Letter to the Editor

Delayed urticaria due to bupivacaine: A new presentation of local anesthetic allergy

Dear Editor,

Local anesthetics (LA) consist of a lipophilic aromatic ring connected to a hydrophilic amine group. The linking chain is used to classify the agents as ester or amide: ester-type, which are derivatives of para-aminobenzoic acid, including cocaine, benzocaine, procaine, proparacaine and tetracaine; and amide-type, including aminoacylamides (bupivacaine, lidocaine, prilocaine, mepivacaine), aminoalkilamides (procainamide) and quinolone derivative (dibucaine).

LA have been widely used to relieve pain in surgical, obstetric, dental and ophthalmic procedures. They provide complete but temporary analgesia, because of their interaction with neural voltage-gated sodium channels, blocking the production and conduction of nerve impulses in sensory fibres.

Adverse reactions related to LA can be broadly defined as either systemic or local. Systemic non-allergic adverse reactions are much more frequent than true allergy. These systemic responses comprise vasovagal or psychomotor reactions, dose-related toxic responses and, in some cases, side effects from added epinephrine in commercially-available solutions. In this context, true allergic manifestations to LA are very scarce, with a rate around 1%, and they can be classified as either immediate or delayed allergic reactions.

Regarding allergic reactions to LA, we present a 54-year-old female who was subjected to a bowel resection due to a colon adenocarcinoma. An analgésic treatment with oral analgesics (metamizole and dexketoprofen) and continuous epidural analgesia with bupivacaine 0.5% and fentanyl was started after this gastrointestinal surgery, developing a generalized urticaria two days later. Then, both continuous epidural and oral analgesia were stopped. Skin lesions disappeared without residual lesions in a few days, after treatment with oral antihistamines and topical corticosteroids. Our patient had previously used metamizole, dexketoprofen and fentanyl, but LA composition was unknown.

An allergic workup was started eight weeks later. After obtaining informed consent, both skin prick test (SPT) and intradermal test (IDT) were performed, using a commercial presentation named Bupivacaina 0.5%™ (Braun, Barcelona, Spain), containing bupivacaine hydrochloride 5 mg/ml, sodium chloride and sodium hydroxide. SPT was made with the undiluted commercial drug, meanwhile a 1:10 dilution in saline solution was used for IDT. Readings were performed at 15–20 min and at 24–48 h, showing both of them negative results at all reading times.

Subsequently, a subcutaneous challenge test was carried out with 1 ml of Bupivacaina 0.5%, with no immediate adverse reaction. However, 18 h after this challenge test, she presented a generalized urticaria that did not improve with oral antihistamines (Fig. 1). Moreover, one day later she developed an urticarial worsening, associated to labial angioedema and, interestingly, multiple purple macular lesions with central hypopigmentation on upper thigh (Fig. 2). Dermatologists considered these lesions consistent with an urticarial vasculitis but, unfortunately, a skin biopsy was not performed. Treatment with oral steroids was prescribed for seven days, with a complete resolution of cutaneous damage in 3–4 days. Then, oral challenge tests with the other drugs involved in this case (i.e., metamizole, dexketoprofen, and fentanyl) were also performed, with negative results.

Going further, possible cross-reactivity among different amide LA was evaluated, trying to search for a safe alternative for the patient. For this purpose, we carried out SPT (undiluted) and IDT (1:10 dilution) with Lidocaina 1%™ (lidocaine hydrochloride 10 mg/ml, glucose monohydrate, sodium chloride and Mepivacaina 2%™ (mepivacaine hydrochloride 20 mg/ml, sodium chloride and sodium hydroxide), both belonging also to Braun-Spain, resulting in negative immediate and delayed readings. Then, subcutaneous challenge tests were performed with both LA, demonstrating good tolerance.

Our final diagnosis was delayed urticaria due to bupivacaine, with morphological data suggestive of urticarial vasculitis, in which good tolerance to other amide LA (namely lidocaine and mepivacaine) was demonstrated. These features suggest that an immunological mechanism, which is not fully clarified, underlies the adverse reaction.

