Trigeminal nerve injury associated with injection of local anesthetics
Needle lesion or neurotoxicity?

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Local anesthetics typically are considered safe for use in healthy people. However, injection-related trigeminal nerve injury reflected in neurosensory disturbance (NSD) does occur. Such NSDs most often are referred to as prolonged paresthesia. A detailed clinical examination may reveal a variety of signs and symptoms of neurological discomfort, such as hypoesthesia, anesthesia, dysesthesia, allodynia, spontaneous pain and abnormalities related to gustation.1-5

Estimates of the incidence of local anesthetic-related NSD (temporary or permanent) in dental practice vary widely, with the order of magnitude ranging from 1:750,000 to 1:42 disturbances per injection.4,6-9 The true incidence is unknown. Some lesions may resolve completely and patients return to normal function through spontaneous healing, whereas other injuries may be permanent, and patients may recover partially or not at all.4-10 Haas11 and Pogrel and Thamby12 suggested that the majority of cases resolve within eight weeks after the injection, but

ABSTRACT

Background. The authors used comprehensive national registry and clinical data to conduct a study of adverse drug reactions (ADRs), in particular neurosensory disturbance (NSD), associated with local anesthetics used in dentistry.

Methods. The study included data sets of annual sales of local anesthetics (from 1995 through 2007), 292 reports to the Danish Medicines Agency, Copenhagen, Denmark, of adverse reactions to local anesthetic drugs, and a clinical sample of 115 patients with NSD associated with local anesthetics. The authors assessed lidocaine 2 percent, mepivacaine 2 percent and 3 percent, prilocaine 3 percent, and articaine 4 percent sold in cartridges.

Results. The study results showed a highly significant overrepresentation of NSDs associated with articaine 4 percent, in particular with mandibular blocks.

Conclusions. The distribution of NSDs was disproportionate to the market share of three of the four drugs in both national registry data and clinical data. These findings indicate that the main cause of injury was neurotoxicity resulting from administration of the local anesthetic rather than the needle penetration.

Clinical Implications. Clinicians may consider avoiding use of high-concentration (4 percent) anesthetic formulations for block anesthesia in the trigeminal area in cases in which there are viable alternatives.

Key Words. Alveolar nerve; local anesthetics; consumer product safety; drugs; pharmacology; facial nerves; lingual nerve; nerve block; risk assessment; safety management; trigeminal nerve.

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longitudinal studies are few. To help prevent NSDs related to such iatrogenic lesions, a clarification of the mechanism of injury and the relative risk profiles of local anesthetics in current use may be of value.

Opinions about the etiology of injection-related trigeminal NSD have been diverse and not always evidence based. Pogrel and colleagues9 suggested three mechanisms:

- mechanical injury caused by a penetrating needle to the conductive structures of the nerve12-14;
- mechanical injury causing intraneural bleeding with subsequent hematoma and granulation tissue formation, with constrictive scarring, hypoxia or both9,11-17;
- neurotoxicity with degeneration of axon or myelin cellular structures or both due to local anesthetics4,10,18-23.

We hypothesized that a distribution of local anesthetic–related trigeminal NSDs that reflects the market share of formulations in current use would suggest a needle trauma etiology or, in other words, an equal risk profile for the four local anesthetics commonly used in Europe (that is, articaine 4 percent, lidocaine 2 percent, mepivacaine 2 and 3 percent and prilocaine 3 percent). Conversely, complications reported to a national registry with a skewed distribution with respect to market share would provide a valid argument against mechanical injury’s being the dominant cause of NSD, thus leaving properties of the injected drug (neurotoxicity) as the most probable mechanism of NSD.

The aim of this study was to report adverse drug reactions (ADRs) and NSDs associated with injection of local anesthetics by using data from the comprehensive national registry of the Danish Medicines Agency (DMA), Copenhagen, Denmark, and examination results from a clinical patient cohort. We also report the market share of each anesthetic. Finally, we discuss the etiology of the underlying nerve lesions.

**PATIENTS, MATERIALS AND METHODS**

We based this study on three data sets: annual sales of local anesthetics, reports of local anesthetic–related ADRs to a national database and a clinical sample of patients.

