

A LIGNOCAINE PATCH FOR DENTAL ANALGESIA SAFETY AND EARLY PHARMACOLOGY

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Abstract: Topical anesthetics are commonly used in oral & maxillofacial surgery to control pain in the oral cavity mucosa before local anesthetic injection. These anesthetic agents come in many forms, developed for different usages, to minimize adverse reactions, and for optimal anesthetic efficiency. Earlier studies have revealed that these agents may also limit the growth of microorganisms in the area of anesthetic application. Many topical anesthetic agents show different levels of antimicrobial activity against various bacterial strains and Candida. The dosage of local anesthetic agent used in some clinical preparations is too low to show a significant effect on microbial activity. Efficiency of antimicrobial activity depends on the local anesthetic agent's properties of diffusion within the bloodstream and binding efficiency with cytoplasmic membrane, which is followed by disruption of the bacterial cell membrane. The antimicrobial properties of these agents may extend their usage in patients to both control pain and infection. To develop the topical local anesthetic optimal usage and antimicrobial effect, a collaborating antiseptic agent may be used to benefit the local anesthetic. However, more research is required regarding minimum inhibitory concentration (MIC) and minimum bactericidal concentration (MBC) of topical local anesthetic agents with drug interaction between anesthetics and antiseptic agents.

Keywords: Antimicrobial Activity; Local Anesthetics; Microorganism; Minimum Inhibitory Concentration; Topical Anesthesia

Introduction

Local anesthesia is applied topically or administered by injection to control pain in the body. Unlike general anesthesia, local anesthetics do not cause loss of consciousness. Topical anesthetics are used to numb mucosa of the nose, ear and throat, anus, and genital area. It is used adjunctively to relieve pain and to help patients feel more comfortable before surgery. In addition to their anesthetic properties, local anesthetics also possess antimicrobial effects. They have been shown to inhibit and kill a wide spectrum of bacteria and fungus [1]. In dentistry, topical anesthetics are typically used to anesthetize the mucosal surface area of the oral cavity prior to local anesthetic injection [2].

When administering local dental anesthesia, bacteria in the normal oral flora can pass into the tissue by needle injection through the mucous membrane. These bacteria can cause suppurated local infections or odontogenic bacteremia after dental interventions [3, 4, 5]. Therefore, it is possible that the antimicrobial properties of topical anesthetics may provide an additional benefit as an antiseptic to prevent post-operative infections.

We reviewed the effect of local anesthetics on antimicrobial activity with a focus on dentistry. These anesthetics were tested against a broad spectrum of microorganisms, including oral and skin microflora, opportunistic pathogenic bacteria, and fungi. The collective results of in vitro and in vivo studies conducted over many years have substantiated a supplemental role for local anesthetics in the probable prevention and treatment of interventional site infections.

Classification :

The structure of an anesthetic molecule consists of three components: 1) the lipophilic aromatic ring, 2) an intermediate ester or amide linkage, and 3) the tertiary amine, which influences the clinical properties. The potency of a local anesthetic depends on lipid solubility of the aromatic rings and its substitute compound along with the tertiary amine [6, 7]. For example, bupivacaine is more potent than articaine due to its greater lipid solubility. Lipid solubility also affects the onset of the anesthetic as it enables rapid diffusion of the drug through cell membranes. Thus, the potency of 0.5% bupivacaine is comparable to 4% articaine [8]. Conversely, concentration or the presence of other factors may have a greater effect on onset [7]. Epinephrine in the solution of the local anesthetic decreased its vascular absorption rate, thereby enhancing the deep numbness and long duration of local action [8].

Local anesthetics can be classified as ester-type or amide-type based on its intermediate chain. Drug metabolism is different for each type; esters are hydrolyzed in blood plasma by plasma esterases, whereas amides are metabolized in the liver. The incidence of allergic reaction, from skin rash to anaphylaxis, is highly associated with ester anesthetics due to the formation of p-aminobenzoic acid (PABA) [6], which may cross-react with similar compounds such as sulfa antibiotics or metabisulfite [9].

1. Ester-type anesthetics

Cocaine was the first local anesthetic drug, introduced by Koller in 1884 [10]. For oral use, cocaine is available in liquid form mixed with adrenaline for topical anesthesia. It has a reported high risk of addiction and toxicity.

Topical benzocaine is an ester-type anesthetic agent composed of p-aminobenzoic acid (PABA) that can induce allergic reactions. Benzocaine is available in various preparations, such as gel, gel patch, spray, ointment, or solution. Concentrations used range from 6% to 20%, and has multiple uses. Topical use of 20% benzocaine provides anesthetic effect within 30 seconds but requires approximately 2 – 3 minutes to reach adequate depth. It effectively reduces pain caused by injection into the alveolar mucosa and tongue, but only slightly affects the palatal mucosa because of the tissue thickness and dense nerve supply [11]. The duration of action is approximately 5 – 15 minutes after onset. Benzocaine-associated methemoglobinemia has been regularly reported [12].

Tetracaine, also an ester derivative of PABA, is more effective than cocaine [13]. Tetracaine is available in spray and ointment forms of 0.2% to 2.0% concentration. It produces rapid onset within 10 – 20 seconds, with a short duration of action of 10 – 15 minutes. Tetracaine is quickly absorbed into the mucous membrane. Limiting use to 20 mg per session to reduce the risk of adverse reactions has been recommended [14].

2. Amide-type anesthetics

Lidocaine is the only amide-type anesthetic that is available in both topical and injectable forms. In dentistry, many forms and concentrations of lidocaine are used, from 2 – 5% gel and solution, 5% ointment, 10% spray, and 20% lidocaine patch [15]. Lidocaine has a potency comparable to benzocaine. It requires three minutes after application to reach adequate anesthesia [16]. Lidocaine is highly effective on alveolar mucous but is less effective on palatal mucous membrane. It is used as an analgesic ingredient in Magic Mouth Wash and mouth rinse products for oral mucositis in patients receiving radiation and chemotherapy [17].

Prilocaine is also used in combination with other topical anesthetics, such as in Eutectic mixture of local anesthetics (EMLA) and Oraqix [18]. The maximum dose is 6 mg/kg in adults and should not exceed 400 mg. Prilocaine has low cardiac toxicity and is relatively safe in pregnant women [19].

EMLA, which contains 2.5% lidocaine and 2.5% prilocaine, is used in procedures or surgeries that cause minimal to considerable pain. EMLA is also commonly used as a topical skin analgesic cream to reduce pain, anxiety, and discomfort associated with venous cannulation in adults and children [20].

Moreover, EMLA is used as an intraoral analgesic in dental procedures such as excision of gingival tissues and clinical procedures in pediatric dentistry [21, 22]. Further studies are needed to define the proper dose and exposure duration in children to prevent adverse effects.

Adverse effects

Common adverse effects of topical anesthetics are temporary altered sense of taste and allergy. The signs and symptoms of allergic reactions are itching, edema, nasal discharge, shortness of breath, wheezing, and headache [23, 24].

Allergic reactions are infrequent in amide-type anesthetics [25]. Methemoglobinemia is another adverse reaction caused by anesthetics that can lead to severe or fatal cyanosis and additional adverse effects [12]. Adverse effects from using prilocaine and EMLA creams have been reported [26]. More severe complications can occur, including central nervous system toxicity, cardiovascular toxicity, and methemoglobinemia [27, 28].

