



REVISTA BRASILEIRA DE ANESTESIOLOGIA

Publicação Oficial da Sociedade Brasileira de Anestesiologia
www.sba.com.br



CLINICAL INFORMATION

Perianesthetic refractory anaphylactic shock with cefuroxime in a patient with history of penicillin allergy on multiple antihypertensive medications



Deb Sanjay Nag*, Devi Prasad Samaddar, Shashi Kant, Pratap Rudra Mahanty

Tata Main Hospital, Department of Anesthesiology and Critical Care, Jamshedpur, India

Received 20 June 2014; accepted 6 August 2014

Available online 27 October 2014

KEYWORDS

Anaphylaxis;
Perianesthetic;
Cefuroxime

Abstract We report a case of perianesthetic refractory anaphylactic shock with cefuroxime in a patient with history of penicillin allergy on regular therapy with atenolol, losartan, prazosin and nicardipine. Severe anaphylactic shock was only transiently responsive to 10 mL of (1:10,000) epinephrine and needed norepinephrine and dopamine infusion. Supportive therapy with vasopressors and inotropes along with mechanical ventilation for the next 24 hours resulted in complete recovery. She was successfully operated upon 2 weeks later with the same anesthetic drugs but intravenous ciprofloxacin as the alternative antibiotic for perioperative prophylaxis. © 2014 Sociedade Brasileira de Anestesiologia. Published by Elsevier Editora Ltda. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

PALAVRAS-CHAVE

Anafilaxia;
Perianestésico;
Cefuroxima

Choque anafilático refratário perianestésico com cefuroxima em paciente com história de alergia à penicilina recebendo vários medicamentos anti-hipertensivos

Resumo Relatamos um caso de choque anafilático refratário no período perianestésico com cefuroxima em paciente com história de alergia à penicilina em terapia regular com atenolol, losartan, prazosina e nicardipine. O choque anafilático grave foi apenas transitoriamente responsivo a 10 mL de epinefrina (1:10000) e precisou de infusão de norepinefrina e dopamina. A terapia de apoio com vasopressores e inotrópicos, juntamente com ventilação mecânica por 24 horas resultaram em recuperação completa. A paciente foi operada com sucesso duas semanas mais tarde, com os mesmos agentes anestésicos, mas com ciprofloxacina intravenosa como antibiótico alternativo para a profilaxia perioperatória.

© 2014 Sociedade Brasileira de Anestesiologia. Publicado por Elsevier Editora Ltda. Este é um artigo Open Access sob uma licença CC BY-NC-ND (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

* Corresponding author.

E-mail: debsanjay@gmail.com (D.S. Nag).

Introduction

Operating room is a unique environment where the patient receives exposure to multiple drugs which can potentially cause anaphylaxis. While antibiotics remain one of the commonest causes of perioperative anaphylaxis, the concurrent antihypertensive medications can make the anaphylactic shock refractory to conventional therapy. Here we report a case of severe refractory anaphylactic shock in a patient on multiple antihypertensive medications. Patient consent has been obtained for this report.

Case description

A 46-year-old (70 kg) lady was scheduled for an open reduction and internal fixation (ORIF) of fracture of lower end of humerus. She had a history of hypertension and hypothyroidism which was controlled on atenolol 25 mg once daily, losartan 50 mg twice daily, prazosin 2.5 mg once daily, nicardipine 20 mg twice daily and thyroxin sodium 100 micrograms once daily.

She had no history of previous surgery or anesthesia exposure but reported allergy to penicillin. However she gave history of oral intake of amoxicillin and erythromycin without any adverse reaction. Pre-anesthesia evaluation was done on admission and all her routine investigations were within normal limits. Except for Losartan, she received all her antihypertensive medication and thyroxin sodium on the morning of surgery. Her initial baseline readings were a pulse rate of 69/min, blood pressure of 171/75 mmHg and room air saturation (SpO₂) of 97%. General anesthesia was induced with fentanyl 100 micrograms, midazolam 1 mg, propofol 140 mg and vecuronium 6 mg intravenously. Patient was intubated and maintained on isoflurane, nitrous oxide and oxygen through the circle system and intermittent positive pressure ventilation.

