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Supplement 2

Treatment of acute renal failure (ARF) and oliguria/anuria in three prematurely delivered infants with fenoldopam – three cases report

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Summary

Background: *Fenoldopam – a dopamine analogue – stimulates postsynaptic D_1 receptors in the renal and splanchnic circulatory vessels and has no activity on D_2 receptors, α and β adrenergic receptors. It increases RBF and urine output, without significant changes in the blood pressure. Due to those effects, we decided to use fenoldopam in the treatment of infants with acute renal failure in oliguric state.*

Case report: *We present the schedule of the therapy of three premature newborns, whom we administered fenoldopam (dose 0.1 $\mu g \times kg^{-1} \times min^{-1}$) in ARF. We observed the improvement in kidney function and urinary output. The first patient suffered from ARF secondary to SIRS and the abdominal aortic embolism. A recovery of renal function and improvement of clinical state have been observed after introduction of a complex therapy including fenoldopam).*

Next patient developed ARF on the third day after delivery. The inborn infection, hepatic failure, and dyspnoea have accompanied ARF. Although he was given a complete treatment and fenoldopam infusion leading to increase in diuresis, he died in the course of DIC.

In the third infant sepsis was the cause of arising ARF on 19th day of life. Two days of using fenoldopam resulted in enlarging urinary output and return of renal function.

Conclusions: *The normalisation of renal parameters depended on the combination of traditional methods of therapy with the administration of fenoldopam. The positive effects of the therapy indicate the safety of usage and proposed dosage of fenoldopam in infants and should be verified in further studies.*

Key words: fenoldopam • acute renal failure • sepsis • neonate

BACGROUND

Acute renal failure in neonate is a condition of a rapid impairment of renal function with diminishing of glomerullar filtration rate. This leads to disturbance in organic fluid homeostasis and is often associated with oliguric or anuric stage. Usually (in about 75% of cases) it appears as prerenal insufficiency connected with the decrease of blood flow in the kidneys, hypotension and anoxia [1,2]. It may also be secondary to thrombosis of renal vessels, disseminated intravascular coagulation (DIC), necrotizing enterocolitis (NEC), and frequently occurs in sepsis. Naturally, it complicates the course, worsen prognosis of above- mentioned illnesses and increases mortality rate.

Eradication of primary condition, which in turn leads to ARF, as well as volume expansion, compensation in electrolytic balance, dilatation of renal vessels are crucial for therapy [3].

Having known the pathophysiology of ARF, one realises that improving the renal perfusion by dilating afferent arterioles in cortex prevents acute tubular necrosis [4]. Drugs, which counteract the constriction of small vessels in renal cortex, caused by diminution in blood flow and hypoxia, have tremendous value in the therapy. That is the reason of using dopamine, although, it has been shown recently, that so-called 'splanchnic dose' is not efficient in dilating renal arterioles [5,6]. Fenoldopam – a new analogue of dopamine, used meanwhile in hypertension and prophylaxis of ARF in adults undergoing cardiac surgery was proved to be more effective [7]. In the dose 0.1 $\mu g \times kg^{-1} \times min^{-1}$ it does not show hypotensive effect, while it improves blood supply especially in the perimedullar area of renal cortex.

The latter effect of fenoldopam seems to be important in premature children, whose perimedullar glomerulli are earlier mature but more susceptible to anoxia [2].

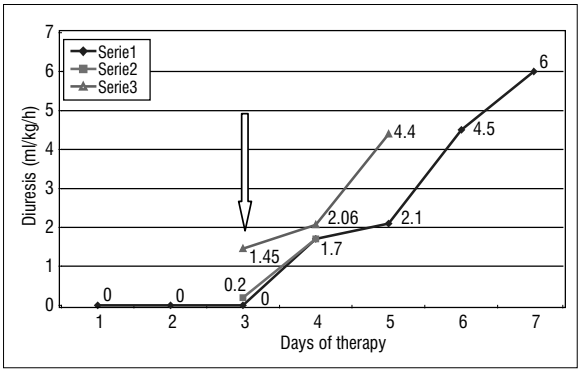
Up to this moment, we have not found any report about this drug administrating to premature infants.