**Annual sales of local anesthetics.** In May 2009, the DMA provided us with unpublished data regarding total annual sales of all local anesthetics in Denmark from 1995 through 2007. The DMA is similar to the U.S. Food and Drug Administration and maintains records of all prescription medicines sold in Denmark. We extracted information about local anesthetics from the national DMA database according to the following Anatomical Therapeutic Chemical codes: N01BB52 (lidocaine), N01BB53 (mepivacaine), N01BB54 (prilocaine) and N01BB58 (articaine). The drugs were sold in cartridges, and volumes were stated in liters (Figure 1).

**Reports of local anesthetic–related ADRs to a national database.** The DMA also maintains reports of adverse effects associated with pharmaceutical products. Health care professionals are required to report to the DMA any

**ABBREVIATION KEY.** ADR: Adverse drug reaction. DMA: Danish Medicines Agency. NSD: Neurosensory disturbance.

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**Figure 1.** Volume (in liters) of local anesthetics sold in cartridges in Denmark from 1995 through 2007. The mean market share for prilocaine was 19.4 percent; for mepivacaine, 11.8 percent; for lidocaine, 27.7 percent; and for articaine, 41.2 percent (Danish Medicines Agency, Copenhagen, Denmark, unpublished data, 2009).

**Figure 2.** Reports to the Danish Medicines Agency (DMA) (Copenhagen, Denmark) of adverse drug reactions (ADRs) associated with local anesthetics sold in cartridges in Denmark from 1995 through 2007 (DMA, unpublished data, 2010). Reports from 2005 may have been affected by a peak in sales volume during 2003 and 2004, as well as by overreporting of ADRs resulting from an antiarticaine campaign during 2005.
suspected or established diagnosis of an ADR associated with prescription medicines. In June 2010, we obtained and analyzed updated data regarding the 292 patient reports related to ADRs and local anesthetics from the DMA's national database for 1995 through 2007 (DMA, unpublished data, 2010) (Figure 2). Reported ADRs are categorized initially according to neurological adverse effects and then according to anatomical region: oral sensory disturbances and pain, taste disturbances and facial sensory disturbances (group A); other cranial nerve effects (that is, blurred vision, diplopia, hearing impairment, facial palsy) (group B); and systemic symptoms such as dizziness, vertigo, headache and migraine, allergic reactions and nonneurological local adverse effects. The results showed significant over-representation of articaine in all three groups.

Clinical sample. One of us (S.H.), who had a specific interest and expertise in trigeminal nerve injuries, recruited patients who had been referred consecutively to two tertiary oral and maxillofacial clinics. From 1995 through August 2001, the practitioner (S.H.) recruited patients from Glostrup Hospital, University of Copenhagen, Glostrup, Denmark, and from September 2001 through 2007, he recruited patients from Rigshospitalet, University of Copenhagen. The clinical sample consisted of 115 patients, each of whom had NSD in one or more oral branches of the trigeminal nerve associated with injection of local anesthetics (Figure 4). The patient, the patient’s dentist or the investigator (S.H.) reported all cases to the DMA.

From 1995 through 2005, almost all patients in the country (which has a population of 5.5 million people) with NSD had been referred to and examined by one of us (S.H.). We excluded all patients with NSD that might have been attributed to surgical, implant or endodontic procedures. In January 2006, we calibrated the technique of colleagues from other regions of the country in performing a standardized neurosensory examination; hence, clinicians in four other centers performed examinations. We did not include in our clinical sample patients examined at these four centers.

We defined an NSD as any abnormality in somatosensory or gustatory perception that persisted for weeks or months beyond the normal duration of local anesthetic effects. We classified nerve injuries that resolved spontaneously as temporary. We considered unresolved disturbances in patients examined less than one year after the injection as potentially permanent and those persisting one year or more after the injection as permanent.

We invited all patients in the sample to undergo a standardized neurosensory examination at the time of referral and again after 12 months. In all cases, the nerve’s distribution in the healthy (uninjured) side served as a paired control. The examination protocol has been described in depth elsewhere.

