

## Is Articaine the Hypoallergenic Anesthetic?

### Letter to the Editor:

Since articaine first became available in Europe in the 1970s, this unique anesthetic has been increasingly utilized in dental and periodontal surgery.<sup>1</sup> More recently, this anesthetic has been used by the dermatologic surgeon. For example, in the March issue of *Dermatologic Surgery*, Schulze and co-workers described the use of articaine as a rapid, effective, and well-tolerated adjunct anesthetic during deep fascial plane dissections in cutaneous surgery.<sup>2</sup> With greater utilization of this anesthetic, awareness of its value in surgery and the implications in allergic patients gain importance.

Local anesthetics have three distinct structural components, namely, an aromatic portion, an intermediate chain, and an amine group.<sup>3</sup> The chemical linkage (backbone) between the aromatic portion and the intermediate chain determines whether the anesthetic is an “amide” or an “ester.”<sup>4</sup> In particular, the ester-based group has a carbon-oxygen-carbon group linkage whereas amides have the carbon-nitrogen-carbon group linkage<sup>5</sup> (Figure 1). It is important to note that since the “esters” are derivatives of the allergenic para-aminobenzoic acids (PABA), which commonly cause delayed type T-cell-mediated type IV hypersensitivity (DTH), they commonly cross-react with each other and similar structural compounds<sup>6,7</sup> (Table 1).

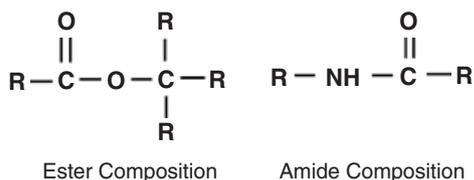
Local anesthetic allergy can be specific to the chemistry of anesthetic agent itself or to a preservative in the vehicle, such as paraben, which is notably a para-hydroxybenzoic acid which cross-reacts with

the esters of PABA.<sup>8</sup> The general rule of thumb is that if a patient is found to have allergic contact dermatitis (ACD) to an “ester,” an anesthetic in the amide class can be considered an alternative anesthetic option<sup>6</sup> (Table 2).

Articaine is a unique amide anesthetic that structurally incorporates both a thiophene ring (to allow for increased solubility) and an adjuvant ester side chain attached to the ring (to allow for rapid metabolism via hydrolysis).<sup>9–11</sup> Because articaine is not a PABA derivative, it does not share the allergenicity of the “esters.” While these distinctive chemical characteristics undoubtedly determine articaine’s promising infiltrative local anesthetic ability, they also play a role in the chemical’s T-cell-mediated immunogenicity, or lack thereof.

It is important to note that immediate IgE-mediated type I hypersensitivity reactions have been reported to all structural classes of topical anesthetics, including articaine.<sup>6,12</sup> These anaphylactoid-type reactions generally occur perioperatively and obviate further use of the implicated anesthetic agent. ACD, on the other hand, may occur 96 hours after the introduction of the anesthetic agent, which makes it more difficult to temporally associate with the implicating allergen. This is especially true in cases where the ACD becomes systematized<sup>13,14</sup> versus the more common intense periwound inflammation, which may promote wound dehiscence.

A review of the English literature demonstrates that there are no reported cases of DTH reactions to



**Figure 1.** Line diagrams of ester and amide anesthetics.

**TABLE 1.** <sup>6,7</sup>Para-Aminobenzoic Acid Derivatives

Ester anesthetics
PABA sunscreens
Sulfonamides/sulfonureas
Aniline dyes or Azo dyes
Paraphenylenediamene (hair dye)

**TABLE 2. <sup>5</sup>Amide and Ester Anesthetic Examples**

<i>Amides</i>	<i>Esters</i>
Articaine	Benzocaine
Cincocaine	Chloroprocaine
Lidocaine	Cocaine
Mepivacaine	Procaine
Prilocaine	Tetracaine

articaine during dental and dermatologic procedures. Lidocaine and mepivacaine DTH reactions, however, have been reported.<sup>15–17</sup> Furthermore, a subset of patients highly sensitized to local amide anesthetics demonstrated cross-reactivity between the amino-acyl derivatives, such as bupivacaine, mepivacaine, and prilocaine. Importantly, these “highly reactive” patients did not react to articaine, suggesting that its novel structure may render it less allergenic.<sup>16,18</sup>

Although amide allergy is a widely accepted rare event, it is not a novel diagnosis at the University of Miami Contact Dermatitis Referral Clinic (probably representing a referral bias). We are frequently asked to differentiate the allergens causing T-cell-mediated anesthetic allergy and recommend alternative anesthetic options, especially in patients allergic to amides. Our experience, along with the important contributions of the authors referenced in this letter, suggest a role for articaine as a hypoallergenic amide in the setting of DTH to anesthetics.

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