RETROSPECTIVE REVIEW OF DENTAL LOCAL ANESTHETIC INDUCED PARESTHESIA IN THE UNITED KINGDOM

by

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A thesis submitted in conformity with the requirements
for the Degree of Master of Science
Graduate Department of Dentistry
University of Toronto

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Master of Science, 2012

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ABSTRACT

Background: While local anesthetics are essential drugs in dentistry, risks such as paresthesia are associated with their use. The purpose of this study was to analyze the reported paresthesia cases in the United Kingdom.

Methods: Voluntary reports of paresthesia from local anesthetic use between 1998 and 2008 obtained from UK’s Yellow Card Scheme were examined. Statistical significance was tested using the Chi-Square analysis, comparing expected frequencies of paresthesia based on the UK dental anesthetic sales data, to the observed reports of paresthesia.

Results: Of the 44 reported cases of paresthesia, 85% of the cases involved the mandible with the lingual nerve being the most often affected. The frequency of observed paresthesia associated with 4% articaine solution, was 5.9 times greater than expected ($\chi^2$, p<0.0001).

Conclusions: These data suggest that paresthesia after the injection of local anesthetic in dentistry is rare, yet more likely to occur if a 4% solution is used.
I owe more than I can imagine to my mother and father, for their unconditional love and support.
ACKNOWLEDGEMENTS

I wish to acknowledge the exemplary work and professionalism of Dr. Daniel Haas for his mentorship of this research project. Dr. Haas is an outstanding scholar and teacher, and I am honored to have had the privilege to be educated under his direction. I have much respect, admiration, and appreciation for Dr. Haas.

My sincere thanks go to other Committee members, Drs. Michael Goldberg and Leslie Laing Gibbard for their valuable input and suggestions. I would like to pay particular gratitude to Dr. Gabriella Garisto, not only for her expertise and guidance through this project, but also her caring support throughout the program.

This research study was based on Dr. Andrew Gaffin’s earlier correspondence with the United Kingdom’s pharmacovigilance office, for which, I am much grateful.
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Statement of Problem</td>
<td>24</td>
</tr>
<tr>
<td>III. Purpose</td>
<td>26</td>
</tr>
<tr>
<td>IV. Objective</td>
<td>27</td>
</tr>
<tr>
<td>V. Research Methodology</td>
<td>28</td>
</tr>
<tr>
<td>VI. Results</td>
<td>33</td>
</tr>
<tr>
<td>VII. Discussion</td>
<td>36</td>
</tr>
<tr>
<td>VIII. Future Directions</td>
<td>47</td>
</tr>
<tr>
<td>IX. Conclusions</td>
<td>48</td>
</tr>
<tr>
<td>X. Tables</td>
<td>49</td>
</tr>
<tr>
<td>XI. Figures</td>
<td>54</td>
</tr>
<tr>
<td>XII. References</td>
<td>63</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table 1. Physiochemical properties of local anesthetics………………..49
Table 2. Example of data obtained from Strategic Data Marketing…………50
Table 2. Percentage of unknown private label sales yearly from 1998 through
2008, based on data from Strategic Data Marketing………………51
Table 3. Observed and expected frequencies of paraesthesia 1998 through 2008
in the U.K………………………………………………………………………………52
Table 4. Observed and expected frequencies of paraesthesia 2001 through 2008
in the U.K………………………………………………………………………………53
<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Figure 1</td>
<td>Example of a Yellow Card supplied line-listing spreadsheet page</td>
<td>54</td>
</tr>
<tr>
<td>Figure 2</td>
<td>Reported cases of non-surgical paraesthesia by year and local anaesthetic drug</td>
<td>55</td>
</tr>
<tr>
<td>Figure 3</td>
<td>UK local anaesthetic sales percentages from 1998 through 2008, based on data from Strategic Data Marketing</td>
<td>56</td>
</tr>
<tr>
<td>Figure 4</td>
<td>UK local anaesthetic sales percentages yearly from 1997 through 2008, based on data from Strategic Data Marketing</td>
<td>57</td>
</tr>
<tr>
<td>Figure 5</td>
<td>Expected and expected frequency distribution per local anaesthetic drug from 1998 through 2008</td>
<td>58</td>
</tr>
<tr>
<td>Figure 6</td>
<td>Distribution of non-surgical paraesthesia cases by age</td>
<td>59</td>
</tr>
<tr>
<td>Figure 7</td>
<td>Distribution of non-surgical paraesthesia cases by gender</td>
<td>60</td>
</tr>
<tr>
<td>Figure 8</td>
<td>Distribution of non-surgical paraesthesia cases by dental arch</td>
<td>61</td>
</tr>
<tr>
<td>Figure 9</td>
<td>Distribution of paresthesia cases by affected area of face</td>
<td>62</td>
</tr>
</tbody>
</table>
I. Introduction

A millennium ago, Persian alchemists Avicenna and Raazi used opium and papaveris as local anesthetics in patients with joint, dental, eye, and ear pain (Al Mazoora et al., 1989). It has been more than a century since cocaine was first used by Karl Koller as an injectable local anesthetic and later by William Halsted and John Hall for nerve block anesthesia in dentistry (Calatayud, 2003). It was indeed this essential discovery of local anesthetics that facilitated pain control without the need for loss of consciousness or inhumane suffering. Subsequently, revolutionary advances such as development of novel anesthetics without the addictive qualities of cocaine, the addition of vasoconstrictors, and alternative methods of delivery have significantly improved the efficacy and potency of local anesthesia, while reducing unwanted adverse events.

The most commonly used local anesthetics in dentistry today are lidocaine, articaine, prilocaine, mepivacaine, and bupivacaine. All these agents reversibly inhibit the excitation-conduction process in targeted nerves, which use sodium channels for action potential generation.

Nerve physiology:

The functional unit of a peripheral nerve is a neuron. A neuron is a cell with multiple small protrusions called dendrites and one larger axon. Dendrites receive signals from other neurons using chemical synapses, which flow out to other neurons using the axon. Most axons are surrounded by a Schwann cell, which has structural and supportive roles,
most significantly on the mode of impulse transmission. In unmyelinated nerves, projections from a single Schwann cell surround several axons. In myelinated nerves, the Schwann cell projections encircle many times around an axon. Thus the axon is surrounded by a sheath formed of multiple double layers of phospholipid cell membrane named the myelin sheath (Wildsmith, 1986). The sheath works as an insulator, blocking ion leakage, and therefore, increases the speed of impulse propagation.

In peripheral nerves, bundles of nerve fibers, made of axons and sheath, are surrounded by longitudinally arranged collagen fibrils, termed endoneurium. Many of these processes are bundled together into groups known as fascicles, each surrounded by multiple concentric layers of myofibroblastic cells, known as the perineurium. The perineurium is a transparent semipermeable membrane, which may be easily separated from other fibers (Sunderland, 1990). The epineurium is made up of longitudinally arranged collagen and elastin fibrils which surround a number of the bundles and in turn, make up the entire peripheral nerve. The epineurium is in contact with the surrounding areolar tissue, through which the blood supply passes to the nerve. The blood supply reaches each individual nerve cell by the interconnecting septa of fibrous connective tissue.

**The nerve impulse:**

The conduction of impulses in the nerve fiber is principally due to changes in the electrophysiological gradient of the nerve membrane. Neuronal cell bodies maintain a negative resting potential of -90 to -60 mV within the cell in comparison with the exterior of the cell membrane, by an electrogenic sodium-potassium pump (White & Katzung, 2007). At rest, the nerve cell cytoplasm has a high concentration of potassium ions and a
low concentration of sodium ions. The opposite is true for the extracellular environment. It is this gradient which accounts for the negative intracellular resting potential. During this period, the cell membrane is more permeable to passage of potassium than sodium. During excitation, a slow phase of depolarization occurs during which the electrical potential within the nerve cell becomes progressively less negative, and when it reaches a critical level, the threshold potential, (about -55mV), voltage gated sodium channels are opened. A fast inward sodium flow suddenly depolarizes the membrane (+40mV), generating an action potential. Thereafter, repolarization begins, with inactivation of sodium channels and outflow of potassium continuing until the intracellular resting potential of -50 to -70 mV is restored (White & Katzung, 2007).

Once a segment of an axon is depolarized, a potential difference exists in comparison to adjacent sections. This causes a local current to flow into the adjacent segments and makes its membrane potential less negative, thereby activating voltage gated sodium channels. This in turn initiates a chain reaction that produces a successive series of depolarizations along the nerve fiber, which propagates along the axon (Evers, 1990). In an unmyelinated nerve, the impulse flows contiguously along the axon, as one depolarized segment activates its adjacent area. However, in a myelinated nerve, sodium channels are found almost entirely in the nodes of Ranvier which are unmyelinated nodal spaces. The impulse jumps from one node to the next node, with the middle nerve section depolarizing. This is known as saltatory conduction and explains the faster rate of impulse transmission in myelinated fibers (Wildsmith, 1986).
Nerve fibers are categorized into three types based on the diameter of the fiber. Type A fibers and their subtypes are heavily myelinated, largest in diameter (2-20 µm), have highest conduction speed, and are responsible for conducting proprioception, pressure, and motor signals. Type B fibers are myelinated, moderate in diameter (1-3 µm), and are visceral sensory and preganglionic autonomic fibers. Type C fibers are unmyelinated, small in diameter (0.3-1.3 µm), and transmit pain and temperature sensations (Wildsmith, 1986). Local anesthetics block type C fibers more easily than type A fibers due the large difference in size. Therefore, patients who are anesthetized from pain sensation still feel pressure and are able to move the affected area, because type A fibers are largely unblocked. Interestingly however, it is found that myelinated nerves are blocked before unmyelinated nerves of the same diameter. This is because myelinated nerves need to be blocked only at nodes of Ranvier and thus require a smaller portion of these nerves to be exposed to the anesthetic.