STATISTICAL METHODS
We calculated the expected number of patients with NSD associated with each formulation under the null hypothesis (that is, ADRs,
including NSDs, would reflect the market share of each formulation). We used frequencies and percentages to describe the distribution of data. When considering all formulations simultaneously, we used the \(\chi^2\) test to examine associations under the null hypothesis. When we examined each formulation individually (that is, one formulation versus the rest [overrepresentation or underrepresentation]), we used the binomial test (two-tailed). We considered differences to be significant at \(P < .05\).

The number of ADR reports peaked in 2005, and there may have been an increased focus on reporting ADRs to the DMA as a result of an antiarticaine press campaign during the summer of 2005. For that reason, we performed midway calculations to avoid a possible bias related to the 2005 NSD numbers.

**RESULTS**

**Annual sales.** Figure 1 shows data regarding sales of local anesthetic drugs from 1995 through 2007. Articaine-based formulations entered the market in 2001, primarily at the expense of lidocaine.

**ADRs in DMA’s national database.** From 1995 through 2007, the DMA received 292 reports (204 [69.9 percent] for women and 88 [30.1 percent] for men) regarding ADRs associated with local anesthetics sold in cartridges. One hundred eighty-two (62.3 percent) of these reports pertained to articaine-based formulations (Figure 2).

For the period from 2001 through 2007 (after the launch of articaine), 181 (75.1 percent) of 241 reports were categorized into group A (oral trigeminal sensory disturbances, pain and taste disturbances), eight reports (3.3 percent) were classified into group B (blurred vision, diplopia, hearing impairment and facial palsies) and 52 reports (21.6 percent) were classified into group C (dizziness, vertigo, headache, migraine, allergic reactions and nonneurological systemic or local adverse effects). Articaine was significantly overrepresented in all groups (Figure 3). The proportion of ADRs in group C attributable to lidocaine, mepivacaine and prilocaine was much higher than the proportion of ADRs in group A attributable to these drugs.

**Clinical sample.** Our study sample was composed of 115 patients referred from 1995

### TABLE 1

<table>
<thead>
<tr>
<th>NERVE</th>
<th>NO. (%) OF AFFECTED BRANCHES</th>
<th>NO. OF TEMPORARY LESIONS</th>
<th>NO. OF POTENTIALLY PERMANENT LESIONS</th>
<th>NO. OF PERMANENT LESIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lingual</td>
<td>86 (65.6)</td>
<td>6</td>
<td>19</td>
<td>61</td>
</tr>
<tr>
<td>Inferior Alveolar</td>
<td>31 (23.7)</td>
<td>2</td>
<td>2</td>
<td>27</td>
</tr>
<tr>
<td>Buccal</td>
<td>8 (6.1)</td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>infraorbital</td>
<td>4 (3.1)</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Mental</td>
<td>2 (1.5)</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>TOTAL</td>
<td>131 (100)</td>
<td>9</td>
<td>26</td>
<td>96</td>
</tr>
</tbody>
</table>

* Complete recovery in less than one year.
† Nonresolving neurosensory disturbance in patients examined less than one year after the injection.
‡ Neurosensory disturbance persisting at one year or later after the injection.

### TABLE 2

<table>
<thead>
<tr>
<th>LOCAL ANESTHETIC</th>
<th>TEMPORARY LESIONS (FULL RECOVERY)</th>
<th>POTENTIALLY PERMANENT LESIONS (&lt; 12 MONTHS AFTER INJECTION)</th>
<th>PERMANENT LESIONS (NO RECOVERY)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients</td>
<td>No. of Nerves</td>
<td>No. of Patients</td>
</tr>
<tr>
<td>Articaine 4%</td>
<td>3</td>
<td>6</td>
<td>13</td>
</tr>
<tr>
<td>Articaine and Other Anesthetic</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Lidocaine 2%</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Mepivacaine 3%*</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Prilocaine 3%</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>TOTAL</td>
<td>5</td>
<td>9</td>
<td>25</td>
</tr>
</tbody>
</table>

* One patient received an injection of mepivacaine 2%.
through 2007 who had NSDs associated with injection of local anesthetic drugs. Eighty-one patients were female (70.4 percent) and 34 were male (29.6 percent). The median age of participants was 47 years (range, 23 through 80 years), with no sex-related difference. Figure 4 shows the distribution of patients according to the year of injury and anesthetic formulation. Clinicians used mandibular block anesthesia in 108 (94 percent) of these patients.