The patient was maintaining stable hemodynamics over the next 15 min when she was positioned and part preparation of the surgical site was done. Within minutes of initiating the intravenous injection of cefuroxime (1.5 g diluted in 20 mL of sterile water) the heart rate dropped to 36/min, peak airway pressures increased to above 40 cm of H₂O and blood pressure became unrecordable. By this time only 750 mg cefuroxime had been administered. Further administration of cefuroxime was immediately stopped. A call for help was given and all anesthetic gases were turned off. The patient was switched to manual ventilation with 100% oxygen. Higher resistance to ventilation was appreciated while squeezing the bag of the anesthesia workstation. The bradycardia was initially non-responsive to 0.6 mg of intravenous atropine, but responded to a second dose with heart rate rising to 112/min. The patient developed maculopapular rash all over her body with evident angioedema causing rapid swelling of eyelids, lips and face.

Anaphylaxis was diagnosed and immediately 1 mL of (1:10,000) Epinephrine was administered intravenously along with rapid transfusion of 1000 mL of normal saline, 200 mg of intravenous hydrocortisone and 25 mg of intramuscular promethazine hydrochloride. Her lower limbs were elevated. Simultaneously 10 puffs of salbutamol were delivered into the endotracheal tube. On observing

no response, incremental doses of 10 mL (1:10,000) intravenous Epinephrine was administered over 10 min. This resulted in an appreciable peripheral pulse and a blood pressure of 81/30 mmHg on the non-invasive blood pressure monitor. Bronchospasm started getting relieved with mild chest expansion and faint breath sounds were audible on auscultation. Saturation (SpO₂) increased to 85–90% over the next 5 min the blood pressure again started dropping with very feeble central pulses and became unrecordable very soon. Central venous access was immediately secured through the subclavian route and dopamine infusion was started at 5 microgram/kg/min and increased to 10 microgram/kg/min, resulting in a blood pressure of 80/39 mmHg over the next 15 min. Suspecting refractory anaphylactic shock, norepinephrine infusion was also started at 2 microgram/min and increased to 5 microgram/min resulting in blood pressure of 92/43 mmHg with heart rate of 146/min. She became conscious, started breathing spontaneously and responded by eye movements in the next 15 min. The decision was made to postpone the surgery and the patient was shifted to the Critical Care Unit (CCU).

In the CCU, she was put on mechanical ventilation and the initial Arterial Blood Gas (ABG) showed mixed metabolic and respiratory acidosis. She was advised intravenous hydrocortisone 50 mg/6 hourly and ranitidine 50 mg/12 hourly. She needed inotropic support with dopamine 10 microgram/kg/min, norepinephrine 5 microgram/min and epinephrine 2 microgram/min with an aim to maintain blood pressure above 70% of pre-shock levels. Norepinephrine was gradually tapered and stopped over the next 2 h. Blood pressure gradually improved from 99/54 mmHg to 140/90 mmHg with heart rate range of 98–113/min by next morning, 24 h after the event. All vasoactive agents were gradually tapered and stopped. She was conscious and responsive to commands. After a T-Piece trial, she was extubated. Post extubation she was able to speak and maintain her vital parameters with oxygen supplementation by mask. Hydrocortisone was stopped on the third day after the event and the patient was shifted to her cabin. Facial swelling gradually reduced and she recovered back to normalcy without any residual effect of the anaphylactic reaction.

Her antihypertensive drugs were restarted 3 days later. She was operated upon after two weeks with perioperative antibiotic coverage of intravenous ciprofloxacin and general anesthesia with propofol, fentanyl and vecuronium for induction and endotracheal intubation, isoflurane, nitrous oxide and vecuronium were used for maintenance of anesthesia. After the surgery, reversal of neuromuscular blockade was done with neostigmine and glycopyrrolate. Following an uneventful intraoperative and postoperative course, she was discharged from the hospital two weeks after her surgery.