**Mechanism of action of local anesthetics**

Local anesthetics block impulse transmission from sensory nerves primarily by blockage of voltage-gated sodium channels. Most of these agents bind the large alpha subunit of the sodium channel, as tissue buffers increase the pH of the agent, releasing some of the lipid-soluble base form of the drug, which is able to diffuse through the lipid cell membrane into the axoplasm where a portion ionizes again. This ionized form of the drug then enters the sodium channel from the inside of the axon and obstructs further channel activation and depolarization (Wildsmith, 1986).

As the concentration of local anesthetic is progressively increased, the excitation
threshold is increased, the transmission rate of impulse is slowed, the upswing of action potential becomes flatter, and ultimately, an action potential is no longer generated (White & Katzung, 2007). The local anesthetic binding to an increasing number of sodium channels is the cause for this progressive effect. The critical length of blockage at which no impulse is further propagated, is found to be 2 to 3 nodes of Ranvier.

Ion channels are believed to exist in one of three phases; resting, active, and inactive. Local anesthetics are shown to have more affinity to sodium channels that are in their active and inactive states compared to those in a resting state. Thus, channel blockage is both voltage and time dependent, meaning they have the greatest effect if the nerve is firing rapidly (White & Katzung, 2007). Furthermore, local anesthetics may also block other ion channels including calcium, potassium, NMDA, and nicotinic acetylcholine channels in the spinal cord. Some have proposed that the clinical differences between various local anesthetic agents may be caused by the blockage of different ion channels (Smith et al., 2002). Interestingly, many general anesthetic agents such as ketamine, volatile gases, and meperidine are also found to block sodium channels to some degree (Butterworth, 1989). However, these agents are much less potent at the voltage gated ions channels than the ligand gated ion channels in the central nervous system. It has been shown that a partial blockade of sodium channels is not sufficient to suggest peripheral conduction blockade as a major mechanism (Scholz, 2002).
Pharmacology of local anesthetics

All local anesthetics have a similar chemical structure consisting of three components. These include an aromatic part with a lipophilic benzene ring, an intermediate ester or amide chain, and a hydrophilic terminal amine. The aromatic ring improves the lipid solubility of the agent, which enhances diffusion through the lipophilic nerve sheath and membranes of individual axons to access the sodium channel receptor. The more lipid soluble a local anesthetic is, the greater is the likelihood that it will enter the nerve fiber, and thus, will have a higher potency (Becker et al., 2006).

The intermediate chain that connects the aromatic and amine segment, is composed of either an amide or an ester linkage. This linkage can be used in classifying local anesthetics into two groups, comprised of amides (lidocaine and its derivatives) and esters (procaine and its derivatives). Esters are relatively unstable in solution and are broken down easily, whereas amides are much more stable (Covino, 1986). The ester anaesthetics are hydrolyzed in plasma by cholinesterase enzyme, whereas the amides undergo enzymatic degradation in the liver.

As discussed above, the potency of local anesthetics is determined by their lipid solubility. Other functional characteristics of local anesthetics are determined by their dissociation constant (pKa) and protein binding. Onset of action depends on lipid solubility as well as the pKa. The pKa is the pH value at which a solution of a local anesthetic is in equilibrium, with half in the non-ionized state (B) and half in the ionized state (BH^+). Because the neutral base form of the anesthetic is more lipophilic, it can
penetrate nerve membranes faster (Morgan et al., 2008). If an anesthetic has a higher pKa, the percentage in the ionized state increases and the onset of the block is slowed. Most anesthetics have a pKa greater than 7.4 and therefore, are weak bases which require addition of hydrochloride salt to become water soluble and injectable. However, the inside of a cell is more acidic and favours the charged state. Thus, it is the ionized form of the molecule in the end which binds the sodium channel and blocks conduction. Furthermore, inflammation in the extracellular space may decrease pH and may slow onset of action.

The duration of action for local anesthetics is determined by lipophilicity and protein binding. Local anesthetics with high lipid solubility remain bound to receptors longer, and are less likely to be taken away by blood flow, resulting in an increased duration of action (Morgan et al., 2008). Those anesthetics with a higher degree of binding to alpha-1-acid glycoproteins and albumin, have a prolonged elimination and also can be displaced from the binding site by other protein-bound drugs. A high affinity for plasma proteins also corresponds to a greater affinity for protein at the receptor site within sodium channels, prolonging the presence of anesthetic at the site of action (Becker et al., 2006). Furthermore, protein binding decreases the availability of free drug in the blood, reducing the potential for toxicity in other organs (Greenblatt et al., 1982). A comparison of the functional characteristics of local anesthetic can be seen in table 1.

Due to the unfavourable clinical profile of esters, they have been replaced by amide local anesthetics. Presently, no ester anesthetic is produced in cartridge form for injection. However, it is still available for dental use as a topical anesthetic.
Vasoconstrictors

The addition of a vasoconstrictor such as epinephrine or levonordefrin to a local anesthetic solution has several potentially beneficial effects. By vasoconstriction of blood vessels at the site of injection, there is a consequent decreased absorption of the agent into blood and thus less redistribution of the drug. Therefore, duration and quality of anesthesia is improved, and the minimum concentration of local anesthetic agent needed for nerve block is decreased (Jastak et al., 1983). As the peak plasma concentration of the local anesthetic agent is decreased, the toxic effects of the drug are also reduced. However, these potential effects of vasoconstrictors are mostly seen with strongly vasodilating agents such as lidocaine.

Local anesthetic adverse effects

All drugs, natural or synthetic, carry risks of complication and side effects with usage. Local anesthetics are no exception. Local anesthetics are the most frequently administered drugs in dentistry. It has been estimated that by adding usage figures from North America, Western Europe and Japan, more than 1 billion injections of local anesthetics occur per year in a dental setting. Thus, it could be expected that local anesthetics would be a major factor in adverse reactions in the dental office. There are reports in the literature stating frequencies of 4.5-26.2% depending on the type of events studied though serious, life-threatening situations are rare (Kaufman et al., 2000).

The three major forms of local anesthetic adverse events are firstly, the systemic effects following absorption of the local anesthetic from the site of administration, secondly, the
direct trauma from injection, and thirdly, neurotoxicity from the drugs locally when administered in close proximity to nerves.

Systemic adverse effects:

Systemic adverse effects of local anesthetic drugs usually occur because of excessive dosage, rapid absorption, or accidental intravascular injection, which is the commonest cause of local anesthetic toxicity (Naguib et al., 1998). The rate of absorption of local anesthetics varies with the site of administration and the presence or absence of a vasoconstrictor. Exposure of a local anesthetic solution to a larger vascular area results in a greater rate and degree of absorption. However, it has been shown that regardless of the site of injection, peak levels are reduced and the rate of absorption are delayed by adding vasopressors such as epinephrine to the local anesthetic solution (Scott et al., 1972).

A prospective study of immediate complications of local anesthetic injection administered to 1,007 consecutive patients showed a rate of positive aspiration in seven percent of inferior alveolar nerve blocks on the first attempt. Furthermore, it was found that if positive aspiration occurred with the first injection, there was a 31.3 percent chance that positive aspiration occurred with the second injection (Lustig et al., 1999). Interestingly, even with thorough aspiration, the study still found 10 cases in which the anesthetic was injected intravascularly.

Following accidental intravascular injection, blood concentration of the anesthetic quickly rises and may lead to systemic toxic reactions, which are manifested by a progressive range of neurological symptoms as the local anesthetic directly enters the
cerebral circulation (Mulroy, 2002). Early symptoms such as circumoral numbness, tinnitus, metallic taste, agitation, and paranoia are consistent with central nervous system excitation. Excitatory signs are a result of initial selective blockade of inhibitory pathways. These symptoms often precede slurred speech, drowsiness, and unconsciousness, consistent with CNS depression, which follows. Interestingly, intravascular injection of lidocaine is routinely used by many anesthesiologists, not only for pre-emptive local anesthesia for phlebitis associated with propofol injection at the site, but also since it has been shown to significantly reduce the minimum alveolar concentration of volatile anesthetics (Senturk et al., 2002). Progression of blood levels may lead to muscle twitching and/or tonic-clonic seizures. Very high blood levels are associated with coma, respiratory arrest, and death. (Morgan et al., 2008). Fortunately, most of these types of reactions seen in the dental office are often the early excitation ones and are short lived because a relatively small amount of drug is used and the blood flow to the brain rapidly removes the drug.

The cardiovascular system is more resistant to local anesthetic toxicity than the central nervous system. While signs consistent with cardiovascular stimulation such as tachycardia and hypertension may occur early reflecting CNS excitation, major cardiac toxicity such as arrhythmias or collapse is usually seen with three times the blood concentration that produces seizures (Morgan et al., 2008). All local anesthetics depress myocardial automaticity and reduce the duration of refractory period and conduction velocity. These effects are a result of sodium channel blockage in membranes of cardiac muscles. Historically, intravascular lidocaine had been used in emergency situations for treatment of ventricular arrhythmias. Bupivacaine, however, has been associated with
severe cardiotoxic reactions after unintentional intravascular injection. Studies have shown that bupivacaine causes more pronounced changes in depolarization than other anesthetics as it firmly blocks cardiac sodium channels and dissociates slowly (Clarkson et al., 1986). It is very important to note, however, that much of the morbidity and mortality occurring in the dental office setting associated with injection of local anesthetic after accidental intravascular injection is due to the cardiovascular effects of epinephrine or other vasoconstrictors on patients at risk for coronary artery disease.

