Occurrence of paresthesia after dental local anesthetic administration in the United States

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Although local anesthetics are safe, effective and essential drugs for dentistry, their use may involve complications. One such potential outcome is paresthesia, which refers to a neuropathy that manifests as persistent anesthesia or an altered sensation ranging from complete numbness to burning, tingling or continual pain.[1-3] Most oral paresthesias are caused by direct trauma associated with a surgical procedure, such as a dental extraction or orthognathic surgery. However, studies have shown that paresthesia also can occur after nonsurgical dentistry.[4-9] The exact cause of this is not known, but it may be one or a combination of several factors: traumatic injury to the nerve via direct contact with the needle, hemorrhage into the nerve sheath, hydrostatic pressure from the injection or potential neurotoxicity from the local anesthetic itself.[2]

The hypothesis that local anesthetics may be neurotoxic is controversial.[10,11] An initial report with results suggesting this possibility was a retrospective examination of nonsurgical paresthesia in Ontario,

ABSTRACT

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Background. Several studies have suggested that the likelihood of paresthesia may depend on the local anesthetic used. The purpose of this study was to determine if the type of local anesthetic administered had any effect on reports of paresthesia in dentistry in the United States.

Methods. The authors obtained reports of paresthesia involving dental local anesthetics during the period from November 1997 through August 2008 from the U.S. Food and Drug Administration Adverse Event Reporting System. They used χ^2 analysis to compare expected frequencies, on the basis of U.S. local anesthetic sales data, with observed reports of oral paresthesia.

Results. During the study period, 248 cases of paresthesia occurring after dental procedures were reported. Most cases (94.5 percent) involved mandibular nerve block. The lingual nerve was affected in 89.0 percent of cases. Reports involving 4 percent prilocaine and 4 percent articaine were 7.3 and 3.6 times, respectively, greater than expected (χ^2, $P < .0001$) on the basis of local anesthetic use by U.S. dentists.

Conclusions. These data suggest that paresthesia occurs more commonly after use of 4 percent local anesthetic formulations. These findings are consistent with those reported in a number of studies from other countries.

Clinical Implications. Until further research indicates otherwise, dentists should consider these results when assessing the risks and benefits of using 4 percent local anesthetics for mandibular block anesthesia.

Key Words. Paresthesia; local anesthetics; prilocaine; articaine; inferior alveolar nerve block; mandibular nerve block.

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Canada, from 1973 through 1993.[4] Investigators in that study found an overall incidence of paresthesia to be 1:785,000, with the two drugs most often implicated being 4 percent prilocaine and 4 percent articaine. The number of annual cases of paresthesia increased beginning in 1985, shortly after the introduction of articaine into the Canadian market. Results from that study also showed that the lingual nerve was affected in 64 percent of all reported cases. Results from a follow-up study in which researchers investigated reports from 1994 through 1998 found, once again, that paresthesia most often was associated with 4 percent prilocaine and 4 percent articaine and that the lingual nerve was involved in 70 percent of the cases.[5] More recently, an analogous study of nonsurgical paresthesia in Ontario during the period from 1999 through 2008 yielded similar results; as before, 4 percent prilocaine and 4 percent articaine were associated more frequently with neuropathy than were any of the other local anesthetics available in dental cartridges.[12] Also as before, the lingual nerve was affected most frequently, being involved 79.1 percent of the time. Thus, all three studies from Ontario had consistent findings.