CASE REPORT

Case 1

The first patient, a premature male infant, with birth-weight 1390 g, was delivered by caesarean section because of premature rupture of membranes) (PROM), after 29 weeks of pregnancy. He gained 7 points in 1 min in the Apgar score. Because of the severe dyspnoea the baby was intubated, ventilated with respirator. Surfactant was administrated within the first day of life. Starting from the second day of life, the breath was supported with the nCPAP system. On the day fourth the clinical condition of the infant deteriorated. The neonate required mechanical ventilation. We observed a sudden impairment of peripheral perfusion in the area of lower limbs and anuria. On the ground of the clinical status and laboratory investigations (results found on the 2nd day of life: PTINR 1.2; aPTT 133sec; plasma fibrinogen level – 3.6 g × l^{-1}. results found on the 4th day of life: Antitrombin III 24%, leucocytosis 24×10^3) thrombotic syndrome was suspected. A catheter was removed from umbilical artery. Heparin (100 iu × kg^{-1} × 6 h^{-1}), antibiotic (meropenem), infusion of dopamine with dobutamine (5 μg × kg^{-1} × min^{-1}) and sufentanyl were administered. The infant was also supplemented with antitrombin III. We monitored fluid balance, but within the next 24 hours no diuresis was observed. Data of laboratory analyses revealed further deterioration in hemostasis, lowering of hematocrit, changes in systemic inflammation indicators. Blood test values were as follows: Hb 11.7 g × dl^{-1}; Hct 23.3%; RBC 3.23×10^6 ; WBC 4.93×10^3, PLT 198×10^3; aPTT 61.8 sec; fibrinogen 1.03 g × l^{-1}; D-dimers 8304 u × l^{-1}; AT III 154%; protein C 2%; electrolytes serum level (mmolxl-1): Na 143; K 5, 7; Ca 2, 08; Ca^{2+} 1, 21; urea serum level (BUN)- 6.6 mmol × l^{-1}. Then, fresh frozen plasma, erythrocyte mass, 20% human albumin, pentaglobin and pentoxifylline were introduced.

Despite this therapy, during the 6th day of life there was no increase in diuresis and potassium serum level increased from 6.7 to 10.2 mmol × l^{-1} as well as plasma creatinine level was 125 μmol × l^{-1}. Because of the disturbances found in ECG, glucose and insulin infusion, followed by infusion with salbutamol was started. Then, peritoneal dialysis was introduced and continued during the next 9 days. Administration of erythrocyte mass, albumin, furosemid, catecholamine were indispensable (Hb 8.2 g × dl^{-1}; Hct 24.3%; RBC 2.47×10^6; WBC 3.66×10^3, PLT 6, 9×10^3; alb 16.9 g × l^{-1}). Further investigations suggested the diagnosis of SIRS (procalcitonin >10 ug/l, IL 6 124 u/l, negative blood culture examination). On the 7th day of life after obtaining informed consent from the parents, we added fenoldopam (0,1 μg × kg^{-1} × min^{-1}) to the therapy. Both diuresis (Figure 1, series 1), and other parameters (creatinine serum level: 93, 86; 75; 38 μmol × l^{-1}; BUN: 17, 6; 16; 11, 9; 7, 2 mmol × l^{-1}; potassium serum level 5, 2; 4, 2; 4, 1 mmol × l^{-1}) of renal function improved on the next two days. Ultrasound examination performed on 6th and 10th day of life revealed significant enlargement and blurred structure of kidneys and the presence of embolus under renal arteries ostiums (in reversed Doppler image), whereas on 37th day it presented only faded medullar-cortical border.



Fugure 1. The rate of diuresis in three patients during treatment. Arrow indicates start of fenoldopam therapy.