When studying the toxicity of a drug, one should also look into the activity of the drug’s metabolites. Lidocaine is biotransformed in the liver to monoethylglycylxylidide (MEGX) and glycylxylidide (GX). These metabolites have been associated with cases of lidocaine toxicity (Becker et al., 2006). Fortunately, these metabolites have been mostly implicated in cases of repeated large doses in spinal anesthesia or intravascular infusion, and thus, not of a major concern in its dental applications (Miyabe et al., 1998).

Methemoglobin is hemoglobin with the iron oxidized to the ferric state, rather than the normal, reduced ferrous state. A metabolite of prilocaine, o-toluidine, can oxidize iron forming methemoglobin which reduces the oxygen carrying capacity of red blood cells. When more than one percent of total hemoglobin has converted to methemoglobin, the condition is called methemoglobinemia. Patients appear cyanotic and become symptomatic when the proportion of methemoglobin exceeds 10 to 15% (Becker et al., 2006). Recommendations based on toxicological and pharmacokinetic data show that doses of prilocaine up to 600 mg (approximately 8 mg/kg) are considered safe (Niesel et al., 1991). For this reason, reports of methemoglobinemia are very rare in dentistry as it is highly unlikely that such large doses are used in dental practice. There have been reports
describing methemoglobinemia in association with benzocaine, an ester used as a topical anesthetic in dentistry, and most cases reported in the literature occurred in infants and very young children (Olson et al., 1981). This adverse event is seldom life threatening and is treated with intravenous methylene blue, which reduces the heme to its normal state.

**Allergy to local anesthetics**

Reports of local anesthetic induced allergic reactions have been reduced significantly since amide local anesthetics usage replaced esters (Finucane, 2003). Ester-type local anesthetics, like procaine, are derived from para-amino benzoic acid (PABA), a known allergen. Furthermore, when ester agents are hydrolyzed by plasma cholinesterases, PABA is formed as a metabolite (Chen, 1998). Although exceptionally rare, reports of allergic reactions to amide local anesthetics have appeared in the scientific literature, but no known cases thus far have confirmed an immunoglobulin E-mediated hypersensitivity reaction (Becker et al., 2006).

Older commercial preparations of local anesthetics included a bacteriostatic agent called methylparaben, which is chemically related to para-amino benzoic acid and is also identified as an allergen (Aldrete et al., 1970). Since local anesthetics in dentistry are available as one time use cartridges, methylparaben is no longer added to the preparation, since the early 1980s, with the exception of the product Ultracaine, which contained it until the mid 1990s. However, another preservative, sodium metabisulfite, is added to all local anesthetics that contain a vasoconstrictor. Bisulfites are antioxidants used to prevent
the early breakdown of epinephrine in dental cartridges. This substance has been found to be a potential allergen that affects a small subgroup of the asthmatic population (Lukawska et al., 2009).

Psychogenic episodes associated with the stress and pain of injection may lead to vasovagal symptoms such as bradycardia, hypotension, and loss of consciousness. Furthermore, reactions to epinephrine especially when injected intravascularly, may include palpitations, tachycardia, arrhythmia, anxiety, headache, tremor, and hypertension. These symptoms may wrongly be self-diagnosed as hypersensitivity.

**Direct trauma from injection**

Peripheral nerve injury is a rare complication of regional anesthesia in both medicine and dentistry. As neurological injuries after peripheral nerve blocks are so uncommon, it is very difficult to obtain reliable data about their incidence. Furthermore, it is quite problematic in most cases to isolate neuronal injury cases caused by trauma to the nerve during injection from those related to neurotoxicity of the local anesthetic. Overall, retrospective studies estimate an incidence of 0.5–1.0% (Liguari, 2004). However, the true incidence depends on the definition of nerve injury. For major complications resulting in permanent nerve damage, a 1.5/10 000 incidence has been reported, while most injuries are transient, or are often subclinical with mild mononeuropathies (Jeng et al., 2010).
There is much debate about the mechanism of localized nerve injury related to the site of injection. Theories are largely divided on hydrostatic pressure from injection, direct mechanical injury to the nerve by the needle, or chemical injury from the local anesthetic solution itself (Haas, 2006). In situ studies have shown that extrafascicular administration of clinically used concentrations of local anesthetic solutions may alter perineurial permeability, causing endoneural edema, increasing endoneurial fluid pressure, causing Schwann cell injury and axonal dystrophy with endoneural fibrotic changes as a late consequence (Myer et al., 1986). As the local anesthetic enters the neural cell membrane, the regulatory function of the perineurial and endothelial blood-nerve barrier is compromised. With increased perineural permeability, accumulation of edema, and increased fluid pressures within the fascicles, the normally hypertonic endoneurial fluid that permeates between the neuronal fibers within the fascicle becomes hypotonic (Hogan, 2008). Thus, a local anesthetic solution applied non-traumatically and externally to a peripheral nerve bundle may cause deleterious effects by increasing intraneural hydrostatic pressure.

Direct mechanical injury to the nerve causes discontinuation of the perineural tissue around the nerve fascicles, ruptures the blood-nerve barrier, leading to subsequent edema of the nerve, and herniation of the endoneural fibers (Hogan, 2008). Peripheral nerves have intrinsic blood vessels in the endoneurium, and an extrinsic plexus of vessels in the epineural space that anastomose with the intrinsic circulation after crossing the perineurium (Jeng et al., 2010). Injury to these vital vessels may cause ischemia and has been identified as one of the causes of peripheral nerve injury. It has also been
hypothesized that by traumatizing the intrinsic blood vessels, an intraneural hematoma will be formed creating much damaging pressure within a rigid space. Furthermore, hemorrhage from extrinsic blood vessels would give rise to a constrictive epineuritis, compressing the nerve fibers (Smith et al., 2006). The release of blood and blood products during hematoma formation leads to fibrosis and scar formation, which may prevent axonal regeneration by disrupting the fascicular architecture.

Accidental intraneural injection of local anesthetics may cause pressure ischemia of the nerve fascicles (Hadzic et al., 2004). Animal studies suggest that it is intrafascicular injection in combination with high injection pressures that result in neural injury and neurological deficit, while injection within the epineurium results in low pressures and preservation of normal neurological function (Jeng et al., 2010). Intraneural, yet extrafascicular injections are characterized by the spread of the drug within as well as leakage of fluid outside the epineurium into the compliant neighboring connective tissues, without creation of excessive pressure (Robards et al., 2009). In contrast, intrafascicular injections lead to pressure buildup within the layers leading to some degree of neurologic impairment (Kapur et al., 2007). Peripheral nerves have a high ratio of extraneural connective tissue to nerve fascicles, and therefore, needle placement is likely to be in the extrafascicular connective tissue compartment. (Barrington et al., 2011). A human cadaver study of beveled needle placement within the sciatic nerve confirmed that the needle tip was more likely to be extrafascicular and not cause fascicular or vascular injury (Sala-Blanch et al., 2009).
In dentistry, nearly all local anesthetic injections are followed by complete return to normal nerve activity within a few hours. However, a small number result in persisting deficits in sensory performance, or in the generation of pain, with the overall altered sensation termed paresthesia. While most cases of paresthesia in dentistry are caused by severing of nerves from surgical procedures such as dental extractions or orthognathic surgery, some are not so easily explained and may occur during routine restorative procedures. Some argue that direct nerve injury from the local anesthetic needle may be to blame. This is observed especially during mandibular injections such as inferior alveolar nerve block, lingual nerve block, or mental block where the dentist unseeingly tries to reach the nerve hidden in the midst of soft tissues with a long sharp beveled needle. One dental study found that the inferior alveolar nerve block did result in permanent paresthesia with an incidence rate of between 1:26,762 and 1:160,571 (Pogrel et al., 2000).

Stacy and Hajjar examined the tips of local anesthesia needles after mandibular blocks and found that the majority of the needles had a barbed tip. After using animal laboratory simulation, they showed that the tips of standard needles would often barb after contacting bone. Furthermore, they related the pattern of this barbing and the direction of the bevel of the needle at the time of its insertion, and found increasing likelihood of lingual or inferior alveolar nerve involvement on withdrawal of the barbed needle (Stacy et al., 1994).

A select number of patients undergoing inferior alveolar, lingual, or mental nerve blocks
report a sudden electric shock sensation as the needle approaches the landmarked area, which is thought to occur when the needle contacts part of the nerve trunk. In the prospective study of 1,007 dental patients as mentioned above, it was reported that patients felt an electric current sensation 40 times with inferior alveolar nerve blocks, 18 times with lingual nerve blocks, four times with mental nerve blocks and one time with a second injection to the same site (Lustig et al., 1999). Other studies have estimated overall incidence figures of 1.3% to 8% of all mandibular block injections (Smith et al., 2006). By examining the large differences in incidence rates between reports of electric shock occurrence and paresthesia, one can see that the former is not always indicative of the latter. While it is suggested that about 15% of the patients who experience electric shock sensations may experience further prolonged localized altered sensations, nearly half of paresthesia cases report no history of electric shock (Harn et al., 1990; Pogrel et al., 2000; Smith et al., 2006).

