ARTICAINE AND PARESTHESIA IN DENTAL ANESTHESIA: NEUROTOXICITY OR PROCEDURAL TRAUMA?

Clinical tip

PIERREL

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Abstract
This article is designed to educate the dental health professional concerning the occurrence and overall incidence of reported local anesthetic-induced paresthesia. In addition, it will serve to illustrate the potential causes of such paresthesia and to investigate whether the use of articaine is related to a higher frequency of occurrences of these adverse events.

The hypothesis that articaine, a local anesthetic with wellestablished effectiveness widely used in dentistry, might have neurotoxic effects is continuously under intense discussion. A number of reports claim to provide a basis for the opinion that articaine is related to a higher frequency of neurologic adverse events like paresthesia, demanding a change in the recommendations for usage.
However, when going into scientific detail, this claim seems to lack the level of evidence needed for such extensive changes.

Therefore, this article aims to summarize the current controversial discussion regarding the use of articaine and to demonstrate that a) evidence for an increased risk of paresthesia with the use of articaine due to potential neurotoxic effects is mostly lacking, and b) the paresthesia cases found after injections of articaine might likewise be attributed to procedural trauma.
In the following, data available from the countries prominent in the articaine debate are presented, afterwards completed by information gained from international studies and reviews.

Date from the U.S.
Pogrel et al. (1995) reviewed 12 cases seen in the Department of Oral and Maxillofacial Surgery at the University of California, San Francisco, in the period from 1988 to 1992.
These patients had altered sensations in the area of distribution of the inferior alveolar nerve (IAN) or lingual nerve (LN) following injection of a local anesthetic in the course of restorative treatment. Eight patients (66.7 percent) received 2% lidocaine with 1:100,000 epinephrine (= adrenaline), three patients (25 percent) 4% prilocaine with 1:200,000 epinephrine and one patient (8.3 percent) 2% mepivacaine with 1:20,000 levonordefrin.
This distribution did not suggest that one local anesthetic is more likely to cause damage than another since the amount of damages occurring with all three dental anesthetics was proportionate to their use. In total, four patients received one injection, four patients two injections, two patients received three injections and two patients more than three injections on the day the nerve damage occurred. Interestingly, the majority of patients were in the course of a dental treatment where they had received a local anesthetic shortly before: seven patients had received a local anesthetic for dental treatment within the three months prior to the supposed damaging injection. Seven patients experienced an electric shock-type sensation during the injection, suggesting that the nerve was injured by the needle.
Five patients reported no such experience. The nerve damage occurred to the LN in nine cases (75 percent) and to the IAN in two cases (16.7 percent); in one most unusual case (8.3 percent), the chorda tympani was affected.

The exact mechanism of the nerve damage was unknown, but three potential theories were proposed:

1) direct trauma to the nerve from the needle;
2) intra-neural hematoma formation;
3) local anesthetic toxicity.

Pogrel & Thamby (2000) conducted a prospective study including patients referred to a tertiary care center with permanent alteration

in the sensation of the IANs, LNs or both, that resulted from an inferior alveolar nerve block (IANB).
Among a trial population of 83 patients, the LN was affected in 79 percent of patients and the IAN in 21 percent. In 47 patients (57 percent), the causative IANB was painful or evoked an electric shock-type sensation when administered.
In the other 36 patients (43 percent), this was not the case. When a single agent was used only, 48 percent of patients received lidocaine, 47 percent received prilocaine and five percent received mepivacaine.

For lidocaine and mepivacaine, this corresponds to national sales figures of 1999 (lidocaine: 62 percent, prilocaine: 13 percent, mepivacaine: 23 percent), but prilocaine was found to be more frequently linked to cases of nerve involvement than the other anesthetics.
Pogrel (2007) conducted a trial including 57 patients referred to the Department of Oral and Maxillofacial Surgery at the University of California, San Francisco, from January 2003 to December 2005 with diagnosed damage of the IAN and/or LN that could have resulted from an IANB only.

