Local anesthetic failure in endodontics:

Mechanisms and Management

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Many patients fear endodontic procedures due to a concern about pain. Although pain treatment is well managed in many endodontic patients, there exists a group of patients who do not receive adequate local anesthesia. This article reviews the mechanisms of local anesthetic failure and focuses on available evidence for developing effective and efficient approaches in local anesthesia.

Introduction

Successful management of pain emergencies is a strong component of clinical excellence. Although clinical studies indicate that comparatively few patients experience pain after endodontic procedures, it has been estimated that about 20% of patients experience moderate-to-severe pain after treatment (1, 2, 3). An additional small fraction of patients (about 1–2%) will experience a sudden 'flare-up' of severe pain or swelling after endodontic treatment. To compound the problem, the clinical management of endodontic patients is often problematic due to inadequate local anesthesia.

Many of these issues will be reviewed in articles in subsequent issues of *Endodontic Topics*, which will summarize the latest clinical research and relevant biological foundations from the perspective of providing guidance for the efficient and effective management of endodontic pain conditions. In this inaugural issue, we will review the problem of local anesthetic failures in endodontic patients. Why are local anesthetics less effective in endodontic pain patients? How can we better identify these patients before treatment? And, more importantly, what is the best current evidence available for recommending strategies in producing clinically acceptable anesthesia in these patients?

Prevalence of local anesthetic failures

When planning dental procedures on teeth with clinically normal (i.e. uninflamed) pulps, effective local anesthesia is the bedrock of dental pain control. Local anesthetics administered by the infiltration route of injection are highly effective in producing clinical anesthesia in normal tissue. Although nerve-block injections are considered more technically difficult, and therefore somewhat less predictable than infiltration injections, clinical studies suggest success rates of about 75–90% or more in patients with clinically normal teeth (4, 5, 6, 7, 8, 9, 10).

However, local anesthetics are generally much less effective when administered to patients with inflamed tissue (11). For the purposes of this review, we will focus on studies that evaluate patients with odontogenic pain due to inflamed pulpal or periradicular tissue. Clinical studies have reported that a single inferior alveolar nerve (IAN) block injection of local anesthetic(1.8 cc) is ineffective in 30–80% of patients with a diagnosis of irreversible pulpitis (5, 12, 13, 14). Figure 1 compares the frequency of anesthetic failures after a single IAN nerve block injection of 1.8cc of 2% lidocaine with 1:100000 epinephrine. Patients with irreversible pulpitis had an 8-fold higher failure of local anesthetic injections in comparison to

normal control patients (5). Thus, local anesthetic failures can occur in a substantial proportion of endodontic pain patients. Similar observations are reported in children undergoing endodontic treatment (9). Understanding the biological basis for this problem is likely to lead to improved clinical outcomes in treating these patients.

Mechanisms of Action of Local Anesthetics

Research conducted in the last 10 years has shed great light onto the mechanisms of action of local anesthetics in blocking sodium channels. Sodium channels are expressed by excitable cells, such as neurons, cardiac cells and skeletal muscle. These channels are classified as voltage-gated sodium channels, and are activated in the presence of an appropriate electrical field. Under physiologic conditions, sodium channels are activated by the depolarization of an adjacent region of a peripheral neuron. This ability to detect electrical fields serves as the basis for electrical pulp testers; the clinical application of a sufficient electrical field onto a test tooth leads to the activation of the sodium channels, neuronal depolarization, and subsequently signals being sent to the brain.

Molecular biology studies have discovered several different types of sodium channels, and their amino acid sequence and protein structure have been deduced (15). As described later in this review, certain types of these sodium channels are found on pain neurons ('nociceptors') and appear to be less sensitive to local anesthetics. Thus, one possible hypothesis for local anesthetic failure is that inflammation evokes an increase in the anesthetic-resistant subpopulation of sodium channels that exist on pain neurons.

Most clinically useful local anesthetics diffuse across the plasma membrane and access the sodium channel from the cytosolic side of the protein. The drug binds together in the inner-pore region of the channel, thereby blocking the inflow of sodium ions, which in turn leads to neuronal depolarization being blockaded (16). Local anesthetics preferentially bind to the sodium channel in the inactivation phase that follows activation and depolarization. When administered to peripheral neurons, of course this blockade prevents signals from being transferred from the periphery to the central nervous system. Molecular studies have led to the channel's pore neuronal depolarization consisting of four
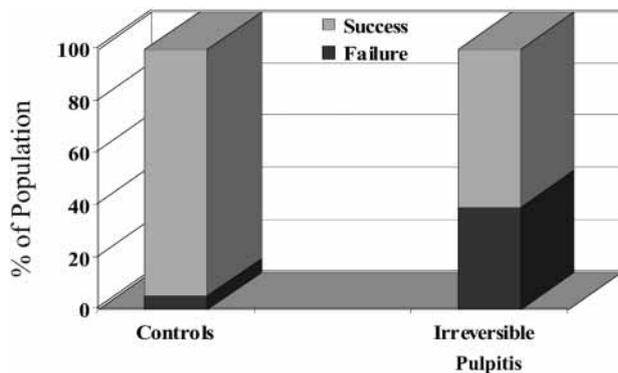
Fig. 1. Comparison of the frequency of failed inferior alveolar nerve block injections in 25 normal patients in comparison to 25 patients with pain due to irreversible pulpitis. All patients presented for dental treatment of a mandibular tooth that was either uninflamed (e.g., presentation for third molar extraction) or inflamed with a diagnosis of irreversible pulpitis. Patients then received 1.8cc of 2% lidocaine with 1:100 000 epineprhine and were assessed for clinical anesthesia over the involved area. (Re-drawn from: Hargreaves *et al. Abs Soc Neurosci* 2001 (Copyright retained by author)).
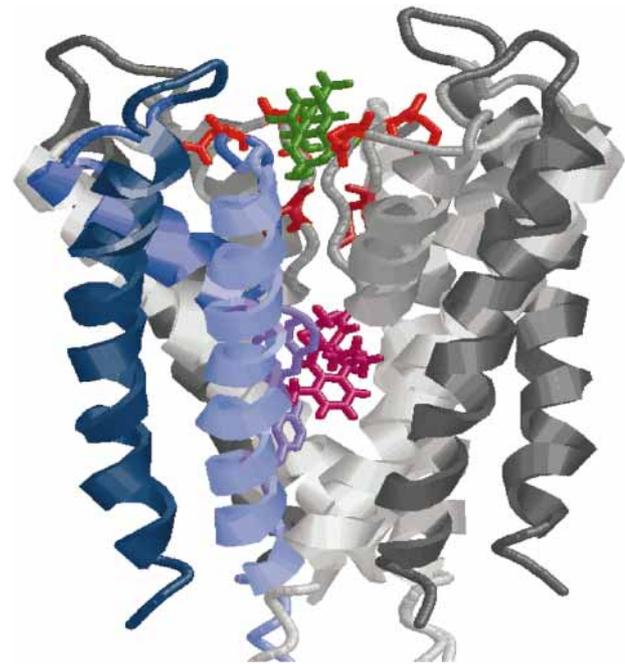
Fig. 2. Schematic illustration of a sodium channel indicating the binding site for local anesthetics. Tetrodotoxin (green) is shown at the outer pore opening, while etidocaine (purple) is shown approaching the local anesthetic binding site in the inner (cytosolic) pore opening. (Reprinted from Catterall W. From ionic currents to molecular mechanisms: the structure and function of voltage-gated sodium channels. *Neuron* 2002; 26: 15, with permission from Elsevier Science).

