Learning From Others:

A Case Report From the Anesthesia Incident Reporting System

Anesthesia Quality Institute
ANESTHESIA INCIDENT REPORTING SYSTEM (AIRS)

Detailed review of unusual cases is a cornerstone of anesthesiology education. Each month, the AQI-AIRS Steering Committee will abstract a case and provide a detailed discussion based on a submission to the national Anesthesia Incident Reporting System. Feedback regarding this item can be sent by email to ***r.dutton@asahq.org****. Report incidents to* ***www.aqiairs.org****.*

Case 2012-7: Fool me once …

"Life can only be understood backwards, but it must be lived forwards." — Soren Kierkegaard (1813-1855)

An ASA IIIE adolescent female, 22 kg, with history of failed cadaveric renal transplant and refractory hypertension was scheduled for transplant nephrectomy. Induction of anesthesia with propofol was uneventful; the patient then received cefazolin and fentanyl. Three minutes later, she developed sudden hypoxemia followed by bronchospasm, cutaneous flushing, hypotension (40 mmHg) and hypocapnea (end-tidal CO_2 8 mmHg). She required escalating doses of epinephrine to improve bronchospasm, ventilation and hypoxia. Hypotension was unresponsive to phenylephrine and improved only after 1,000 ml crystalloid plus epinephrine 100 mcg. She was given hydrocortisone 50 mg and diphenhydramine 25 mg. An arterial line was placed, which showed blood pressure of 49/38 mmHg. Support was continued with epinephrine at 0.3 mcg/kg/min, norepinephrine 0.3 cg/kg/min and vasopressin 0.5 units/min. Her condition stabilized and she was transported to the ICU. The nephrectomy was performed three days later; no cefazolin was used and the procedure was completed without incident.

Background

The patient had undergone multiple previous procedures with anesthesia and had received cefazolin many times. Six months earlier the patient had anesthesia for peritoneal dialysis catheter placement. At that time she suffered cardiovascular collapse several minutes after tracheal intubation, characterized by ET CO_2 of 5 mmHg and blood pressure 30-40 mmHg, but with no evidence of bronchospasm. She responded to a 500 ml fluid bolus, 200 mcg epinephrine in 50 mcg boluses and hydrocortisone 20 mg. She stabilized with an epinephrine infusion 0.04 mcg/kg/min. Full neurological function returned with no focal deficits 35 minutes after anesthesia was discontinued.

The drug that caused this initial allergic reaction was not clear. The patient had received cefazolin, propofol and fentanyl in the period prior to the adverse event, and the surgical site had been prepped with chlorhexidine. Cefazolin was considered an unlikely culprit because at the time the patient was taking oral cephalexin for a urinary tract infection. Radioallergosorbent testing (RAST) for serum-specific immunoglobulin E (IgE) showed no reaction to any agent used during the procedure. Subsequent to this initial reaction the patient had two uneventful general anesthetics, but did not receive cefazolin or propofol on either occasion.

Discussion

It appears clear in hindsight that the patient suffered a severe allergic reaction to cefazolin on both of these occasions. In this and many other cases, identification of the allergen is reached only after a lengthy process of deduction and elimination. After the first reaction, there were several potential culprits; the patient had received fentanyl, propofol, cefazolin and sevoflurane for anesthesia. In addition, chlorhexidine prep solution had been applied to the patient's skin (Garvey, Roed-Petersen et al. 2001), and an endotracheal tube sterilized by ethylene oxide (Bache, Petersen et al. 2011) had been placed. A severe allergic reaction to any of these is possible.

The anesthesia team for the second event was misled into thinking it was safe to administer cefazolin by a couple of factors. First was a note following the initial event stating that cefazolin was unlikely to have caused the allergic reaction because the patient was taking oral cephalexin concurrently with the first operation. However, being able to safely take one cephalosporin does not rule out allergy to another. Cross-reactivity between cephalosporins is side-chain, not beta-lactam, specific (Igea, Fraj et al. 1992). Cefazolin and cephalexin have quite different side-chains and cross-reactivity may not occur. It is quite possible for a patient to have IgE specific sensitization to one drug, cefazolin, and not to the other, cephalexin.

The second factor giving the anesthesia team a false sense of safety was the RAST test performed after the first incident, which did not identify an allergy to cefazolin. In a patient such as this, even following a severe IgE mediated anaphylactic reaction, sensitivity of the RAST is only 75 percent, i.e., a false-negative test is quite possible (Fontaine, Mayorga et al. 2007).

In reality, it can be difficult to identify the cause of an allergic reaction in the operating room. The patient is exposed to many substances over a brief period of time, and identifying the true allergen is not always possible. Following a serious intraoperative allergic reaction, the drug reported as the most likely cause was

shown to be wrong 73 percent of the time (Kroigaard, Garvey et al. 2005). This is in part because of reporting bias based on old and outdated concepts.