It was excluded that other procedures could have been responsible for the nerve impairment.
The numbers of nerve damage cases of the individual anesthetics were linked with the U.S. national sales figures, which provide a measure for the frequency of use for the respective drug (Table 1).
Lidocaine was associated with 35 percent of nerve damage cases while having 54 percent U.S. sales.
Articaine was related to 29.8 percent of the cases with 25 percent of U.S. sales, whereas prilocaine caused 29.8 percent of cases having just six percent of the U.S. sales.
Obviously, the frequency of nerve damage cases associated with articaine was proportional to its use, whereas for prilocaine,

Table 1: Nerve Damage Cases in Relation to U.S. National Sales Figures

Anesthetic	Number of Cases (%)	Approximate % of Sales*
Lidocaine alone	20 (35)	54
Prilocaine alone	17 (29.8)	6
Articaine alone	17 (29.8)	25
Others	3 (5.25)	15

**Total: 260 million cartridges/year*
Data from Pogrel, 2007

a remarkably higher frequency of cases was found compared to the expectation based on the proportion of sales.

Moore et al. (2006) conducted two double-blind, ulticenter, randomized, controlled trials (RCTs) to determine the efficacy and clinical characteristics of 4% articaine hydrochloride (HCl) with 1:200,000 epinephrine (A200) compared to those of 4% articaine HCl with 1:100,000 epinephrine (A100) and 4% articaine HCl without epinephrine (Aw/o) used to induce either IANB with 1.7ml (trial one, N = 63) or maxillary infiltration anesthesia with 1ml articaine (trial two, N = 63).
In each trial, one case of associated numbness and tingling was documented: for the subject in trial one (A100) symptoms resolved within 24 hours, for the subject in trial two, (A200) it was six hours.
No case of paresthesia was reported.
Garisto et al. (2010) conducted a retrospective analysis on 248 cases of paresthesia involving dental local anesthetics extracted from the U.S. Food and Drug Administration Adverse Event Reporting System for the period from 1997 to 2008.
They compared the reported frequency of paresthesia to the expected frequency derived from U.S. sales figures.
Garisto et al. found that anesthetic solutions used in dentistry with a high concentration of active substance (4%) i.e. prilocaine and articaine, have a significantly higher association (factors: prilocaine 7.3, articaine 3.6,p <0.0001) with the development of paresthesia than those of lower concentration (2%, e.g. lidocaine).

Date from the Canada

Haas & Lennon (1995) performed a retrospective analysis examining every report of paresthesia following the injection of local anesthetics recorded by Ontario's Professional Liability Program (PLP) from 1973 to 1993. Only those cases without surgery were considered resulting in 143 reports of paresthesia.

All reports involved anesthesia of the mandibular arch, with the tongue most frequently reported to be affected, followed by the lip.

Pain was reported in 22 percent of the cases. Most paresthesia events were reported following the injection of articaine and prilocaine.

There were 14 case reports of paresthesia not associated with surgery in 1993 alone. This can be extrapolated to a frequency of 1:785,000 injections.

Articaine was administered in 10 of these cases, prilocaine in the remaining four cases.

The observed frequencies of paresthesia following the administration of articaine ($p < 0.002$) or prilocaine ($p < 0.025$) were significantly greater than the frequencies expected for these agents, based on the distribution of the use of local anesthetics in Ontario in 1993.

Gaffen & Haas (2009) performed a review of paresthesia cases associated with local anesthetic injection and not related to surgery that were reported to Ontario's PLP during the period from 1999 to 2008. Of 182 PLP reports of paresthesia following non-surgical procedures made, all but two were associated with mandibular block injection.

The LN was affected significantly more often than the IAN ($p < 0.001$).

According to Table 2, articaine alone was associated with 109 reported cases of paresthesia (59.9 percent), prilocaine with 29 cases (15.9 percent), lidocaine with 23 cases (12.6 percent) and mepivacaine with six cases (3.3 percent). In 15 cases (8.2 percent), multiple anesthetic drugs were administered.

The importance of the reported paresthesia frequencies for the different anesthetics depends on the relative use of these agents by Ontario dentists.

