Case Reports/Case Series

Case report: Treatment of rocuronium-induced anaphylactic shock with vasopressin

[Présentation de cas : traitement d'un choc anaphylactique provoqué par le rocuronium avec de la vasopressine]

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Purpose: To report the use of vasopressin to treat a patient who, after failing to respond to volume expansion and epinephrine administration, experienced an anaphylactic reaction to rocuronium.

Clinical features: A 17-yr-old female was scheduled to undergo transnasal, transsphenoidal resection of a pituitary tumour. Shortly after induction of general anesthesia, for which rocuronium 50 mg *iv* was administered to facilitate tracheal intubation, the patient developed severe hypotension and diffuse erythema. This severe,allergic response was refractory to the administration of intravenous fluids, epinephrine, and phenylephrine. However, arginine vasopressin, administered intravenously as a bolus of two units, followed by an infusion of 2 $U \cdot hr^{-1}$, rapidly corrected the hemodynamic instability. Her recovery from this episode was uneventful, but surgery was cancelled. Skin testing, performed six weeks later, was positive for rocuronium and negative for cisatracurium and latex, as well as all other medications administered. Eight weeks later, the surgical procedure was performed, uneventfully, using cisatracurium as the muscle relaxant.

Conclusions: Vasopressin may be effective in the resuscitation of anesthetized patients, with hemodynamic instability associated with anaphylaxis resistant to epinephrine and alpha-agonists.

CAN J ANESTH 2008 / 55: 7 / pp 437–440

Objectif *: Rendre compte de l'utilisation de vasopressine pour traiter une patiente qui a présenté une réaction anaphylactique au rocuronium, réfractaire à l'expansion volumique ou à l'administration d'épinéphrine.*

Éléments cliniques *: Une résection trans-nasale, trans-sphénoïdale d'une tumeur de l'hypophyse était prévue chez une jeune femme de 17 ans. Peu après l'induction de l'anesthésie générale comportant l'administration de 50 mg iv de rocuronium afin de faciliter l'intubation trachéale, la patiente a développé une hypotension grave ainsi qu'un érythème diffus. Cette réaction allergique grave s'est avérée réfractaire à l'administration de liquides intraveineux, d'épinéphrine et de phényléphrine. Toutefois un bolus de deux unités d'arginine-vasopressine administrée en intraveineuse, suivi par une perfusion de 2 $U \cdot hr^{-1}$, a permis de corriger rapidement l'instabilité hémodynamique. Il n'y a pas eu d'événement durant le rétablissement de la patiente, mais la chirurgie a été annulée. Un test cutané effectué six semaines plus tard a montré des résultats positifs pour le rocuronium et négatifs pour le cisatracurium et le latex ainsi que pour les autres médicaments administrés. Huit semaines plus tard, l'intervention chirurgicale a eu lieu, sans complications, en utilisant du cisatracurium comme curare.*

Conclusions *: La vasopressine peut être efficace pour réanimer les patients anesthésiés présentant une instabilité hémodynamique associée à une anaphylaxie résistante à l'épinéphrine et aux alpha-agonistes.*

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Competing interests: None declared.

Accepted for publication March 17, 2008.

Revision accepted March 31, 2008.

THE reported incidence of anaphylactic reactions during anesthesia varies from 1:6,000 to 1:20,000.[1] Muscle relaxants are believed to be responsible for 2/3 of the cases,[2] with rocuronium frequently being implicated.[3] Anaphylaxis during anesthesia is often life-threatening, with a mortality rate of 3–6%.[4] Due to the life-threatening nature of anaphylaxis, rapid recognition and immediate management are essential to prevent mortality and morbidity. The standard descriptions of the treatment of anaphylactic and anaphylactoid reactions advise the use of resuscitation with intravenous fluids and epinephrine.[1] In the case described, we report the use of vasopressin to treat a patient with an anaphylactic reaction to rocuronium, who did not respond to volume expansion and epinephrine administration. Consent for publication was obtained in accordance with the authors' local institutional guidelines.

