

Topical Analgesic and Anesthetic Agents

Drug Class Review

Benzocaine (Anbesol[®], Cepacol[®], others)
Benzocaine/Butamben/Tetracaine (Cetacaine[®])
Benzyl Alcohol (Ulesfia; Zilactin)
Capsaicin (various)
Dibucaine (Nupercainal)
Diclofenac (Flector[®], Pennsaid[®], Voltaren[®], others)
Dyclonine (Dyclocaïne[®], Sucrets[®])
Ethyl Chloride
Hexylresorcinol (Sucrets[®])
Lidocaine (Akten, AneCream, Lidoderm, Xylocaine, others)
Lidocaine/Prilocaine (EMLA[®], Oraqix[®])
Lidocaine/Tetracaine (Synera[®])
Methyl Salicylate/ Menthol (BenGay[®]; Icy Hot[®], others)
Pramoxine (Itch-X, Proctofoam, others)
Proparacaine (Flucaine)
Tetracaine (Altacaine[®], Pontocaine[®], others)
Trolamine (Arthricream, Myoflex, others)

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Executive Summary

Introduction: Thirteen topical analgesic and anesthetic agents are currently available for use in the United States and are indicated in the treatment or temporary relief of pain. The topical agents are available as aerosols, creams, gels, lotions, lozenges, ointments, patches, solutions and rectal products. Each of the agents are available in different formulations, have varying potencies and may have different indications and uses.

The topical analgesic and anesthetic agents are indicated in the treatment of pain associated with minor procedures and in the symptomatic relief of pain associated with various localized muscle, joint, or skin disorders, including burns, abrasions, sore throat, post-herpetic neuralgia, arthritis, and hemorrhoids. Efficacy of the topical analgesic and anesthetic agent can vary depending on the disorder being treated. In general, treatment of pain is determined by clinical judgment based upon location of procedure/pain, prior treatment, and complicating conditions (infection present, age of patient).

Clinical Efficacy: The comparative clinical evidence available for the topical analgesic and anesthetic agents is limited. The majority of the evidence evaluates the agents in placebo-controlled trials. The limited head-to-head clinical evidence demonstrates comparable clinical efficacy for lidocaine products, diclofenac and ethyl chloride. According to clinical experience, the topical analgesic and anesthetic agents are useful in the treatment of pain associated with minor procedures and muscle, joint, or skin disorders. Success of treatment varies depending on accurate diagnosis, agent delivery vehicle, frequency of application, duration of treatment, and adverse effects.

Special Populations: Very little evidence is available for use of topical analgesic and anesthetic agents in pediatric patients or the geriatric population. Pediatric and geriatric patients may be at increased risk of adverse events due to characteristics that increase penetration of the topical agents including: reduced ability to metabolize rapidly and thinner skin. Overall, caution should be used when using topical analgesic and anesthetic agents in these populations

Adverse Drug Reactions: The topical analgesic and anesthetic agents may be associated with both local and systemic adverse events. Rate of adverse events tends to increase with increased duration of use. Local adverse effects reported with topical analgesic and anesthetic use include: burning and stinging at the site of administration. Systemic adverse effects reported with topical analgesic and anesthetic use include: seizure, CNS depression and cardiovascular toxicity. Long-term use of topical analgesic and anesthetic agents is not recommended.

Summary: Overall, selection of a topical analgesic and anesthetic preparation should be based on both patient-related and drug-related factors including age of the patient, the extent and location of the body surface area to be treated and the presence or absence of infection.

Introduction

The analgesic and anesthetic agents are available as aerosols, creams, gels, lotions, lozenges, ointments, patches, solutions and rectal products.^{1,2} Thirteen topical analgesic and anesthetic agents are currently available for use in the United States: benzocaine, benzyl alcohol, capsaicin, dibucaine, diclofenac, dyclonine, ethyl chloride, hexylresorcinol, lidocaine, pramoxine, proparacaine, tetracaine and trolamine. Many of the agents are available as over-the-counter products and in mucosal formulations for the treatment of pain associated with mucous membranes and rectal formulations for the treatment or temporary relief of pain associated with hemorrhoids. All of the topical agents are indicated in the treatment or temporary relief of pain and itching associated with minor surgeries, burns, cuts, abrasions, post-herpetic neuralgia, arthritis, and other muscle, joint, or skin irritations. A number of combination analgesic and anesthetic products are also available for use in the United States: benzocaine/butamben/tetracaine (Cetacaine®), lidocaine/prilocaine (EMLA®, Oraqix®), lidocaine/tetracaine (Synera®), methyl salicylate/menthol (BenGay®, Icy Hot®, others). Table 1 compares all of the available topical analgesic and anesthetic agents.^{1,2}