Regarding this, T-cell-mediated immunity has been involved in this kind of delayed reactions, expressing both memory and activation markers on CD4 cells, and to a lesser degree on CD8 cells, but possible Th1/Tc1 and/or Th2/Tc2 involvement remains a matter of discussion. Th1-cytokine pattern has been reported, with increases in IL-2, IFN-γ, and TNF-α expression, together with IL-4 downregulation. Increased levels of perforin, granzyme B and FAS-L, produced by both CD4 and CD8 cells, have been also notified. In addition, a Th2-cytokine pattern, with variable amounts of IL-4 and IL-5, has been also notified regarding drug-induced delayed reactions, with a specific report involving lidocaine.

Possible association of this delayed urticaria with vasculitis, which is suggested by the type of skin lesions presented by our
patient, could be related to the involvement of humoural immunity, through specific IgG against bupivacaine. Mast cell membrane receptors may recognize Fc-portion of IgG, resulting in delayed mast cell activation, with subsequent release of mediators, such as chemotactic and activating cytokines. In this context, TNF upregulates ICAM-1 and E-selectin, facilitating eosinophil and neutrophil migration, then leading to proteolytic enzyme release. Thus, vascular damage involving a leukocytoclastic vasculitis may take place6

Delayed-type allergy to LA has been previously reported and can be diagnosed by patch testing.7 It usually presents with eczematous lesions from 2 to 24 h after LA contact, and generally lasts for several days. However, a LA-induced delayed urticaria, such as our case, is considered exceptional. Late LA-reactions are mainly due to type IV hypersensitivity to para-aminobenzoic acid (PABA) component of ester-type LA,8 but some reports have also implicated amide-type LA, regarding its subcutaneous administration.9

On the other hand, immediate-type allergic reactions to LA are extremely rare.10 Although there have been reports with ester agents,11 amide compounds has now become the main triggers of immediate allergic reactions, probably because they are increasingly preferred in clinical practice.1

When you evaluate a possible allergy to LA, a detailed clinical history, along with skin tests with implicated drugs, are usually needed. However, skin tests have a limited value, because low molecular weight drugs could need to bind a protein carrier to achieve allergenicity, and unknown drug metabolites could also be relevant antigens.12 Meanwhile LABs are used for SPT, they are not recommended for IDT due to its high false positive rate, which is estimated to be within 8–15%.13 Even so, we decided to make them in our patient, in order to allow their delayed readings, by assuming that immunologic response could involve other components, besides mast cells or IgE. Unfortunately, IDT were negative, both in immediate and delayed readings. Therefore, a challenge test was recommended, given that it is the gold standard test to study drug hypersensitivity.

In order to perform challenge tests, preservative-free LA have been recommended, to avoid confusion with paraben allergy. In this regard, we would like to emphasise that we have used preservative-free commercially-available preparations of LA to study our patient.

Little is known about LA cross-reactivity, and unclear patterns have been suggested. It is more referenced in delayed-type hypersensitivity,14 despite being described also in immediate reactions.15 Usually, when an allergy to ester agents is evident, all LA belonging to ester group should be avoided, since cross-reactivity among them has been described.9 On the other hand, amide-type LA present a lower cross-reactivity, both in immediate and delayed allergy. This limited cross-reactivity into amide group is confirmed in our patient, who tolerated several amide LA other than bupivacaine.

In conclusion, and to the best of our knowledge, this is the first report on delayed urticaria related to bupivacaine administration, and probably including cutaneous vasculitis. Further investigations should be carried out to search for the underlying immunologic mechanisms involved in this kind of lesion.

Conflict of interest
The authors have no conflict of interest to declare.

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References


Fig. 1. Generalized urticaria showed at 18 h.

Fig. 2. Purple macular lesions with central hypopigmentation, suggested of vasculitis, showed at 48 h.


Received 14 March 2016
Received in revised form 5 May 2016
Accepted 12 May 2016
Available online 16 June 2016