transmembrane domains, much like staves forming a barrel. Local anesthetics bind to sites located on all four of these domains and thereby block sodium inflow (Fig. 2) (11, 17). Knowledge of the properties of these binding sites has provided important clues in the development of new local anesthetic drugs (18).

Local anesthetics display a higher binding affinity to sodium channels that are in an inactivated form. This property predisposes local anesthetics to produce a use-dependent blockade and indicates that these drugs are especially effective in blocking rapidly firing nerves (19, 20) (Fig. 3). Since faster firing rates means that the sodium channel goes through the inactive form more often as it goes through the cycle, there is increased opportunity for local anesthetic binding. This is believed to be the basis for the effectiveness of systemic local anesthetics in treating chronic pain patients, since the local anesthetic would block the most rapidly firing neurons which are, presumably, nociceptors. However, this property does not explain local anesthetic failures in odontogenic pain patients, as such theories predict that these drugs would actually work even more effectively under conditions where peripheral nerves are rapidly firing. Thus, other mechanisms must be considered in order to explain the clinical problem of local anesthetic failure.

Although dental textbooks report that local anesthetics show differential blockade of nerves, our understanding of this process continues to evolve. Many of us may remember learning that the unmy-elinated C fibers are the most sensitive to local anesthetic blockade, followed by the lightly myelinated neurons (A-delta fibers), with the heavily myelinated neurons (A-beta fibers) being the least sensitive to these drugs (7). Under normal conditions, pain perception is mediated by the C and A-delta fibers, whereas touch and proprioception are mediated by the A-beta fibers. As textbooks have suggested that a positive lip sign (i.e. lack of touch sensation due to the blockade of A-beta fibers) predicts that pulpal pain fibers are anesthetized and the patient is ready for treatment, this has classic dental implications (7).

However, this classic lesson is based on research conducted in the 1930s using an older method of whole nerve recording of shorter fiber lengths (21, 22). More recent studies have re-tested this hypothesis using a single fiber recording technique (23, 24). Under these experimental conditions, the results indicate that local anesthetics block the heavily myelinated A-beta fibers and lightly myelinated A-delta fibers at much lower concentrations than unmyelinated C-fibers (24) (Fig. 4). Moreover, this finding is supported by careful behavioral studies conducted in animals. Injection of lidocaine into the sciatic nerve produces a complete blockade of innocuous touch at doses that only partially block nociception (25). Therefore, these data indicate that local anesthetics can block myelinated fibers preferentially over the unmyelinated fibers.

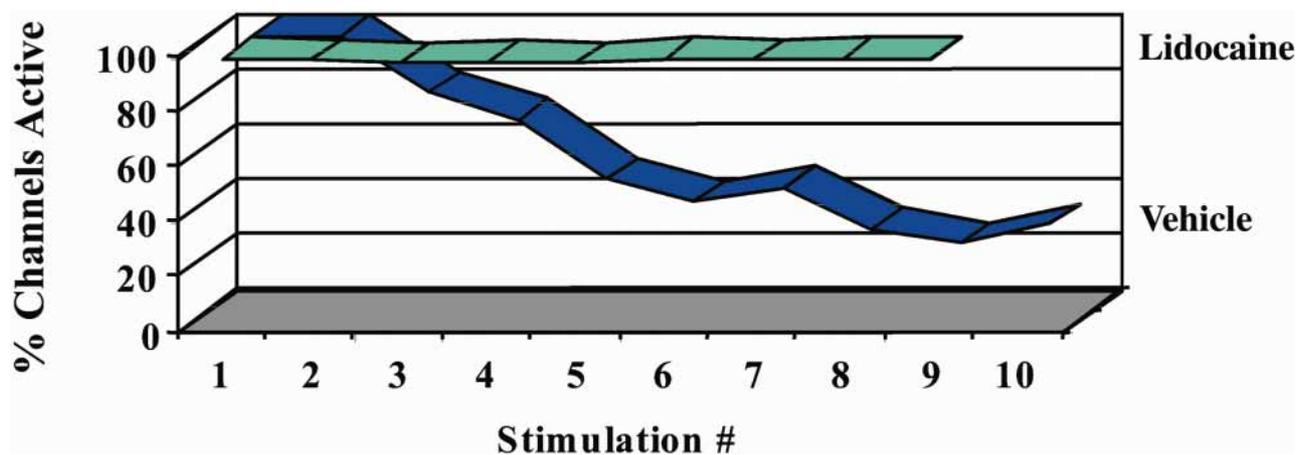Clinical research also does not support the classic