The topical analgesic and anesthetic agents are available in different formulations, have varying potencies and may have different indications and uses.¹⁻⁴ In general, the topical products exhibit minimal absorption and have few systemic adverse reactions or drug interactions. Limited data is available comparing the efficacy and/or safety of the topical analgesic and anesthetic agents. In general, treatment of pain associated with minor procedures and muscle, joint, or skin irritations is determined by clinical judgment based upon location of procedure/pain, prior treatment, and other complicating conditions (infection, age of patient, duration of action). This is a report of the available data evaluating the topical analgesic and anesthetic agents in the treatment or temporary relief of localized pain.¹⁻⁴

Disease Overview

Topical analgesic and anesthetic agents are indicated in the treatment of pain associated with minor procedures and in the symptomatic relief of pain associated with various localized muscle, joint, or skin disorders, including burns, abrasions, sore throat, post-herpetic neuralgia, arthritis, and hemorrhoids.^{3,4} Efficacy of the topical agents can vary depending on the disorder being treated. In general, the topical analgesic and anesthetic agents are most effective in the temporary relief of pain associated with minor disorders. Systemic analgesic agents tend to be more effective in the treatment of pain but the topical agents are often preferred as they are associated with fewer systemic adverse effects. Systemic adverse events associated with analgesic use include constipation, sedation and respiratory depression. While analgesic and anesthetic agents are effective in treating pain, they are not curative. The cause of the underlying pain should be identified and treated or eliminated in addition to temporary relief of the pain symptoms.^{3,4}

Individual topical analgesic and anesthetic agents may vary in efficacy as a result of differences in potency, vehicle formulation, frequency of application, site of application, disease

or pain being treated, individual patient characteristics and whether or not an occlusive dressing is used.¹⁻⁴ For example, occlusive vehicles, like ointments, may increase analgesic activity as they provide increased skin hydration and increased skin permeability. Using a transdermal formulation may also increase analgesic activity. The solubility of the topical agents can affect penetration into the epidermis; propylene glycol is a solvent found in many topical preparations that tends to increase the potency of the agent. Peanut oil is added to some topical agents to form a preparation that is thinner and easier to apply while maintaining the hydrating properties. Creams have increased amounts of petrolatum, are less oily, and may be more cosmetically appealing but less hydrating. Lotions, solutions, and gels have less penetration but may be more useful in treating diseases in hair-bearing areas. Other formulations, like patches, foams or sprays, may increase convenience.^{3, 4}

