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Articaine and paresthesia in dental anaesthesia: neurotoxicity or procedural trauma?

The hypothesis that articaine, a local anesthetic with well-established 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 may 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.

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%) received 2% lidocaine with 1:100,000 epinephrine (= adrenaline), 3

patients (25.0%) 4% prilocaine with 1:200,000 epinephrine and 1 patient (8.3%) 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 was 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%) and to the IAN in two cases (16.7%); in one most unusual case (8.3%), 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) intraneural 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% of patients and the IAN in 21%. In 47 patients (57%), the causative IANB was painful or evoked an electric shock-type sensation when administered. In the other 36 patients (43%) this was not the case. When a single agent was used only, 48% of patients received lidocaine, 47% received prilocaine and 5% received mepivacaine. For lidocaine and mepivacaine, this corresponds to national sales figures of 1999 (lidocaine: 62%, prilocaine: 13%, mepivacaine:

23%), 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 US national sales figures, which provide a measure for the frequency of use for the respective drug (Table 1). Lidocaine was associated with 35% of nerve damage cases while having 54% US sales. Articaine was related to 29.8% of the cases with 25% of US sales, whereas prilocaine caused 29.8% of cases having just 6% of the US sales. Obviously, the frequency of nerve damage cases associated with articaine was proportional to its use, whereas for prilocaine, 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, multicenter, 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 1.7 ml (trial 1, N = 63) or maxillary infiltration anaesthesia with 1 ml articaine (trial 2, N = 63). In each trial, one case of associated numbness and tingling was documented: for the subject in trial 1 (A100) symptoms resolved within 24 hours, for the subject in trial 2 (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 US 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 US 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).

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 anaesthesia of the mandibular arch, with the tongue most frequently reported to be affected, followed by the lip. Pain was reported in 22% 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. 182 PLP reports of paresthesia following non-surgical procedures were 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%), prilocaine with 29 cases (15.9%), lidocaine with 23 cases (12.6%) and mepivacaine with six cases (3.3%). In 15 cases (8.2%), 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 may 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 6 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 7 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 (CADRMP Adverse Reaction Database). Remembering the PLP reports (*Gaffen & Haas, 2009; Haas & Lennon, 1995*), the discrepancies compared to the Health Canada reports become obvious.

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 has 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®. 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.

Table 1: Nerve damage cases in relation to US national sales figures (data from Pogrel, 2007)

Anaesthetic	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		

Until October 1st, 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.

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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 listed 82 different reactions. Sensory disturbances were the most commonly reported adverse reaction (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*).

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The Medicines Evaluation Board of the Netherlands (February 2010) stated in the Public Assessment Report on Loncarti 40/0.005 mg/ml and Loncarti 40/0.01 mg/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.

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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*).

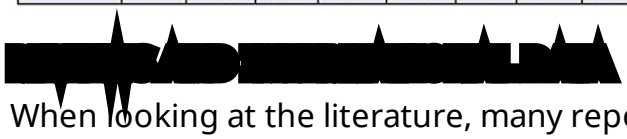
Jerjes *et al. (2006)* conducted a prospective trial in order to evaluate the proportion of permanent sensory impairment of IANs and LNs and the factors influencing such frequency after the removal of mandibular third molars under local anaesthesia. From 1998 to 2003, there were 1,087 patients having their mandibular third molars removed under local anaesthesia. Frequency of IAN injury was 4.1% up to one w
eek after surgery and decreased to 0.7% after two years of follow-up, whereas alteration in tongue sensation occurred in 6.5% of patients up to one week after surgery and decreased to 1.0% after two years of follow-up. The experience of the dentist was found to be a significant factor in determining both, permanent IAN ($p = 0.026$) and LN ($p = 0.022$) paresthesia.

Jerjes *et al. (2010)* conducted another prospective trial in the UK involving 3236 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%; for the LN, it was 1.8%. These figures decreased over time and 18 to 24 months postoperatively. The frequency of permanent dysfunction of the IAN was 0.6%, for the LN it was 1.1%. 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.

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% were classified as local reactions including symptoms like hematoma, hemorrhages, hypesthesia, and paresthesia. The frequencies for the individual symptoms were not given.