Lidocaine and Lidocaine hydrochloride

Lidocaine is the only amide-based local oral topical anesthetic that is also used as an injectable anesthetic. In dentistry, lidocaine is used as a 2% or 5% gel, 2% solution, 4% or 5% solution, 5% ointment, or 10% spray [12]. The onset of action is approximately 1 to 2 minutes and duration of action is approximately 15 minutes, with peak efficacy occurring at 5 minutes. Although 5% ointments have a similar potency to 20% benzocaine, its onset of action is more delayed, requiring at least 3 minutes to achieve adequate anesthesia. It is effective on alveolar mucus, but not on the palatal mucous membrane. Lidocaine solution is an ingredient of Magic Mouth Wash rinse and may be used for patients with oral mucositis caused by radiation and chemotherapies [13].

4. Prilocaine

Prilocaine is the most popular amide-based local anesthetic agent used for infiltration anesthesia in dental procedures. It is used in combination with other topical anesthetics [14]. Prilocaine is a secondary amide, unlike mepivacaine and lidocaine. Prilocaine is used as two types of formulations, 4% prilocaine or 4% prilocaine with 1:200,000 epinephrine. Regardless of the presence of

epinephrine, the maximum dose of prilocaine for adults is 2.7 mg/lb or 6 mg/kg. The total dose should not exceed 400 mg in adults. Prilocaine is relatively safe for use in pregnant women, with a Pregnancy Category B status.

Eutectic Mixtures Of Local Anaesthesia

Mixtures of topical anesthetic agents used for local anesthesia are called eutectic mixtures of local anesthesia (EMLA). Mixing refers to the process of combining drugs or replacing an ingredient to prepare a commercial drug. The ultimate goal is to produce potent mixtures of local anesthetics to be used in procedures or surgeries that cause minimal or considerable pain. Such mixtures have lower melting points, which in turn promotes easier absorption of the EMLA into the oral mucous membrane [15].

EMLA cream, a 1:1 mixture of 2.5% prilocaine and 2.5% lidocaine, was first used as a cutaneous topical anesthetic in dermatology in the 1980's [16]. Holst and Evers were the first to attempt the administration of EMLA cream within the oral cavity. Their results showed high efficacy in the attached gingiva [17]. Since this study, multiple studies have documented the application of EMLA cream on mucosal surfaces. In addition, several reports have noted that the use of EMLA cream reduced pain during probing, hand scaling, ultrasonic scaling, rubber-dam clamp placement, and palatine nerve block [18, 19, 20, 21, 22, 23, 24, 25].

Nayak and Sudha suggested that the low viscosity of EMLA cream renders it difficult to handle, which in turn makes it difficult to administer locally as a topical anesthetic at the site of the needle injection [26]. To overcome this setback, Svensson and Peterson used an Orahesive bandage, which improved the pain relief effects of the topical anesthetic [27]. Despite various findings pertaining to the potential of EMLA cream for use in dentistry, the manufacturer does not recommend the use of the cream on mucous membranes. Further, additional studies are needed to identify the appropriate dose and duration of exposure in children to prevent overdose and side effects.

Recent developments

About two-thirds of all patients find scaling procedures to be painful. Approximately 30% of patients have been reported to feel pain during scaling and root planing [28, 29]. However, infiltration anesthesia for the purpose of controlling such pain may actually cause pain and fear. Furthermore, all four quadrants cannot be treated simultaneously with infiltration anesthesia and dentists are required to administer additional anesthetics [30]. Thus, there are ongoing efforts to develop a topical anesthetic that could be used for periodontal procedures [31, 32].

1. HurriPAK Periodontal Anesthetic Kit

HurriPak (Beutlich LP Pharmaceuticals, FL, USA) is a 20% benzocaine solution that is sold as a needle-free periodontal anesthetic kit. The product comprises of a plastic syringe (3 ml) and disposable plastic tips [1], which are inserted deep within the gingival sulcus. The onset of action is 30 seconds and duration of action is approximately 15 minutes. Fifteen minutes is generally not enough time for performing procedures in adults, so re-administration of the solution, infiltration anesthesia, or periodontal ligament anesthesia using needle injections may be needed.