As data on drug use were available for the period from 2006 to 2008, 15 paresthesia cases from these three years were subjected to further analysis. When considering the combined reports from 2006 to 2008, only articaine and prilocaine had a significantly higher frequency of paresthesia than expected based on their market share (articaine: 42 observed vs. 26.5 expected; prilocaine: eight observed vs. 4.1 expected; $p < 0.01$).

The authors concluded that these data suggest that local anesthetic neurotoxicity might be at least partly involved in the development of post-injection paresthesia.

A search on 4% and 2% local anesthetics in the Health Canada Adverse Reaction Reports (1983-2008) in the Canadian Adverse Drug Reaction Monitoring Program (CADRMP) database on adverse reactions revealed only six cases explicitly declared as "paresthesia" and 14 more with symptoms that could be a paresthesia, but were not labeled as such.

None of these 20 reports indicated the exact duration of the events. For seven reports, outcomes were given as "recovered without sequelae."

Considering about 30 million dental local anesthetic injections per year in Canada, 20 adverse reactions of paresthesia in 25 years have to be classified as negligible.

Remembering the PLP reports (Gaffen & Haas, 2009; Haas & Lennon, 1995), the discrepancies compared to the Health Canada reports become obvious.

Data from Europe

1) Denmark

In 2006, the Danish Medicines Agency examined the risk of nerve damage from dental local anesthetics.

The examination was initiated because articaine, as one of the anesthetics, was suspected to bear a greater risk of nerve damage than others. Together with the European Pharmacovigilance Working Party (PhVWP), the agency found no basis for strengthening the warnings for using articaine,

since the product information already contains a warning on the potential long-term disruption of the nerve transmission.
But based on several articles in this area published by Danish researchers, the agency decided to review the safety again. In the new review, data from all countries where local anesthetics with articaine are marketed will be included.

The Danish Medicines Agency therefore asked the marketing authorization holders of the original articaine products to send an extraordinary safety update report by the end of 2011.

Currently, there are five products with articaine on the Danish market: Dentocaine, Septanest, Septocaine, Ubistesin and Ubistesin Forte. By the time of writing this article, the report is under review.

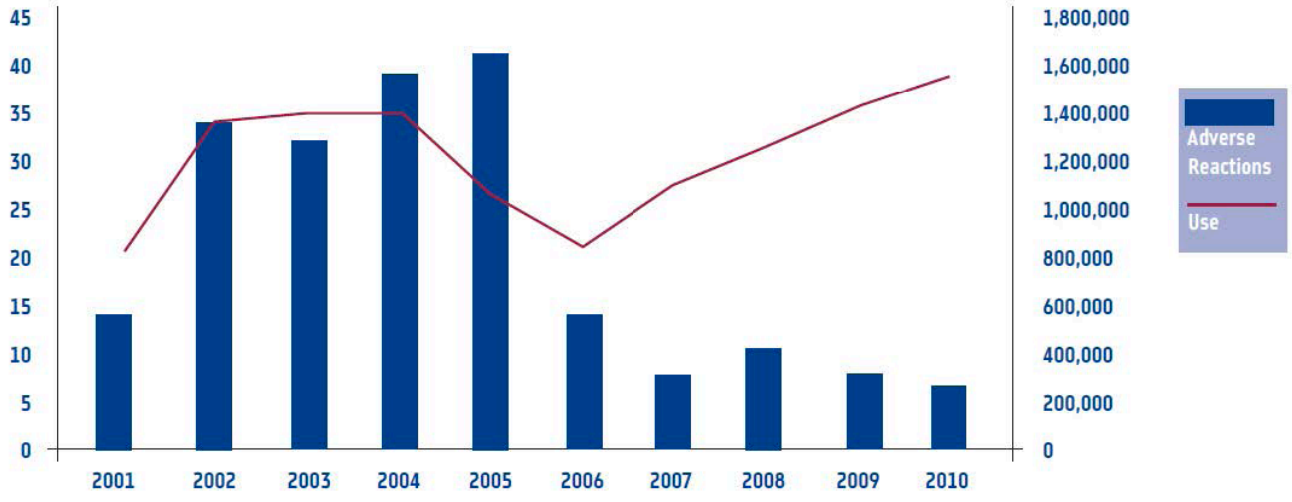
The Danish Medicines Agency's database of side effects contains 160 reports on adverse reactions against articaine that occurred in the period from 2001 to 2005.