The results of a study conducted in northern California before the release of articaine in the United States showed that 4 percent prilocaine was reported more often than other local anesthetics with respect to permanent paresthesia after local anesthetic administration.[6] Results of another study conducted in northern California showed that there were more reports of 4 percent prilocaine's being associated with paresthesia, and reports of 4 percent articaine's association and 2 percent lidocaine's association were proportional to and lower than, respectively, those predicted on the basis of their estimated use.[13]

In Denmark, investigators found that 88 percent of reports of nerve injuries involved articaine.[8] Results of another study conducted in Denmark showed an increase in cases of paresthesia after the market introduction of 4 percent articaine and that the lingual nerve was affected in 78 percent of cases.[9]

To summarize, reported studies of paresthesia have been conducted in Ontario, Canada; Denmark; and northern California. Yet, no comparable assessment has been done in the United States as a whole. Therefore, our purpose in this study was to determine if the type of local anesthetic administered had any effect on reports of paresthesia in dentistry in this country. We accomplished this by retrospectively analyzing cases of nonsurgical paresthesia associated with dental local anesthetics that were voluntarily reported to the U.S. Food and Drug Administration (FDA) from November 1997 through August 2008.

METHODS

We obtained ethics approval for this study from the University of Toronto Health Sciences Research Ethics Board. We obtained voluntarily submitted adverse event reports involving the dental local anesthetics currently available in the United States—namely, articaine, bupivacaine, lidocaine, mepivacaine and prilocaine—from the FDA's Adverse Event Reporting System (AERS). The AERS is a computerized information database designed to support the FDA's postmarketing safety surveillance program for all approved drug and therapeutic biological products. The FDA began entering adverse event reports into the AERS on Nov. 1, 1997. The system relies on voluntary reports submitted by health care professionals, consumers or others who become aware of a possible drug-related adverse event. This information is available to the public at large through the Freedom of Information Act.[14]

We examined all reports during this period that denoted a neuropathy, including paresthesia, hyperesthesia, hypoesthesia, dysesthesia, dysgeusia, ageusia and a burning sensation. Inclusion criteria were all of the following three items: an oral paresthesia; a dental procedure; a case in the United States. Exclusion criteria included any one of the following: a surgical procedure such as extraction, implant placement or periodontal surgery, because such procedures can cause paresthesia; use of an intraosseous device, which can traumatize the nerve directly; a local anesthetic such as etidocaine that is no longer available in dental cartridges in the United States; or a case report obtained only from the scientific literature. We extracted the following case parameters and subjected them to descriptive statistical analysis by using software (SPSS, version 17, SPSS, Chicago): the local anesthetic's generic name; the year in which the adverse event occurred; the age and sex of the patient; the route

ABBREVIATION KEY. AERS: Adverse Event Reporting System. **FDA:** Food and Drug Administration.

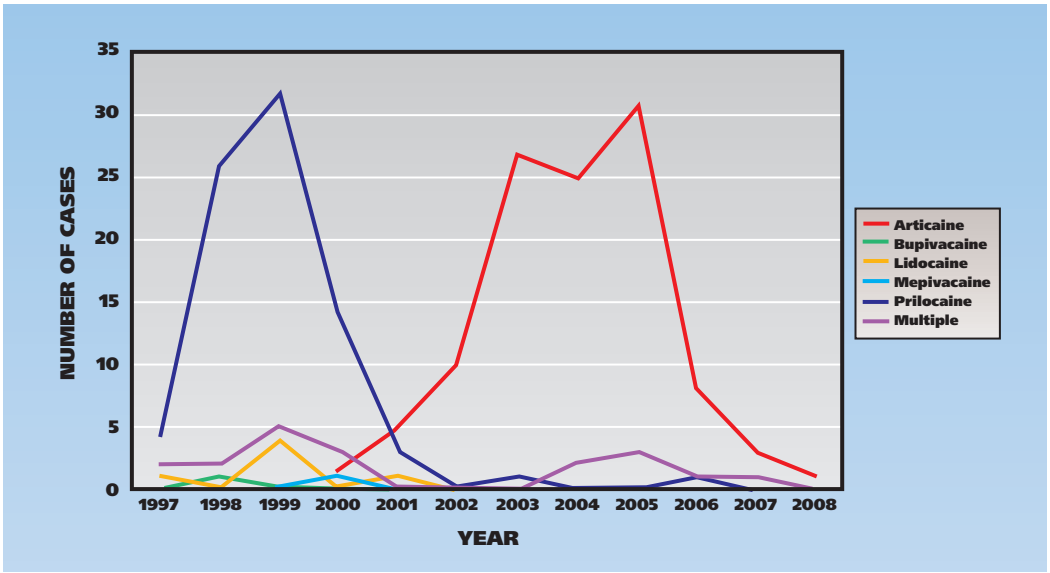

Figure 1. Reported number of cases of nonsurgical paresthesia, according to year and local anesthetic drug.