Fig. 3. Demonstration of use-dependent block by lidocaine (80 μM) to sodium channels. Lidocaine or vehicle were continuously exposed to separate groups of channels and the channels were stimulated by electrical pulses (200 ms pulses at 60 mV). These data indicate that the binding site for local anesthetics is available only after activation of the sodium channel. Thus, local anesthetics exhibit greater blocking activity in rapidly firing neurons. This property is termed use-dependent inhibition. (Data redrawn from: Grant *et al. Circulation Res* 1989; 65: 1247–62).

interpretation. In dental patients receiving an IAN block, lip numbness indicates the lack of A-beta mediated touch. In a clinical trial in 40 normal subjects after IAN block with 3% mepivacaine, 100% of the subjects reported lip numbness, but only 80% of these subjects had pulpal anesthesia (defined as no response to electrical testing). In another study on 30 normal subjects, an inferior alveolar nerve block with 2% lidocaine (and epinephrine at either 1 : 100 000, 1 : 80 000 or 1 : 50 000) produced 100% lip numbness, but only about 50–75% incidence of pulpal anesthesia in molars (26). Similar discrepancies between lip numbness and pulpal anesthesia in normal subjects have been reported in other clinical trials (4, 27, 28).

However, a positive lip sign is even more misleading in endodontic pain patients. In a clinical trial of 61 patients with irreversible pulpitis of a mandibular molar, 100% of the patients reported lip numbness after IAN anesthetic block, but only 62% of these patients had pulpal anesthesia (as defined by no response to thermal testing) (12). In a study on 26 patients with mandibular pulpitis, IAN block (2% lidocaine with 1 : 100 000 epinephrine) resulted in a 100% incidence of lip numbness, but only a 38% incidence of pulpal anesthesia (13). These studies indicate that IAN anesthetic blocks given to patients with irreversible pulpitis in a mandibular tooth have, on average, a 55% incidence of pulpal anesthesia, even in the presence of 100% lip numbness. Thus, a positive lip sign (i.e. lack of touch sensation) does not necessarily indicate pulpal anesthesia in the endodontic pain patient.

The results of other studies have also brought into question another classical belief of local anesthetics. In 1942, Takeuchi and Tasaki (29) reported that complete anesthesia occurs when three consecutive nodes of Ranvier are blocked, and this finding continues to be reported in dental textbooks today (7). According to this view, conduction blockade occurs regardless of the length of the nerve anesthetized – just as long as three nodes of Ranvier are included in the area of local anesthetic administration. However, recent studies have demonstrated that anesthetic blockade can be cumulative along the axon length, resulting in a gradual reduction in conduction velocity that eventually leads to a complete blockade (30, 31). This is shown in Fig. 5, where the lidocaine-mediated reduction in conduction velocity increases with the length of the nerve exposed to the drug. This work has called into question the traditional view that the three nodes of Ranvier should be blocked (30).

The clinical implication of this finding is that the success of clinical anesthesia may be increased by increasing the length of the nerve exposed to the local anesthetic. This finding might suggest that, if an IAN block fails, then the clinician may wish to perform a second injection via the Gow-Gates technique, as this would lead to an increase in the length of IAN bathed in local anesthetic (the classic technique fills the inferior pterygomandibular space). Alternatively, other studies have shown that an increased speed of injection leads to a greater distribution of the drug in the tissues (due to increased pressure), and this may lead to longer sections of nerve being exposed to local anesthetic (32). Given the potential for discomfort, this technique might be administered as a second IAN injection into anesthetized soft tissue, using appropriate aspiration methods. These hypotheses should first be tested in clinical trials on pulpitis patients.

Hypotheses for Local Anesthetic Failure

Despite the large prevalence of local anesthetic failures in endodontic pain patients, there have been comparatively few studies that have attempted to determine the mechanism(s) for this effect. This is an important problem, as identification of the mechanism(s) mediating local anesthetic failure are likely to
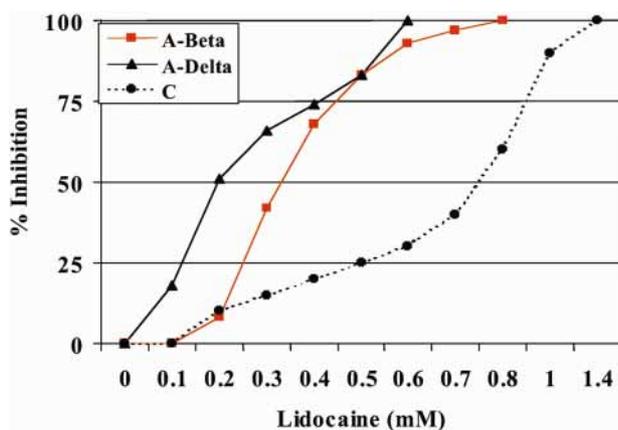
Fig. 4. Demonstration of the relative susceptibility of peripheral neurons to lidocaine using single fiber recording technique. The myelinated A-beta fibers (squares) and A-delta fibers (triangles) are the most sensitive to lidocaine. The unmyelinated C fibers (circles) are the most resistant to lidocaine. $N = 45$. (Data re-drawn from: Huang *et al. J Pharm Expt Therap* 1997).

have immediate and long-term benefits in revealing techniques that will provide more effective pain control to these patients. As well as our own hypotheses that we have developed based on a review of contemporary pain physiology to explain local anesthetic failures, listed below are several leading hypotheses advanced in the dental literature. Clearly, this is an area that needs continued research. For each hypothesis, we review the proposed mechanism and the clinical implications for improved anesthetic success in endodontic pain patients.

1. Anatomical Causes for Anesthetic Failures

While one could argue that the inability of the operator to deposit anesthetic solution in close proximity to the targeted nerve would lead to inadequate blockade in both normal and uninflamed states, it may be possible that a partial blockade would be adequate in neurons that were not sensitized by inflammatory mediators (see below). Thus, it is critical to know the nerve supply to the tissue to be anesthetized, as well as the anatomy of the injected site and its variations. Because anatomic variation would have a lesser impact on infiltration anesthesia (commonly used in the

maxilla), this discussion will be limited to mandibular anesthesia.