The adverse reactions were mainly sensory impairments and nerve damages.
Since 2005, a decrease in the number of reports of new adverse reactions was recorded.

Figure 1 displays the number of reports of suspected adverse reactions listed according to the year they occurred.
For comparison, the chart also shows the development of dentists' use of articaine. Until October 1, 2011, the Danish Medicines Agency has received two reports on suspected adverse reactions from articaine, which occurred in 2011. In both cases, the patients experienced a sensory impairment after treatment with articaine.
According to the Danish Medicines Agency's Annual Pharmacovigilance Report 2010, the agency received 49 reports concerning the use of articaine in 2010.
The vast majority of the side effects reported concerned nerve damage and loss of or changed mouth sensitivity after treatment.
During 2010, the Danish Medicines Agency reviewed the data on articaine with regard to suspected nerve damage. In this context, a number of cases have been reported of which a large proportion pertained to side effects occurring before 2010.

Considering the overall international experience, the PhVWP concluded that there is no basis for adding further warnings to articaine's summary of product characteristics, and the balance between benefits and risks is still assessed to be positive.

Figure 1: The Number of Reports of Suspected Adverse Reactions to Articaine



The number of suspected adverse reactions reported to the Danish Medicines Agency for articaine. (year = year a reported adverse reaction began, use = use of articaine in dental practices in mL) (taken from: http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/side-effects/news/number-of-suspected-adverse-reactions-re---articaine)

2) Finland

The Finnish National Agency for Medicines has received 84 reports of adverse reactions to dental local anesthetics up to the end of October 2007.

Of these, 52 involved products containing articaine and epinephrine and listing 82 different reactions.

Sensory disturbances were the most commonly reported adverse reactions (N=12) followed by nausea or vomiting (N=11), urticaria or other rash (N=9), anaphylaxis (N=8) and palpitations (N=8). The sensory disturbances comprised numbness or paresthesia involving the face, lips or tongue.

These symptoms were not reported in association with other dental local anesthetics (WHO Pharmaceutical Newsletter 2008, 1).

3) The Netherlands

The Medicines Evaluation Board of the Netherlands (February 2010) stated in the Public Assessment Report on Loncarti 40/0.005mg/ml and Loncarti 40/0.01mg/ml (articaine with epinephrine) solution for injection that, in spite of safety reports in the literature suggesting that articaine use might be associated with prolonged paresthesia (Haas and Lennon, 1995; Van Eeden & Patel, 2002), the overall risk was estimated as obviously small, being 1:785,000 (see also section Data from Canada, and Haas & Lennon, 1995; Malamed et al, 2001).

Further, for the 28 reports of suspected nerve damage after articaine use evaluated by the Danish Medicines Agency (see Section I - Denmark), the causality of paresthesia was assessed as unclear.

The prolonged paresthesia may have been rather due to the interventions than articaine.

4) United Kingdom

In the United Kingdom, where some allegations about paresthesia related to articaine were made through letters to the editor of a journal (Meechan, 2003; Pedlar, 2003a and 2003b), a search of the reports made by the Yellow Card Scheme of the Medicines and Healthcare Products Regulating Agency of the Ministry of Health shows no reports for adverse reactions caused by articaine (Diaz, 2010) Jerjes et al. (2006) conducted a prospective trial in order to evaluate the proportion of permanent sensory impairment of IANs and LNs and the factors influencing such frequency after the removal of mandibular third molars under local anesthesia. From 1998 to 2003, there were 1,087 patients having their mandibular third molars removed under local anesthesia.

Frequency of IAN injury was 4.1 percent up to one week after surgery and decreased to 0.7 percent after two years of followup, whereas alteration in tongue sensation occurred in 6.5 percent of patients up to one week after surgery and decreased to one percent after two years of follow-up.

The experience of the dentist was found to be a significant factor in determining 6 both permanent IAN ($p=0.026$) and LN ($p=0.022$) paresthesia.

Jerjes et al. (2010) conducted another prospective trial in the UK involving 3,236 patients who underwent surgical removal of impacted third molars in order to identify the risk factors and frequency of IAN and LN paresthesia at one, six and 18-to-24 months postoperatively.

At one month, the frequency of IAN paresthesia was 1.5 percent; for the LN, it was 1.8 percent. These figures decreased over time and 18-to 24 months postoperatively.

The frequency of permanent dysfunction of the IAN was 0.6 percent, for the LN it was 1.1 percent. With regard to IAN paresthesia, risk factors included the patient's age (26-30 years), horizontally impacted teeth, close radiographic proximity to the inferior alveolar canal (IAC) and treatment by trainee surgeons. With regard to the LN, risk factors included male gender, distoangular impactions, close radiographic proximity to the IAC and treatment by trainee surgeons.

Thus, one of the main risk factors of developing permanent sensory dysfunction in the distribution of these nerves is the experience of the surgeon or dentist.

5) Germany

Rahn and Ball (2001) reviewed the adverse effects reported to the manufacturer of articaine in Germany for the period from 1975 to 1999.
In total, 3,335 reports on adverse reactions were found.
With 775 million cartridges of articaine sold in the respective time period, this leads to a frequency of one reaction in 232,558 injections.
Out of these 3,335 adverse reactions, 14 percent were classified as local reactions, including symptoms like hematoma, hemorrhages, hypesthesia and paresthesia.
The frequencies for the individual symptoms were not given.

Reviews and International Data

When looking at the literature, many reports suggesting that articaine has an increased risk of neurotoxicity are based on retrospective data. That way they are biased in data recruitment and have a questionable level of evidence (Diaz, 2010).
Hence, these cannot be considered suitable for strong recommendations on the use of articaine. In order to prove claims of increased paresthesia, the current frequency of paresthesia events associated with anesthetics has to be established clearly and further studies are needed to determine a significant increase in paresthesia associated with articaine, if existing at all. In this regard, RCTs would be the method of choice, as they will provide the highest level of evidence, their design maximizing the control over the environment, thus providing the most reliable results (Yapp et al., 2011).
To date, there is only one publication on the safety of articaine fulfilling these requirements (Malamed et al.,2001).
This paper summarizes three identical single dose, double-blind, parallel-group, active controlled trials comparing the safety of articaine (4% articaine with epinephrine 1:100,000) with that of lidocaine (2% lidocaine with epinephrine 1:100,000) for dental procedures in a total of 1,325 patients. These trials showed that articaine and lidocaine were comparable in many ways, including the frequencies of paresthesia, which were less than one percent in both treatment groups.
The results did not offer any hint that articaine might be associated with an increased risk of paresthesia (Malamed et al, 2001).
The trials conducted by Malamed were part of the approval process for articaine, which became available in the U.S. in early 2000.
Despite the fact that the Food and Drug Administration (FDA) approved articaine based on these findings, there has been an ongoing discussion on the subject of paresthesia allegedly caused by Septocaine in the U.S. (Diaz, 2010).
Other literature shows that there is neither a significant clinical advantage nor a significant risk of developing a paresthesia when using articaine for an IANB instead of other dental anesthetics, e.g. lignocaine (Wells & Beckett, 2008; Yapp et al., 2011).
In 2010, Katyal published a systematic review comparing the efficacy and safety of articaine versus lignocaine in maxillary and mandibular infiltrations and block anesthesia in patients presenting for routin dental treatments.
Trial selection was limited to RCTs in patients requiring non-complex routine dental treatments comparing 4% articaine (1:100,000 epinephrine) and 2% lignocaine (1:100,000 epinephrine).
Outcome measures had to contain anesthetic success, post-injection adverse events or post-injection pain.
Katyal found that there is no difference in post injection adverse events between articaine and lignocaine.
However, articaine injection resulted in a slightly higher score for pain at the injection site after anesthetic reversal compared to lignocaine as measured by a visual analog scale.
The clinical impact of these higher post-injection pain scores compared to lignocaine is negligible considering that both drugs appear to have similar adverse effect profiles.
Additionally, since articaine is more effective than lignocaine in providing anesthetic success

in first molar region routine dental procedures, articaine was recommended as anesthetic to be preferred over lignocaine for use in routine dental procedures.

