Author's response to reviews

Title: Role Of Vasopressin In The Treatment Of Anaphylactic Shock In A Child Undergoing Surgery For Congenital Heart Disease: Case Report

Authors:

Luca Di Chiara (dichiaraluca@libero.it)
Giulia V Stazi (giuliavaleria@tiscali.it)
Zaccaria Ricci (zaccaria.ricci@fastwebnet.it)
Angelo Polito (angpolito@hotmail.com)
Stefano Morelli (s.zeus@inwind.it)
Chiara Giorni (c_giorni@yahoo.it)
Ondina La Salvia (dichiaraluca@libero.it)
Vincenzo Vitale (ezio.vitale@tin.it)
Eugenio Rossi (zaccaria.ricci@fastwebnet.it)
Sergio Picardo (picardo@opbg.net)

Version: 3 Date: 16 November 2007

Author's response to reviews: see over
Reviewer #1's report
Title: Role Of Vasopressin In The Treatment Of Anaphylactic Shock In A Child Undergoing Surgery For Congenital Heart Disease: Case Report
Version: 2 Date: 9 November 2007
Reviewer: Constantinos Chrysostomou
I am familiar with the literature and believe that this case meets one of the 7 criteria for evaluation in the journal: Unreported or unusual side effects or adverse interactions involving medications
Has the case been reported coherently?: Yes
Is the case report authentic?: Yes
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: Yes
Does the case report have diagnostic value?: Yes
Will the case report make a difference to clinical practice?: Yes
Comments to authors:
General
This is a well written case report about the use of Vasopressin in vasoplegic shock. This and other case reports increase the awarness about epinephrine and norepinephrine resistant shock and early administartion of vasopressin.Dr.Di Chiara has nicely reviewed the pathomechanism of this type of shock and gives us a brief explanation why the use of vasopressin is applicable in this setting.
-------------------------------------------------------------------------------
Revisions necessary for publication
Some grammar revisions are necessary for publication
1. Page 4, par 1, line 6: change "hemodinamic" to "hemodynamic"
2. Page 5, par 1, line 4: change "patophysiologic' to "pathophysiologic"
3. Page 5, par 1, line 18: Change the sentence to "Moreover, vaopressin raises the vasoconstrictive effect of norepinephrine, the plasma concentration of which is markedly elevated, in the course of vasodilatory shock"
4. Page 5, par 1, line 22: add the word "shock" after anaphylactic.
5. Page 6, par 1, line 3: change "diuresis contraction" to "contraction diuresis"
6. Page 6, par 2, line 2: delete "treatment in" and delete "s" from corticosteroids
7. Page 6, par 2, line 3: delete "e" from Vasopressine
8. Page 6, par 2, line 5: I would change the last sentence fom ".....and eventually to death." to "and cell death"
What next?: Accept after minor revisions
Quality of written English: Needs some language corrections before being Published

All revisions suggested by the reviewer have been corrected in the text.

Reviewer #2's report
Title: Role Of Vasopressin In The Treatment Of Anaphylactic Shock In A Child Undergoing Surgery For Congenital Heart Disease: Case Report
Version: 2 Date: 13 November 2007
Reviewer: stefano romagnoli
I am familiar with the literature and believe that this case meets one of the 7 criteria for evaluation in the journal: An unexpected event in the course of observing or treating a patient

Has the case been reported coherently?: Yes
Is the case report authentic?: Yes
Is this case worth reporting?: Yes
Is the case report persuasive?: Yes
Does the case report have explanatory value?: Yes
Does the case report have diagnostic value?: No
Will the case report make a difference to clinical practice?: Yes

Comments to authors:

General
The authors describe the case of a patient who was undergoing pediatric heart surgery with an anaphylactic reaction to heparin that was refractory to epinephrine infusion but effectively treated with arginine-vasopressin. This report is interesting since the arginine-vasopressin has been rarely administered to treat a vasodilatory shock due to anaphylactic reaction and it never has been administered in pediatric heart surgery.

Revisions necessary for publication

Major comments:
Page 3; line 13-14
“In order to re-establish hemodynamic stability, volume resuscitation was started (30 ml/Kg) and two intravenous (i.v.) boluses of 500 mcg of epinephrine were given…”

In consideration to the specific setting (Cardiac Surgery operating room), how did you establish the doses? How much time elapses from the first dose?

Page 3; line 19-20
As correctly suggested by the reviewer we specified this notion and added to the text: “by institutional protocol: 25 mcg/kg every 5 minutes”

“The finding of metabolic acidosis (pH 7.23) with increased lactate levels (9 mmol/L) suggested inadequate systemic oxygen delivery”. According to the above sentence, a raising of blood lactate, indicating tissue hypoxia, is caused by an inadequate DO2 (anaerobic metabolism). Nonetheless, the amount of oxygen available to the cells is determined by a number of central and peripheral factors. Central factors are related to the cardiorespiratory function (cardiac index and PaO2) and to the Hb concentration (DO2 = CI × CaO2); peripheral factors are related to the distribution of cardiac output to the various organs and to the regulation of the microcirculation that can be substantially altered in several conditions (i.e. distributive shock) where local control of vascular tone is altered and the formation of edema may contribute to damage the distribution of blood flow.