Traditionally, the pulps of mandibular teeth have been anesthetized by a blockade of the inferior alveolar nerve via an intraoral approach to deliver the local anesthetic to the pterygomandibular space. In the classic technique, the needle is advanced to a point where a pool of anesthetic is deposited near the mandibular foramen, which lies below the lingula, and in the sulcus colli mandibulae (33). Because the bony prominence of the lingula projects medially, it is often difficult to place the tip of the needle in the sulcus colli, and it has been suggested that the bevel should be orientated towards the midline in order to take advantage of the lateral deflection that would be provide via tissue resistance (34). However, even when needle placement is optimized with ultrasound guidance, failure of the inferior alveolar nerve block occurs (35). This may be due to the erratic post-injection distribution of anesthetic solution in the pterygomandibular space over which the operator has no control (36).

Accessory innervation to the mandibular teeth from several sources has also been suggested as the cause for inadequate anesthesia. In particular, the nerve to
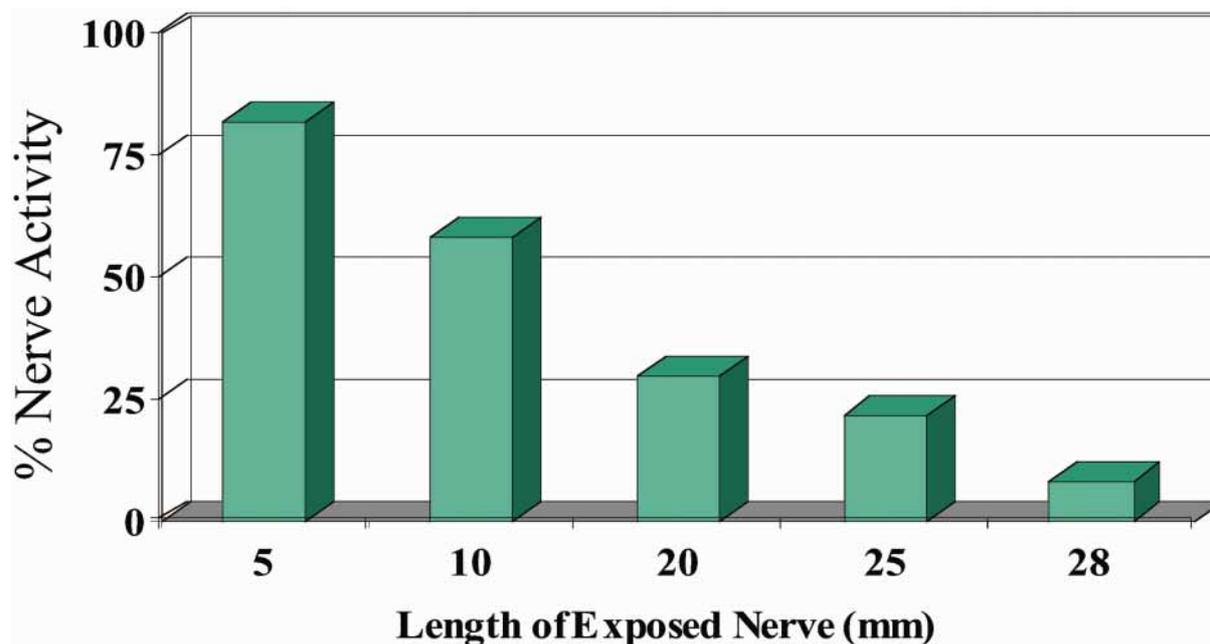

Fig. 5. Demonstration that lidocaine blockade of nerve conduction depends, in part, upon the length of the nerve exposed to the anesthetic solution. Lidocaine (0.8 mM) was exposed to varying lengths of frog sciatic nerve with the compound action potential being measured. (Figure redrawn from: Raymond S, Steffensen S, Gugliano L, Strichartz G. *Anesth Analg* 1989; 68:563–70).

the mylohyoid muscle has been implicated in carrying afferent fibers from the mandibular teeth (37, 38, 39). In a study of 37 cadavers, Wilson *et al.* (39) found the point at which the mylohyoid nerve branched from the inferior alveolar nerve to be an average of 14.7 mm above the mandibular foramen; a distance which may be great enough to prevent a blockade of the mylohyoid nerve when the classic technique is used. To overcome accessory innervation from the mylohyoid nerve, the clinician has several options, including the use of a block technique that deposits anesthetic solution higher in the pterygomandibular space (i.e. Gow-Gates or Akinosi), infiltration on the lingual surface of the mandible adjacent to the tooth operated, or techniques that deposit anesthetic solution in the medullary space surrounding the operated tooth, such as the intraligamentary or intraosseous routes of injection.

Other nerves which have been suggested as supplying afferent impulses from mandibular teeth include the lingual, buccal, and transverse cervical (for review see [40]); however, convincing evidence for these innervation sources does not exist. Regardless of the origin, the technique that would predictably block *all* sources of accessory innervation to the mandibular teeth would be one in which the anesthetic solution is deposited at the apices of the teeth in question (i.e. intraligamentary or intraosseous routes). While both of these techniques appear to increase the efficacy of inferior alveolar block anesthesia, randomized clinical trials show a greater duration of lower molar pulpal anesthesia (as determined by a reading of 80 on an electric pulp tester) to be provided by the intraosseous technique (41, 42).

2. Acute Tachyphylaxis of Local Anesthetics

It is well known in pharmacology that administration of receptor agonist drugs often leads to reduced responsiveness to a subsequent administration of the drug; an effect called tachyphylaxis. Because local anesthetics are often administered together with vasoconstrictors, there is the possibility that the drug persists in the tissue for a sufficient amount of time to produce tachyphylaxis at the sodium channel. It has been proposed that this contributes to reduced anesthetic effectiveness, especially after repeated injections (43).