of drug administration; dental arch; side; specific anatomic structures affected (to allow us to determine which branch of the trigeminal nerve was involved); injection-associated events, such as pain, electric shock or positive aspiration of blood; any additional symptoms; the dental procedure involved; multiple drugs injected; vasoconstrictor use; and resolution of the adverse event.

We obtained data regarding the sales of dental local anesthetic cartridges in the United States, yearly from 1997 through 2008, from a research company (Strategic Data Marketing, Rochelle Park, N.J., unpublished data, 2009).

We used statistical analysis to test the null hypothesis that each local anesthetic had no effect on the frequency of reporting of cases of dental paresthesia. We used the χ^2 test to compare the expected frequencies of oral paresthesia, on the basis of sales data, with observed reports of such paresthesia made to the AERS. When the expected frequency in any one group was less than five, we considered χ^2 to be less reliable, so we used the exact binomial probability distribution instead to compare outcomes. All statistical tests were two-tailed and interpreted at the 5 percent level. If inspection of these data revealed that reporting frequencies were higher than expected for any one drug, we then analyzed the data further with that drug excluded.

RESULTS

During the period from November 1997 through August 2008, 11,003 adverse events were reported to the FDA's AERS for the five local anesthetics of interest. The FDA provides line listings that summarize the information about individual adverse events. Actual hard-copy reports containing further details can be obtained on request. Our review of each of these listings provided information that warranted requesting 533 detailed reports. Further analysis of these 533 reports revealed that 248 of them satisfied our inclusion and exclusion criteria. In addition to these 248, there were 19 cases involving dental care in which surgery was specified, one of which involved the use of multiple agents. In 89 of the 248 cases, nonsurgical dentistry was specified. For the 159 of the 248 cases for which no procedure was listed, we assumed that they involved nonsurgical dentistry. Single agents were used in 226 of the 248 cases, and 22 involved the use of multiple drugs, all of which included either prilocaine or articaine. In reports involving only one drug, a total of 116 (51.3 percent) cases involved 4 percent articaine, 97 (42.9 percent) involved 4 percent prilocaine, 11 (4.9 percent) involved 2 percent lidocaine, one (0.4 percent) involved 0.5 percent bupivacaine and one (0.4 percent) involved 3 percent mepivacaine. We excluded one case in which an intraosseous injection (Stabident, Fairfax Dental, Miami) was used, as it may directly traumatize the nerve.

Figure 1 shows the observed cases of paresthesia per local anesthetic drug according to year. Data for 1997 represent only two months because the AERS began in November of that year, and data for 2008 involve only eight months because we requested adverse event reports up to and including August 2008. Articaine was introduced into the U.S. market in May 2000. Therefore, as expected, no cases were reported for this drug before this time. As shown in Figure 1, the majority of adverse events reported before the year 2000 involved prilocaine. After 2000, the

number of reported cases involving articaine increased markedly, and articaine became the local anesthetic most reported to be associated with paresthesia across the entire study period.

We obtained the yearly U.S. sales of local anesthetics from 1997 through 2008; Figure 2 shows the relative percentage of each anesthetic's market share during this period. These sales data provided a basis for determining an expected distribution of paresthesia reports if the null hypothesis was correct and the type of local anesthetic administered had no effect on the development of this condition.