Table 1. Comparison of the Topical Analgesic and Anesthetic Agents^{1,2}

Topical Agent	Dosage Form	Indications	Dosing Recommendations	Generic Availability
Benzocaine (Anbesol® [OTC], Cepacol® [OTC], others)	Aerosol, Gel, Liquid, Lozenge, Ointment, Solution, Mouth Strip, Mouth Swab	Temporary relief of pain associated with pruritic dermatosis, pruritus, minor burns, acute congestive, bee stings, insect bites, mouth/gum irritations, sunburn, and hemorrhoids; used as anesthetic lubricant for passage of catheters and endoscopic tubes.	Apply topically 2-4 times daily; Lozenge can be taken up to every 2 hours	Product dependent
Benzocaine/ Butamben/ Tetracaine (Cetacaine®)	Aerosol, Gel, Liquid	Topical anesthetic to control pain in surgical or endoscopic procedures; anesthetic for accessible mucous membranes except for the eyes.	Aerosol: Apply for ≤1 second Gel: Apply ~1/2 inch x 3/16 inch Liquid: Apply 6-7 drops	No generic available
Benzyl Alcohol (Ulesfia; Zilactin [OTC])	Gel, Lotion	Gel: Temporary relief of pain from cold sores/fever blisters. Lotion: Treatment of head lice infestation.	Gel: Apply to affected area up to 4 times/day Lotion: Apply, leave on for 10 minutes, rinse; repeat in 7 days	No generic available
Capsaicin (various)	Cream, Gel, Liquid, Lotion, Patch	Patch: Management of post-herpetic neuralgia (PHN). OTC labeling: Temporary relief of minor pain.	Patch: Apply to affected area up to 3-4 times/day for up to 8 hours for 7 days Topical products (cream, gel, liquid, lotion): Apply to affected area 3-4 times/day	Generic only available for Cream
Dibucaine (Nupercainal [OTC])	Ointment (topical and rectal)	Fast, temporary relief of pain and itching due to hemorrhoids or minor burns.	Apply to affected areas; <30 g for adults or <7.5 g for children in 24-hour	Generic
Diclofenac (Flector®, Pennsaid®, Voltaren®, others)	Solution (ophthalmic), Transdermal (gel, patch,	Ophthalmic: Treatment of postoperative inflammation following cataract extraction or corneal refractive surgery.	Ophthalmic: 1-2 drops prior to surgery, following surgery, and continue 4 times/day, up to 2 weeks	Ophthalmic: Generic Transdermal:

	solution)	Transdermal: Relief of osteoarthritis pain, acute, localized joint/muscle injuries, actinic keratosis, and pain due to minor strains, sprains, and contusions.	Transdermal gel/solution: Apply to affected area 4 times/day Transdermal patch: Apply 1 patch twice daily	Product dependent
Dyclonine (Dycloaine®, Sucrets® [OTC])	Lozenge	Temporary relief of pain associated with oral mucosa.	One lozenge every 2 hours as needed (maximum: 10 lozenges/day)	No generic available
Ethyl Chloride	Aerosol	Local anesthetic in minor operative procedures, minor sport injury, bruises, myofascial and visceral pain syndromes.	Spray for a few seconds until the tissue becomes white (3-10 seconds)	Generic
Hexylresorcinol (Sucrets® [OTC])	Lozenge	Minor antiseptic and local anesthetic for sore throat	One lozenge every 2 hours as needed (maximum: 10 lozenges/day)	No generic available
Lidocaine (Akten, AneCream [OTC], Lidoderm, Xylocaine, others)	Cream, Gel (topical, ophthalmic), Kit, Lotion, Ointment, Patch, Solution	Rectal: Temporary relief of pain and itching due to anorectal disorders Topical: Local anesthetic for oral mucous membrane, minor surgeries, minor burns, cuts, and abrasions of the skin Oral topical solution: Topical for irritated oral mucous membranes Ophthalmologic: To provide local anesthesia to ocular surface during procedures Patch: Relief of allodynia, chronic pain in post-herpetic neuralgia, and temporary relief of localized pain	Cream, Gel, Lotion, Ointment, Solution: Apply 2-4 times daily Patch: Place for up to 12 hours in any 24-hour period	Product dependent
Lidocaine/Prilocaine (EMLA®, Oraqix®)	Cream, Gel (periodontal)	Cream: Topical anesthetic for use on normal intact skin to provide local analgesia for minor procedures Periodontal gel: Topical anesthetic for use in periodontal pockets during dental procedures	Apply to skin for 10 minutes to two hours	Cream: Generic Gel: No generic available
Lidocaine/Tetracaine (Synera®)	Transdermal (patch)	Topical anesthetic for use on normal intact skin for minor procedures	Prior to procedure, apply to intact skin for 20-30 minutes	No generic available