However, it is not clear that local anesthetics produce substantial, or in fact any, tachyphylaxis under clinical conditions. Several clinical trials have evaluated repeated or continuous local anesthetic administration to treat chronic pain patients. Despite continuous infusion or daily administration for periods of up to several years, these studies have not reported tachyphylaxis to local anesthetics (44, 45). Thus, this hypothesis may have comparatively little merit for explaining local anesthetic failures.

3. Effect of Inflammation on Local Tissue pH

As described above, most clinically useful local anesthetics diffuse across the cell membrane and then block the sodium channel by accessing the protein from the cell's cytoplasm. This action requires the drug to shift between its acid form (an ionized or charged molecule) and its base form (an uncharged molecule). The pH of most local anesthetics in cartridge form is purposefully low (pH = 3–4), because the charged, acid form of the molecule is more stable (as is the vasoconstrictor) at a low pH, and thus gives a longer shelf life (7, 46). Once injected, the local tissue pH and the drug's strength as an acid (measured as the pKa value) regulate the distribution of the local anesthetic between the acid and base forms according to the well-known Henderson-Hasselbalch equation (pH − Pka) = log (Base/Acid). The proportion of the drug that exists in the uncharged base form is available to diffuse across the cell membrane. Once inside the cell, the drug repartitions into the acid and base forms, and it is the acid form of the drug that blocks the sodium channel.

This is a potentially important issue because inflammation-induced tissue acidosis may cause 'ion trapping' of local anesthetics. According to this hypothesis, the low tissue pH will result in a greater proportion of the local anesthetic being trapped in the charged acid form of the molecule and, therefore, unable to cross cell membranes. This hypothesis has been advanced as a major mechanism for local anesthetic failures in conditions such as endodontic pain (6, 7). This calculated relationship for lidocaine, mepivacaine and bupivacaine is presented in Figure 6. As the figure shows, the reduction in tissue pH results in a substantial proportion of the drug being trapped in the charged acid form. A second interpretation of this data is that tissue pH does not equally ion trap all

local anesthetics as they differ in their pKa properties. Thus, over the pH range of 7.4–6.6, in comparison to lidocaine or bupivacaine, mepivacaine is relatively resistant to ion trapping. To the extent that this hypothesis explains local anesthetic failure, mepivacaine represents a logical local anesthetic for use in patients with irreversible pulpitis.

However, there are considerations that may limit the local pH hypothesis. First, the acidosis may be minor in magnitude. Although severe forms of liquefaction necrosis (e.g. an abscess) may have pH levels as low as 4–5, the affected area is restricted to the actual abscess. Studies on cutaneous inflammation indicate that tissue pH may be only marginally reduced to pH values of about 5.8–7.2 (46). In addition, inflamed tissue possesses greater buffering capacity than normal tissue (possibly due to extravasation of protein or erythrocytes into the inflamed tissue) (46). Thus, the actual pH change may not be large enough to produce substantial ion trapping of local anesthetics. In addition, a reduction in tissue pH is likely to be a localized event and, with the exception of mandibular second and third molars, most probably does not involve distinct fascial space compartments that isolate the site for an IAN nerve block from the mandibular teeth. Thus, even in severe forms of inflammation, local tissue pH may explain problems with infiltration anesthesia in maxillary teeth, but is unlikely to explain local anesthetic failures in nerve block anesthesia.

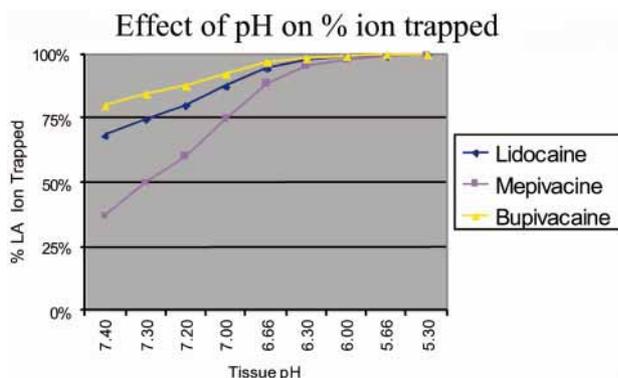To the extent of its validity, the local pH hypothesis

Fig. 6. The relationship between the proportion of local anesthetic in the cationic acid form of the drug as a function of tissue pH. Note that the cationic acid form cannot diffuse across cell membranes and is referred to as the 'ion trapped' proportion of the molecule. This proportion is derived from the Henderson-Hasselbach equation and the pKa value for each drug.

has at least two clinical implications. Firstly, it suggests that local anesthetics with lower pKa values are likely to be more effective in endodontic pain patients. As seen in Fig. 6, the data suggests that 3% mepivacaine might be able to produce greater anesthesia in patients with irreversible pulpitis. This recommendation is based on the physical properties and available formulations of these drugs, and it should be evaluated in a prospective clinical trial. Secondly, the temporary adjustment of tissue pH may be used to augment clinical anesthesia. This strategy has been employed by anesthesiologists with sodium bicarbonate to alkalinize the local anesthetic and tissue pH and thereby enhance local anesthesia (47, 48). Addition of sodium bicarbonate also raises the pCO_2 of the anesthetic solution bathing the nerve. When CO_2 crosses the nerve membrane and decreases the intracellular pH, the ionized form of the drug is favored, and as mentioned previously, it is *this* form that binds to the sodium channel to effect blockade.

Although alkalinization may have theoretical utility, there is a paucity of clinical trials in dental pain patients to support its use. In one study, compared with a standard lidocaine formulation, a buffered lidocaine formulation demonstrated no significant difference when given by infiltration injection into inflamed maxillary incisors (49). Although other formulations may warrant testing in additional studies, there does not appear to be a preponderance of clinical evidence to support the use of alkalinization of local anesthetic solutions.

4. Effect of Inflammation on Blood Flow

Inflammation has several other effects on local tissue physiology. For example, it has been proposed that peripheral vasodilation induced by inflammatory mediators would reduce the concentration of local anesthetics by increasing the rate of systemic absorption (43). This is a potentially important mechanism, because local anesthetics are well-recognized vasodilators that, in most cases, require formulation with vasoconstrictor agents. Although inflamed dental pulp experiences regional changes in blood flow (50), less is known about inflammation-induced vascular changes in periradicular tissue. Moreover, it is likely that this vasodilation may be localized and not evident at distant sites of injection (i.e. nerve block injection sites). Thus, this hypothesis may have greater utility in explaining difficulties with infil-

tration anesthesia when compared with nerve block anesthesia.