Wells & Beckett (2008) performed a focused literature search to assess the safety and suitability of articaine as a substitute for lignocaine.

The authors consider that practitioners should be aware of a possible, as yet unproven, link between the concentrations of local anesthetic solutions (4% vs. 2%) and nerve damage.

In contrast, Diaz (2010) emphasized in his review regarding articaine that direct damage to the nerve caused by anesthetics containing 4% active substance has never been scientifically proven. He mentioned other studies such as published by Hoffmeister (1991), showing that 4% solutions are not capable of damaging the nerve, even after direct injection.

His investigations demonstrated that no morphologically detectable toxic lesions were microscopically observable after direct injection of 4% articaine. He used a volume of articaine in proportion to the size of the animal nerves employed in his trial and concluded that these neurosensory disturbances were the result of fibrosis following intra-neural hematomas. There are various studies, such as those published by Krafft & Hickel (1994) or Harn & Durham (1990), supporting his findings. They observe a frequency of direct needle trauma to the nerve during traditional IANBs of 7.7 percent and 3.62 percent, respectively and that the injection itself has a significantly higher risk of causing damage to the nerve than the anesthetic, especially since in the traditional IANB the LN lies directly in the path of the needle.

Diaz (2010) promotes the use of alternative techniques to the traditional IANB, but not the need to switch anesthetics.

He found no reports of paresthesia in the scientific literature where alternative block techniques were used. Additionally, Diaz (2010) supports SF Malamed, a worldwide acknowledged specialist for dental anesthesia.

Malamed stated as well “there is absolutely no scientific evidence to demonstrate there is a greater risk of paresthesia associated with the administration of a 4% local anesthetic” (Malamed 2006a) and “allegations that 4% local anesthetics are associated with a greater risk of paresthesia are based solely on anecdotal reports” (Malamed 2006b).

For additional information, we reviewed all case reports from the Pierrel Safety Database for products containing 4% articaine with 1:100,000 and 1:200,000 epinephrine and elsewise identical unit compositions [Articaina con Adrenalina Pierrel, Orabloc, and Karticaine (Forte)] (Pierrel Safety Database).

The database contains related reports from the U.S., Canada, and Italy (i.e. the countries where these anesthetics are on the market), covering the period from January 2009 to May 2012. There were 26 case reports (US: N=13, Canada: N=9, Italy: N=4), none of which were related to paresthesia, with an overall sales volume of about 12 million cartridges (Canada and U.S.: four million, Italy: eight million).

Conclusion

All studies or reports suggesting articaine having an increased risk of neurotoxicity are retrospective, biased in data recruitment and of low level of evidence. Hence, they are not suitable to promote strong recommendations. In order to prove claims of increased paresthesia following articaine injection, the actual frequency of paresthesia associated with other anesthetics needs to be clearly demonstrated and further trials are needed to determine a significant increase in paresthesia associated with articaine, if existent. These trials should be RCTs as their design will provide the highest level of evidence and maximum control over the experimental environment, that way yielding most reliable results (Yapp et al., 2011). Though reports exist, claiming that articaine is frequently related to paresthesia diverse literature reported that other anesthetics, e.g. prilocaine and lidocaine (often comparators for articaine), are associated with paresthesia events with comparable or even higher frequency. Many analyses seem to overestimate the risk.

This is obviously caused by calculations resulting in statistically significant higher risks for paresthesia events with articaine injections, even though the risk itself is extremely low (up to 1:785,000), especially when compared to other “everyday life”-risks like death by car accident (1:11,236) or strike by lightning (1:250,000).

