DOI: 10.55522/jmpas.v6i3.0137 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

A extensively second-hand drugs: Topical agents

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Received – 20 March 2017**, Revised** - 25 April 2017, **Accepted** – 23 May 2017 **(DD-MM-YYYY)**

Refer This Article

Kiran Jagtap, Ramesh Agarwal, Lata.Kale, Nilofar Zaidi, Sonia.Sodhi, Shaikh Tauseeef Ahmed, Sayyed Mohammed Qadri, Pratik C Parkarwar, Kirandevi C Puranik, Swati Rathod, 2017. A extensively second-hand drugs: Topical agents. Journal of medical pharmaceutical and allied sciences, V 6 - I 3, Pages -508 – 513. Doi: https://doi.org/10.55522/jmpas.V6I3.0137.

ABSTRACT

The skin & mucosa form the largest organ system in the body. There are many dermatologic conditions that affect the skin of the face & perioral areas. Several diseases that are primary to the oral mucosa or systemic diseases with oral manifestation that may require topical agents.

Keywords: Topical, Face, Perioral, Dermatologic, Skin, Mucosa.

INTRODUCTION

Topical agents deliver the medication directly to the target organ that needs treatment and provides high concentration of the desired medication to the specific site with less risk of provoking systemic side effects.Several vehicles deliver a drug topically, and vehicle is important part of effectiveness of the drug.

Topical pharmaceuticals are used for the following purposes.

Protecting an injured area from the environment so as to permit the rejuvenation of the skin.

Providing skin hydration or for an emollient effect

Providing a method of conveying a medication to the skin or mucosa for a specific effect either topical or systemically.

List of common topical vehicles

Creams- Semisolid emulsions of oil & water intended for external application that contains medicaments dissolved or suspended in water soluble cream base. They are usually soft, white, and non-greasy & they vanish when rubbed into skin.

Ointment- Semisolid emulsions of water droplets suspended in oil. They are occlusive & form a film on skin or mucosa that creates a membrane that causes an increase in the local skin temperature & its water content. This effect makes it easier for the topically applied substance to melt at body temperature & penetrate the skin's outer protective layer.

Solution -Liquid preparations that contain soluble chemicals dissolved in either water or alcohol

Gels -Semisolid emulsions that liquefy at body temperature when applied to the skin or mucous membrane

Lotions -Either suspension of insoluble powder in liquid (Calamine lotion) or pourable emulsions of oil in water. They are easily applied; their effects are short acting & they tend to wear off faster than creams/ ointments [1].

The decision to use a cream, ointment, gel, or lotion depends on the degree of skin penetration desired, the characteristics of the skin, the characteristics of the area to which the medication is applied & the properties of the medication. The amount of drug that penetrates & vigor of rubbing, the surface area covered, the condition of the skin, & the occlusive effect of the base.

Creams are usually applied to areas in which they can be rubbed vigorously into the skin or to moist, weeping lesions because they produce drying by having the exudate absorbed into the aqueous external phase of the cream.

Ointments are generally used on dry scaly lesions because they stay on longer & their emolient properties aid in rehydration

Pastes are thick, stiff ointments that do not flow at body temperature & serve as protective coatings over the area to which they are applied.

Orabase is one such agent. It is widely used dental paste that is agent

for several topical medications that are used intraorally. It contains gelatin, pectin, &carboxymethylcellulose sodium in plastibase (plasticized hydrocarbon gel, a polyethylene & mineral oil gel base).

Classification

Corticosteroid

Immunomodulators

Analgesics

Antibacterial

Antiviral

Antifungal

Topical steroids

It possesses anti-inflammatory &antimitotic activity& are corner stone of treatment for many inflammatory skin & mucosal conditions.They are absorbed at different rates from different parts of body, for E.g – from eyelids & genitals is 30%, face- 7% forearm – 1%, palm -0.1%. It's available in cream, ointment, gel, & liquid vehicle. When comparing different forms of the steroid preparation, ointment is generally stronger than creams because they penetrate better & absorbed best [2].

Usage

It needs to be in contact with the mucosa for some minutes for it to have any significant effect.

Patients should not eat or drink for 30min after using the steroid, in order to prolong contact with the lesion.

The steroid can usefully be applied in a plastic splint worn overnight for treatment of desquamative gingivitis.

Topical steroids in OLP in increasing order of potency

Triamcinolone acetonide 0.1% (Tess, Ledocort, Kenocort) tid/day for 1month

Fluocinolone acetonide 0.025% (fluzone) tid/day for 2months with tapering dose

Clobetasone propionate 0.05% (clobetol cream, cosvate gel) bid/day for 2months

RAS-Topical steroid like flucinonide, betamethasone, or clobetasol, placed direcly on ulcer reduces healing time.

Oral lesions of lupus erythematosis -0.05% flucinonide & 0.05%clobetasol gel placed on lesion bid for 2weeks

Bullous pemphigoid -High potency topical steroids, clobetasol, betamethasone.

Adverse reactions

Local -Skin atrophy, striae, telangiectasia, acneiform eruption & perioral dermatitis & hypersensitivity reactions

Systemic- When large amounts of steroids are absorbed through the skin, fluid retention, raised blood pressure, & secondary diabetes may develop or it may aggravate these conditions in pateints already in therapy. Supression of the hypothalamic-pituitary-adrenal axis with the use of topical steroids is uncommon. