Cardiac failure following inadvertent administration of high-dose epinephrine subcutaneously

Kim A. Tran^a, Douglas D. Fraser^{a,b}, Krista Hawrylyshyn^c and Kambiz Norozi^{a,d,*}

^a*Department of Pediatrics, University of Western Ontario, London, ON, Canada*

^b*Department of Pediatrics, Centre for Critical Illness Research, London, ON, Canada*

^c*University of Western Ontario, London, ON, Canada*

^d*Department of Pediatric Cardiology, Medical School Hannover, Hannover, Germany*

Received 11 May 2012

Revised 14 November 2012

Accepted 19 November 2012

Abstract. Our aim is to report the consequences of epinephrine toxicity leading to cardiac failure in a child and the successful management with dopamine and milrinone. A previously healthy 13-year-old girl undergoing a left tympanomastoidectomy was inadvertently administered 10 mL of 1:1000 epinephrine subcutaneously (0.175 mg/kg) on the left post auricular region in lieu of lidocaine. She developed sudden supraventricular tachycardia, hypertension and flash pulmonary edema. She was initially treated with propofol, nitroglycerin and increased peak end-expiratory pressure. Within 4 h, she remained tachycardic, but was hypotensive with an increased central venous pressure. Electrocardiogram and echocardiogram investigations showed ST changes indicative of myocardial ischemia and globally reduced function, respectively. Dopamine infusion was administered, together with milrinone, resulting in a gradual improvement of cardiac function within 3 days. She was transitioned to enalapril and discharged home. This case highlights the clinical features of high dose epinephrine toxicity secondary to iatrogenic subcutaneous overdose followed by hypotension and pulmonary edema as a possible late effect of epinephrine and the successful management of secondary cardiac failure with administration of dopamine, milrinone and enalapril.

Keywords: Epinephrine, drug toxicity, dopamine, milrinone, myocardial ischemia, pulmonary edema

1. Introduction

Epinephrine is an important drug used in the treatment of cardiac arrest, bradycardia, hypotension, anaphylactic reactions and bronchospasm. It acts on both alpha and beta-adrenergic receptors to exert inotropic

and chronotropic effect on the heart. In the pediatric population, high dose epinephrine (0.1 mg/kg or greater) can lead to a biphasic reaction of tachyarrhythmias, hypertension, pulmonary edema followed by hypotension and rarely myocardial ischemia [1,2]. There are several reports indicating accidental administration of epinephrine in pediatric patients, however the majority of these cases epinephrine were given intravenously [3,4]. We report a pediatric patient who received high dose epinephrine subcutaneously requiring resuscitation and intensive care therapy.

*Corresponding author: Kambiz Norozi, Paediatric Cardiology, Office Room B1-152, Department of Pediatrics, University of Western Ontario, 800 Commissioners Road East, London, ON, N6A 5W9, Canada. Tel.: +1 519 685 8500; Ext. 56062; Fax: +1 519 685 8156; E-mail: kambiz.norozi@lhsc.on.ca.

2. Case report

In a peripheral hospital, a previously healthy 13-year-old girl (weight: 57 kg and height: 163 cm) with an unremarkable past medical history or family history, underwent a left tympanomastoidectomy for left chronic ear disease and a cholesteatoma. During the operation, she was inadvertently administered 10 mL of 1:1000 epinephrines subcutaneously (0.175 mg/kg) on the left post auricular region in lieu of lidocaine. This dosage represents 17 times the normal recommended dose for subcutaneous epinephrine in the intact circulation (i.e. anaphylaxis). The operation was halted when the patient developed supraventricular tachycardia with a heart rate of 160 beats per min and hypertension of 240/140 mmHg. Anesthetic medications including propofol and fentanyl were increased and carotid massage was attempted with no effect. A nitroglycerin patch was placed immediately, followed by the initiation of a nitroglycerin infusion (2 µg/min). Flash pulmonary edema occurred with 700 mL of frothy blood tinged fluid suctioned from the endotracheal tube. The patient was then transferred from a peripheral hospital to our pediatric critical care unit (PCCU).

At arrival to our PCCU 4 h later, she was intubated and ventilated (oxygen saturation 96% with fraction of inspired oxygen 0.85), she was hypotensive with a blood pressure (BP) of 80/40 mmHg and she had sinus tachycardia with a heart rate of 150 beats per min. Her first gas (capillary) showed a pH 7.11, partial pressures of carbon dioxide 61 Torr (8.13 kPa), bicarbonate 19 mmol/L and base excess -11.9 mmol/L. Her troponin-T and lactate levels were elevated at 0.58 µg/L (normal <0.03 µg/L) and 5.0 mmol/L (normal <2.4 mmol/L) respectively. Her PCCU admission chest X-ray was consistent with pulmonary edema (Fig. 1.A1). The ventilation mode was Synchronized Intermittent Mandatory Ventilation with Pressure-Regulated Volume Control and a positive end-expiratory pressure of 10 cmH₂O. As she clinically improved, we reduced the fraction of inspired oxygen to 0.40 and positive end-expiratory pressure to 5 in the following 2 days. Shortly before extubation on day 3, the ventilation mode was weaned to pressure support ventilation. She was started on morphine infusion (10 µg/kg/h) and this weaned off after 2 days. A PCCU admission electrocardiogram showed ST depression in leads V3 and V4 (Fig. 1.A2). The initial echocardiogram (ECHO; Fig. 1.A3) revealed globally reduced left ventricular pump function with an ejection fraction (EF) of 41%. Hemodynamic resuscitation included 20 mL/kg intravenous bolus of isotonic

saline without any effects on arterial pressure, but the central venous pressure increased to 20 mmHg. The nitroglycerin patch was removed and nitroglycerin infusion was discontinued. Dopamine was started at 3 µg/kg/min but rapidly titrated to 12 µg/kg/min in order to maintain systolic BP of greater than 85 mmHg. Milrinone was then started at 0.5 µg/kg/min. After 2 days, dopamine was discontinued. On the 3rd day, milrinone was discontinued, followed by introduction of angiotensin-converting-enzyme (ACE) inhibitor, enalapril. Her chest X-ray showed resolution of the pulmonary edema (Fig. 1.B1). Her electrocardiogram changes resolved by day 3 (Fig. 1.B2) and her troponin-T level trended to normal by day 5. Cardiac status improved with central venous pressure of 10 mmHg, heart rate of 115 beats per min, BP of 90/60 mmHg and the EF on ECHO increased from the initial 41% to 63% (Fig. 1.B3). She was eventually extubated on day 3. On day 5, she was transferred from the PCCU to the general hospital ward and discharged home on day 8.

3. Discussion

In our case, we describe the toxic effects of high-dose subcutaneous epinephrine on a previously healthy adolescent female. The clinical presentation first included tachyarrhythmia, hypertension and pulmonary edema, followed by severe hypotension, elevated troponin I, and global hypokinesia of the left ventricle with decreased EF.

There are several case reports of accidental administration of epinephrine in pediatric patients; however, epinephrine was given intravenously in the majority of these cases [1–5]. Only two cases in the literature describe epinephrine overdoses given subcutaneously. In these latter cases, both pediatric patients (14-year-old female and a 5-year-old male) presented with tachyarrhythmia and ST-segment depression [1,2]. However, neither of these cases aggravated to severe hypotension requiring inotropic support. The more severe effects on our patient were likely dose-dependent. In addition, the nitroglycerine treatment may have transiently contributed to the severe hypotension on PCCU admission. Cases of nitroglycerine treatment in acute myocardial infarction have reported severe systemic arterial hypotension as a consequence of decreased left ventricle filling pressure [6].