The mechanical injury theory has met significant criticism over past years. Some contend that while the lingual nerve averages 1.86 mm in diameter and the inferior alveolar nerve between 2 and 3 mm in diameter, the diameter of a 25 gauge long needle used for a block is a small fraction at 0.45 mm. Others argue that the diameter of the needle is 500 to 1000 times greater than the 0.5 to 1.0 micron nerve fascicle for pain, cold, or heat, and the large discrepancy in size suggests that it is not possible to selectively injure the small pain fibers present in a 2 to 3 mm wide nerve, while leaving the larger touch, pressure, and proprioceptive fibers intact (Nickel, 1990).

Although it may be common sense that fascicular injury may occur once the nerve is pierced with a sharp object such as a needle, there has been little convincing evidence in
directly examining the mechanism by which needle injury disrupts the biophysics of peripheral nerves. Furthermore, some studies even suggest that needle tip trauma of the nerve may not itself be the cause of the clinical complications. One study noted no significant functional changes after the passage of a needle into the human ulnar nerve if local anesthetic was not injected intraneurally (Lofstrom et al., 1966). Another study found no changes in microscopic anatomy or function within the nerve following penetration of the fascicle with a needle and the injection of saline solution (Gentili et al., 1980).

In another study in which surgical exploration of some permanent paresthesia cases secondary to injection with local anaesthetic was undertaken, it was concluded that there was no evidence of macrotrauma caused by the anaesthetic needle (Pogrel and Thamby, 2000). It was observed that there was minor increase in adhesions surrounding the nerve and the nerve in the area of the injection had a whiter appearance compared to elsewhere along the nerve. None of these changes were noted to be caused by the direct trauma to the nerve by the needle.

**Neurotoxicity of Local Anesthetics**

Since nerve damage to the lumbar and sacral sections of the spinal cord, also known as ‘cauda equina syndrome’, in spinal anesthesia was linked with usage of 5% lidocaine, many have become concerned about the risk of long term neurological sequelae caused by high concentrations of local anesthetics (Rigler et al., 1991). All local anesthetics seem to be involved in clinical reports of neural complications. To explain the possible mechanisms of neurotoxicity, many biochemical, electrophysiological, and histopathologic studies have been performed. Recent findings suggest that the anesthetic
itself may cause localized chemical damage to the nerve, which may manifest itself clinically (Smith et al., 2006). Local anesthetic agents are shown to generate cytotoxic effects in cell cultures, such as inhibition of cell growth, motility, and even produce morphological changes (Sturrock et al., 1979). Furthermore, cytotoxicity has been directly related to the duration that the nerves are exposed to the local anesthetic solution as well as the increasing local anesthetic concentrations (Hogan, 2008).

In in-vitro models using isolated nerves, spinal cord, or neuronal cells, it has been shown that all local anesthetics may cause loss of action potential, increase of intracellular calcium, conduction blocks, apoptosis, and cell death (Friederich et al., 2002 & Perez-Castro et al., 2009). Using crayfish giant axons, it was shown that highly concentrated lidocaine induced a complete loss of resting membrane potential, and an irreversible conduction block (Kanai et al., 1998). A number of studies have revealed concentration dependent mitochondrial dysfunction by collapsing the mitochondrial membrane potential, uncoupling oxygen consumption, and adenosine diphosphate-phosphorylation, releasing cytochrome c, and activating caspases, which may all lead to apoptotic cell death (Johnson et al., 2004 & Kamiya et al., 2005 & Perez-Castro et al., 2009). One mechanism for these effects has been that local anesthetics bind to more calcium channels at higher concentrations, alter the neuronal calcium homeostasis and cause a sustained increase in cytoplasmic calcium. Supporting this theory, it was shown that lidocaine at 0.5% and 1% concentrations caused minimal changes in calcium homeostasis and no neurotoxicity, whereas 2.5% and 5% concentration of lidocaine lead to toxic level of cytoplasmic calcium, causing cell death (Johnson et al., 2002).
In addition, different local anesthetics may have different mechanisms of neurotoxicity. While lidocaine has been shown to have a degenerative effect on the myelin, bupivacaine has been found to kill the Schwann cells more effectively than lidocaine (Lirk et al 2006 & Park et al., 2005). However, all local anesthetics are found to significantly decrease cell viability in a concentration-dependent fashion even at subclinical concentrations, as lidocaine 0.4%, bupivacaine 0.03%, and mepivacaine 0.6% were found to kill 50 percent of human neuroblastoma cells after a 10 minute exposure (Perez-Castro et al, 2009).

While neurotoxicity observed with in-vitro studies does not necessarily correlate with the incidence of poor sequelae in the clinical setting, evidence about the mechanism of injury might be obtained.

Another concentration dependent theory for the mechanism of neurotoxicity in nerve injury is that neural membrane lyses due to the detergent properties of local anesthetics (Kitagawa et al., 2004). Using four different agents it was shown that local anesthetics form molecular aggregations like other chemical surfactants. At osmotic pressures, which should be insufficient to affect the nerve membrane, local anesthetics caused membrane disruption. Thus, dissolving of the nerve membrane by highly concentrated local anesthetics may cause irreversible neural injury.

An in-vivo study using histopathologic quantification of local anesthetic-induced endoneurial edema, nerve fiber injury and Schwann cell damage on the sciatic nerve of rats showed a concentration dependent increase in cellular injury with all of the agents used (Kalichman et al, 1989). Another in-vivo study on infraorbital nerve in rats examined sensory nerve fiber inhibition by exposing the nerve to 1, 2, and 4% lidocaine, with and without epinephrine and found a concentration, and epinephrine dependent
delay in axonal transport recovery. (Fink and Kish, 1976)

As mentioned earlier, epinephrine is added to the local anesthetic to cause local vasoconstriction and to inhibit the absorption of the drug away from its primary site of action. However, epinephrine’s role in causing nerve ischemia and injury is unproven (Partridge, 1991). It is plausible that vasoconstriction and limitation of blood flow into the nerve would result in metabolic stress, ischemia, and injury.

**Local anesthetic neurotoxicity in dentistry**

Reports of dental local anesthetic-induced neurotoxicity manifesting as paresthesias have been presented over the last two decades. Given the *in-vitro* and *in-vivo* research studies presented above, it is not surprising that many of the dental reports have found a concentration dependent linkage between local anesthetics and incidence of paresthesia. This was first reported by a retrospective examination of voluntary reported nonsurgical paresthesia cases in Ontario, Canada during the period of 1973 to 1993 (Haas and Lennon, 1995). The two local anesthetics most often implicated with paresthesia were the higher concentrated 4% articaine and 4% prilocaine. In this study, the overall incidence of paresthesia was determined to be 1:785,000. It is interesting to note that the number of reported cases of paresthesia increased dramatically following the introduction of 4% articaine into the Canadian market in 1985. Two follow-up studies examining further reports of paresthesia from 1994 to 1998, and 1999 to 2008 had similar findings, further implicating the highly concentrated local anesthetics 4% articaine and 4% prilocaine with paresthesia (Miller and Haas, 2000; Gaffen and Haas, 2009).
In 2005, a Danish study conducted a retrospective review of reports of paresthesia from 2002-2004, similar in methods to the Canadian studies, and reported that 4% articaine was implicated in 88% of injury cases (Legarth, 2005). A more recent clinical and registry study based on the Danish Medicines Agency’s national database on adverse drug reactions indicated that neurotoxicity of the injected substance is the causative factor rather than the needle penetration as the majority of nerve injuries were associated with 4% articaine and a substantial increase in the number of injection injuries followed its introduction to the Danish market (Hillerup and Jensen, 2011).

In the United States, a randomized, double-blind, multicenter trial of 1,325 patients on the efficacy and safety of 4% articaine found that paresthesia was reported by 0.9% of the articaine group compared to 0.45% of the lidocaine group (Malamed et al., 2001). Two other studies based in California have been published in 2000 and 2007. In the former study, which was published prior to the release of articaine into the American market, 4% prilocaine was found to be involved more frequently than other anesthetics (Pogrel and Thamby, 2000). In the latter study from the same author, it was observed that while paresthesia reports with prilocaine were higher than expected, articaine was proportional to that predicted based on their estimated usage data (Pogrel, 2007). Finally, in a recent study of retrospective reports of paresthesia involving local anesthetics between 1997 through 2008 obtained from the U.S. Food and Drug Administration, it was found that cases involving 4% prilocaine and 4% articaine were 7.3-times and 3.6- times, respectively, greater than expected (Garisto et al., 2010).
While all the above studies found a significant relationship between 4% anesthetics and incidence of paresthesia, they also unanimously found that the lingual nerve was most often affected during mandibular anesthesia as compared to the inferior alveolar nerve.
II. Statement of Problem

While Haas and Lennon found the incidence of local anesthetic induced paresthesia to be 1 in 785,000 injections, Garisto et al reported a rate of 1 in 13,800,970. Other studies fall mostly within this range. Thus, it can be said that although local anesthesia induced paresthesia may be a very debilitating adverse effect, it is a rather uncommon complication. However, given the profession’s main principle of ‘do no harm’, one must thoroughly compare the risks and benefits of drugs before administering them.