To the extent that this hypothesis predicts local anesthetic failure, there are clinical implications that may improve the success of local anesthesia. If vasodilation leads to increased drug absorption, then the use of higher concentrations of vasoconstrictors may produce more profound or longer duration anesthesia. Thus, in patients who can tolerate it, the use of 1:50 000 epinephrine may improve clinical success in anesthetizing patients with endodontic pain. However, to date, the results from clinical trials have been equivocal. The use of 1:50 000 epinephrine produces a greater degree of vasoconstriction in patients than 1:100 000 epinephrine (51), and yet, there is no difference in the magnitude or duration of clinical anesthesia in normal subjects (26). In this latter study, the clinical anesthesia for 2% lidocaine was the same, regardless of whether the epinephrine was present at 1:50 000, 1:80 000 or 1:100 000 (26). Knoll-Kohler and Fortsch, however, showed a dose-dependent relationship between the onset and duration of anesthesia and the concentration of epinephrine (1:200 000, 1:100 000, 1:50 000) when used with 2% lidocaine for infiltration anesthesia (52). It should be noted that these studies were conducted in normal subjects and, to date, no clinical trial has tested whether these higher concentrations of epinephrine alter anesthesia in endodontic pain patients in whom tissue vasodilation may be increased.

5. Effect of Inflammation on Nociceptors

Substances released from inflamed tissue have two major effects on nociceptive ('pain detecting') neurons (53). Firstly, they change the functional activity of these neurons. As might be expected, nociceptors are thought to be quiescent throughout much of our lives and only discharge in the presence of stimuli strong enough to damage the tissue or chemicals that stimulate receptors on these neurons. Inflammatory mediators activate or sensitize these neurons by interacting with specific receptors. An example of a mediator that activates nociceptors is bradykinin: its administration causes a brisk firing of unmyelinated C nociceptors via activation of cell surface bradykinin receptors (BK1 or BK2). Prostaglandin E_2 is an example of a mediator that sensitizes nociceptors: administration of PGE_2 reduces the threshold for firing

to the point where gentle stimuli can now activate these neurons. For example, the throbbing nature of pulpal pain is thought to be due to pulpal nociceptors sensitized to the point where they discharge in response to the patient's heartbeat. Thus, activation and sensitization are two major mechanisms by which inflammatory mediators alter the activity of these normally quiescent neurons. Although local anesthetics display use-dependent blockading properties, peripheral sensitization and activation have been reported to cause an increase in the resistance of nerves to anesthetics (54).

In addition, inflammatory mediators, including certain growth factors, have a profound effects on these neurons by altering their structural properties. In particular, the elegant studies by Byers and her colleagues have led to the realization that the terminals of peripheral nerves literally grow ('sprout') into areas of inflammation in dental pulp and periradicular tissue (55). Clinical studies have confirmed that a similar sprouting occurs in inflamed human dental pulp. This increase in nerve terminals in inflamed tissue increases the size of their receptive field, indicating that pain neurons may now be more easily activated by a spatial summation of stimuli (56).

Inflammation also changes the synthesis of several proteins in nociceptors, leading to an increase in neuropeptides, such as substance P and calcitonin gene-related peptide. These neuropeptides play important roles in regulating pulpal inflammation (57). In addition, tissue injury may alter the composition, distribution or activity of sodium channels expressed on nociceptors (58, 59, 60). The effect of inflammation on these sodium channels may have profound implications in local anesthetic failures.

As mentioned earlier in the review, several types of sodium channels have been discovered over the last decade. One particular group of channels is characterized as being resistant to the puffer fish toxin, tetrodotoxin (TTX). At least two channels are members of the TTX-resistant class, including the PN3 (also known as SNS, or $Na_V 1.8$) and NaN (also known as the SNS2 or $Na_V 1.9$) sodium channels. The TTX-resistant class of sodium channels is of interest since they are less sensitive to lidocaine (61) (Fig. 7). As Fig. 7 demonstrates, increasing concentrations of lidocaine provides increasing blockade of the sodium channels. However, the TTX-resistant channels are about four times less sensitive to lidocaine (imagine

trying to inject 1/4 of a dental cartridge to obtain anesthesia). The TTX-resistant class of sodium channels is expressed on nociceptors under normal conditions (62). In addition, their activity more than doubles after being exposed to prostaglandin E_2 (59)(Fig. 8). Thus, we hypothesize that the TTX-resistant class of sodium channels represents a logical
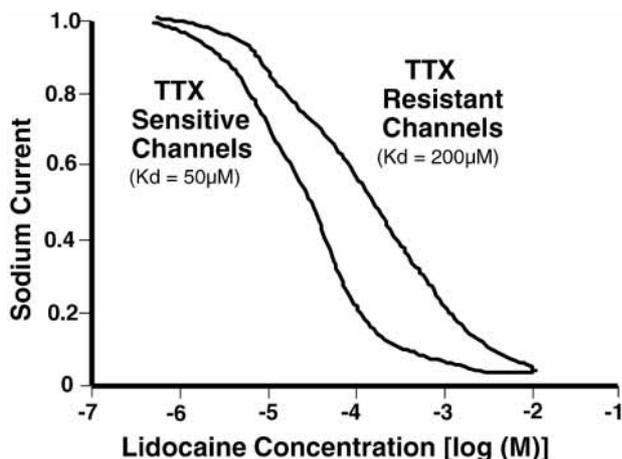