According to conventional wisdom, neuromuscular-blocking drugs are responsible for most of the severe intraoperative allergic reactions (Hepner and Castells 2003). This belief needs to be re-examined. In Denmark, the Danish Anaesthesia Allergy Center conducts a formal and rigorous follow up on all reports of severe intraoperative allergic reactions anywhere in the nation. Their analysis shows that muscle relaxants are not the most common cause of intraoperative allergic responses (Garvey, Roed-Petersen et al. 2001). The three most common allergens were, in descending order, chlorhexidine, antibiotics and latex (Garvey, Roed-Petersen et al. 2001; Kroigaard, Garvey et al. 2005). Only one case of neuromuscular blocker sensitivity was identified, and that was to cisatracurium. The Danish results have since been confirmed by a study in the United States (Gurrieri, Weingarten et al. 2011).

The incidence of life-threatening allergic reactions during anesthesia varies by country from 1/6,000 in Norway to 1/34,000 (a likely underestimate) in the United States (Gurrieri, Weingarten et al. 2011). These estimates would extrapolate to any given anesthesiologist seeing one to two cases every decade of clinical practice. In the United Kingdom, 10 percent of severe allergic reactions associated with anesthesia are fatal. Compare this with malignant hyperthermia, a much less common complication with a current mortality of around 5 percent (Rosero, Adesanya et al. 2009).

Lessons

What lesson does this case have for the clinician? The most obvious is that allergies can present despite previous negative screening tests and that no patient's care can be taken for granted. In other words, the previous history of an allergic event should have increased concern more than the subsequent negative testing reduced it.

A more generic lesson is the importance of preparing for an allergic reaction at any moment. Allergic reactions in the O.R. must be treated aggressively. Severe allergic responses have a significant morbidity and mortality. The cornerstones of treatment are rapid recognition, aggressive intravascular resuscitation and early use of epinephrine (Garvey, Belhage et al. 2011; Lee and Vadas 2011).

Another lesson is that the presentation may be limited to one system only, the most common being cardiovascular collapse (Lee and Vadas 2011). Lack of pulmonary or cutaneous manifestations does not rule out an allergic reaction. With the first event, severe hypotension was the principal feature. In the second incident, pulmonary and cutaneous manifestations also presented.

As they do for malignant hyperthermia, hospitals should develop an a priori plan, the "anaphylaxis drill," for management of severe allergic reactions (Kroigaard, Garvey et al. 2007; AAGBI 2009). Having such a plan and activating it early may improve outcome (Axon and Hunter 2004) and may serve as the basis for team-based simulator training. In addition, the plan can include recommendations for formal post-hoc testing, e.g., drawing blood for a tryptase assay, and consultation with allergy experts.

Propagating communication of the patient's allergies should be a core function of electronic health care records (EHR). In addition to making sure that a previous reaction is not forgotten or overlooked, the EHR could integrate expert opinion (the pharmacist who would know about cephalosporin side-chain differences) and decision support ("the patient has had a previous anaphylactic reaction"). More advanced systems can integrate with syringe bar-code technology to reduce the risk of even accidental administration of a contraindicated medication.

Finally, in the management of severe allergic reactions, it is not useful to worry about whether the underlying mechanism is or is not IgE mediated – the anaphylactic/anaphylactoid question. Regardless of the mechanism, the event can be severe and life-threatening, and clinical management is the same. Some experts suggest doing away with the differentiation and just using the term "anaphylactic."

Bibliography:

- Harper NJ, Dixon T, Dugué P, et al.; Association of Anaesthetists of Great Britain and Ireland. Suspected anaphylactic reactions associated with anesthesia. *Anaesthesia*. 2009;64(2):199-211.
- Axon AD, Hunter JM. Editorial III: anaphylaxis and anaesthesia--all clear now? *Br J Anaesth*. 2004;93(4):501-504.
- Bache S, Petersen JT, Garvey LH. Anaphylaxis to ethylene oxide - a rare and overlooked phenomenon? *Acta Anaesthesiol Scand*. 2011;55(10):1279-1282.
- Fontaine C, Mayorga C, Bousquet PJ, et al. Relevance of the determination of serum-specific IgE antibodies in the diagnosis of immediate beta-lactam allergy. *Allergy*. 2007;62(1):47-52.
- Garvey LH, Belhage B, Krøigaard M, Husum B, Malling HJ, Mosbech H. Treatment with epinephrine (adrenaline) in suspected anaphylaxis during anesthesia in Denmark. *Anesthesiology*. 2011;115(1):111-116.
- Garvey LH, Roed-Petersen J, Husum B. Anaphylactic reactions in anaesthetised patients - four cases of chlorhexidine allergy. *Acta Anaesthesiol Scand*. 2001;45(10):1290-1294.
- Garvey LH, Roed-Petersen J, Menné T, Husum B. Danish Anaesthesia Allergy Centre - preliminary results. *Acta Anaesthesiol Scand*. 2001;45(10):1204-1209.
- Gurrieri C, Weingarten TN, Martin DP, et al. Allergic reactions during anesthesia at a large United States referral center. *Anesth Analg* 2011;113(5):1202-1212.
- Hepner DL, Castells MC. Anaphylaxis during the perioperative period. *Anesth Analg*. 2003;97(5):1381-1395.
- Igea JM, Fraj J, Davila I, Cuevas M, Cuesta J, Hinojosa M. Allergy to cefazolin: study of in vivo cross reactivity with other betalactams. *Ann Allergy*. 1992;68(6):515-519.
- Kroigaard M, Garvey LH, Gillberg L, et al. Scandinavian Clinical Practice Guidelines on the diagnosis, management and follow-up of anaphylaxis during anaesthesia. *Acta Anaesthesiol Scand*. 2007;51(6):655-670.
- Kroigaard M, Garvey LH, Menné T, Husum B. Allergic reactions in anaesthesia: are suspected causes confirmed on subsequent testing? *Br J Anaesth*. 2005;95(4):468-471.
- Lee JK, Vadas P. Anaphylaxis: mechanisms and management. *Clin Exp Allergy*. 2011;41(7): 923-938.
- Rosero EB, Adesanya AO, Timaran CH, Joshi GP. Trends and outcomes of malignant hyperthermia in the United States, 2000 to 2005. *Anesthesiology*. 2009;110(1):89-94.

SEE Question

Which of the following is MOST likely true regarding etomidate?

- ❑ (A) The median lethal dose to median effective dose ratio (LD_{50}/ED_{50} ratio) is significantly higher than other general anesthetics (i.e., there is a larger margin of safety).
- ❑ (B) Etomidate effectively blocks the sympathetic response to laryngoscopy.
- ❑ (C) An induction dose of etomidate is as likely to cause apnea as an induction dose of propofol.
- ❑ (D) Etomidate is a gamma-aminobutyric acid (GABA) receptor antagonist.

One measure of the safety of a drug is its LD_{50}/ED_{50} ratio. A drug has a large margin of safety if the LD_{50} is many times higher than the ED_{50}. Etomidate has a high LD_{50}/ED_{50} ratio. Early studies of etomidate in rats found that it had a favorable ratio of approximately 12 and later work suggested it may be as high as 26. In comparison, the LD_{50}/ED_{50} ratio for barbiturates ranges from three to five. The safety of etomidate administration is related to its minimal ability to cause hemodynamic instability and a tendency to maintain spontaneous breathing after administration of the drug.

Etomidate does not directly affect sympathetic tone or depress myocardial function in normal volunteers. For this reason, etomidate is often the drug of choice in patients with ischemic heart disease, decreased ejection fraction or valvular heart disease. However, etomidate does not block the sympathetic response to laryngoscopy because it does not alter sympathetic tone. Generally, opioids are administered with an induction dose of etomidate to prevent tachycardia and hypertension during intubation. In addition, etomidate is associated with myoclonus, pain on injection, and nausea and vomiting. In patients with a high sympathetic tone, such as trauma patients with pain and hypovolemic shock, etomidate will decrease catecholamine production and may precipitate hemodynamic collapse. As with all induction agents in this situation, the cautious use of a reduced dose is recommended.

It is well established that the molecular target of etomidate is the GABA type A ($GABA_A$) receptor. GABA is the major inhibitory neurotransmitter in the nervous system, and many anesthetics facilitate GABA effects either directly or indirectly. Etomidate positively modulates $GABA_A$ receptor activation by endogenous agonists, resulting in $GABA_A$ receptor activation at lower concentrations of GABA than would normally be required. Additionally, etomidate slows the postsynaptic current decay mediated by endogenous GABA, resulting in prolonged inhibition. Etomidate enhances activation of extrasynaptic $GABA_A$ receptors. Etomidate also has direct effects on the $GABA_A$ receptor and can act as an allosteric agonist, although this is generally seen at supraclinical dosages.

Bibliography

- Forman SA. Clinical and molecular pharmacology of etomidate. *Anesthesiology*. 2011; 114(3):695–707.

Answer: A

Interested in becoming a question writer for the SEE Program? Active ASA members are encouraged to submit their CVs for consideration to Richard Dutton, M.D., M.B.A., SEE Editor-in-Chief, at r.dutton@asahq.org.