The symptoms observed following the Epinephrine overdose are consistent with previous cases. Epinephrine, when used at a high dose, results in beta-adrenergic

Fig. 1. A) Investigations on the reported patient obtained shortly after presentation. A chest radiograph illustrating a normal cardiac silhouette with severe pulmonary edema (A1). An electrocardiography (A2) demonstrating acute ischemia. Note the significant ST depression in leads V3 and V4. An M-mode echocardiography of the left ventricle in the para-sternal long axis (A3) showing global reduction of left ventricle pump function (ejection fraction 41%). B) Day 3 investigations on the reported patient obtained shortly after presentation. A chest radiograph illustrating a normal cardiac silhouette and significant improving of pulmonary edema (B1). Normal electrocardiography (B2) showing resolution of ST depression in leads V3 and V4. An M-mode echocardiography of the left ventricle in the para-sternal long axis (B3) showing normal pump function on left ventricle (ejection fraction 63%).

stimulation affecting diastolic function negatively [7]. Increased myocardial oxygen demand and decreased oxygen supply may lead to myocardial ischemia as noted in our patient. The initial systemic hypertension causes increased left ventricular filling pressure thereby increasing the pulmonary capillary pressure [7–9]. This increase impairs the endothelium and basement membrane, and subsequent extravasation of fluid, protein and red blood cells from pulmonary vasculature into

the interstitial and alveolar space resulting in pulmonary edema [7]. As epinephrine level begins to decrease, arterial vasodilation and subsequent hypotension ensue. Left ventricular dysfunction, as a consequence of increase in afterload and ischemia, contributes to the hypotension as observed in our patient.

This case reports the combined use of dopamine and milrinone in treating the left ventricular dysfunction and severe hypotension. Dopamine at doses of

10–15 µg/kg/min exert more alpha receptor stimulation leading to vasoconstriction, thereby improving cardiac contractility thereby increasing cardiac output. However, increase of systemic vascular resistance needed to be offset by the vasodilating effects of milrinone.

Milrinone acts through selective inhibition of phosphodiesterase III, leading to elevation of intracellular adenosine 3',5'-cyclic monophosphate level. By acting on peripheral phosphodiesterase, it decreases systemic vascular resistance, resulting in decreased left ventricular afterload and filling pressure. It also has a direct action on the heart, increasing cardiac contractility [10]. In addition, milrinone contributes to left ventricular relaxation, increased filling time and decreased coronary resistance, thereby improving cardiac output and perfusion [11]. Since milrinone's effects are independent of adrenergic stimulation, it is a favorable choice for treatment.

Interestingly, milrinone has been shown in a randomized controlled trial in the pediatric population to reduce the risk of low cardiac output syndrome in post-operative congenital heart repair [12]. However, to date, there has not been any randomized controlled trial in the pediatric population with milrinone as treatment of cardiogenic pulmonary edema. In fact, lung compliance improves with milrinone use in the adult population receiving mechanical ventilation for cardiogenic pulmonary edema [13]. In an experimental study of animal models, milrinone has been found to attenuate post resuscitation myocardial dysfunction [11].

The positive effect of combined high dose dopamine and milrinone with respect to cardiac function, and changes in heart rate and mean arterial pressure has already been reported in adult patients [14]. In addition, in a study on newborn hypoxic-re-oxygenated piglets, systemic hemodynamics was improved when milrinone was added to dopamine [15]. Here we report the use of this combination in the second phase of epinephrine toxicity where left ventricular dysfunction leads to severe hypotension. Following the patients treatment with dopamine and milrinone infusions, the ECHO showed improved cardiac function with an EF of 63%. Oral administration of ACE inhibitor (enalapril) was started during milrinone weaning. It is well known that ACE inhibitors have beneficial effects in heart failure by not only hemodynamic actions, but also from the prevention of harmful myocardial and vascular remodeling initiated by the renin-angiotensin-aldosterone system [16,17]. The patient's EF further increased to 75% following 2.5 mo on enalapril.

