal replacement therapy. Fenoldopam was weaned to 0.1 mcg/kg per minute on POD 12 and stopped on POD 20. She subsequently died 4 months later while awaiting cardiac transplantation.

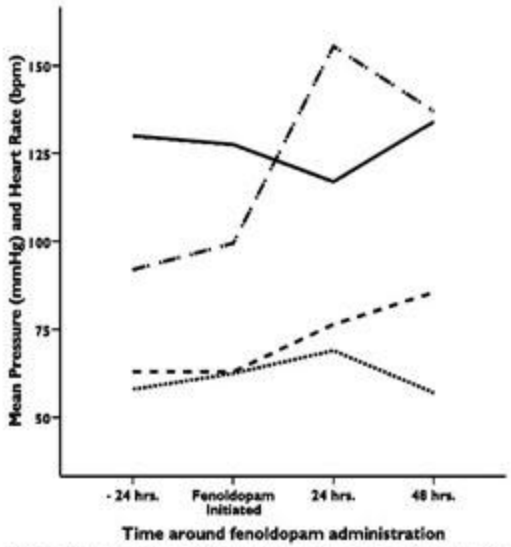

Fig. 1 Mean systemic arterial pressure and heart rate before and after fenoldopam administration. *Dashed and dotted line*: case 1 heart rate; *solid line*: case 2 heart rate; *dashed line*: case 1 mean arterial pressure; *dotted line*: case 2 mean arterial pressure

Case 2

A 7-week-old boy with idiopathic dilated cardiomyopathy, respiratory failure, and severely diminished cardiac function was placed on an EXCOR pediatric left-ventricular assist device (Berlin Heart AG, Berlin, Germany) while awaiting heart transplantation. He was managed with continuous IV infusions of furosemide at 0.08 mg/kg per hour, nitroprusside, nitroglycerin, and dobutamine immediately postoperatively, and he subsequently developed AKI. Coagulase-negative staphylococcal sepsis further complicated the postoperative clinical course.

Urine output decreased significantly to approximately 1 ml/kg per hour by POD 1 and continued to decline despite increasing furosemide to 0.3 mg/kg per hour and adding twice-daily IV chlorothiazide at 20 mg/kg per dose. Increases in BUN from 32 to 44 mg/dl and SCr from 0.5 to 0.6 mg/dl were also observed on POD 1. SNa, UNa, and UCr concentrations were 142 mmol/l, 41 mmol/l, and 18 mg/dl, respectively, and calculated FENA was 0.96%. The urinalysis demonstrated 30 mg/dl protein, 387 RBC/ HPF (Foley catheter in place), and one hyaline cast/hpf. Fenoldopam was initiated at 0.2 mcg/kg per minute on POD 1. Further elevations of BUN to 74 mg/dl and SCr to 1 mg/dl, were noted on POD 2, and fenoldopam was increased to 0.3 mcg/kg per minute. Changes in his BUN, SCr, and urine output before and after fenoldopam was initiated are described in Table 1.

Improvements in urine output to 3.6 and 3.4 ml/kg per hour were observed on POD 2 and 3, respectively, as the patient remained on 0.3 mcg/kg per minute of fenoldopam. However, the improvement in urine output was transient and his urine output declined to 1.5 ml/kg per hour on POD 4. Despite upward titration of fenoldopam to 0.5, 0.75, and 1.5 mcg/kg per minute on POD 5, 6, and 7, respectively, but the patient's BUN and SCr continued to increase and urine output decrease. MAP and HR are illustrated in Fig. 1 and were not clinically different from values prior to fenoldopam initiation. HR remained unchanged over the course of fenoldopam therapy despite escalating doses.

By POD 7, the patient became generally fluid-overloaded, with poor peripheral perfusion, and he became unresponsive to diuretic therapy by POD 8. A hemodialysis catheter was placed on POD 8, and continuous venovenous hemofiltration was commenced. Fenoldopam was weaned to 0.3 mcg/kg per minute on POD 9 and discontinued on POD 10. The patient subsequently died of sepsis and multiorgan failure on POD 13.