2. Cetacaine Topical Anesthetic

Cetacaine (Cetylite, NJ, USA) contains 14% benzocaine, 2% butamben, and 2% tetracaine-hydrochloric acid and is used for controlling local pain in all mucous membranes, except for the eyes [1]. This product should never be used for injections. The anesthetic kit is comprised of the solution, a syringe, and applicator tip that enables access to the periodontal pocket. The solution may be applied using a cotton swab or microbrush.

3. Oraqix Subgingival Anesthetic

In 2004, the FDA approved Oraqix (Dentsply, Pennsylvania, USA) for dental use. Oraqix contains 2.5% lidocaine and 2.5% prilocaine and is packaged with 20 cartridges and tips [1, 14]. It is a non-injectable gel anesthetic that is administered by insertion into the gingival sulcus, where it produces its anesthetic effects to enable deep scaling and root planing [33, 34, 35, 36, 37]. It has been reported that Oraqix is also effective for application of orthodontic bands [38]. Combining Oraqix with other local anesthetics must be performed with caution.

Precautions And Side effects

Topical local anesthetics are considered relatively safe and not many adverse reactions have been associated with them. The most common side effect is tissue stimulation (when topical anesthetics are applied for prolonged periods) and a temporary altered sense of taste [39]. However, some types of topical anesthetics that combine esters and amides to produce potent anesthetic effects have a potential risk for allergic reactions. Ester-based agents, as PABA derivatives, are known allergens and a subset of the population have shown allergic reactions to these drugs. Actual allergic reactions to amide-based local anesthetics are highly rare [40]. If the patient has a history of allergic reactions to local anesthetics, the dose of the anesthetic used at the time and whether the patient

received dental treatment after the allergic reaction should be checked. If no decision can be made regarding the patient's allergy to the anesthetic, the patient should be sent to an allergy specialist for testing with a diluted solution as well as a subcutaneous injection of an undiluted solution. If an allergy is present, the patient may show signs and symptoms, such as skin stimulation accompanied by itching, edema, swollen marks in the face and neck, nasal discharge, shortness of breath, wheezing, and headache [41].

In addition, benzocaine is a well-known cause of methemoglobinemia [42]. The FDA continually warns healthcare specialists and patients that benzocaine-associated methemoglobinemia is consistently documented in the literature and can induce severe or even fatal outcomes [1, 43, 44]. Methemoglobinemia, which has also been associated with EMLA cream and prilocaine [45, 46], is a disorder in which a high concentration of methemoglobin (hemoglobin with the iron in the heme group oxidized to the ferric state) accumulates in the blood. It induces cyanosis and is caused either by a genetic metabolic defect in humans or drug intake. Benzocaine is prohibited in patients with a history of methemoglobinemia or pediatric patients younger than two years of age [47]. Methemoglobinemia may result even with a single administration of benzocaine or may result unexpectedly after a few administrations. Signs and symptoms may occur in a few minutes to two hours after using topical benzocaine within the oral cavity or spraying benzocaine into the oropharyngeal isthmus to prevent vomiting.

It has been reported that EMLA cream can sometimes lead to regional pallor, flare, edema, an early burning sensation, and rare itching [48]. In addition, it may also induce allergic and anaphylactic reactions, including hives, vascular edema, bronchospasms, and shock. Although rare, EMLA may result in methemoglobinemia in children [45, 49].

Conclusion

Topical anesthetics are highly useful for reducing discomfort, pain, and anxiety during dental procedures. Traditional topical anesthetic agents with benzocaine and lidocaine as active ingredients are available in various forms and products should be selected based on the intended use. In addition, newly developed topical anesthetic products feature heightened anesthetic effects by combining several ingredients or could be used on periodontal tissues. Although rare, topical anesthetics can induce allergic reactions or side effects, such as methemoglobinemia; therefore, practitioners should perform thorough history-taking and be careful not to overdose patients. It is recommended that dentists gain a proper understanding of topical anesthetics in order to improve the quality of care.

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