The median time from injury to examination was 12 months (range, one to 64 months), with no significant differences between the four local anesthetics. We noted a substantial increase in the number of new cases after 2000, which coincided with the introduction to the Danish market of local anesthetics based on articaine 4 percent (Figure 4). The NSDs affected a total of 131 branches of the trigeminal nerve in the 115 patients (Table 1).

At the one-year follow-up examination, one of us (S.H.) diagnosed permanent NSDs in 85 patients (73.9 percent) who exhibited disturbed neurosensory function. Five patients (4.3 percent) experienced a complete recovery, as evidenced by a return to normal neurosensory function. Twenty-five patients (21.7 percent) did not attend their one-year follow-up visit, and we classified their conditions as potentially permanent. Table 2 shows the distribution of patients with neurosensory injuries according to type of injury and anesthetic formulation.

**Association with market share.** In the analyses below, we address the relative incidence of local anesthetic–associated permanent NSDs on the basis of data collected from 2001 through 2007 to allow us to compare all four drugs.

As shown in Table 3, we found a highly significant overrepresentation of permanent oral NSDs associated with articaine 4 percent on the basis of our clinical data. Table 4 shows the data reported to the DMA regarding patients with NSDs. We found a significant underrepresentation of NSDs associated with lidocaine and prilocaine on the basis of both the DMA data and the examination results from our clinical sample. Data from the DMA reports and our clinical sample show that the proportion of NSDs related to mepivacaine was in reasonable accord with the drug's market share.

**Double injuries.** In 11 patients with permanent NSDs, two trigeminal branches were affected simultaneously via an injection in one site (typically a mandibular block). One of these patients had received an injection of lidocaine, whereas the remaining 10 patients received injections of articaine 4 percent. This overrepresentation of double injuries in patients receiving articaine (that is, 10 of 11 patients), and in light of the expected outcome based on the drug's market share of 41.2 percent, also is highly significant ($P < .001$; binomial, two-tailed).

**Relative risk.** The risk related to each local anesthetic was expressed by the distribution of NSDs according to sales volume (in liters) across the years. The relative risk for articaine versus that for the other drugs in relation to market share ranges between 3.1 and 8.6 (Table 5). The increased number of NSDs in 2005 may reflect a peak in sales during 2003 and 2004, as well as overreporting resulting from an antiarticaine campaign during the summer of 2005. Thus, to avoid possible bias associated with the 2005 numbers, we performed a midway calculation—from 2001 through 2004—that showed that articaine-related NSDs occurred 6.2 times more often than did those related to all of the other drugs. For the entire study period (2001-2007), articaine-associated NSDs were 5.0 times
more frequent than were those associated with the other drugs (Table 5). From 2001 through 2007, the relative risk of an NSD with articaine was 3.1 times higher than that with mepivacaine, 6.3 times higher than that with lidocaine and 5.5 times higher than that with prilocaine.

**DISCUSSION**

**Methodological considerations.** As Gaffen and Haas,25 Haas26 and Hillerup and Jensen10,27 reported, analyzing the cause of trigeminal nerve injury related to injection of local anesthetics is methodologically difficult. Moreover, ADRs, including NSDs, associated with local anesthetics probably are underreported.17 Because of the rarity of permanent lesions, a randomized controlled study is unfit as proof of safety28; the required number of participants in test and control groups would be totally unrealistic. Consequently, researchers must rely on other methodologies (such as open observational studies,8,10 animal experiments21-23,29 and use of data from central registries4,25).

**Study limitations.** The DMA data used in our study lack precision with regard to temporary or permanent lesions, and they may be skewed by referral bias for 2005. Likewise, some of the systemic ADRs may reflect conditions unrelated to the action of the drug (such as vasovagal syncope). Still, the DMA database of ADRs covers the entire Danish population, which we might conceive of as a cohort of 5.5 million participants.