Case report

A 17-yr-old female was scheduled to undergo a transnasal transsphenoidal resection of a pituitary tumour. The pituitary tumour had been discovered during investigation of a previous syncopal episode. The patient had no other symptoms and took no medications. Apart from a mildly elevated growth hormone level, all laboratory investigations were within normal limits. The patient had received no previous anesthetics, and there was no family history of any problems with anesthesia. After the event, the patient's mother admitted to developing swelling of the tongue and lips following codeine ingestion.

The patient was seen in the holding area and, because of her needle phobia, an inhalational induction with sevoflurane was planned. She was transferred to the operating room where standard monitors were applied, and general anesthesia was induced, uneventfully, with nitrous oxide and sevoflurane via face mask. After intravenous access was obtained, propofol 100 mg *iv*, lidocaine 100 mg *iv*, fentanyl 100 µg, and rocuronium 50 mg *iv* were administered in sequence. Endotracheal intubation was successfully performed 90 sec later, and intermittent, positive pressure ventilation was started, with minute ventilation adjusted to maintain eucarbia. General anesthesia was continued with sevoflurane in oxygen, and a remifentanil infusion was adjusted to maintain the bispectral index monitor score below 50.

Within minutes of anesthetic induction, an erythematous rash was observed over the patient's entire body, and her blood pressure decreased to 62/38 mmHg. The electrocardiogram showed sinus-tachycardia at rates varying between 119–138 beats·min^{-1}. Chest auscultation revealed clear breath sounds and no wheezing. Airway pressures were normal and remained unchanged.

The patient was placed in the Trendelenburg position. Over the next ten minutes, multiple boluses of neosynephrine (to a total of 200 µg *iv*) and epinephrine (to a total of 1200 µg *iv*) were administered, in addition to 2 L of 0.9% sodium chloride solution. However, the patient's condition remained unchanged (blood pressure, 50/30 mmHg; sinus-tachycardia, 136 beats·min^{-1}). At that point, two units of arginine vasopressin was administered intravenously, as an initial bolus, followed by an infusion at a rate of 2 U·hr^{-1}. Within two minutes of the bolus administration, the patient's blood pressure and heart rate returned to respective, baseline values (blood pressure, 112/64 mmHg; heart rate, 95 beats·min^{-1}) A radial arterial line was inserted, and the arterial blood gases were within normal limits (pH 7.39, pCO_2 40 mmHg, pO_2 298 mmHg, and HCO_3^- 23 mmol·L^{-1}). In view of the preceding events, surgery was cancelled, and anesthesia was converted to a propofol infusion, titrated to permit continued positive pressure ventilation. The patient was transferred to the postanesthesia care unit. Approximately 90 min after the initial event, the patient developed marked swelling of the lips and tongue; consequently, her trachea remained intubated while ventilation was continued for an additional 24 hr. Chlorpheniramine 50 mg *iv*, dexamethasone 10 mg *iv*, and famotidine 10 mg *iv* were administered and were repeated at eight-hour intervals for the next 48 hr.

By the following day, the swelling of the patient's tongue and lips had resolved and her chest *x-ray* was normal. With the patient fully stabilized, her trachea was extubated, and 48 hr after the event, she was discharged well to home.

Six weeks later, the patient received followed up by the Allergy and Clinical Immunology Clinic. Skin allergy testing to all the administered drugs, including cisatracurium and latex, demonstrated negative results at all dilutions, with the exception of rocuronium, which was positive at the first dilution (1:100 dilution). Serum tryptase levels were not available, as blood samples had not been obtained within sufficient time. A letter was written to the patient informing her of the results, and she was advised to wear a medic alert bracelet warning of the rocuronium allergy. Eight weeks after the initial event, the patient underwent the originally scheduled surgical procedure under general anesthesia, using cisatracurium as the muscle relaxant. The anesthetic course was unremarkable.

Discussion

The clinical features, response to treatment, and sub-

sequent test results suggest that our patient suffered anaphylaxis to rocuronium. While the diagnosis of anaphylaxis, in this case, was partially circumstantial, in the absence of documented elevation of serum tryptase levels, the successful use of low-dose vasopressin in the management of anaphylaxis to rocuronium has not been described previously.