Methyl Salicylate/ Menthol (BenGay® [OTC]; Icy Hot® [OTC], others)	Aerosol, Balm, Cream, Patch, Stick	Temporary relief of minor aches and pains of muscle and joints associated with arthritis, bruises, simple backache, sprains, and strains	Patch: Apply to affected area for up to 8 hours not more than 3-4 times daily Topical products: Apply to affected area up to 3-4 times/day	No generic available
Pramoxine (Itch-X [OTC], Proctofoam [OTC], others)	Foam (rectal), Gel, Lotion	Temporary relief of pain and itching associated with hemorrhoids, burns, minor cuts, scrapes, or minor skin irritations	Apply to affected area up to 3-5 times daily	Product dependent
Proparacaine (Fluaine)	Solution (ophthalmic)	For use in ophthalmic procedures when a topical disclosing agent is needed along with an anesthetic	Instill 1 drop in each eye just before procedure and every 5-10 minutes for 5-7 doses, if needed	Generic
Tetracaine (Alcaine®, Pontocaine®, others)	Solution (mouth, ophthalmic)	Applied to nose and throat for diagnostic procedures Local anesthesia for various ophthalmic procedures of short duration	Mouth/throat solution: 0.25-0.5% solution by direct application or nebulization; total dose <20 mg Ophthalmic: 1-2 drops into affected eye prior to procedure and every 5-10 minutes, if needed, up to 5 doses.	Mouth solution: No generic available Ophthalmic solution: Generic
Trolamine (Arthricream [OTC], Myoflex [OTC], others)	Cream, Lotion	Relief of pain of muscular aches, rheumatism, neuralgia, sprains, arthritis on intact skin	Apply to affected area as needed up to 3-4 times/day	Product dependent

Mechanism of Action

Each type of topical anesthetic and analgesic has a distinct mechanism of action. The agents identified broadly as local anesthetics include benzocaine, proparacaine, tetracaine, articaine, dibucaine, lidocaine, prilocaine, pramoxine and dyclonine. This group of agents is further categorized according to molecular type: esters, amides or ethers. While the agents have different molecular makeups, the mechanism of action is the same for each. The local anesthetics work by blocking the permeability of sodium ions to the neuronal membrane, thus stabilizing the electric potential of the neuron.⁵⁻⁷ Stabilizing the neuron effectively blocks the initiation and conduction of nerve impulses, and leads to 'numbing' of the affected area. Generally, these agents have little to no systemic absorption through the skin. However, if the skin is broken or damaged or if applied to mucous membranes, the topical anesthetics can be well absorbed systemically.

The other topical analgesic agents have widely varied mechanisms of action and absorption. Diclofenac is a nonsteroidal anti-inflammatory drug with both oral and topical formulations. It works by inhibiting cyclooxygenase (COX), which is an early component of the arachidonic acid cascade.⁸ Diclofenac is poorly absorbed through the skin compared to oral doses with only about 10% of the drug being absorbed topically at maximum. Inhibiting the COX enzyme results in the reduced production of prostaglandins, thromboxanes, and prostacyclin. Trolamine is a salicylate and works very similarly to diclofenac in that it inhibits the COX enzyme. It also has very little absorption and has not resulted in systemic levels of salicylate.⁹ Capsaicin was originally thought to solely work through a counter-irritant effect, but further research has shown that capsaicin is an agonist of the TRPV1 cation channels on nociceptive nerve fibers. Repeated exposure to capsaicin results in desensitization of the sensory axons and the inhibition of pain transmission.¹⁰ Ethyl chloride is used as a cryoanalgesic. When the spray is applied to the skin, it causes a freezing and numbing sensation with no systemic absorption.¹¹ See table 2 for a summary of the pharmacokinetic data available for the topical analgesic and anesthetic agents.

Table 2. Summary of Pharmacokinetics of the Topical Analgesic and Anesthetic Agents ⁵⁻¹⁶