Conversely, our clinical data are fairly precise. Thus, it is fair to conclude that the distribution of ADRs (including NSDs) is not consistent with a drug’s market share in the DMA data, as well as in our clinical sample of

### Table 4

<table>
<thead>
<tr>
<th>LOCAL ANESTHETIC</th>
<th>NO. OF REPORTS TO DMA PER YEAR</th>
<th>TOTAL NO. (%) OF REPORTS</th>
<th>MARKET SHARE (%) OF DRUG, 2001-2004</th>
<th>P VALUE†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2001</td>
<td>2002</td>
<td>2003</td>
<td>2004</td>
</tr>
<tr>
<td>Articaine 4%</td>
<td>8</td>
<td>25</td>
<td>24</td>
<td>28</td>
</tr>
<tr>
<td>Lidocaine 2%</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Mepivacaine 2% and 3%</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Prilocaine 3%</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td>12</td>
<td>26</td>
<td>30</td>
<td>33</td>
</tr>
</tbody>
</table>

* DMA: Danish Medicines Agency.
† Source: DMA (unpublished data, 2010).
‡ P values are binomial test values showing the significance of overrepresentation or underrepresentation of the drug.
§ Not applicable.

### Table 5

<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Sales Volume, in Liters</td>
<td>No. of NSDs</td>
</tr>
<tr>
<td>Articaine 4%</td>
<td>7,787</td>
<td>85</td>
</tr>
<tr>
<td>Lidocaine 2%</td>
<td>3,899</td>
<td>6</td>
</tr>
<tr>
<td>Mepivacaine 2% and 3%</td>
<td>1,959</td>
<td>6</td>
</tr>
<tr>
<td>Prilocaine 3%</td>
<td>3,168</td>
<td>4</td>
</tr>
</tbody>
</table>

* NSDs: Neurosensory disturbances.
† Source: DMA (unpublished data, 2010).
patients with NSDs. Moreover, there is a significant variation in the risk profile of the four anesthetics. All of the data we assessed (that is, DMA reports, clinical data and double injuries) point to overrepresentation of NSDs with injection of articaine 4 percent.

**Clinical sample.** Our sample is distinctive in that every patient underwent a systematic examination of neurosensory function, not merely an interview. This enabled us to assess systematically the severity of patients’ loss of function, as well as maintain records of their specific neuropathic dysfunction. The median time to referral of patients from injury to initial examination was 12 months. This may have led to the exclusion of a number of cases in which recovery had taken place. Nothing is known about the number and distribution of anesthetic formulations in such cases. The decline in the number of adverse effects reported to the DMA after 2005 most likely reflects dental practitioners’ switch from 4 percent formulations to lower-concentration anesthetic formulations for block anesthesia. In addition, the decline in the number of patients referred to our center after 2005 reflects the referral of patients residing outside Copenhagen to other centers for neurosensory examinations.

In accordance with the study results reported by Haas and Lennon,4 Gaffen and Haas25 and Garisto and colleagues,30 the results of our study showed that mandibular blocks accounted for the overwhelming majority (94 percent) of NSDs.

**Needle lesions.** Needle lesion is an interesting possible cause of nerve injury, and several researchers in fields other than oral local anesthesia have conducted studies of the influence of the angle of the needle bevel. Cornelius and colleagues19 and Hillerup and colleagues23 found that intrafascicular nerve penetration and injection of saline solution into the sciatic nerve in rats had no measurable influence. The results of an experimental study by Fried and colleagues31 of the effects of microneurographic electrode penetration in the rat sciatic nerve showed small perineural and endoneural lesions that exhibited a “vigorous” regenerative response. Needle lesions, like mechanical lesions in third molar surgery,24,32 probably are associated with a fair potential for spontaneous recovery.

We found only a few studies in which investigators examined the association between needle lesions and oral trigeminal branches.6,9,12 Harn and Durham33 reported that the electric shock sensation resulting from needle contact was a probable cause of injury. However, in a prospective study, Kraft and Hickel6 found that 856 (7 percent) of 12,104 patients experienced an electric shock–like sensation, but none experienced temporary or permanent NSDs. Pogrel and colleagues9 found it “difficult to understand how a needle that is smaller than 0.5 mm in diameter could cause such profound damage to the entire nerve,” and they concluded that “direct trauma from the needle is probably not responsible for the nerve damage.”