Retrospective studies are the best tools available in studying uncommon adverse effects. However, as correlation from retrospective studies does not imply causation, there is an enormous need for the gathering of data from multiple sources in order to construct an accepted conclusion.

While mounting evidence from previous retrospective studies link 4% solutions with significantly higher incidence of paresthesia, there continues to be ongoing uncertainty in dentistry fueled by disagreement among academics about whether sufficient evidence has been thus far presented (Malamed et al 2001, Haas 2006, Hillerup and Jensen 2006, Malamed 2006, Dower 2007, Malamed 2007). As such, many have called for further studies to be done in this regard to find whether similar findings are found elsewhere.

In 2002, four years following the release of 4% articaine in the United Kingdom, Drs. Van Eeden and Patel of Royal Berkshire Hospital, penned a letter to the British Journal of Oral and Maxillofacial Surgery, regarding an unusual number (four) of patients having presented complaining of persistent and long-standing paresthesia following an inferior alveolar nerve block with articaine for routine dentistry. The duo called on studies to ascertain whether their observation was isolated, or if it is mirrored across the United
Kingdom (Van Eeden et al., 2002). Furthermore, Dr. Pedlar of Leeds Dental Institute confirmed similar observations of this apparent increase in dysesthesia following regional nerve block injections associated with the use of articaine, and asked for a wide scale survey of adverse events to clarify the significance of this apparent adverse reaction (Pedlar, 2003).
III. PURPOSE

While thus far, studies of differences in the incidence of paresthesia among available local anesthetics in dentistry have been conducted with data from Canada, United States and Denmark, no such assessment has been done for the UK. Therefore the purpose of the proposed study was to retrospectively analyze cases of non-surgical paresthesia associated with local anesthetics that were voluntarily reported to the UK Medicines and Healthcare Products Regulatory Agency’s Yellow Card database over the period 1998 to 2008.
IV. OBJECTIVE

The objective of this study was to test the following null hypothesis:

Null Hypothesis (H₀): The type of local anesthetic used has no impact on the rate of voluntarily reported non-surgical paresthesia in dentistry. The frequency of reported cases of non-surgical paresthesia associated with each local anesthetic agent will be proportional to the relative usage of each local anesthetic.
V. RESEARCH METHODOLOGY

The study design was a retrospective review of the reported cases of paresthesia in dentistry, which were voluntarily reported to the UK Medicines and Healthcare Products Regulatory Agency’s Yellow Card Scheme. The study also reports on the distribution of usage among the four dental local anesthetic drugs currently available in the U.K.

Ethics approval for this study was obtained from the University of Toronto Health Sciences Research Ethics Board.

Retrospective analysis of cases of non-surgical paresthesia in dentistry in the U.K.

The Medicines and Healthcare regulatory agency is an executive agency of the Department of Health in the United Kingdom, which protects and promotes public health and patient safety by ensuring that medicines, healthcare products, and medical equipment meet appropriate standards of safety, quality, performance and effectiveness, and are used safely. The safety of medicines is monitored using the Yellow card Scheme which has been in existence since 1964 after the famous thalidomide tragedy. The Yellow Card Scheme is a computerized information database, containing over half a million reports of adverse drug reactions, and stored in a database known as the Adverse Drug Reaction On-line Information Tracking (ADROIT) system. In May of 2006, the database was transferred to a new MHRA information management system called Sentinel. Voluntary reports of reactions on Yellow Cards constitute a vital source of information on adverse effects of medicines. The scheme acts as a detection and warning system for
the identification of previously unrecognized reactions and enables identification of risk factors, outcomes of the adverse drug reactions (ADR) and other factors that may affect clinical management. The value of the scheme has been demonstrated many times and it has helped to identify many safety issues such as linkage of black cohosh and liver toxicity. Reports from healthcare professionals, patients and the pharmaceutical industry are all entered onto the MHRA’s adverse drug reaction. The basis of this study was the adverse event line listings from the database of voluntary reports to the Yellow Card involving the dental local anesthetics currently available in the U.K.

Yellow Card summarizes the information of individual adverse event reports in line listings. Researchers are able to obtain a copy of these detailed summaries after approval of application by the Independent Scientific Advisory Committee (ISAC) for the MHRA database research and demonstration of research ethics approval. Some of this information, albeit further summarized and tabulated, is also available to the public through the MHRA website and is listed as Drug Analysis Prints (DAPs). These DAPs are a tally of all adverse drug reactions reported since the drug was made available in the U.K.

For the purposes of this research project, the database was accessed and searched by an ISAC representative for suspected ADR cases based on the local anesthetic drug active ingredients being one of articaine, benzocaine, bupivacaine, carticaine, levobupivacaine, lidocaine, lignocaine, mepivacaine, prilocaine, ropivacaine, and tetracaine, between January 1\textsuperscript{st}, 1997 to December 31\textsuperscript{st}, 2009. The listings were also filtered for neurological
signs and symptoms, paresthesias and dysesthesias, and other sensory abnormalities, which included hyperesthesia, hypoesthesia, dysgeusia, aguesia, or burning sensation. Figure 1 shows an example of line listings provided by the MHRA.

Once these data were received by the University of Toronto, Faculty of Dentistry, Discipline of Anesthesia, it was evaluated based on previously set inclusion and exclusion criteria as to comply with the applications made to the University of Toronto Health Sciences Research Ethics Board and MHRA Yellow Card Scheme. Thus ADR data were further filtered to include only those procedures which were dentally related, had sensory adverse effects limited to the oral region, and occurred during the period of January 1st, 1998 to December 31st, 2008. 4% articaine was introduced in the U.K market in 1998. Furthermore, since lidocaine, articaine, prilocaine, and mepivacaine are the local anesthetics available for injectable dental use in the U.K. only these local anesthetics and their trade names were included for further analysis. Unfortunately, the case reports did not describe the nature of the dental procedure that was being undertaken at the time and thus, surgical cases could not be identified.

For the cases that fulfilled the above inclusion criteria, where available, the following case parameters were entered into an Excel spreadsheet and subjected to descriptive statistical analysis using SPSS® (version 17, Chicago, IL): generic name of the local anesthetic; year of the adverse event; age and gender of the patient; and the site of the nerve injury.
**Dental local anesthetic usage in the U.K.**

Yearly sales data of dental local anesthetic cartridges in the U.K., during the period of 1998 through 2008, were purchased from the dental research company Strategic Data Marketing (Strategic Data Marketing, Rochelle Park, N.J., unpublished data, 2010). Yearly sales data were provided by anesthetic drug trade name and per 50 units of anesthetic cartridges. An example showing data for year 2000 is shown in Table 2. The table was arranged based on year of sales and the generic drug name, as the totals for each trade name drug of the same generic formula were combined. For example, Lignostab®, Xylocaine®, Xylo tox E80®, Eurocaine®, Lignospan® are all trade names for lidocaine and thus, their sales data were combined under lidocaine.

For each year, a small portion of sales was reported as private label, which was comprised of drugs lidocaine and articaine. Table 3 lists the percentage of private label data that was undifferentiated between articaine and lidocaine per year. In order to include the unknown private label sales data, an assumption was made that the ratio of undifferentiated lidocaine to articaine private label sales would reflect that of the total known lidocaine to articaine sales. The number of unknown sales was then added to that of the known sales numbers (Table 2). This method was also used by Garisto et al (2010).

**Statistical analysis**

Statistical analysis (all statistical tests were 2-tailed and interpreted at the 5% level) was used to test the null hypothesis that the particular local anesthetic had no impact on the frequency of reporting of cases of dental paresthesia. Chi-Square goodness-of-fit test was
used to compare the observed frequency of paresthesia for each drug, obtained from the
reports of oral paresthesia submitted to the Yellow Card Scheme to the expected
frequency of reported cases. The expected frequency was calculated by multiplying the
overall percentage of each local anesthetic usage based on the sales data, and the total
number of included cases. A limitation of the chi-square test is that the expected
frequencies must not be less than five to ensure accuracy. If expected frequencies were
less than five, the exact binomial probability distribution test should be performed and
thus, this was carried out in this study as applicable.

Furthermore, descriptive statistics was performed on gender, age, and location of
paresthesia based on available data to show significance of differences where found.
VI. RESULTS

Search of the Yellow Card Scheme’s database for the periods of January 1998 through August 2008 yielded 1872 line listings comprised of 193 cases of sensory and neurological adverse events related to the local anesthetic agents. Review of the provided information from each of these 193 cases revealed that there was a total of 45 cases that satisfied the inclusion and exclusion criteria. In one case, both articaine and lidocaine were used and as with previous similar studies, this case was discarded from the final tabulation, leaving 44 cases. It should be noted that three cases involving lidocaine were reported on the same date of 10/29/2008, all of which had identical accompanying data. However, since the three cases were given three different case reference numbers, they could not be discarded as they fulfilled the inclusion criteria.

Of the 44 cases a total of 34 (77.3%) cases involved articaine, seven (15.9%) involved lidocaine, two (4.5%) involved prilocaine, and one (2.3%) involved mepivacaine. Thus, articaine was the most implicated in paresthesia cases by a dental local anesthetic over the entire study period as it was reported 3.4 times the number of the combined reports for the other three anesthetics. Figure 2 shows the observed cases of paresthesia of each local anesthetic drug for each year of study.