Type	Agents	Mechanism	Route	Systemic Absorption	Onset of Action	Duration	Metabolism	Excretion	
Esters:	Benzocaine	Blocks the initiation and conduction of nerve impulses by decreasing permeability to sodium ions in the neuronal membrane	Topical, rectal,	Poor through intact skin; Well absorbed from mucous membranes	<5 minutes	15-45 min?	Hepatic and plasma esterases	Urine (metabolites)	
	Proparacaine		ophthalmic	NR	rapid	10-20 min	Plasma esterases	urine	
	Tetracaine		Ophthalmic, topical	NR	5-10 minutes (rhinolaryngology)	30min (rhinolaryngology)	Hepatic, plasma esterases	urine	
Amides	Articaine		Injection only						
	Dibucaine		Topical/rectal	Poor through intact skin; well absorbed through mucous membranes	15 min	2-4 hours	hepatic	Urine	
	Lidocaine		Topical	~3-5% transdermal, depends on exposure	3-5 minutes in mucous membrane and damaged skin	45 min	90% hepatic; Active metabolites	Urine (<10% as unchanged drug)	
	Prilocaine		Topical (with Lidocaine)	Depends on duration of application and site: 6-33.5% prilocaine over 24 hours	1 hour More rapid in mucosa	1-2 hours after removal 15-20 min in mucosa	Hepatic, and hydrolyzed by amidases	Urine	
	Ether		Pramoxine	Topical, rectal	Minimally absorbed	3-5 minutes	NR	hepatic	NR

Ketone	Dyclonine (Dyclocaine) (Sucrets) (OTC)		Oral lozenge	NR	<10 min	<60 min	NR	NR
NSAID	Diclofenac	Inhibits cyclooxygenase, resulting in the reduced formation of prostaglandins, thromboxanes and prostacyclin.	Topical	Gel: 6-10% Solution: 2-3%	NR	NR	Hepatic	<1% renal
Salicylate	Trolamine	Inhibits cyclooxygenase, resulting in the reduced formation of prostaglandins, thromboxanes, and prostacyclin	Topical	Minimal	NR	NR	NR	NR
Capsaicinoids	Capsaicin	Activates TRPV1 cation channels on nociceptive nerve fibers. Repeated exposure results in desensitization of the sensory axons and inhibition of pain transmission	Topical cream/patch	Minimal	Slow	long	hepatic	NR
Cryoanalgesic	Ethyl Chloride	Freezes and numbs the skin	Topical spray	NR	Rapid	Seconds to 1 minute	NR	NR
Other	Hexylresorcinol (Sucrets)	Blocks voltage-gated neuronal sodium channels to inhibit initiation and conduction of nerve impulses	Oral lozenge	NR	Rapid	NR	NR	NR

Methods

A literature search was conducted to identify articles addressing clinical safety or efficacy of the analgesic and anesthetic agents, searching the MEDLINE database (1950 – 2013), the Cochrane Library, and reference lists of review articles. For the clinical efficacy section, only clinical trials published in English and indexed on MEDLINE prior to 12/2013, evaluating efficacy of the agents are included. Trials evaluating the analgesic and anesthetic agents as monotherapy or combination therapy where adjunctive medications remained constant throughout the trial are included. Trials comparing monotherapy with combination regimens are excluded.¹⁷⁻³⁶

Clinical Efficacy

Clinical evidence evaluating the topical analgesic and anesthetic agents is limited. The majority of clinical evidence available for the analgesic and anesthetic agents are placebo-controlled trials. Comparative clinical trials evaluating various lidocaine products, diclofenac and ethyl chloride were identified for evaluation.³⁷⁻⁴² According to the clinical evidence, the analgesic and anesthetic agents are more efficacious than placebo in treating or reducing localized pain. Differences may exist in duration of effect, patient preferences and other secondary outcomes.

Comparative clinical evidence comparing lidocaine/prilocaine to lidocaine demonstrates similar rates of efficacy.^{37, 38, 41} One clinical trial comparing topical lidocaine/prilocaine, lidocaine and placebo reported no differences in efficacy between treatment groups.^{40, 42} A trial comparing topical lidocaine to ethyl chloride spray demonstrated reduced pain intensity in the topical lidocaine treatment group.³⁹ A number of placebo-controlled trials evaluating the efficacy of lidocaine patches in the treatment of post-herpetic neuralgia reported significant pain relief, higher rates of patient preference, and less use of rescue medication in patients using the lidocaine patches.^{21, 30, 32, 41} The diclofenac epolamine patch was also evaluated in numerous placebo-controlled trials. In patients with a sports-related injury, statistically significant improvement in pain were reported in favor of the diclofenac patch.²⁰ Similar outcomes were reported in placebo-controlled trials evaluating the diclofenac patch in patients with a minor soft tissue injury and osteoarthritis of the hands and knees.^{19, 23-25, 29, 31, 34}

Special Populations

Geriatric Patients^{1, 2}

In general, topical analgesic and anesthetic agents are safe and effective in the geriatric population when a low-potency preparation is used for short periods of time. No evidence of differences in safety or efficacy has been reported between elderly and younger adult patients. Elderly patients may have thin skin, which can lead to increased penetration of analgesic and anesthetic agents and increase in both systemic and local adverse events.