Discussion

While the incidence of perioperative anaphylaxis has been reported to be between 1 in 10,000–20,000 anesthesia procedures, it is responsible for 3–10% of the perioperative fatalities.¹ Anaphylaxis therefore is of major concern to the

anesthesiologists who administer multiple drugs with potential to cause fatal hypersensitivity to any drug.² Anaphylaxis has been defined as “a serious, life-threatening generalized or systemic hypersensitivity reaction” or “a serious allergic reaction that is rapid in onset and might cause death.”³ Allergic reactions to anesthetic drugs usually occur within 10 min of the drug exposure but can also occur as late as 30 min to several hours later.⁴ However, more than 90% of reactions evoked by intravenous drugs occur within 3 min of its administration.⁵ In this case the patient was maintaining good hemodynamic parameters till cefuroxime injection was started. Therefore it appears that cefuroxime was the cause of this anaphylactic reaction. The subsequent uneventful administration of general anesthesia two weeks later using the same drugs (except cefuroxime) before incision reaffirmed our belief that it was cefuroxime induced anaphylaxis.

There is adequate literature evidence about the safety of cephalosporins (including cefuroxime) in patients reporting allergy to penicillin.^{6,7} Although skin testing could have been done prior to administration of cefuroxime, no validated diagnostic test (including skin testing) is of sufficient sensitivity for evaluating of IgE-mediated allergy to antibiotics other than penicillin.⁸ Even in patients who are truly allergic to penicillin, the risk of a reaction from a cephalosporin with side chains different from penicillin/amoxicillin is so low that its use is “justified and medico-legally defensible by the currently available evidence”.⁹

In our patient, anaphylaxis was diagnosed by the “clinical criteria for diagnosing anaphylaxis” as suggested by Sampson et al.¹⁰ Bradycardia is an uncommon presentation during anaphylaxis. In our patient, premedication with beta blocker and severe hypoxia could be the probable reason for this uncommon presentation.¹¹

There are numerous cases of severe anaphylactic shock refractory to catecholamines.¹² ACE inhibitors have been reported to be associated with increased risk for more severe reaction from venom immunotherapy or field sting.¹³ There are isolated case reports of resistance to epinephrine in patients on alpha adrenergic blockers.¹⁴ Resistance to exogenous catecholamines in patients on beta-blockers is not only due to desensitization of adrenergic receptors, it also involves nitric oxide which plays a pivotal role in the pathophysiology of anaphylaxis. Increased nitric oxide synthesis has been found to be responsible for the vasodilatory shock resistant to vasopressors.¹⁵ Greater risk of anaphylaxis exists in patients on ACE inhibitors and angiotensin receptor blockers as they “inhibit the metabolism of angiotensin, bradykinin, and substance P” and derange the compensatory activation of the rennin-angiotensin system.¹³ ACE inhibitors also cause impaired breakdown of bradykinin (a vasoactive mediator causing hypotension in severe anaphylaxis).¹³ Possibly, the synergistic effect of all the concurrent antihypertensive drugs (atenolol, losartan, prazosin, nicardipine) contributed to the refractory anaphylactic shock with only transient response to 10 mL of (1:10,000) epinephrine in our patient.

In refractory anaphylactic shock, norepinephrine, metaraminol, methylene blue or glucagon has been recommended.^{1,15} Although an infusion of dopamine and norepinephrine was started in our patient, “no clear superiority of dopamine, dobutamine, norepinephrine,

phenylephrine, or vasopressin (either added to epinephrine alone, or compared with one another), has been demonstrated in clinical trials”.¹⁶ Based on the clinical response, epinephrine infusion was added in the CCU and norepinephrine was subsequently tapered off. In suspected anaphylaxis, blood samples for estimation of tryptase should be sent between 15 and 180 min and for histamine between 15 and 60 min from the onset of symptoms. The specificity of these tests has been questioned and normal values do not rule out anaphylaxis.¹⁶ It has been suggested that skin testing should be performed 4–6 weeks after the reaction to identify the specific allergy.¹⁷ There is evidence that in cases of conclusive clinical history and strong temporal association with the implicated drug, skin tests or in vitro specific IgE, and/or challenge tests may not be warranted.¹² Facilities for these tests were unavailable at our setup, therefore not considered for further evaluation.