Local anesthetic usage, shown as a relative percentage based on the yearly U.K. local anesthetics sales data for the period of 1998 though 2008 is shown in Figure 3. Nearly 70% of the local anesthetic sales were of lidocaine which would reflect its usage by dentists. Year by year local anesthetic sales can be seen in Figure 4. It is clearly evident that although lidocaine still remains the most widely used local anesthetic, articaine usage
has been steadily increasing, as it overtook prilocaine and became the second highest selling dental local anesthetic in the U.K since 2004. Over the 11-year focus of this study, approximately 436,426,100 cartridges of local anesthetic were sold in the U.K. Thus, each year approximately 39,675,100 cartridges are used in dentistry. With the working assumption that all sold local anesthetics were used clinically on dental patients, the incidence for reported cases of local anesthetic induced paresthesia was calculated. The overall reported incidence was 1 in 9,698,358, which included the one case where both lidocaine and articaine were used. Excluding this case, the overall incidence was 1 in 9,918,775. The reported incidence for each local anesthetic was: articaine 1:1,684,132; prilocaine 1:24,368,600; mepivacaine 1:27,414,150; and lidocaine 1:43,287,748.

The observed cases of paresthesia compared to the expected frequencies of each local anesthetic are shown in Figure 5. If the null hypothesis of no difference between local anesthetics was correct, each drug would have the same number of observed and expected paresthesia cases. However, it can be seen that articaine has a much higher observed than expected cases while the other three local anesthetics had lower observed than expected reports. Observed cases with articaine were 5.9-times greater than expected.

Chi-square goodness-of-fit analysis of the cases from 1998 to 2008 showed that articaine had a higher than expected frequency of paresthesia compared to the three other local anesthetics combined, and this was statistically significant (p<0.0001) based on market share, as shown in Table 4.

**Patient age and gender**
The distribution of the paresthesia cases based on the patient’s age category is shown in Figure 6. The mean age of affected patients was 42.9 years with a median of 44 years and the age range was 18 to 65 years. Most of the cases reported involved patients in fourth, fifth, and sixth decades.

The distribution of affected patients by gender, where reported, can be found in figure 7. Overall, 28 cases were found in females (63.6%), compared to 16 males (36.4%). This difference although appearing large, was not found to be statistically significant due to the small sample size (p=0.07).

**Maxilla versus mandible**

When comparing arches in regards to the location of paresthesia, the mandibular arch was affected in 22 (84.6%), compared to 4 (15.4%) patients with maxillary paresthesia. This difference was statistically significant (p< 0.001) and can be seen in Figure 8. None of the cases reported paresthesia of both arches.

**Affected area**

Out of 44 total case reports, 30 had identified an affected anatomical structure. The tongue which is innervated by the lingual nerve, was reported in 16 cases. The lower lip, innervated by a branch of the inferior alveolar nerve, was reported in 6 cases. None of the cases had both of these structures affected. The upper lip, the chin, cheek, side of the face and oral mucosa were also found to be affected in different cases. The distribution of sites affected is shown in Figure 9.
VII. DISCUSSION

These findings are consistent with previous retrospective studies investigating differences among local anesthetics in the incidence of paresthesia, as once again the higher concentrated 4% articaine solution was significantly implicated (Haas and Lennon, 1995; Miller and Haas, 2000; Legarth, 2005; Hillerup and Jensen, 2006; Gaffen et al, 2009; Garisto et al, 2010). Supporting this finding is the growing number of in-vitro and in-vivo experimental evidence of a dose-dependent local anesthetic induced neurotoxicity (Fink and Kish, 1976; Kalichman et al., 1989; Rigler and Drasner, 1991; Lambert and Hurley, 1991; Kalichman, 1993; Selander, 1993; Lambert, et al., 1994; Kanai, et al.,1998; Cornelius, et al., 2000; Friederich et al., 2002; Johnson, et al., 2004; Kitagawa et al., 2004; Perez-castro et al., 2009).

However, in this study, with only 2 cases of reported paresthesia, prilocaine was rarely associated. A review of the literature yielded an interesting finding as to a possible explanation for the above result. A survey of local anesthetic use among general dental practitioners in the UK for period of 2002-2003 found that 81% of practitioners selected lidocaine/epinephrine, while 10% selected articaine/epinephrine, and 4% selected prilocaine/felypressin as their first choice for an anesthetic agent for healthy patients (Corbett et al., 2005). In medically compromised patients prilocaine/felypressin was most commonly selected (43%) for patients, compared with lidocaine/epinephrine being used in 40% of cases. Although, plain solutions such as prilocaine and mepivacaine are indicated in patients with cardiovascular conditions, they were selected by only 7% of practitioners in such cases. Furthermore, the commonly used prilocaine/felypressin formulation is actually a 3% anesthetic solution in the UK, while the rarely used plain
prilocaine is a 4% solution. Taking into account the ratio of healthy versus medically compromised patients, these usage data are quite similar with those found in this study through the data from Strategic Dental Marketing (SDM) for the considered years. During the period of 2002-2003, using SDM data, lidocaine had 68% of the market share, while articaine and prilocaine had 13% and 15%, respectively. While SDM data did not differentiate between 3% and 4% formulations of prilocaine, using the results of Corbet et al., it can be assumed that as 4% prilocaine is very seldom used in the United Kingdom, prilocaine has a lower observed than expected rate of paresthesia. Thus, this further supports previous studies, which state that it is indeed the concentration, not the drug per se, that is causing higher incidence of paresthesia associated with certain local anesthetic agents.

Much like its predecessor studies, this research had a retrospective design based on a spontaneous voluntary reported database of an adverse effect. (Haas and Lennon, 1995; Miller and Haas, 2000; Hillerup and Jensen, 2006; Gaffen and Haas, 2009; Garisto et al., 2010). The necessity of a way to identify unexpected and uncommon adverse effects of drugs, especially those newly released, has been illustrated many times. Examples include acetylsalicylic acid (aspirin) and Reye’s syndrome, bupropion and seizures, streptomycin and permanent deafness, amiodarone and pulmonary fibrosis, all of which were discovered by reviews of adverse event databases. According to Health Canada’s voluntary adverse drug effect database, MedEffect, voluntary reporting by health professionals of suspected reactions is the most common way to monitor the safety and effectiveness of marketed health products. These individual reports may be the only source of information concerning previously undetected adverse reactions or changes in
product safety and effectiveness profiles to marketed health products. The Yellow Card Scheme, used specifically in this study, was prompted by the severe adverse drug reaction associated with the drug thalidomide. Introduced originally in West Germany in 1956, thalidomide was marketed in 1958 in the United Kingdom as Distaval® (Layton and Cox, 2007). An effective advertising drive led to worldwide usage of the drug for treatment of anxiety, insomnia, and morning sickness. First suspicions of a serious problem were raised more than three years following its release, after investigations at obstetric units in West Germany showed a great increase in the number of children born with limb deformities. By the time thalidomide was withdrawn in 1964, over 10,000 babies had been born severely deformed. Due to this appalling human toll, worldwide attention was focused on developing databases to track adverse drug reactions that may be missed with the relatively small sample sizes of premarketing clinical trials. In May 1964 the Yellow Card Scheme was launched within the United Kingdom. In the forty years of the Yellow Card Scheme, other unexpected effects have been identified from drugs that had been carefully tested and assessed before being licensed for general use (MHRA, 2004). Indeed, some uncommon effects may only be identified from continued monitoring. Thus, as these databases of voluntary reported adverse drug reactions are a collection of case-reports with an advantage of covering entire geographic populations, they are a scientific yet cost-effective, method of monitoring drug safety (Hazell and Shakir, 2006).

The purpose of ADR databases such as the MHRA and the Yellow Card Scheme is to regularly and systematically review all the data for individual drugs or products, looking for reactions of potential concern. However, an alternative approach is to bring together
the data for a particular adverse drug reaction and review the drugs which have been suspected of producing the reaction and the numbers of cases, such as has been done in this retrospective study. This approach is likely to be more useful for regulatory bodies when comparing drugs of the same class, or those used for similar outcomes (Waller and Lee, 1999).

Thus, the utility of spontaneous adverse drug reactions reporting schemes and formal studies in the identification of drug safety issues is well established. However, these schemes have a number of limitations. One widely acknowledged limitation in using voluntary reported databases for research is the under-reporting phenomenon. A recent systemic review to estimate the extent of under-reporting of adverse drug reactions to spontaneous reporting systems in 12 countries found that approximately 6% of all potentially reportable reactions are reported (Hazell and Shakir, 2006). Furthermore, the reporting rates for suspected reactions of a life threatening nature, is found to be much higher than other adverse events, such as paraesthesia. There is other evidence indicating that the spontaneously reported cases is even lower, and may represent only 1% of true cases (Rodriguez et al., 2001, Rogers et al., 1988, Jorup-Ronstrom et al., 1983). Specifically in the United Kingdom, it has been estimated that approximately 2% of adverse event data is reported (Fletcher, 1991). It has been recognized that a major deterrent in reporting was the unavailability of the Yellow Card reporting forms (Lawson, 1990, Belton et al., 1995). As these forms are commonly available in pharmacy departments of hospitals, monthly index of medical specialties, and medical data sheet compendiums, dentists in general may not have convenient access and thus it can be expected to have even lower reporting rates than their medical colleagues.
Thus, it can be concluded that the rate of under-reporting is quite substantial. In this study, the incidence rate for local anesthetic induced paresthesia was found to be 1 in 9,698,358 injections. However, this rate is significantly underestimated due to the limitations of the study. Firstly, as illustrated above, the numerator is only a small fraction of the true value, due to the general under-reporting. The number of paresthesia reports from the UK is a very small fraction of that reported in the province of Ontario in Canada, where cases of paresthesia are reported to a specific dental Professional Liability Program (PLP) database instead of a combined adverse drug reaction database like UK’s Yellow Card scheme (Haas and Lennon, 1995; Miller and Haas, 2000; Gaffen and Haas, 2009). While both databases are based on voluntary reporting, the PLP likely has higher reporting rates since it is a group insurance program that is specifically geared to licensed Ontario dentists and serves in their interest to report should claims arise in the province.