Although this comparison might appear somewhat blunt, it makes clear that the clinical significance of these results is questionable. Furthermore, direct damage to the nerve caused by anesthetics containing four percent of active substance has never been scientifically proven (Diaz, 2010), and prolonged paresthesia might rather be due to the interventions than articaine because the experience of the surgeon was found to be a significant factor in determining both, permanent LN (p=0.022) and permanent IAN paresthesia(p=0.026).

Diaz (2010) supports the use of alternative techniques to the traditional IANB, but not the need to switch anesthetics. There are no reports of paresthesia in the scientific literature when using alternative mandibular block techniques. Health Canada Adverse Reaction Reports revealed that in about 25 years, there are only 20 cases that are associated with paresthesia-like events related to the use of 4% and 2% local anesthetics. In a country where approximately 30 million dental local anesthetic injections are given per year, this number should be deemed negligible. Remembering the PLP reports (Gaffen & Haas, 2009 and Haas & Lennon, 1995), a discrepancy compared to the Health Canada reports and the overall situation regarding the estimation of the risk of paresthesia with articaine as dental anesthetic becomes obvious. The fact that even within one country contrary findings are reported should raise reasonable doubt in the dentist community about the suggestion that articaine is associated with an increased frequency of paresthesia.

Current information on adverse reactions related to all articaine products marketed by Pierrel in the U.S., Canada, Russia and Italy was retrieved from the respective marketing authorization holders for the period from 2009 to 2012 (Pierrel Safety Database). There were 31 reports on adverse reactions, none of which was related to paresthesia. Considering the total sales volume of about 20 million cartridges (U.S., Canada, Russia and Italy), this result seems to support the conclusion that articaine products are likely to generate a negligible number of adverse reactions and bear no increased risk for paresthesia. Overall, when it comes down to scientifically sound research and data, no general, clear evidence can be found to support the claim that articaine is associated with increased paresthesia because of its inherent characteristics.

Additionally, a clear causal relationship between anesthetic agent and neurological complications like paresthesia cannot be confirmed from the literature (Yapp et al., 2011). Based on the findings presented, procedural trauma appears to be a valid alternative explanation for the reported neurological complications.