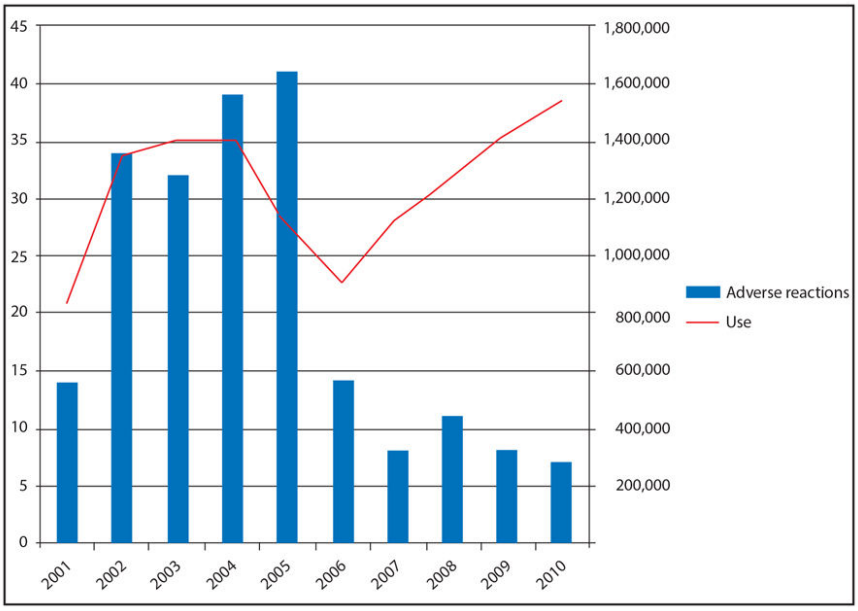
Table 2 Cases of paresthesia not related to surgery by year and anesthetic drug (data from Gaafen & Haas, 2009)

	Cases of paresthesia [N (%)]										
Anesthetic	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
Articaine	7 (43.8)	17 (70.8)	11 (47.8)	9 (50.0)	9 (69.2)	7 (87.5)	7 (43.8)	20 (74.1)	12 (60.0)	10 (58.8)	109 (59.9)
Lidocaine	4 (25.0)	3 (12.5)	4 (17.4)	1 (5.6)	3 (23.1)	1 (12.5)	1 (6.2)	4 (14.8)	1 (5.0)	1 (5.9)	23 (12.6)
Mepivacaine	0	1 (4.2)	1 (4.3)	0	0	0	0	0	1 (5.0)	3 (17.6)	6 (3.3)
Prilocaine	4 (25.0)	2 (8.3)	5 (21.7)	5 (27.8)	0	0	5 (31.2)	1 (3.7)	5 (25.0)	2 (11.8)	29 (15.9)
Multiple	1 (6.2)	1 (4.2)	2 (8.7)	3 (16.7)	1 (7.7)	0	3 (18.8)	2 (7.4)	1 (5.0)	1 (5.9)	15 (8.2)
Total	16 (100)	24 (100)	23 (100)	18 (100)	13 (100)	8 (100)	16 (100)	27 (100)	20 (100)	17 (100)	182 (100)



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 can not 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*).

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 1325 patients. These trials showed that articaine and lidocaine were comparable in many ways, including the frequencies of paresthesia, which were less than 1% 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 US 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 US (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 anaesthesia in patients presenting for routine 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 analogue 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 the 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 intraneural hematomas. There are various studies, such as those published by Krafft & Hickel *(1994)* or Harn & Durham *(1990)*, s upporting his findings. They observe a frequency of direct needle trauma to the nerve during traditional IANBs of 7.7% and 3.62%, 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 Malamed, a world-wide acknowledged specialist for dental anaesthesia. Malamed stated as well that “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 US, Canada, Russia, Poland and Italy covering the period from January 2009 to Decemeber 2014. There were three case reports related to paresthesia, none of them classified as permanent, with an overall sales volume of more than 40 million cartridges. One case of non-permanent paresthesia every 13.3 million injections.

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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, in the author's opinion, 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 (Haas & Lennon*, 1995; WHO Pharmaceutical Newsletter,* Gaffen & Haas*, 2009; Garisto 2010*), 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 (Pogrel*, 1995;* Pogrel & Thamby*, 2000;* Pogrel*, 2007*).

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, see Haas & Lennon; 1995), especially when compared to other "everyday life"-risks like death by car accident (1:11,236) or strike by lightning (1:250,000) (*Transport Canada, 2004; Environment Canada, 1995*). Although this comparison may 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 4% of active substance has never been scientifically proven (Diaz*, 2010*), and prolonged paresthesia may rather be due to the interventions than articaine (*Public Assessment Report of the Medicines Evaluation Board in the Netherlands on Loncarti 40/0.005 mg/ml and Loncarti 40/0.01 mg/ml, February 2010*) 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 ($p = 0.026$) (Jerjes *et al., 2006;* Jerjes *et al., 2010*).

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 which 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 relelated to all articaine products marketed by Pierrel in the US, Canada, Russia, Poland and Italy was retrieved from the respective marketing authorization holders for the period from January 2009 to December 2014 (Pierrel Safety Database). There were three case reports related to paresthesia, none of them classified as permanent. Considering the total sales volume of more than 40 million cartridges (one case every 13.3 million injections) this result supports 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 can not be confirmed from the literature (Yapp *et al., 2011*). Based on the findings presented above,

procedural trauma appears to be a valid alte3rnative explanation for the reported neurological complications[redacted]

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Oral Health welcomes this original article.

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