Secondly, the denominator, which is the overall number of cartridges used, may be overestimated. The denominator is the number of local anesthetic cartridges that was sold in the United Kingdom during the study period as per data purchased from Strategic Dental Marketing. However, this assumption may be an exaggeration since not every cartridge of local anesthetic that is sold, is actually used. Due to these reasons, it may be argued that from a population perspective, voluntary case report data should not be used for estimating incidence rates (Rodriguez et al., 2001).

Another limitation of the study in relation to the data purchased from SDM was the portion of ‘unknown’ private label sales. In every year, there was a number of
undifferentiated private label sales comprised of lidocaine and articaine. For the purpose of this study, it was decided that the number used for unknown cartridges of anaesthetic would be proportional to reflect the ratio of lidocaine to articaine in the known yearly sales totals. On average, these unknown data only represented less than 1.8% of the yearly sales.

Considering the observed rates of paresthesia associated with articaine, as illustrated in figure 2, it may be suspected that the high peak in the number of cases of paresthesia attributed to articaine, which occurred during period of 1999-2000, is due to the ‘Weber Effect’ in reporting. The Weber effect, a trend first noticed during a study of nine nonsteroidal anti-inflammatory drugs marketed in the United Kingdom during the late 1970s and early 1980s, is an epidemiologic phenomenon stating that the number of reported adverse reactions for a drug rises until approximately the middle to end of the second year of marketing, peaks, and then steadily declines to the level of other similar drugs (Weber, 1984). Various studies have analyzed the Weber effect in different classes of drugs and have even been successful in duplicating the original study using different adverse drug databases from around the world (Fung et al., 1998, Wallenstein and Fife, 2001, Hartnell and Wilson, 2004). During the first three years following the release and marketing of 4 percent articaine, there were 11 reported cases of paresthesia associated with this drug compared with two cases associated with the other local anesthetics. However during the next eight years, there were 23 cases of paresthesia associated with articaine, compared with eight cases total for the remaining anesthetics.
In order to rule out a possible bias of data caused by the Weber Effect that could affect study results, Chi-square analysis was repeated with all reported cases of paresthesia for the first three years following release of articaine omitted and usage data from SDM adjusted to reflect the period of 2001-2008 (Table 5). There was no major change, and all results remained statistically significant (p<0.0001).

Furthermore, the drop from the peak of the number of reports seen in year 2000 may not have been caused by the Weber effect. In the UK newly marketed drugs have packages marked with an inverted triangle by the British National Formulary, and health care providers are asked to report any adverse drug reactions that might conceivably be related to the newly released drug. For other products health professionals are only requested to report very serious or life threatening ADR (Griffin, 1986). The Black Triangle status is usually placed for the first two years after release of a new drug. Thus, the reason for the high peak and the subsequent relative drop in reported rates of paresthesia after injection of articaine may be due to the removal of the black triangle from the package after the first two years. However, a survey of UK health professionals regarding their attitudes towards reporting of adverse reactions using Yellow Card showed that over half of the responders did not know the precise meaning of the black triangle (Belton et al., 1995).

Another limitation of the study was the inability to rule out surgically caused paresthesia directly. In some of the previous retrospective studies, the nature of the procedure undertaken by the dentist following the administration of local anesthetic was known and thus surgical procedures such as an extractions or implant placements were excluded as
that may have been the cause of the paresthesia (Gaffen and Haas, 2009, Garisto et al., 2010). In this study, the dental procedure was not described in line listings received from the Yellow Card database and thus, surgical procedures were not excluded directly. However, two postulations are made in regards to these data to alleviate skepticism regarding its cause. Firstly, as spontaneous reporting schemes are passive investigation systems, reliance is placed on the ability of health professionals to recognize possible adverse drug reactions and to distinguish these from symptoms related to the underlying procedure. For example, it should be assumed that a dental surgeon would not voluntarily report a case of paresthesia following surgical extraction of a mandibular third molar to an adverse drug reaction database. Secondly, this assumption is made for all local anesthetics in use, and thus, it would not bias towards any specific local anesthetic.

As found in previous retrospective studies on local anesthetic induced paresthesia in dentistry (Haas and Lennon, 1995; Pogrel and Thamby, 2000; Hillerup and Jensen, 2006; Gaffen and Haas, 2009; Garisto et al., 2010) most cases in this study affected the lingual nerve rather than the inferior alveolar nerve. An explanation as to why the lingual nerve is more likely to suffer damage is simply related to its structure. The lingual nerve branches from the third division of the trigeminal nerve after it exists the foramen ovale. It carries with it taste fibers from the chorda tympani that supply the anterior two thirds of the tongue. The lingual nerve may vary in shape but also in size from 1.53mm to 4.5mm. At the region of the lingula, close to the landmarked area for the mandibular block injection, the lingual nerve is either monofascicular or oligofascicular (Graff-Radford and Evans, 2003). This is unlike the inferior alveolar nerve, which is multifascicular in this
region. This structural difference may explain why the lingual nerve is more susceptible than the inferior alveolar nerve to injection damage. If a nerve was unifascicular at the point of injection, as 33% of lingual nerves are found to be, then any injury at this point automatically would affect the whole nerve. Furthermore, if the nerve has only one fascicle there would be no opportunity for remaining fascicles to compensate and minimize the impairments caused by an injured fascicle (Pogrel and Thamby, 2003).

This study found a greater incidence of paresthesia amongst the female gender (63.6%) although this was not statistically significant due to the small sample size. Previous studies had either not found a gender specific predilection (Haas and Lennon, 1995; Gaffen and Haas, 2009), or found that females were more likely to be affected. (Pogrel and Thamby 2000; Hillerup and Jensen 2006; Garisto et al., 2010). Epidemiologic and survey research has classically demonstrated greater frequencies of sensory related symptoms among females than males in the general population (Fillingim, 2000). Nevertheless, if females are more affected, this difference may be explained by discrepancy in reporting rates, as females are more likely to visit their health care provider, report an injury, or seek referral to specialists (Kandrack et al., 1991; Weir et al, 1996). Alternatively, gender differences in biological vulnerability and physiologic response to peripheral nerve injury may also exist (Hillerup and Jensen, 2006). Women are over-represented in a variety of chronic pain conditions. Conditions such as migraine and tension-type headaches, temporomandibular joint disorders, fibromyalgia are all found to be more prevalent in women, with female to male ratios ranging from 2:1 to 9:1 (Lipton and Stewart, 1998; Schwartz et al., 1998; LeResche, 1997; Wolfe et al., 1995).
Interestingly, the mean age of affected patients was 42.9 years as most of the reported cases involved patients in their fourth, fifth, and sixth decades of life. This was consistent with other recent studies which had found the mean age of affected patients to be 41.9 to 43.8 years (Gaffen et al., 2009; Garisto et al., 2010). It can be speculated that this observed age-related higher reporting of cases of paresthesia, likely mirrors the increased need and utilization of dental services of this age group.

The results of this study and those previously, have shown that administering 4% local anesthetics carry a higher risk of paresthesia especially for mandibular blocks. Prudent practitioners must always weigh the risks and benefits in administration of all drugs and procedures. As such, the benefits of using 4% solutions such as articaine have been extensively studied. With respect to maxillary infiltration anesthesia, some studies have found 4% articaine to be more effective than 2% lidocaine for lateral incisors but not molars (Evans et al., 2008), while others reported no clinical superiority for this injection (Oliveira et al., 2004; Vähätalo et al., 1993). However, a recent randomized controlled trial found a statistically significant difference supporting use of 4% articaine in place of 2% lidocaine for buccal infiltration in patients experiencing irreversible pulpitis in maxillary posterior teeth (Srinivasan et al., 2009). However, for mandibular block anesthesia, randomized controlled clinical trials have thus far not shown any superiority for successfully achieving the inferior alveolar nerve block with either prilocaine or articaine when compared to 2% lidocaine (Malamed et al., 2001; Claffey et al., 2004; Mikesell et al., 2005; Sherman et al., 2008; Tortamano et al., 2009). Moreover, studies comparing different concentrations of articaine have revealed no superiority of 4%
articaine for onset of effect and depth of anaesthesia compared with 2% articaine in either infiltration or block anesthesia (Winther and Nathalang, 1972; Hintze et al., 2006)

A recent experimental study using rat sciatic nerves to examine the effects of needle penetration with injection of saline solution versus articaine in different concentrations found concentration-dependent neurotoxic injuries after injection of articaine with a significant difference between 2% and 4% formulations (Hillerup et al., 2011). Furthermore, the mechanical injury of needle penetration with saline injection had no significant effect on nerve conduction or histomorphology. Thus, if the risk of nerve injury is greater with 4% solutions, with no apparent benefit, then usage of these agents for inferior alveolar blocks should be avoided.
VIII. FUTURE DIRECTIONS

The chief limitation of this study was the under-reporting phenomenon similarly seen in other pharmacovigilance studies, which are based on voluntary reported adverse drug reactions. It would be inappropriate to apply a standard ‘correction factor’ based on previous studies of under-reporting rates, since surely there is substantial variation in rates for different drugs and types of adverse reactions, in different populations and at different points in time (Hazell and Shakir, 2006). In the United Kingdom, further efforts must be made in promotion of the Yellow Card Scheme, facilitation of reporting, and education about the benefits of adverse drug reactions reporting. In some countries, such as Sweden, France and Italy, reporting of adverse reactions is compulsory possibly leading to higher success rates. (Waller and Bahri, 2002).