Figure 3 shows the observed cases of paresthesia compared with the expected frequencies per drug. χ^2 analysis showed that articaine and prilocaine were the only two drugs associated with a higher-than-expected frequency of paresthesia ($P < .0001$ for each) on the basis of market share (Table 1). Cases involving prilocaine were 7.3 times more numerous than expected and those involving articaine 3.6 times more numerous than expected. Given these findings, and in an attempt to more accurately identify whether each of these two drugs had individual significance, we then analyzed data for both articaine and prilocaine with the other drug excluded from calculations to determine if significance remained. Table 2 shows the results of this further analysis: the χ^2 values for prilocaine and for articaine increased, demonstrating a highly significant difference when we compared the observed reports of paresthesia with the expected reports. Because articaine was introduced into the U.S. market in 2000, we repeated the analysis from that year on, as Table 3 (page 841) shows. Once again, χ^2 analysis showed that each of these two drugs was reported to have caused neuropathy significantly more frequently than expected ($P < .0001$).

Given this finding, as before, we analyzed these two drugs separately to test for any statistically significant associations. This analysis revealed that paresthesias associated with articaine and prilocaine were significantly greater than expected ($P < .00000001$) on the basis of market share (Table 4, page 841). A number of reports did not specify the year of the adverse event occurrence. These cases were included in the overall analysis from 1997 through 2008, shown in Tables 1 and 2, as we know that they occured within this study period, but we omitted them in the subanalysis from 2000 through 2008, shown in Tables 3 and 4, because of the uncertainty of the year. Among cases reported from 1997 through 2008, no year of occurrence was specified for four cases involving articaine, four cases involving lidocaine and 16 cases involving prilocaine. Although the cases involving articaine almost certainly occurred from 2000 onward, we used n = 112 instead of n = 116 in the subanalyses shown in Tables 3 and 4 to be consistent with the

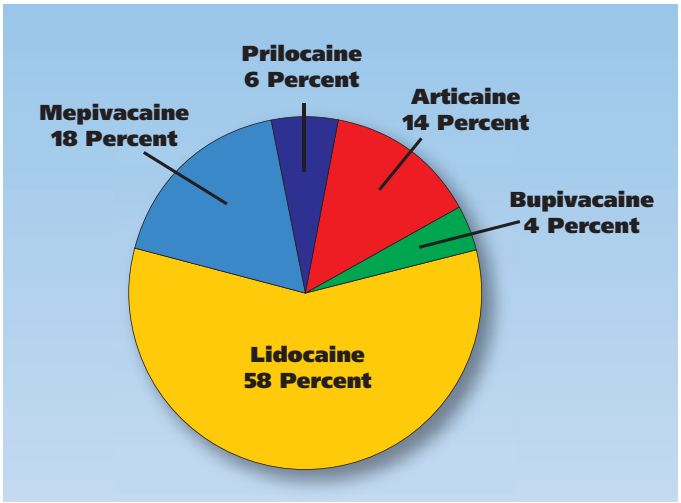

Figure 2. U.S. local anesthetic sales percentages from November 1997 through 2008. Source: Strategic Data Marketing, unpublished data, 2009.