Our case highlights the clinical features of high dose epinephrine toxicity secondary to iatrogenic subcutaneous overdose followed by hypotension and pulmonary edema as a possible late effect of epinephrine. However, our case may have been confounded by the initial treatment with nitroglycerin and its possible contribution to the subsequent hypotension.

Acknowledgment

We wish to thank Dr. Herschel Rosenberg (Western University, London, Canada) for his critical reviewing of this manuscript.

References

- [1] Davis CO, Wax PM. Prehospital epinephrine overdose in a child resulting in ventricular dysrhythmias and myocardial ischemia. *Pediatr Emerg Care* 1999;15(2):116–8.
- [2] Campbell RL. Cardiovascular effects of epinephrine overdose: case report. *Anesth Prog* 1977;24(6):190–3.
- [3] Dybvik T, Halvorsen P, Steen PA. Accidental intravenous administration of 50 mg of racemic adrenaline in a 2-year-old boy. *Eur J Anaesthesiol* 1995;12(2):181–3.
- [4] Bennie RE, Miyamoto RT. Epinephrine-induced ventricular fibrillation during anesthesia for myringotomy and tube insertion. *Otolaryngol Head Neck Surg* 1994;111(6):824–6.
- [5] Tajima K, Sato S, Miyabe M. A case of acute pulmonary edema and bulbar paralysis after local epinephrine infiltration. *J Clin Anesth* 1997;9(3):236–8.
- [6] Come PC, Pitt B. Nitroglycerin-induced severe hypotension and bradycardia in patients with acute myocardial infarction. *Circulation* 1976;54(4):624–8.
- [7] Dünser MW, Hasibeder WR. Sympathetic overstimulation during critical illness: adverse effects of adrenergic stress. *J Intensive Care Med* 2009;24(5):293–316.
- [8] Mazzocca AD, Meneghini RM, Chhablani R, Badrinath SK, Cole BJ, Bush-Joseph CA. Epinephrine-induced pulmonary edema during arthroscopic knee surgery. A case report. *J Bone Joint Surg Am* 2003;85-A(5):913–5.
- [9] Wanamaker HH, Arandia HY, Wanamaker HH. Epinephrine hypersensitivity-induced cardiovascular crisis in otologic surgery. *Otolaryngol Head Neck Surg* 1994;111(6):841–4.
- [10] Duggal B, Pratap U, Slavik Z, Kaplanova J, Macrae D. Milrinone and low cardiac output following cardiac surgery in infants: is there a direct myocardial effect? *Pediatr Cardiol* 2005;26(5):642–5.
- [11] Niemann JT, Garner D, Khaleeli E, Lewis RJ. Milrinone facilitates resuscitation from cardiac arrest and attenuates postresuscitation myocardial dysfunction. *Circulation* 2003;108(24):3031–5.
- [12] Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003;107(7):996–1002.
- [13] Takeda S, Matsumura J, Ikezaki H, Kim C, Sato N, Nakanishi K, et al. Milrinone improves lung compliance in

- patients receiving mechanical ventilation for cardiogenic pulmonary edema. *Acta Anaesthesiol Scand* 2003;47(6):714–9.
- [14] Karasawa F, Okuda T, Tsutsui M, Matsuoka N, Yamada S, Kawatani Y, et al. Dopamine stabilizes milrinone-induced changes in heart rate and arterial pressure during anaesthesia with isoflurane. *Eur J Anaesthesiol* 2003;20(2):120–3.
- [15] Manouchehri N, Bigam DL, Churchill T, Joynt C, Vento M, Cheung PY. Milrinone is preferred to levosimendan for mesenteric perfusion in hypoxia-reoxygenated newborn piglets treated with dopamine. *Pediatr Res* 2012;71(3):241–6.
- [16] Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med* 1987;316(23):1429–35.
- [17] Momma K. ACE inhibitors in pediatric patients with heart failure. *Paediatr Drugs* 2006;8(1):55–69.