Pediatric Patients^{1, 2}

Topical analgesic and anesthetic agents may be a useful alternative to injection of analgesic and anesthetic agents in children undergoing minor procedures. In general, safety and efficacy of the topical analgesic and anesthetic agents in children have not been established. Dosage adjustment may be required and some studies have shown less overall benefit in children <7 years of age. Overall, the topical analgesic and anesthetic agents should be used with caution in the patient population.⁴³

Adverse Drug Reactions

The topical analgesic and anesthetic agents are associated with both local and systemic adverse events.¹⁻⁴ Rate of adverse events tends to increase with increase duration of use. Local adverse effects are more prevalent than systemic reactions. Local adverse events most frequently reported with the topical analgesic and anesthetic agents include: Burning or stinging at the administration site and allergic reactions. Elements found in topical agents that may cause an allergic reaction include: propylene glycol, sorbitan sesquioleate, methylchloroisothiazolinone or methylisothiazolinone, lanolin, parabens, or formaldehyde releasing preservatives (imidazolidinylurea/diazolidinylurea).¹⁻⁴

Usually, up to 99% of the topical analgesic and anesthetic agent is cleared from the skin and only 1% is therapeutically active and only a very small portion of that, if any, is systemically absorbed.¹⁻⁴ Penetration can vary depending on stratum thickness, frequency of application, and use of an occlusive barrier. Agents used in the mouth can cause significant adverse events if swallowed and these agents are not recommended for use in children. Systemic adverse effects that can result from topical analgesic and anesthetic agents include: seizure, central nervous system (CNS) depression, and cardiovascular toxicity. Continued use of topical analgesic and anesthetic agents may lead to tachyphylaxis, especially with capsaicin use. Long-term use of topical analgesic and anesthetic agents is not recommended. Topical analgesic and anesthetic agents should not be used on ulcerated, atrophic, or infected skin. Caution should be used when using topical analgesic and anesthetic agents on certain body areas (e.g., intertriginous areas) or in pediatric/geriatric populations.¹⁻⁴

Summary

Thirteen topical analgesic and anesthetic agents are currently available for use in the United States and are indicated in the treatment or temporary relief of localized pain. The topical agents are available as aerosols, creams, gels, lotions, lozenges, ointments, patches, solutions and rectal products. Each of the agents has varying potencies and rates of skin penetration and, subsequently, different clinical uses. In general, treatment with a topical analgesic and anesthetic agent is determined by clinical judgment based upon location of pain, prior treatment, and complicating conditions (infection, age of patient).

The comparative clinical evidence available for the topical analgesic and anesthetic agents is limited. The majority of the evidence evaluates the agents in placebo-controlled trials. The limited data demonstrate comparable clinical efficacy for the agents. According to both clinical evidence and experience, topical analgesic and anesthetic agents are useful treatments for localized pain and success of treatment can vary depending on an accurate diagnosis, treatment of underlying disorder, agent delivery vehicle, frequency of application, duration of treatment, and adverse effects. The topical analgesic and anesthetic agents may be associated with both local and systemic adverse events. Local adverse effects include: burning and stinging at the site of administration. Systemic adverse effects include: seizure, CNS depression and cardiovascular toxicity. Long-term use of topical analgesic and anesthetic agents is not recommended. Caution should be used when using the topical analgesic and anesthetic agents in children or the geriatric population.

Overall, selection of a topical analgesic and anesthetic agent and preparation should be based on both patient-related and drug-related factors including age of the patient, the extent and location of the body surface area to be treated and the presence or absence of other complicating factors.

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