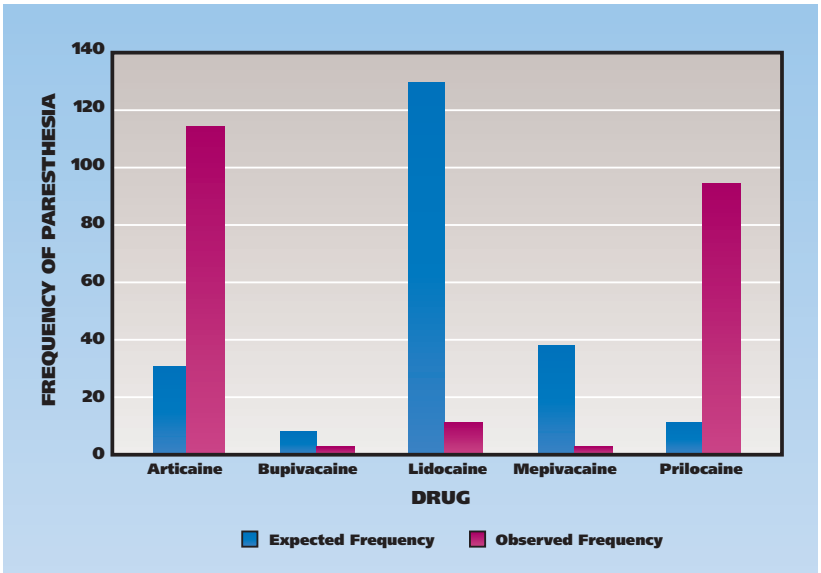

Figure 3. Expected versus observed frequency distribution per local anesthetic drug from November 1997 through August 2008.

TABLE 1

Observed and expected* frequencies of paresthesia as reported to the Adverse Event Reporting System involving dental local anesthetics from 1997 through 2008 in the United States.†

LOCAL ANESTHETIC	OBSERVED FREQUENCY	EXPECTED FREQUENCY
Articaine Comparison‡		
Articaine	116	31.86
Other anesthetics	110	194.14
TOTAL	226	226
Prilocaine Comparison§		
Prilocaine	97	13.26
Other anesthetics	129	212.74
TOTAL	226	226

* Observed frequency: Number of cases. Expected frequency: Total number of cases × fractional use of specific drug.
† Does not include cases involving the use of more than one agent (n = 22).
‡ The difference was statistically significant ($\chi^2_1 = 258.7$, $P < .0001$).
§ The difference was statistically significant ($\chi^2_1 = 561.8$, $P < .0001$).

TABLE 2

Observed and expected* frequencies of paresthesia as reported to the Adverse Event Reporting System involving articaine and prilocaine from 1997 through 2008 in the United States, analyzed with the other significant drug excluded from the calculations.†

LOCAL ANESTHETIC	OBSERVED FREQUENCY	EXPECTED FREQUENCY
Articaine Comparison‡		
Articaine	116	19.32
Other anesthetics minus prilocaine	13	109.68
TOTAL	129	129
Prilocaine Comparison§		
Prilocaine	97	7.51
Other anesthetics minus articaine	13	102.49
TOTAL	110	110

* Observed frequency: Number of cases. Expected frequency: Total number of cases × fractional use of specific drug.
† Does not include cases involving the use of more than one agent (n = 22).
‡ The difference was statistically significant ($\chi^2_1 = 569.0$, $P < .0001$).
§ The difference was statistically significant ($\chi^2_1 = 1{,}144.5$, $P < .0001$).

analyses of the other drugs from 2000 onward. The result remains statistically significant either way.

We calculated the overall reported incidence of paresthesia on the basis of the number of reports to the AERS and the total number of cartridges sold in the United States during this 12-year period. The reported incidences were as follows: prilocaine, 1:2,070,678; articaine, 1:4,159,848; bupivacaine, 1:124,286,050; lidocaine, 1:181,076,673; and mepivacaine, 1:623,112,900. The overall reported incidence was 1:13,800,970.

Patients' age and sex. The mean age of affected patients was 41.9 years, and the age range was 15 to 78 years. Most of the cases reported involved patients in their third, fourth or fifth decades of life. In all, in cases in which the sex of the patient was reported, 130 involved female patients (61.0 percent), which was significantly greater than the 83 cases involving male patients (39.0 percent) ($P < .01$).

Injection technique, arch and side. The particular injection technique used was reported in 219 of the 248 cases. Of these, 207 (94.5 percent) involved a mandibular nerve block, two (0.9 percent) involved a mental nerve block and 10 (4.6 percent) involved infiltration. In 213 cases, the mandibular arch was affected (95.1 percent), in 10 cases the maxillary arch was affected (4.5 percent) and in one case both arches were affected (0.4 percent). Leaving out the one case in which both arches were affected, significantly more cases involved the mandibular arch than the maxillary arch ($P < .0001$). There was no predilection in terms of affected side (when it was reported), with 46 cases (52.3 percent) involving the right side and 42 cases (47.7 percent) involving the left side ($P = .67$).

