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Amikacin, bupivacaine, fentanyl and Kounis syndrome

Drugs administered during anesthesia can act as antigens able to induce anaphylactic reactions. Such reactions may appear during various stages and especially during induction, maintenance, and post anesthesia care. It is known that anaphylaxis occurs when 2000 nearby antibodies attached to mast cell surface are bridged by corresponding

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antigens and make the critical number of 1000 bridges. On the other hand, IgE antibodies with different specificities can have additive effects and small, even subthreshold numbers of them can join forces and trigger the cells to release their mediators.^[1]

In the very interesting paper published in this Journal,^[2] a 59-year-old healthy male developed rashes in his upper limb, chest, and abdomen followed by breathlessness, tachycardia, severe hypotension, and cardiovascular collapse 2 min after intravenous injection of 1 g amikacin. Amikacin was injected 18 min after subarachnoid injection of 2.5 ml of bupivacaine heavy 0.5% with 25 mcg fentanyl for subarachnoid block. The authors correctly attributed the anaphylactic shock to amikacin administration and treated the patient accordingly with excellent results. However, they stated that bupivacaine has never been reported as an agent causing anaphylaxis and they did not comment on the role of fentanyl as antigen. Indeed, this patient was exposed, apart from amikacin, which is rarely acting as antigen, to both bupivacaine and fentanyl, which could have joined forces as antigens to induce anaphylactic shock and Kounis anaphylaxis-associated coronary syndrome.^[3]

Bupivacaine is an amide-type of local anesthetic, chemically and biologically different from the older ester-type local anesthetics like procaine. This drug has been reported to induce hypersensitivity reactions and anaphylaxis on some occasions. In a retrospective analysis of 500 patients with adverse drug reactions who sought treatment and were submitted to single-blind, placebo-controlled drug provocation tests when indicated between 2006 and 2010, two severe reactions were observed: Cephalexin-induced anaphylactic shock and bupivacaine-induced anaphylaxis without shock. The authors of this study concluded that drug provocation tests are safe for use in clinical practice, but they should be placebo-controlled and should be performed under the supervision of an allergist.^[4] Bupivacaine has induced also delayed type IV hypersensitivity reaction, 3 days after epidural infusion when the treated patient developed an itchy, vesicular, eczematous reaction on the back and trunk up to the neckline.^[5] In another patient with an initial negative skin prick test with undiluted 0.75% bupivacaine a second subcutaneous challenge test (simple blind) with 0.1 ml dose (1:100 diluted) rendered mild symptoms such as heavy feeling in her arms and itching in the eyes. When this patient was rechallenged 1 month later with bupivacaine, under the same protocol, he developed again symptoms as heavy feeling, cough, sneezes, and itching in the eyes.^[6] Furthermore, levobupivacaine which is the S enantiomer of bupivacaine has been incriminated also for inducing anaphylactic shock during regional anesthesia.^[7]

Intravenous fentanyl, which is a potent, synthetic opioid analgesic used extensively for anesthesia and analgesia has

been also incriminated for inducing allergic reactions and anaphylaxis. There are reports of anaphylactic shock in a 29-year-old female nurse following intravenous fentanyl postoperatively confirmed with intradermal skin test^[8] and in a 25-year-old man with positive lymphocyte transformation test for fentanyl.^[9]

Multidose vials of bupivacaine frequently contain either methylparaben or sodium metabisulfite as preservatives.^[10] Methylparaben resembles para-aminobenzoic acid that is found in ester-type local anesthetic, and sodium metabisulfite is a known allergen, found in wines, which used to be sprayed on salad bars to keep the greens fresh, until too many people had suffered allergic reactions. The same seems to apply for amikacin preparations, which contain the same preservatives methylparaben (0.08% v/v) and propylparaben (0.02% v/v) named Lupamik (Lupin Ltd., Mumbai, India). We agree with the authors of the published report^[2] that para-aminobenzoic acid or methylparaben may be the causative agent triggering anaphylaxis. Therefore, the described patient was exposed to three agents namely, amikacin, bupivacaine, fentanyl and their preservatives that all together could act as allergens able to induce anaphylaxis and Kounis anaphylaxis-associated syndrome.^[3] It must be remembered that simultaneous exposure of several allergens has an additive effect on multisensitized mast cells and basophils.^[11] All patients who suffer perioperative anaphylaxis need a complete and detailed examination for drug allergy. The evaluation should include a precise clinical history, consideration of risk factors, and *in vitro* and *in vivo* drug allergy tests.

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