During the described condition, the “macrocirculatory” parameters were adequately controlled (high-flow CPB and adequate Hct) but the increase in blood lactate concentration was only partially controlled, indicating that a normal or elevated DO2 felt below a critical value, with successive VO2 reduction, mainly due to an altered oxygen extraction capabilities. The authors should therefore remark in the discussion that the observed metabolic acidosis was derived from a poor tissue perfusion due to severe
hypotension-low perfusion pressure (CPB perfusion pressure 20 mmHg with SVRI 470 dyne×sec/cm5/m2) rather than an inadequate DO2 only.

In the revised manuscript these parts have been added to the case report section and discussion section, respectively:

The finding of metabolic acidosis (pH 7.23) with increased lactate levels (9 mmol/L) suggested a poor tissue perfusion due to severe hypotension-low perfusion pressure with inadequate oxygen delivery at peripheral tissues.

Metabolic acidosis is mainly derived from a poor tissue perfusion due to severe hypotension-low perfusion pressure rather than an inadequate systemic oxygen delivery only: distribution of cardiac output to the various organs and to the regulation of the microcirculation that can be substantially altered in several conditions (i.e. distributive shock) where local control of vascular tone is altered and the formation of edema may contribute to damage the distribution of blood flow.

Page 3; line 23
“Moreover, epinephrine infusion was started at a dose of 0.1 mcg/Kg/min in order to achieve a perfusion pressure of 40 mmHg” and “…weaning from CPB failed because of severe hypotension despite epinephrine administration was titrated up to 0.3 mcg/Kg/min”. Vasoplectic shock requiring vasopressor support is a recognized and relatively common complication during and after cardiopulmonary bypass. In the case described in your manuscript the pathogenesis of vasodilatory shock is rather different or nevertheless multifactorial. An association of two or more drugs is a frequent measure used to treat a resistant vasodilatory shock (norepinephrine, high dose dopamine, phenylephrine, angiotensin II, methylene blue); taking into account the existing controversy on which agent should be preferably used, why was arginine-vasopressin your first-line intervention after epinephrine?

In the revised manuscript this part has been added to the discussion section
Given the the existing controversy on which agent should be preferably used in case of vasoplectic shock [13], our decision to use vasopressin was related to other recent available experiences [12], the above described pharmacological rationale and the choice of avoiding escalating therapy with alpha agonists.

Page 4; line 10
“Vasopressin was progressively reduced and stopped after 6 hours infusion and epinephrine reduced and stopped in 12 hours” What was the mean arterial pressure (or other) target you chose where de-escalating the arginine-vasopressin and epinephrine infusion? What was the mean reduction per hour of arginine-vasopressin and epinephrine doses? Did you monitor heart function by means of echocardiography during the weaning from epinephrine?

In the revised manuscript this part has been added to the case report section
Vasopressin was progressively reduced by 0.0001 U.I./Kg/min every 2 hours, controlling SAP to more than 80/40 mmHg, and stopped after 6 hours infusion. Epinephrine was reduced and stopped in 12 hours with the same hemodynamic goal.
Ecography was not monitored during weaning, being all the metabolic and haemodynamic parameters normalized.

Page 4; line 17-19 - Page 3; line 15
“The cardiovascular collapse due to anaphylaxis is a vasodilatory shock, characterized by an abrupt fall in systemic vascular resistance, enhanced vascular permeability and intravascular volume depletion”. In the text you state: “CPB was instituted in 5 minutes in order to improve patient organ perfusion”. Please specify in the discussion section what is the mechanism(s) by which CPB could restore organ perfusion in the setting of vasodilatory shock.

The discussion section has been revised as follows:
Our decision to start CPB might have been questionable since the patient might have been stabilized with epinephrine and vasopressin and the case rescheduled. Nevertheless, our choice was made in order to urgently restore adequate ventilatory parameters and to improve organ perfusion with the extracorporeal circuit before the clinical picture of severe vasoplegic shock was completely defined. It must be considered that CPB might also have initially worsened the clinical picture since, once the inflammatory system is activated, it is likely that CPB will add further activation. However, only the administration of low dose vasopressin was effective in restoring adequate systemic vascular resistance and allowed for a successful CPB weaning and stable postoperative hemodynamic parameters.

Minor comments:
Page 2; line 25
Please replace 0,2 with 0.2; 0,2 with 0.2; 0,5 with 0.5.
Page 2; line 26
Please insert (i.v.) after intravenous (and delete i.v. in page 3; line 13)
Page 3; line 1
Please replace 0,25-0,5 with 0.25-0.5; 0,2 with 0.2; 0,2 with 0.2.
Page 3; line 11-12
“Airway pressure increased to 38 mmHg with the clinical finding…”
The International System of Units (Guide for the Use of the International System of Units. BN Taylor 1995) indicate to express Pressures in Pa. Please substitute mmHg in Pa or in the widely accepted cmH2O. 38 mmHg = 54.6 cmH2O = 5.06 KPa.
Page 3; line 16
Please replace 3,3 with 3.3.
Page 3; line 16
Please replace pH 7,23 with pH 7.23.
Page 3; line 18
Please substitute the symbol of seconds (sec) with s (SI base units)
Page 3; line 24
Please replace 5,1 with 5.1.
Page 3; line 25
Please replace vital parameter with vital parameters.
Page 3; line 26
Please replace minute with minutes.
Page 4; line 4
Is MAP for mean arterial pressure? Is it the perfusion pressure? Please specify.
Page 4; line 5
Please substitute the symbol of seconds (sec) with s (SI base units)
Page 4; line 6
Please replace hemodynamic with hemodynamic.
Page 4; line 23
Please replace resistence with resistance.

All revisions suggested by the reviewer have been corrected in the text.

What next?: Revise and resubmit
Quality of written English: Acceptable