Affected area. Figure 4 (page 842) shows the affected sites. Of 191 reports in which an affected anatomical structure was identified, 170 cases involved the tongue, which is innervated by the lingual nerve. In 14 cases, the lower lip, innervated by a branch of the inferior alveolar nerve, was affected. In seven cases, both were affected.

Injection events and other symptoms. Positive aspiration of blood or the feeling of electric shock, which may indicate direct contact of the

needle with the nerve during injection, was reported in 18 cases (7.3 percent). Although all cases involved paresthesia, some of the reports indicated further symptoms—specifically, taste disturbance in 44 cases (17.7 percent) and dysesthesia in 54 cases (21.8 percent).

Type of dental procedure. We assumed that if the treatment was not listed, surgery was not performed. Therefore, we performed the primary analysis described above on the 226 single-drug cases to which this assumption applied. Of the 89 instances in which nonsurgical dental treatment was identified, restorative dentistry was most common, being performed in 66 cases (74.2 percent). Scaling was reported in 10 cases (11.2 percent) and endodontic treatment was reported in 13 cases (14.6 percent). To control for the possibility that there were unidentified surgical cases within the unknown procedures, we repeated analysis among the five drugs after eliminating all cases with unknown procedures in addition to the known surgical cases. When we analyzed the data for the 89 known procedure cases only, we found that both prilocaine and articaine still produced a greater-than-expected reported incidence of neuropathy on the basis of market share than did the other anesthetics ($P < .0001$), which was the same finding as that in the primary analysis (n = 226). Finally, we performed an analysis including the 18 surgical cases in which only one agent was used (n = 244), with the results once again showing the same statistically significant difference for prilocaine and articaine ($P < .0001$).

Multiple drug injections. There were 22 cases of multiple drug injections. The ordering of administration was listed in only eight of these. In one case, the clinician had used the lower-concentration drug first, then the 4 percent solution. In the other seven cases, the clinician had used the 4 percent concentration first.

Vasoconstrictor. Prilocaine and mepivacaine are marketed in formulations that are plain or contain a vasoconstrictor. Where this distinction was reported, prilocaine plain constituted 28 of the single-drug cases, and prilocaine with

TABLE 3

Observed and expected* frequencies of paresthesia as reported to the Adverse Event Reporting System involving dental local anesthetics from 2000 through 2008 in the United States.†

LOCAL ANESTHETIC	OBSERVED FREQUENCY	EXPECTED FREQUENCY
Articaine Comparison‡		
Articaine	112	25.01
Other anesthetics	22	108.99
TOTAL	134	134
Prilocaine Comparison§		
Prilocaine	19	7.87
Other anesthetics	115	126.13
TOTAL	134	134

* Observed frequency: Number of cases. Expected frequency: Total number of cases × fractional use of specific drug.
† Does not include cases involving the use of more than one agent (n = 10).
‡ The difference was statistically significant ($\chi^2_1 = 372.0$, $P < .0001$).
§ The difference was statistically significant ($\chi^2_1 = 16.7$, $P < .0001$).

TABLE 4

Observed and expected* frequencies of paresthesia as reported to the Adverse Event Reporting System involving articaine and prilocaine from 2000 through 2008 in the United States, analyzed with the other significant drug excluded from the calculations.†

LOCAL ANESTHETIC	OBSERVED FREQUENCY	EXPECTED FREQUENCY
Articaine Comparison‡		
Articaine	112	22.81
Other anesthetics minus prilocaine	3	92.19
TOTAL	115	115
Prilocaine Comparison§		
Prilocaine	19	1.59
Other anesthetics minus articaine	3	20.41
TOTAL	22	22

* Observed frequency: Number of cases. Expected frequency: Total number of cases × fractional use of specific drug.
† Does not include cases involving the use of more than one agent (n = 10).
‡ The difference was statistically significant ($\chi^2_1 = 435.0$, $P < .0001$).
§ The difference was statistically significant ($\chi^2_1 = 205.5$, $P < .0001$), but there was an expected value of less than 5. The difference was statistically significant ($P < .00000001$ according to exact binomial testing that was two-sided and used the method of small P values).