Case 2

Our next patient was a male, SGA (small for gestational age) premature newborn, delivered via caesarean section after 28 weeks of pregnancy. The Apgar score was 6 in the first minute of life. The respiratory distress syndrome developed and ventilatory support was introduced. Also, surfactant was instilled. On the ground of clinical state and extremely low birth-weight (540 g) as well as obstetrical anamnesis (significant intrauterine growth retardation and PROM), we suspected the inborn infection. This hypothesis was partially proved by the following data of laboratory analysis: increased of plasma CRP level – 10.6 mg × l^{-1}, PLT 49×10^3, Hb 14.6 g × dl^{-1}; Hct 43.7%; RBC 3.38×10^6; WBC 2, 83×10^3. On the second day of life significant deterioration in clinical condition was found. Pulmonary bleeding, and anuria (0.2 ml urine × kg^{-1} × h^{-1}) were observed. It was correlated with the changes in plasma urea (4.0–5.2 mmol × l^{-1}) and creatinine (64–72 μmol × l^{-1}) concentrations. The following aberrations in blood cell counts and parameters of hemostasis were found: HCT 22.5%; Hb 7, 5 g/dl; RBC 1.74×10^6; WBC 22.5×10^3; PLT 28×10^3, PT INR 1.86; aPTT 81.7 sec; fibrinogen 0.79 g × l^{-1}; D-dimers 1080, protein C 3%; ATIII 10.5%. Then, FFP, ATIII, ceprotin, ampiciline+sulbactam (unasyn), tobramycine, albumin, furosemid, dopamine (2.5 μg × kg^{-1} × min^{-1}) were given. In order to enlarge urinary output (anuria 1.7ml of urine × kg^{-1} × h^{-1}) we administered fenoldopam. The improvement in diuresis rate is presented in Figure 1. Nevertheless, because of liver insufficiency, DIC, haematological disorders (Hb 8.4 g × dl^{-1}; HCT 24%; RBC 2.17×10^6; WBC 25.5×10^3; PLT 54×10^3; ATIII 39%) and despite of fluid infusion, inotropic and vasopressor support the infant died.

Case 3

In the third case, premature (27+5 weeks of pregnancy) female twin, delivered via caesarean section, whose Apgar score was estimated for 6 points, with birth weight 710 g, ARF occurred in the course of sepsis on the 19th day of life. During the first few days the neonate needed a support of nCPAP and applying of surfactant, antibiotics (unasyn+tobramicyne – CRP 23–41 mg × l^{-1}) and erythrocytes concentrate because of anaemia. The clinical status of the girl was stabilized; she could breathe spontaneously for another three days. However, on the 19th day some episodes of dyspnoea and impairment of peripheral perfusion was observed. The infant needed ventilatory support with a respirator. The laboratory investigation results were as follows: Hct 30, 6%; Hb 10.5 g × dl^{-1}; RBC 3.22×10^6; WBC 9.9×10^3; PLT 20.6×10^3; CRP 31.7; potassium level 4.6 mmol × l^{-1}; BUN 2.7 mmol × l^{-1}; creatinine serum level 46 × mol × l^{-1}, hemostatic indexes: ATIII 43%; protein C 39%; PT INR 1.1; aPTT 106.2; fibrinogen 3.5 g × l^{-1}. Urinary output was 1.45 ml × kg^{-1} × min^{-1}. Enterococcus faecalis was found in blood culture and Acinetobacter cacoaceticus baumani complex in tracheal aspiration culture. The girl was treated with unasyn. Then on the ground of blood culture results it was changed for vancomycine. Also, dobutamine (5 μg × kg^{-1} × min^{-1}), aminofilline, and fenoldopam were introduced. The increase in diuresis (from 2.06 ml × kg^{-1} × h^{-1} to 4.4 ml × kg^{-1} × h^{-1}) on the first day of Fenoldopam administration was found (Figure 1 series 3). At the moment the infant is still being hospitalised.

DISCUSSION

Acute renal failure is life threatening clinical condition in newborn infants.

Premature infants suffer most often from the prerenal type of ARF, in which the dysfunction of nephrons is associated with ischemia [8]. Low renal perfusion pressure and release of renal vasoconstrictor compounds, such as endothelin increase the risk of renal ischemia and acute tubular necrosis. The renal and splanchnic circulatory vessels are very prone to hypoxic insult due to their microvascular anatomy, and they may provide early evidence of altered oxygen metabolism, changes in mean arterial pressure, cardiac output and volume imbalance [7].