If we assume a 1:10,000 (order of magnitude) risk of experiencing physical injury via needle penetration of one nerve branch, the probability of damaging two nerve branches during the same injection of local anesthetic is exceptionally low. Our results with regard to multiple injuries per injection, combined with the distribution of trigeminal NSDs disproportionate to three of the four anesthetic drugs’ market shares, strongly suggest that needle lesions are not a significant cause of injury resulting in permanent NSDs.

Thus, although we cannot rule out needle trauma as a cause of direct fascicular injury or intraneural bleeding with a subsequent negative influence on nerve conduction,18 we found no studies in which investigators documented needle lesions as a cause of permanent trigeminal nerve injury.

**Neurotoxicity.** We need to consider systemic...
toxicity related to the injected dose.34 Investigators in several studies have demonstrated dose-and concentration-dependent neurotoxic effects of local anesthetics.19,21,22 The results of these and other studies showed a dose-and-concentration relationship for lidocaine22 and articaine,19,23,29 indicating a significant neurotoxicity for 4 percent solutions compared with that for lower-concentration solutions.

In 1995, Haas and Lennon4 raised the issue of neurotoxicity’s causing NSDs associated with local anesthetics after their experience with 4 percent formulations of prilocaine and articaine in Canada. In a recent study of 182 cases of non-surgical paresthesia from 1999 to 2008, Gaffen and Haas25 reported an overrepresentation of 4 percent formulations of articaine and prilocaine administered as local anesthetics in dentistry.

Formulations in current use in Europe are based on lidocaine 2 percent, prilocaine 3 percent, mepivacaine 2 percent and 3 percent, and articaine 4 percent (all sold in cartridges for dental use). The articaine-related injuries may not be due solely to its 4 percent concentration; a covariation with its lipid solubility, protein binding and/or other properties related to its chemical composition may contribute to its neurotoxicity. The relative lack of prilocaine-associated ADRs and NSDs in our study compared with those in studies by Haas and Lennon1 and Gaffen and Haas25 may be because the drug concentration is 4 percent in North America, whereas it is 3 percent in Europe.

Neurotoxicity is a sensitive issue for companies, clinicians and patients. A number of communications address this controversy.8,10,16,19,35 Still, a sufficiently large number of prospective studies in which patients are recruited consecutively is lacking and probably will remain so.26 The harmful effects of local anesthetic–related neurotoxicity include demyelination and axonal degeneration.20,22,23 Further animal studies in which researchers demonstrate and quantify neurodegenerative features, such as demyelination and axonal degeneration, associated with different formulations of local anesthetics may enable them to better understand the underlying mechanisms of neurotoxicity.

Safety. Malamed and colleagues28 included 1,325 participants in their prospective study of the relative safety of articaine 4 percent and lidocaine 2 percent. Given the risk of a permanent nerve injury of approximately 1:10,000, the chance of including one injured patient in their study was 10 percent. Thus, we must interpret with some concern the authors’ conclusion that formulations based on articaine 4 percent are safe. Reports of complications and adverse effects by dental practitioners and patients, as well as the results of reported studies, constitute enough data to indicate that articaine 4 percent formulations are not safe for mandibular blocks compared with other local anesthetics in use. Garisto and colleagues30 recently reported outcome data on neurologic ADRs to local anesthetics used in the United States that were remarkably similar to our study results. However limited the risk may seem, prudent practitioners and informed patients may opt for alternative formulations.

CONCLUSION

In answer to the question posed earlier about needle lesion or neurotoxicity, all of the clinical data in our study, as well as data from the DMA, point in the same direction. The distribution of ADRs and NSDs was out of proportion to the market share of three of four formulations in current use; this rules out physical needle lesions as a major causative factor and indicates a causal link with properties of the injected substance. The significant overrepresentation of NSDs associated with articaine 4 percent is related mainly to mandibular blocks. The statistically significant overrepresentation of articaine 4 percent formulations in so-called “double injuries” indicates that properties of the injected substance are the causative agent through neurotoxicity. The prudent approach is to avoid high-concentration anesthetic formulations (that is, 4 percent) for block anesthesia in the trigeminal area.

Disclosure. None of the authors reported any disclosures.

The authors thank Lægemiddelstyrelsen (Danish Medicines Agency, Copenhagen, Denmark) for providing data regarding market share of local anesthetics, as well as the reports of adverse drug reactions.