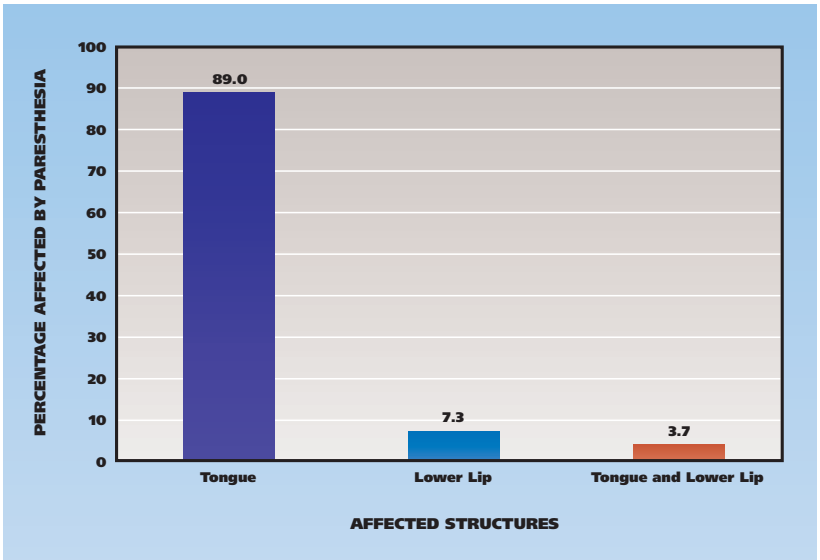

Figure 4. Distribution of structures affected by paresthesia.

1:200,000 epinephrine constituted 61 cases. Our database for sales of prilocaine did not distinguish between these two formulations, so we could not determine significance from these data. There was only one single-drug report for mepivacaine, which was the 3 percent plain solution. This low number does not allow significance to be determined.

Resolution. The duration of oral paresthesia was reported in 108 of the 248 cases. This period ranged from as little as one day to as many as 736 days. Confirmed resolution of paresthesia was reported in only 34 of the 108 cases. Of the cases of paresthesia that did resolve, 25 did so in less than two months, with the remaining nine resolving within 240 days.

DISCUSSION

Our results are consistent with those of reports from Canada and Denmark.[4,5,8,9] Furthermore, they corroborate earlier findings that suggested that the use of either prilocaine alone,[6,13] articaine alone[8,9] or both drugs[4,5,12] may be associated with an increased risk of developing paresthesia. We believe it is important to note that articaine and prilocaine are the only dental local anesthetics formulated as 4 percent solutions in the United States, with all others being of lower concentration (bupivacaine is 0.5 percent, lidocaine is 2 percent and mepivacaine is either 2 or 3 percent).

Databases used. We used two databases for this study. The source for the reports of paresthesia was the FDA's AERS. This system became available for entering adverse event reports on Nov. 1, 1997. It replaced an earlier system, the Spontaneous Reporting System, that held reports from 1968 through October 1998. Because reports to AERS are voluntary, there is the likelihood of underreporting, and the true incidence most likely is higher than that found in this study. This phenomenon already has been noted in the literature, with results from one meta-analysis showing a median underreporting rate of 94 percent, meaning that only 6 percent of adverse events were reported.[15] Furthermore, many dentists may not know that the AERS exists and that they can report paresthesia to this national database. These factors likely could explain the large difference in incidence reported by others.[4-9] As a result, readers should consider the paresthesia rates calculated here only as an absolute minimum estimate of incidence. Nevertheless, the AERS is the only U.S. national database for this information, and its usefulness in corroborating the results of other studies has been stated.[16]