Dopamine was thought to act renoprotective in 'renal dose', but recent studies failed to demonstrate this mechanism [9,10]. Moreover, it proved, that dopamine may constrict the vessels already in a dosis 5 μg × kg^{-1} × min^{-1} [11], probably due to its nonselective agonism to D_1, α_1, β receptors. That is the reason of searching for another potent vasodilatators. Fenoldopam, developed by chemical modification of the dopamine molecule, has specificity for the postsynaptic D_1 receptor with no direct or indirect effects on either α or β receptors. Lack of these activities is beneficial for renal, mesenteric and coronary perfusion. Fenoldopam was reported to be 6 times more effective vasodilatator as dopamine [12]. It improves the blood flow in renal medulla significantly more than in renal cortex. The finding connected with the flow rate of 0,1 μg × kg^{-1} × min^{-1}, revealing good creatinine clearance not associated with haemodynamic instability [13], encouraged us to administer this medication in described above three cases. Although, fenoldopam being hypotensive drug, may cause tachycardia, or hypotension), we did not observe these side effects [14]. In the light of predominantly favourable reports on fenoldopam preventing ARF in patients undergoing abdominal aortic aneurysm repair and coronary arteries bypass graft and information about using this drug in pediatric anaesthesia, we made decision to include fenoldopam to the therapy of ARF [15,16].

We suggest, that improvement in renal function, measured by urinary output rate, sodium excretion, and creatinine clearance was partially caused by fenoldopam infusion. However, the beneficial effects of fenoldopam in the treatment of ARF should be verified in further randomised studies.

CONCLUSIONS

1. Fenoldopam can be useful in the treatment of acute renal failure in premature infants.

2. When given in the dose 0.1 μg × kg^{-1} × min^{-1} fenoldopam does not decrease in arterial blood pressure.

REFERENCES:

1. Norman J. editor, Pediatrics NY, 1979; 63: 475
2. Gouyon J, Guignard JP: Menagement of acute renal failure in newborns. Pediatr Nephrol, 2000; 14: 1037-44
3. Brandt I, Stichor EJ, Lentze MJ: Preterm infants- mental developement to adulthood. J Pediatr, 2003; 142: 463-68
4. Ackerman DM, Blumberg AL, McCafferty JP, et al: Potential usefulness of renal vasodilatators in hypertension and renal disease. Federation Proceedings, 1983; 42: 186-90
5. Lassnigg A: Lack of renoprotective effects of dopamine and furosemide during cardiac surgery .J Am Soc Nephrol, 2003; 11: 97-104
6. Myles PS, Buckland MR, Schenk NJ et al: Effect of 'renal dose' dopamine on renal function following cardiac surgery. Anaesthesia and Intensive Care, 1993; 21: 56-61
7. Halpenny M, Lakshmi S, O'Donnel A et al: Fenoldopam: renal and splanchnic effects in patients undergoing coronary artery bypass grafting. Anaesthesia, 2001; 56: 953-61
8. Sladen RN, Prough DS: Perioperative renal protection. Problems in Anesthesia, 1997; 9: 314-31
9. ANZICS CTG, Lancet, 2000; 356: 2139-43
10. Marik PE: Low dose dopamine: systematic review. Int Care Med, 2002; 28: 877-83
11. Van den Berghe, Crit. Care Med, 1996; 24: 1580-90
12. Mathur VS, Swan SK, Lambrecht LJ et al: The effects of Fenoldopam on systemic and renal hemodynamics in normotensive subjects. Crit Care Med, 1999; 27: 1832-37
13. Murphy MB, McCoy CE, Weber RR et al: Augmentation of renal blood flow and sodium excretion in hypertensive patients during blood pressure reduction by intravenous administration of Fenoldopam. Circulation, 1987; 76: 1312-18
14. Tobias JD: Fenoldopam for controlled hypotension during spinal fusion in children and adolescents. Paediatr Anaesth, 2000; 10: 261-72
15. Gilbert TB, Hasnain JU, Flinn WR et al: Fenoldopam infusion associated with preserving renal function after aortic cross clamping for aneurysm repair. J Cardiovasc Pharmacol Ther, 2001; 6: 31-36
16. Strauser LM, Pruitt RD, Tobias JD: Initial experience with fenoldopam in children. Am J Ther, 1999; 6(5): 283-88