Of the reported cases of anaphylaxis in the perioperative period, there is a wide variation in the estimated incidence associated with muscle relaxants (6%–70%).[5,6] Studies from France and Norway demonstrate that rocuronium is frequently the precipitating factor.[7,8] The management of anaphylaxis consists of withdrawing the offending drug; interrupting the effects of the mediators that were released in the response to the antigen; and preventing further mediator release.[9] Rapid, effective therapy of anaphylaxis is essential to avoid cardiovascular collapse and a poor outcome. Epinephrine is recommended for treatment of anaphylaxis, because it has both alpha and beta adrenergic effects, which increase vascular tone, improve cardiac output, and relax bronchial smooth muscle.[10] Also, by inhibiting the release of histamine and bradykinin from basophils and mast cells, epinephrine decreases further vasodilation and bronchial constriction. However, our patient did not respond adequately to epinephrine and volume expansion, while vasopressin proved to be effective.

Vasopressin is a peptide synthesized in the hypothalamus, and its primary role is fluid homeostasis. The physiological effects were first described in 1895[11], and it was first synthesized in 1954.[12] Indications for its administration include treatment of diabetes insipidus, bleeding disorders, esophageal varices, and most recently, cardiopulmonary resuscitation (CPR), where it has been recognized as an adjunct treatment for cardiac arrest. The latest CPR guidelines of the American Heart Association and the European Resuscitation Council state that vasopressin 40 U *iv* are equally effective as epinephrine 1 mg in the treatment of adults with shock-refractory ventricular fibrillation.[13,14] Jochberger *et al.*[15] suggested the use of vasopressin for intraoperative anaphylaxis as a potent adjunct vasopressor agent in advanced shock states unresponsive to conventional therapy.

Three case reports describe the successful administration of vasopressin in four patients with anaphylactic shock induced by: succinylated gelatin solution, aprotinin, and hornet and wasp stings.[16–18] All authors reported rapid hemodynamic stabilization after vasopressin bolus injection (2–10 IU). In one report, the injection of vasopressin 10 IU was followed by a continuous infusion of vasopressin (40 IU over 60 min). The current patient responded to a bolus of vasopressin 2 IU, followed by a continuous infusion at a rate of 2 IU·hr^{-1}. The use of low-dose vasopressin infusions has become an accepted alternative for the management of vasodilatory shock refractory to catecholamines. Prospective studies indicate that low-dose vasopressin infusions might be useful in treating hypotension in patients with vasodilatory shock refractory to catecholamines. The recommended infusion rate for vasopressin, in the treatment of shock in adults, is 0.01–0.04 U·min^{-1}.[19,20]

Vasopressin has been shown to have beneficial effects in the settings of septic and vasodilatory shock.[21] Dellinger *et al.*[22] have even postulated that vasopressin may be superior to other vasoconstrictors for the treatment of vasodilatory shock. It increases arterial pressure by more than one mechanism, and in the vascular smooth muscle, vasopressin inactivates kATP channels, which function to inactivate calcium channels. Thus, vasopressin allows calcium to enter smooth muscle cells and to bind to the actin-myosin complex, causing an increase in smooth muscle tone and, thereby, constriction of the vessels. Also, by inhibiting the synthesis of nitric oxide, vasopressin inhibits the vasodilation caused by nitric oxide's action on the phosphorylation of myosin. Moreover, vasopressin may be beneficial because, during resuscitative efforts for hypotension, it can improve perfusion of the vital organs by shunting blood flow from muscle, skin, adipose tissue, and the gastrointestinal system, towards the heart and the brain.[23]

In a recent animal study,[24] early treatment with epinephrine, followed by continuous epinephrine or vasopressin infusion, resulted in an excellent survival rate in a rat model of anaphylactic shock. In a rabbit model of systemic anaphylaxis, the effects of vasopressin to improve cardiovascular depression and bronchoconstriction, after the induction of anaphylaxis, were investigated. This study revealed that vasopressin was able to improve survival rates and severe hypotension provoked by systemic anaphylaxis.[25]

In conclusion, while the efficacy of vasopression for the treatment of refractory shock has been well documented, experience is limited with this drug in treating anaphylaxis in patients under general anesthesia. We describe the successful use of low-dose vasopressin, in the management of anaphylaxis to rocuronium, in a patient with no previous exposure to neuromuscular blocking drugs.

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