Fig. 7. Concentration response curve, illustrating the effect of increasing concentrations of lidocaine on the activation of both TTX-sensitive and TTX-resistant classes of sodium channels. Lidocaine is about 1/4 as potent in blocking the TTX-resistant channels in comparison to the TTX-sensitive channels. (Figure redrawn from: Roy, *J Neuroscience* 1992; 12:2104).
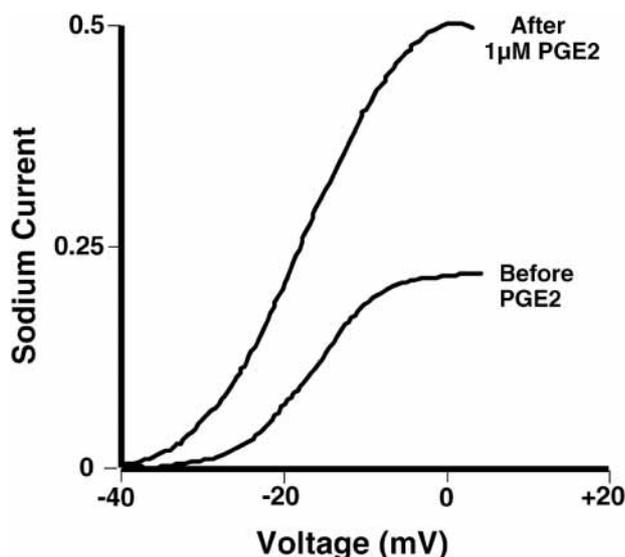

Fig. 8. Effect of application of prostaglandin E2 (PGE2 at 1 µM) on the sodium current generated from TTX-resistant sodium channels. Application of PGE2 increases peak current by more than two-fold and reduces the threshold voltage for activation. (Figure redrawn from: Gold, *Proc Natl Acad Sci* 1996:93:1108).

mechanism for local anesthetic failures: the channels are relatively resistant to lidocaine, they are expressed on nociceptors, and their activity is increased with PGE_2.

Clinical trials conducted in pain patients have evaluated whether the TTX-resistant class of sodium channels is increased after tissue injury. In one study on neuropathic pain patients, there was a substantial increase in the $Na_V 1.8$, but not $Na_V 1.9$, subtype of sodium channels in patients (58). This has led to the suggestion that these and other channels may mediate some forms of persistent pain (63). Our recent clinical studies have demonstrated that human dental pulp contains at least two types of the sodium channel, including $Na_V 1.8$ (53). Thus, the development of selective and potent antagonists to $Na_V 1.8$ may offer particular advantage in treating pain patients, including patients with endodontic pain. One such agent under investigation is the benzomorphan derivative, BIII 890 CL (18).

6. Effect of Inflammation on Central Sensitization

Inflammation also induces changes in the central nervous system's pain processing system. Activation and sensitization of nociceptors in pulpal and periradicular tissue results in a barrage of impulses sent to the trigeminal nucleus and brain. This barrage, in turn, produces central sensitization. Central sensitization is the increased excitability of central neurons and is thought to be a major central mechanism of hyperalgesia (64). Under conditions of central sensitization, there is an exaggerated CNS response to even gentle peripheral stimuli. A common example is sunburn, where even the innocuous stimulation of wearing a t-shirt is considered painful. Similarly, percussing a tooth with an inflamed periodontal ligament (e.g. acute apical periodontitis) may produce an exaggerated pain response which is due, in part, to central sensitization.

Although we often consider central sensitization when discussing endodontic pain mechanisms (65), this same process may contribute to local anesthetic failures. Under normal conditions, many patients tolerate dental procedures, even though a slight or occasional sensation may still be felt. In other words, under normal conditions, a local anesthetic injection that blocks most of the fibers (say, 90%) may still be

clinically successful. This has been reported in other clinical models (for example, IV cannulation of the arm), where patients treated with a topical anesthetic reported that they did not experience pain, even though their visual analog pain scores were greater than zero (66). However, under conditions of central sensitization, there is an exaggerated response to peripheral stimuli and, under these conditions, the same 90% block may permit sufficient signaling to occur to lead to the perception of pain. Thus, central sensitization may contribute to local anesthetic failures.

Unfortunately, there are no selective drugs for blocking central sensitization. The only clinical implication would be to reduce the afferent barrage and thereby reduce central sensitization. This is done routinely by clinicians via cleaning and shaping techniques, but this is a conundrum, as the endodontic treatment is performed after local anesthesia. One interesting study has demonstrated that intraosseous injection of steroid (methylprednisolone acetate 40 mg) reduces endodontic pain in 24 h (67). If confirmed, then this approach may reduce peripheral and central mechanisms sufficiently to obtain predictable local anesthesia.

7. Psychological Factors

Patient anxiety may also contribute to local anesthetic failure. Experienced clinicians understand that apprehensive patients have a reduced pain threshold and are more likely to report an unpleasant dental experience (68, 69, 11, 70). Fear of seeing and/or feeling the needle and the sound of the dental handpiece are routinely cited as causative agents in the creation of anxiety in the dental patient (71). Moreover, patients may be particularly anxious about impending root canal therapy (72). Investigators have also demonstrated that patient anxiety predicts a poor outcome for clinical procedures involving local anesthetics applied to the arm before IV cannulation (66). Thus, patient anxiety should be considered when managing the endodontic pain patient.

Several methods have been advocated for managing anxious emergency pain patients (69, 11). First, the clinician should establish a positive and confident relationship and avoid exposing the patient to obvious fear-producing stimuli. Many clinicians report that a sense of humor often helps to relax apprehensive patients. For extremely fearful patients, cognitive behav-

ior-based programs have shown significant long-term reduction in predental treatment anxiety (73). Other studies have demonstrated that instructing patients to focus on sensory stimuli significantly reduces intraoperative endodontic pain (74, 75). This effect was most evident in patients who were characterized as having a high desire for control and a low perceived control over their clinical care.

Second, pharmacologic agents can be administered to control patient anxiety. While these agents can be delivered via oral, inhalation (N_2O) or intravenous routes, a decreased likelihood of serious morbidity, reduced monitoring and demonstrated efficacy have made oral or a combination of oral and inhalation routes attractive (76, 77). Kaufman *et al.* (46) showed that oral triazolam 0.25 mg was equally effective in comparison to intravenous diazepam in reducing anxiety in patients undergoing oral surgery.