A potential concern is the possibility that reported rates of paresthesia may differ among drugs because of a recognition bias, a reporting bias or both. This bias occurs when practitioners preferentially report adverse reactions associated with certain drugs owing to recent attention in the media or scientific literature.[17,18] However, this bias would not explain the high rates of reporting for prilocaine in the late 1990s. This bias cannot be ruled out entirely for the reports involving articaine, but the magnitude of the increase, as shown in Figure 1, would tend to reduce the likelihood of this being the sole cause of the marked increase. Furthermore, we repeated the data analysis for all dental procedures conducted with and without surgery, as well as for all years and then for 2000 onward only, and the results showed that both prilocaine and articaine were reported as being involved significantly more often than any other local anesthetic for all of these analyses. Thus, no matter how we analyzed the data, the same association between prilocaine or articaine administration and increased risk of experiencing paresthesia remained.

The second database was the information obtained by a marketing company, Strategic Data

Marketing. The market share information provided by this company closely matches that already reported in the literature. Investigators in one study reported that the 2005 market shares were 47 percent for lidocaine, 26 percent for articaine, 15 percent for mepivacaine and 6 percent for prilocaine, with the reference cited as Septodont (Lancaster, Pa.), October 2006.[10] In another study, the market shares cited for 2006 were 54 percent for lidocaine, 25 percent for articaine, 15 percent for mepivacaine and 6 percent for prilocaine, with the reference quoted as a September 2006 personal communication from Septodont.[13] The data we obtained from Strategic Data Marketing listed the 2005 market shares as 53.2 percent for lidocaine, 23.4 percent for articaine, 13.5 percent for mepivacaine and 6 percent for prilocaine. For 2006, the shares the company listed were 55.4 percent for lidocaine, 25 percent for articaine, 12.9 percent for mepivacaine and 6 percent for prilocaine. Thus, our data were close to the estimates provided independently by investigators in two other studies,[10,13] and therefore we can assume that these numbers are valid.

Nerve involvement in paresthesia. Our results showed that the lingual nerve was involved in 89.0 percent of the reports, consistent with findings of previous studies.[4,5,9,12] To determine why the lingual nerve is most commonly affected, investigators in a study published in 2003 examined the histologic characteristics of lingual nerves at the level of the lingula in 12 cadavers.[19] That study's results showed a range in the number of fascicles present, and the authors speculated that a unifascicular nerve may be injured more easily than one with multiple fascicles. Four of the 12 lingual nerves had one fascicle, whereas the inferior alveolar nerve was always multifascicular. To date, this appears to be the most plausible explanation for the finding of the predilection of the lingual nerve to develop paresthesia.

The mechanism underlying nonsurgical paresthesia is not known. In a 2000 study, five patients with permanent paresthesia secondary to injection with local anesthetic underwent surgical exploration of their injuries; in all cases, there was no evidence of damage to the nerve caused by the anesthetic needle.[6] Thus, mechanical trauma alone appears to be an unlikely cause. Could nerve damage be caused by neurotoxicity of the local anesthetic in combination with a minor trauma created by the needle? This is unknown, although results from previous studies suggest it may be the cause.[4,9] Supporting this theory is the finding that there is a great deal of in vitro and in vivo experimental evidence of a dose-dependent neurotoxicity associated with local anesthetics.[20-29]

To date, results from randomized controlled clinical trials generally have not shown that either 4 percent prilocaine or 4 percent articaine is superior to 2 percent lidocaine in achieving mandibular nerve block.[30] Practitioners should take this equivalent benefit into account when comparing the relative risks of these drugs.

CONCLUSION

The findings of our study confirm that paresthesia arising from a local anesthetic injection alone is a rare event. Nevertheless, the findings we report herein support those published previously[4-9] and show that the 4 percent anesthetic solutions used in dentistry, namely prilocaine and articaine, are more highly associated with the development of paresthesia than are those of lower concentration. Therefore, dentists should consider these results when assessing the risks and benefits of using 4 percent local anesthetics for mandibular block anesthesia. ■

Disclosure. None of the authors reported any disclosures.

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