References

1. Diaz M. Is it safe to use articaine? Team Work 2010, 2 (2), 28-35.
2. van Eeden SP, Patel MF. Prolonged paraesthesia following inferior alveolar nerve block using articaine. Br J Oral Maxillofac Surg. 2002;40(6):519-20.
3. Gaffen AS., Haas DA. Retrospective review of voluntary reports of nonsurgical paresthesia in dentistry. J Can Dent Assoc. 2009;75(8):579-579f.
4. Garisto GA, Gaffen AS, Lawrence HP, Tenenbaum HC, Haas DA. Occurrence of paresthesia after dental local anesthetic administration in the United States. J Am Dent Assoc. 2010;141(7):836-44.
5. Haas DA, Lennon D. A 21 year retrospective study of reports of paresthesia following local anesthetic administration. J Can Dent Assoc. 1995;61(4):319-20, 323-6,329-30.
6. Harn, SD, Durham TM. Incidence of lingual nerve trauma and postinjection complications in conventional mandibular block anaesthesia. J Am Dent Assoc. 1990;121(4):519-23.
7. Hoffmeister B, Morphological changes of peripheral nerves following intraneural injection of local anaesthetic, Dtsch Zahnarztl Z. 1991;46(12):828-30.
8. Jerjes W, Swinson B, Moles DR, El-Maaytah M, Banu B, Upile T, Kumar M, Al Khawalde M, Vourvachis M, Hadi H, Kumar S, Hopper C. Permanent sensory nerve impairment following third molar surgery: a prospective study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2006; 102(4):e1-7.
9. Jerjes W, Upile T, Shah P, Nhembe F, Gudka D, Kafas P, McCarthy E, Abbas S, Patel S, Hamdoon Z, Abiola J, Vourvachis M, Kalkani M, Al-Khawalde M, Leeson R, Banu B, Rob J, El-Maaytah M, Hopper C. Risk factors associated with injury to the inferior alveolar and lingual nerves following third molar surgery-revisited. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010; 109(3):335-45.
10. Katyal V. The efficacy and safety of articaine versus lignocaine in dental treatments: a meta-analysis. J Dent. 2010; 38(4):307-17.
11. Krafft TC, Hickel R. Clinical investigation into the incidence of direct damage to the lingual nerve caused by local anaesthesia. J Craniomaxillofac Surg. 1994;22(5):294-6.
12. Malamed SF. Nerve injury caused by mandibular block analgesia. Int J Oral Maxillofac Surg. 2006a;35(9):876-7; author reply 878.
13. Malamed SF. Local anesthetics: dentistry's most important drugs, clinical update 2006. J Calif Dent Assoc. 2006b;34(12):971-6.
14. Malamed SF, Gagnon S, Leblanc D. Articaine hydrochloride: a study of the safety of a new amide local anesthetic. J Am Dent Assoc. 2001;132(2): 177-85.
15. Meechan JG, Re: Prolonged paraesthesia following inferior alveolar nerve block using articaine. Br J Oral Maxillofac Surg. 2003;41(3):202.
16. Moore PA, Boynes SG, Hersh EV, DeRossi SS, Sollecito TP, Goodson JM, Leonel JS, Floros C, Peterson C, Hutcheson M. The anesthetic efficacy of 4 percent articaine 1:200,000 epinephrine: two controlled clinical trials. J Am Dent Assoc. 2006;137(11):1572-81.
17. Pedlar J, Prolonged paraesthesia Br Dent J. 2003a; 195(3):119.
18. Pedlar J, Re: Prolonged paraesthesia following inferior alveolar nerve block using articaine. Br J Oral Maxillofac Surg. 2003b;41(3):202.
19. Pogrel MA, Thamby S. Permanent nerve involvement resulting from inferior alveolar nerve blocks. J Am Dent Assoc. 2000; 131(7):901-7.
20. Pogrel MA, Bryan J, Regezi J. Nerve damage associated with inferior alveolar nerve blocks. J Am Dent Assoc. 1995; 126(8):1150-5.
21. Pogrel MA. Permanent nerve damage from inferior alveolar nerve blocks—an update to include articaine. J Calif Dent Assoc. 2007;35(4):271-3.
22. Rahn R, Ball B. Local Anesthesia in Dentistry - Articaine and Epinephrine for Dental Anesthesia. 3M ESPE 2001:27-29.
23. Wells JP, Beckett H. Articaine hydrochloride: a safe alternative to lignocaine? Dent Update. 2008;35(4):253-6.
24. Wynn RL. Articaine, Local Anesthetics, and Paresthesia. ADA Continuing Education Recognition Program.
25. Yapp KE, Hopcraft MS, Parashos P. Articaine: a review of the literature. Br Dent J. 2011;210(7):323-9.
26. CADRMP Adverse Reaction Database, http://www.hc-sc.gc.ca/dhpmps/medeff/databasdon/search-recherche-eng.php
27. Danish Medicines Agency's Annual Pharmacovigilance Report, 2010. http://laegemiddelstyrelsen.dk/en/topics/side-effects-and-trials/sideeffects/news/numberof- suspected-adverse-reactions-re—-articaine
28. Articaine-containing local anaesthetics. Reports of sensory disturbances. WHO Pharmaceuticals Newsletter 2008, 1, 5.
29. Public assessment report of the Medicines Evaluation Board in the Netherlands. Loncarti 40/0.005 mg/ml and Loncarti 40/0.01 mg/ml, solution for injection.
30. Environment Canada, Thunder, lightning and hail storms (brochure), Catalogue Number En57-24/22-1995E. ISSN 0715-0040. ISBN 0-662-22989-4.
31. Transport Canada, Injury Surveillance, Health Canada and Road Safety, 2004, ISBN 0-662-36440-6.
32. Pierrel Safety Database, January 2009 to May 2012.

Author Bios

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Today he is the CEO at Pierrel Pharma.