Epinephrine remains the only first line medication in anaphylaxis and refractory anaphylactic shock should be considered in patients on multiple antihypertensive medications. As peri-anesthetic anaphylaxis is becoming more common,¹⁸ vigilance and early recognition of anaphylaxis is of paramount importance to reduce its adverse outcome.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Dewachter P, Mouton-Faivre C, Emala CW. Anaphylaxis and anesthesia. *Anesthesiology*. 2009;111:1141–50.
2. Mertes PM, Laxenaire MC, Lienhart A, et al. Reducing the risk of anaphylaxis during anaesthesia: guidelines for clinical practice. *J Invest Allergol Clin Immunol*. 2005;15:91–101.
3. Johansson SGO, Bieber T, Dahl R, et al. Revised nomenclature for allergy for global use: report of the nomenclature review committee of the World Allergy Organization, October 2003. *J Allergy Clin Immunol*. 2004;113:832–6.
4. Hepner DL, Castells MC. Latex allergy: an update. *Anesth Analg*. 2003;96:1219–29.
5. Blas M, Briesacher KS, Lobato EB. Bacitracin irrigation: a cause of anaphylaxis in the operating room. *Anesth Analg*. 2000;91:1027–8.
6. Apter AJ, Kinman JL, Bilker WB, et al. Is there cross-reactivity between penicillins and cephalosporins? *Am J Med*. 2006;119:254, e11–9.
7. Engelman R, Shahian D, Shemin R, et al. The Society of Thoracic Surgeons practice guideline series: antibiotic prophylaxis in cardiac surgery. Part II: Antibiotic choice. *Ann Thorac Surg*. 2007;83:1569–76.
8. Bernstein IL, Li JT, Bernestein DI, et al. Allergy diagnostic testing: an updated practice parameter. *Ann Allergy Asthma Immunol*. 2008;100:S1–142.
9. Pichichero ME. Cephalosporins can be prescribed safely for penicillin-allergic patients. *J Fam Pract*. 2006;55:106–12.
10. Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report – Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol*. 2006;117:391–7.
11. Brown SGA. Cardiovascular aspects of anaphylaxis: implications for treatment and diagnosis. *Curr Opin Allergy Clin Immunol*. 2005;5:359–64.

12. Lieberman P, Nicklas RA, Oppenheimer J, et al. The diagnosis and management of anaphylaxis practice parameter: 2010 update. *J Allergy Clin Immunol.* 2010;126:477–80, e1–42.
13. Cox L, Nelson H, Lockey R, et al. Allergen immunotherapy: a practice parameter third update. *J Allergy Clin Immunol.* 2011;127 Suppl.:S1–55.
14. Watson A. Alpha adrenergic blockers and adrenaline. A mysterious collapse. *Aust Fam Phys.* 1998;27:714–5.
15. Evora PR, Simon MR. Role of nitric oxide production in anaphylaxis and its relevance for the treatment of anaphylactic hypotension with methylene blue. *Ann Allergy Asthma Immunol.* 2007;99:306–13.
16. Simons FER, Arduzzo LRF, Bilò MB, et al. World Allergy Organization Guidelines for the Assessment and Management of Anaphylaxis. *World Allergy Organ J.* 2010;4:13–37.
17. Guttormsen AB, Harboe T, Pater G, Florvaag E. Anaphylaxis during anaesthesia. *Tidsskr Nor Laegeforen.* 2010;130:503–6.
18. Chacko T, Ledford D. Peri-anesthetic anaphylaxis. *Immunol Allergy Clin North Am.* 2007;27:213–30, vi.