

# Bronchospasms After Infusion of a Cephalosporin in Anesthetized Patients: What Is the Culprit?

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Anaphylaxis is characterized by life-threatening upper airway obstruction, bronchospasm and/or hypotension. This once highly fatal IgE-mediated event has entered a new era with extremely low mortality as a result of early recognition and effective treatment.<sup>1</sup> However, this is not the case in patients who have anaphylaxis during anesthesia because of deep sedation, interaction of multiple medications, and complex cardiac and respiratory physiology during ventilation, which hamper the diagnosis. The anaphylactic reaction during anesthesia carries a mortality of 3–6% and results in 2% of patients with significant residual brain damage.<sup>2</sup> However, a study has reported that none of 42 anesthesiologists tested on a simulator made the correct diagnosis and treatment during the first 10 minutes of anaphylaxis,<sup>3</sup> which further emphasizes the importance of early recognition of this uncommon but deadly reaction. Kuo et al rapidly identified a series of anesthetized patients with elevation of airway pressure as having anaphylaxis-related bronchospasm, after excluding the other possibilities, such as problems with the breathing circuit, anesthetic machines and the patient's condition.<sup>4</sup>

Although the most common culprit medications for anaphylaxis in sedated patients are neuromuscular blocking agents (69.2%) followed by latex (12.1%),<sup>5</sup> a new brand of cephalexin (Roles; Gentle Pharmaceutical Corporation Kashin Medicines Co., Ltd., Yunlin, Taiwan), a first-generation cephalosporin, has been incriminated based on time sequence and statistical analyses. Although penicillins are notorious for immediate reactions, events caused by cephalosporins have increased with their use as the first drug of choice for a wide variety of infections and prophylaxis in many surgical procedures. Cephalosporins are semi-synthetic antimicrobial agents that are derived from *Cephalosporium acremonium* and have a  $\beta$ -lactam ring attached

to a 6-member dihydrothiazine ring. Substitution at side chains R1 in the C7 and R2 in the C3 position allows for variation in the antimicrobial spectrum and pharmacokinetic properties. Cephalosporin-induced anaphylaxis is an immediate reaction mediated by IgE antibodies, which can react with different portions of cephalosporins, ranging from a small region to a full side chain, a side chain conjugated with a protein, or the whole cephalosporin molecule.<sup>6</sup> Uncertainty about the antigenic determinant of cephalosporins has hindered studies of recognition of IgE-specific antibodies and development of *in vitro* and *in vivo* diagnostic tests to preclude the patients at risk. A recent study has indicated that the R1 acyl side chain and the  $\beta$ -lactam fragment that are linked to the carrier protein are one of the IgE-binding determinants, because the R2 side chain can be lost during metabolism of cephalosporins.<sup>7</sup> In that same study, use of cefazolin, which has different R1 and R2 side chains from cephalexin, was not associated with anaphylaxis, which indicated that the cephalosporin nucleus should not be blamed. No adverse events have been reported in our institution after use of cephadrine, another common prophylactic antibiotic with the same R1 side chain as cephalexin. Subsequent administration of another brand of cephalexin did not result in such a high incidence of bronchospasm. The results indicated that the R1 side chain might not be responsible for the bronchospasms. Furthermore, the low incidence of anaphylactic reactions to cephalosporins (0.0001–0.1%)<sup>6</sup> makes the occurrence of cephalosporin-induced anaphylaxis in such large numbers of patients and within such a short period less possible. Furthermore, most of the patients had no history of allergy to  $\beta$ -lactam antibiotics. Bronchospasm might not be the result of allergy to cephalexin but to other components in the drug formulation because excipient- or additive-related bronchospasm has



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been reported in the literature.<sup>8</sup> Another consideration is the rapidity of administration of Roles. Red man syndrome, caused by a degranulation effect of vancomycin on mast cells and basophils has also been reported in patients receiving ciprofloxacin, amphotericin B, rifampicin, and teicoplanin.<sup>9</sup> The histamine release was highly associated with rapid infusion of the causative agent. However, further studies are needed to elucidate the relationship between Roles and this phenomenon.

Available laboratory tests of mast cell and basophil activation products in clinical practice include tests for histamine and total tryptase. The utility of  $\beta$ -tryptase, mast cell carboxypeptidase A3, chymase, platelet-activating factor and other cytokines is under investigation. However, their use is limited in the diagnosis of acute anaphylaxis, with suboptimal specificity and sensitivity. Of great concern are those patients who have a history of previous penicillin allergy but who will receive cephalosporin for prophylaxis during surgery. The possible severe sequelae preclude *in vivo* testing such as skin and challenge tests. As mentioned above, lack of knowledge of the exact chemical structure of cephalosporin allergenic determinants has hampered the development of *in vitro* diagnostic testing to anticipate anaphylaxis. Thorough history taking and physician alertness are essential for early diagnosis and treatment of anaphylaxis. Termination of the possible offending cephalosporin is the right way to settle the problem. However, if there is genuine cephalosporin anaphylaxis in a patient, avoidance of further administration of any  $\beta$ -lactam antibiotics might be warranted, because it is hard to identify the exact determinant that causes

anaphylaxis. When it is still necessary to prescribe  $\beta$ -lactam antibiotics, one should at least avoid those with a similar R1 side chain. For example, one should avoid the use of (to name a few) cephadrine, cefaclor and even ampicillin<sup>6</sup> in patients who have an anaphylactic reaction to cephalixin.

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