An important finding in this study was that the local anesthetic prilocaine was not associated with increased rates of reported paresthesia in the United Kingdom. Thus, a 1% reduction in the formulation of prilocaine, from 4% to 3%, significantly reduced the incidence of paresthesia associated with this drug. In Germany, 2% articaine has been made available in market. Thus far, studies have shown similar efficacy between both populations (Winther and Nathalang, 1972; Hintze et al., 2006). Future studies will address whether a reduction in percentage of articaine will have similar reduction in incidence of paresthesia with this drug.
IX. CONCLUSIONS

Fourty four cases of dental local anesthetic induced paresthesia reported to the United Kingdom’s Yellow Card Scheme from 1998 to 2008 were reviewed. The majority of cases were related to the mandibular block injection and lingual nerve was most often affected. For articaine, a 4% local anesthetic, the observed frequencies of reported cases of paresthesia from 1998 to 2008 were significantly greater than expected compared to other local anesthetics. While local anesthetic induced paresthesia is found to be an uncommon event, the findings support those of previous studies (Haas and Lennon, 1995; Miller and Haas, 2000; Pogrel and Thamby, 2000; Dower, 2003; Legarth, 2005; Hillerup and Jensen, 2006; Gaffen and Haas, 2009; Garisto et al., 2010) and show that the 4% solutions of anesthetics used in dentistry are associated with higher risk of paresthesia than those of lesser concentrations. As previous research has not supported additional benefit of using 4% solutions for mandibular block anesthesia, it appears difficult to justify using such agents given the underlying risks. Prudent practitioners should always assess the risks and benefits of all drugs they prescribe or administer to upkeep their oath; *primum non nocere.*
**X. TABLES**

**Table 1. Physiochemical properties of local anesthetics**

<table>
<thead>
<tr>
<th>Agent</th>
<th>Chemical Configuration</th>
<th>Molecular Wt</th>
<th>pKa</th>
<th>Partition Coefficient</th>
<th>Protein Binding (%)</th>
<th>Onset</th>
<th>Relative Potency</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ester</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Procaine</td>
<td></td>
<td>236</td>
<td>8.9</td>
<td>0.02</td>
<td>6</td>
<td>Slow</td>
<td>2</td>
<td>Short</td>
</tr>
<tr>
<td>Amide</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lidocaine</td>
<td></td>
<td>254</td>
<td>7.9</td>
<td>2.9</td>
<td>64</td>
<td>Rapid</td>
<td>4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Mepivacaine</td>
<td></td>
<td>246</td>
<td>7.0</td>
<td>0.8</td>
<td>78</td>
<td>Fast</td>
<td>4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Bupivacaine</td>
<td></td>
<td>288</td>
<td>8.1</td>
<td>27.5</td>
<td>96</td>
<td>Moderate</td>
<td>16</td>
<td>Long</td>
</tr>
<tr>
<td>Prilocaine</td>
<td></td>
<td>220</td>
<td>7.9</td>
<td>0.9</td>
<td>55</td>
<td>Fast</td>
<td>4</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Articaine</td>
<td></td>
<td>321</td>
<td>7.8</td>
<td>17</td>
<td>94</td>
<td>Rapid</td>
<td>5</td>
<td>Intermediate</td>
</tr>
</tbody>
</table>

- Adapted from Covino et al., 1986 with additions from articaine package insert, 1996
Table 2.  Example of data obtained from Strategic Data Marketing

<table>
<thead>
<tr>
<th>Year</th>
<th>VendorName</th>
<th>BrandName</th>
<th>Units by 50 cartridges</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>ASTRA</td>
<td>CITANEST</td>
<td>119636</td>
</tr>
<tr>
<td>2000</td>
<td>ASTRA</td>
<td>LIGNOSTAB</td>
<td>126274</td>
</tr>
<tr>
<td>2000</td>
<td>ASTRA</td>
<td>XYLOCAINE</td>
<td>140934</td>
</tr>
<tr>
<td>2000</td>
<td>ASTRA</td>
<td>XYLOTOX E80</td>
<td>52388</td>
</tr>
<tr>
<td>2000</td>
<td>DEPROCO</td>
<td>EUROCAINE</td>
<td>13804</td>
</tr>
<tr>
<td>2000</td>
<td>DEPROCO</td>
<td>LIGNOSPAN</td>
<td>252570</td>
</tr>
<tr>
<td>2000</td>
<td>DEPROCO</td>
<td>SCANDONEST</td>
<td>38324</td>
</tr>
<tr>
<td>2000</td>
<td>DEPROCO</td>
<td>SEPTANEST</td>
<td>54655</td>
</tr>
<tr>
<td>2000</td>
<td>DEPROCO</td>
<td>UTILYCAINE</td>
<td>712</td>
</tr>
<tr>
<td>2000</td>
<td>PRIVATE LABEL</td>
<td>PRIVATE LABEL</td>
<td>34490</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Year</th>
<th>BrandName</th>
<th>Type</th>
<th>Units by 50 cartridges</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>PRIVATE LABEL</td>
<td>ARTICAINE/LIGNOCAINE</td>
<td>15080</td>
</tr>
<tr>
<td>2000</td>
<td>PRIVATE LABEL</td>
<td>LIGNOCAINE</td>
<td>19410</td>
</tr>
</tbody>
</table>
Table 3. Percentage of unknown private label sales yearly from 1998 through 2008, based on data from Strategic Data Marketing.

<table>
<thead>
<tr>
<th>Year</th>
<th>Unknown private label Sales (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1998</td>
<td>2.58%</td>
</tr>
<tr>
<td>1999</td>
<td>2.35%</td>
</tr>
<tr>
<td>2000</td>
<td>1.81%</td>
</tr>
<tr>
<td>2001</td>
<td>1.45%</td>
</tr>
<tr>
<td>2002</td>
<td>1.25%</td>
</tr>
<tr>
<td>2003</td>
<td>1.50%</td>
</tr>
<tr>
<td>2004</td>
<td>1.67%</td>
</tr>
<tr>
<td>2005</td>
<td>2.77%</td>
</tr>
<tr>
<td>2006</td>
<td>1.21%</td>
</tr>
<tr>
<td>2007</td>
<td>1.23%</td>
</tr>
<tr>
<td>2008</td>
<td>1.88%</td>
</tr>
<tr>
<td><strong>Average</strong></td>
<td><strong>1.79%</strong></td>
</tr>
</tbody>
</table>
Table 4. Observed and expected frequencies of paraesthesia involving the dental local anaesthetic articaine from 1998 through 2008 in the United Kingdom

<table>
<thead>
<tr>
<th>Local Anesthetic Drug</th>
<th>Observed Frequency</th>
<th>Expected Frequency (total # cases x fractional use of specific drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine</td>
<td>34</td>
<td>5.77</td>
</tr>
<tr>
<td>Others</td>
<td>10</td>
<td>38.23</td>
</tr>
<tr>
<td>Total</td>
<td>44</td>
<td>44</td>
</tr>
</tbody>
</table>

Does not include a case involving the use of more than one agent (n = 1). A statistically significant difference could be demonstrated (chi-square = 158.893, df = 1, p < 0.0001)
Table 5. Observed and expected frequencies of paraesthesia involving the dental local anaesthetic articaine from 2001 through 2008 in the United Kingdom

<table>
<thead>
<tr>
<th>Local Anesthetic Drug</th>
<th>Observed Frequency</th>
<th>Expected Frequency (total # cases x fractional use of specific drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Articaine</td>
<td>23</td>
<td>5.24</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>25.76</td>
</tr>
<tr>
<td>Total</td>
<td>31</td>
<td>31</td>
</tr>
</tbody>
</table>

Does not include a case involving the use of more than one agent (n = 1).
A statistically significant difference could be demonstrated (chi-square = 72.439, df = 1, p < 0.0001)
XI. FIGURES

Figure 1. Example of a Yellow Card supplied line-listing spreadsheet
Figure 2. Reported cases of local anesthetic induced paraesthesia by year and local anaesthetic drug.
Figure 3. UK local anaesthetic sales percentages from 1998 through 2008, based on data from Strategic Data Marketing
Figure 4. UK local anaesthetic sales percentages yearly from 1998 through 2008, based on data from Strategic Data Marketing.
Figure 5. Expected v. Observed frequency distribution per local anaesthetic drug from 1998 through 2008
Figure 6. Distribution of non-surgical paraesthesia cases by age.
Figure 7. Distribution of non-surgical paraesthesia cases by gender

- Female: 61%
- Male: 39%
Figure 8. Distribution of paresthesia cases by dental arch

- Maxilla: 15%
- Mandible: 85%
Figure 9. Distribution of paresthesia cases by affected area of face

- Tongue: 53%
- Lower Lip: 20%
- Upper Lip: 7%
- Other: 20%
XII. REFERENCES


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