One could certainly consider an integrated approach that involves both non-pharmacologic and pharmacologic techniques. Regardless of the technique utilized, providing some means of anxiety control should enhance the clinician's ability to provide adequate local anesthesia for endodontic pain patients.

Therapeutic Approaches for Managing Local Anesthetic Failures

Before using the best current evidence to deal with the problem of clinically inadequate local anesthesia in endodontic patients, the clinician would do well to first identify those patients who are likely pose such a problem. This includes individuals who present with signs and symptoms of irreversible pulpitis and/or acute periradicular periodontitis, secondary to either an apical extension of pulpal inflammation or pulpal necrosis and bacterial invasion. It also includes patients with a history of experiencing inadequate local anesthesia for dental procedures and those with an obviously high level of anxiety over the pending treatment.

In the above-mentioned patients, the clinician should consider the modifications discussed below *before* beginning treatment, as repeated painful stimuli caused by endodontic therapy initiated in the presence of inadequate anesthesia will, for reasons already discussed, tend to make the problem worse.

1. Supplemental Local Anesthesia

In the endodontic pain patient without an inordinate level of anxiety, supplemental local anesthesia has been the obvious first choice for dealing with potential anesthetic failures. Supplementing a single-cartridge inferior alveolar block has the potential to deal with failures created by several of the hypotheses previously put forth. By increasing the dose of local anesthetic, one could expose a greater length of the inferior alveolar nerve (IAN) and increase the likelihood of conduction blockade (23). Increased dosage would also help to block the population of TTX-resistant sodium channels that may be elevated in the inflamed state (61). By using an anesthetic with a lower pKa, such as 3% mepivacaine, one could decrease the potential for ion trapping. This would increase the concentration of local anesthetic molecules in the base form necessary for diffusion across the nerve membrane, enhancing blockade and increasing the onset of anesthesia (7). Delivering the second cartridge of anesthetic higher in the pterygomandibular space would have the effect of increasing the length of nerve exposed, as well as possibly blocking the nerve to the mylohyoid muscle before it branches from the IAN (39).

As mentioned previously, supplemental anesthesia can also be provided via other routes. Both intraligamentary and intraosseous techniques deliver the anesthetic to the cancellous bone surrounding the apices of injected teeth (6, 79). While the intraligamentary injection can be provided with no additional armamentaria, there are limitations to the volume of anesthetic deposited, and a significant incidence of postoperative pain may ensue (80). The intraosseous route does afford the possibility of delivering higher doses but requires cortical perforation and delivery of the anesthetic via specialized instruments. It also has the potential to cause perforation of nearby tooth roots if used incorrectly. Clinical trials indicate that the intraosseous route of injection significantly enhances pulpal anesthesia after IAN block injection in endodontic pain patients (42)

The intrapulpal injection is generally used as a final option for the patient who is comfortable until the pulp is exposed (or nearly exposed) (6). This technique delivers the solution directly into inflamed pulpal tissues and requires some means of preventing back flow (81, 82). With this in mind, a limited access opening to the pulp to provide a narrow channel for the intrapulpal injection might be considered (e.g. using a #2 round bur to bore an opening into the pulp chamber); the final access preparation can be accomplished after the pulp has been anesthetized.

As previously discussed, in order to evaluate the depth of pulpal anesthesia provided by any technique, prior to initiating endodontic treatment (i.e. prior to placement of the rubber dam), the clinician should test the tooth in question rather than rely on a positive lip sign. Probably the simplest way to do this would be to repeat the cold test. A lack of response gives both the operator and the patient a certain degree of confidence and, thus, reduces anxiety during the operation.

2. Adjunctive Drugs or Techniques

The first part of this review has highlighted evidence that has allowed a greater appreciation of the effects of inflammation on peripheral nociceptors, as well as central nervous system processing of pain signals. It is very likely that inflammation contributes to local anesthesia failure in inflamed dental pulps via both mechanisms. With this in mind, the astute clinician may consider the use of fast-acting anti-inflammatory drugs as an adjunct to the provision of local anesthesia to teeth with inflamed pulps and/or periradicular tissues.

Reducing pulpal levels of the inflammatory mediator PGE_2 would be beneficial in two ways. Firstly, decreasing pulpal nociceptor sensitization would mitigate an increase in resistance to local anesthetics (54). Secondly, it may diminish a prostanoid-induced stimulation of TTX-resistant sodium channel activity (Fig. 8); these channels also display relative resistance to lidocaine (59, 61). Reduction of PGE_2 could be accomplished with either NSAIDS or steroids. Double-blind clinical trials have shown that the injectable non-steroidal anti-inflammatory drug ketorolac tromethamine, when injected intraorally or intramuscularly, produces significant analgesia in patients with severe odontogenic pain prior to definitive treatment (83, 84). Although it has yet to be evaluated in endodontic pain patients, ibuprofen in a liquid gel formulation (e.g. Advil Liquid Gel® (White-Hall Robbins, Madison, NJ)) may have similar effects. In patients with a diagnosis of irreversible pulpitis, a double-blinded, randomized clinical trial showed that, for the 7 day period preceding endodontic therapy, subjects that received an intraosseous injection of

40 mg methylprednisolone experienced significantly less pain and required significantly less pain medication than those receiving the placebo (67). Finally, for the overtly fearful patient, reducing anxiety by methods previously discussed, such as sublingual triazolam (78) or nitrous oxide (76), and a caring chairside manner, should actually increase the likelihood of effective local anesthesia in endodontic pain patients.

Conclusions

Hopefully the reader has found this review to be informative and practical. Our objectives were to review the pharmacological mechanisms of local anesthesia and pain from the perspective of identifying potential mechanisms for local anesthetic failures. These mechanisms provide the basis for evidence-based treatment strategies and, importantly, point out areas where future research is needed. Given the greater understanding of acute pain mechanisms that we currently enjoy and the ongoing research efforts in pain laboratories throughout the world, it is not too difficult to imagine a time when local anesthesia will be as predictable in inflamed teeth as it is in the normal, uninflamed tooth.

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