

ORNIPRESSIN FOR THE TREATMENT OF ADRENALINE-RESISTANT ANAPHYLAXIS

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Background:

Anaphylaxis is defined as “a serious allergic reaction that is rapid in onset and might cause death”^{1,2} and involves the respiratory and/or cardiovascular system. Adrenaline is the first-line treatment for anaphylaxis. In rare cases, anaphylactic shock may not respond to adrenaline.³⁻⁶ We report on a patient who developed intraoperative anaphylaxis that did not respond to treatment with intravenous adrenaline, but subsequently responded to ornipressin.

CASE REPORT

A 36 year old female developed anaphylaxis intraoperatively while undergoing a bilateral knee arthroscopy under general anaesthesia. She was known to have hypothyroidism on Eltroxin and to have allergic rhinitis with sensitisation to cat and dog hair. She also reported an allergic reaction, with mostly skin manifestations, to penicillin a month prior to surgery. She was not asthmatic and had not previously reacted to aspirin or non-steroidal anti-inflammatory agents.

Previous general anaesthetics during childhood were uneventful. Her last Caesarean section was done under spinal anaesthesia, but was complicated by prolonged hypotension that required extensive fluid administration. There were no skin or other respiratory manifestations and she was told that it was related to the spinal anaesthetic.

During induction, she had received ketamine, propofol and sufentanil. Anaesthesia was maintained with 2-3% sevoflurane in an air/oxygen mix. Clindamycin, granisetron, dexamethasone and ketorolac were administered during the following ten minutes and prior to tourniquet inflation. Two minutes after skin incision, she developed flushing, bronchospasm, bradycardia and hypotension. The diagnosis of anaphylaxis was made and treatment initiated. Intravenous adrenaline was administered in 0.5 mg doses every two minutes. She also received 6 mg of etilefrine,

1 mg of atropine and 2 litres of Ringer's lactate. Despite 2 mg of adrenaline and 1 mg atropine intravenously, she remained hypotensive with a bradycardia. She was also given 200 mg of hydrocortisone, 25 mg of promethazine and 50 mg of ranitidine intravenously. As a last resort, 1 IU of ornipressin was administered intravenously. This resulted in restoration of arterial blood pressure and an increase in heart rate. Subsequent doses of 50-100 µg of adrenaline resulted in a significant increase in blood pressure and heart rate.

A blood-gas performed at this stage revealed an increase in haemoglobin to 19.3 mg/dl and an elevated serum lactate value of 4.3 mmol/l. Unfortunately, blood was not taken to determine the serum tryptase. The only abnormality revealed by focussed transthoracic echocardiography was significantly underfilling of both ventricles. Volume expansion was continued and circulation maintained with low dose adrenaline infusion. Arthroscopy of the first knee was completed urgently.

Forty five minutes later the reaction reoccurred and once again responded poorly to treatment with boluses of adrenaline. Administration of 1 IU of ornipressin restored haemodynamics promptly once again. Surgery was abandoned and the patient transferred to ICU. An adrenaline infusion of 0.02 to 0.05 µg/kg/min and another 5 litres of intravenous fluid was required over the next six hours after which she completely stabilised. She was discharged from hospital three days later.

ImmunoCAP testing was performed six weeks after discharge from hospital and was positive for latex specific IgE with a value of 5.06 IU/ml. ImmunoCAP and CAST tests are not available for the drugs that were administered to her and in view of the severity of the reaction, it was not considered safe to perform skin prick testing or a drug challenge. While the anaphylaxis may possibly have been due to latex, the cause remains unknown.

She was given a MedicAlert bracelet warning of probable latex allergy and possible allergy to the anaesthetic agents she received. She was also advised that should she require anaesthesia in the future, she should inform the anaesthetist of the reaction that occurred and ask him to contact one of the authors of this case report.

DISCUSSION

Successful treatment of anaphylaxis depends on early recognition of the condition. Removal of the suspected allergen should be done as soon as possible. Further treatment aims to maintain the airway and ventilation and restore circulation. This is done by restoring circulating volume, restoring vascular tone to address relative hypovolaemia, preventing interaction of mediators with their various receptors and prevention of further mediator release. The most important intervention though, is the early administration of adrenaline.^{1,2} Adrenaline restores vascular tone, increases myocardial contractility, induces bronchodilatation and also stabilises membranes of mast cells and basophils, reducing the further release of histamine and other mediators.¹

While virtually every drug used in anaesthesia has been reported to cause an anaphylactic reaction, muscle relaxants are the most frequently implicated, accounting for 50-70% of reactions, followed by latex (12-16.7%) and antibiotics, usually beta-lactams and vancomycin (15%).³ Our patient did not receive a muscle relaxant and was given clindamycin for antibiotic prophylaxis.

Although the use of vasopressin for the treatment of adrenaline-resistant anaphylaxis has been reported in the literature,⁴⁻⁷ this drug is not available in South Africa. Ornipressin is a synthetic vasopressin analogue, that is used locally to induce ischaemia and haemostasis at operative sites during ENT, gynaecologic and urologic procedures.⁸ It has a potent and specific non-adrenergic constrictor effect on the microcirculation and veins through its actions on the vasopressin 1 receptor which is equal to, if not greater than, that of vasopressin.⁴ However it does not have the antidiuretic effect of vasopressin.⁹

Ornipressin holds no indication for intravenous administration and the use of intravenous ornipressin is therefore an off-label application of this agent.¹⁰ There are however a number of reports where intravenous ornipressin had been used. These indications include the management of severe catecholamine resistant vasoplegia in cardiac surgery,⁴ improvement of renal function in patients with hepatorenal syndrome¹¹ and the counteraction of neuraxial anaesthesia induced hypotension.¹²

Infusion of ornipressin causes a rise in arterial blood pressure by increasing the venous tone and decreasing the capacity of the peripheral circulation, thus increasing peripheral vascular resistance and shunting blood back to the vital organs and the central circulation. It produces vasoconstriction in the skin, skeletal muscle, intestine and fat, with relatively less constriction of the coronary and renal vasculature, and causes cerebral vasodilatation.⁴ When used as an infusion of 2.5 IU over 30 minutes, it does not produce changes in heart rate, rhythm, cardiac output or intracardiac pressures and does not have a significant effect on coronary blood flow.⁴ In this patient, 1 IU of ornipressin was administered as a rapid intravenous bolus. The clinical effect was adequate and further hypotension was treated with adrenaline. Large doses of ornipressin administered rapidly can result in coronary or cerebral vasospasm and are therefore reserved for life-threatening episodes of cardiovascular instability not responding to adrenaline.

The predominant pathophysiological mechanisms of cardiovascular failure in anaphylactic shock are vasodilatation and hypovolaemia resulting from increased endothelial permeability.⁹ Tsuda *et al* found that adrenaline was only partially effective in reversing histamine-induced vascular relaxation while vasopressin was able to completely reverse histamine-induced vasodilation.¹³ It is these properties of vasopressin and its synthetic analogues ornipressin and terlipressin that make them logical last resort therapy in refractory anaphylaxis.

Vasopressin or ornipressin should be considered for the treatment of adrenaline-resistant anaphylactic shock before resuscitation is discontinued.

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