Discussion

These are the first reports of fenoldopam administration in children receiving VAD therapy with prerenal and/or ischemic hypoxic AKI. Treatment with fenoldopam appeared to be successful in avoiding the need for RRT for one of our patients. Because our patients were receiving diuretic therapy, it is difficult to precisely determine if they had prerenal failure or if they had progressed to ischemiainduced AKI. As each had a bland urine sediment (except for hematuria that was attributable to an indwelling catheter), it is likely that each had prerenal failure at the time fenoldopam was initiated. It is also likely that the patient in case 2 progressed to ischemic AKI over the next several days.

Successful bridge to transplantation with VAD support in children ranges from 58-77% [1,2]. However, AKI and the need for RRT while on VAD therapy is associated with poor survival, carrying a 93% 6-month mortality in adults [3]. Similar data is not available in pediatric patients.

In the past, medical management of AKI has commonly included therapy with "renal-dose dopamine" in the attempt to increase renal blood flow and enhance urine output. Several well-controlled studies and a meta-analysis have demonstrated that renal-dose dopamine is ineffective in AKI in adult patients [10-12]. As fenoldopam is a selective dopamine (DA)-1 receptor agonist, it might enhance renal blood flow and increase urine output compared with DA, which is a nonselective DA receptor agonist.

Fenoldopam causes peripheral and renal vasodilation through potent and selective DA-1 receptor-agonist activity [13]. Diuresis, natriuresis, and an increase in glomerular filtration rate (GFR) also result [14, 15]. The renal protective effects of fenoldopam have been predominantly evaluated in adult patients.

In contrast to the negative studies with DA described above, several studies have demonstrated that fenoldopam decreases the need for renal replacement therapy in adults with AKI. Landoni and colleagues conducted a meta-analysis of 16 randomized controlled trials, encompassing 1,290 patients, of fenoldopam vs. placebo or other treatment to determine the effect of fenoldopam on AKI [4]. Fenoldopam compared with controls significantly reduced the use of RRT, risk of death from any cause, duration of intensivecare-unit stay, and time to hospital discharge. Fenoldopam therapy was also found to decrease the incidence of AKI in critically ill adult patients at risk for AKI [4].

Reported experiences with fenoldopam in pediatric patients are quite limited. Retrospective studies and case reports have characterized fenoldopam administration in 46 neonates and 16 children (age range 3-17 years) for indications of severe hypertension (n =1), controlled hypotension during spinal fusion (n = 10), control of mean arterial pressure (n=4), renal

insufficiency due to septic shock (n = 1), and augmentation of diuresis after cardiopulmonary bypass in neonates (n=46) [5-9].

Moffett et al. describe an increase in urine output and avoidance of RRT after fenoldopam administration in a 17-year-old patient with septic-shock-associated renal insufficiency [5]. Fenoldopam was infused at 0.03-0.08 mcg/kg per minute for approximately 7 days [5]. A retrospective study of 46 neonates showed a 61% increase in urine output 24 h after fenoldopam initiation (P=0.001) [6]. Although fenoldopam was utilized to enhance diuresis in these patients after cardiac surgery, none of the patients demonstrated clinical signs of AKI.

The patient in case 1 initially showed transient improvements in renal function with conservative pharmacologic management but ultimately failed that approach. After fenoldopam administration, urine output, BUN, and SCr improved substantially. This patient did not require RRT after fenoldopam, and renal function subsequently recovered. In case 2, urine output increased, albeit marginally, after fenoldopam initiation, but his BUN and SCr failed to improve even with considerable escalation in fenoldopam dosing. This patient ultimately required continuous venovenous hemofiltration, suggesting that fenoldopam therapy added no additional benefit.

Our patients were quite different in age, weight, and illness severity. The patient in case 2 had sepsis and multiorgan failure, and it is likely that this played a role in his lack of sustained response to fenoldopam. Our patients also had no significant side effects from the fenoldopam infusion. Side effects in adult patients have included hypotension that was more common in adults receiving fenoldopam compared with DA [16]. It is likely that the use of VADs in our patients provided a protective role to blunt or prevent the development of hypotension.

These case reports offer additional data for fenoldopam usage in children, including those with AKI. Additional studies evaluating the risks and benefits of fenoldopam in children with AKI are warranted before general recommendations for its use can be developed in children with AKI.

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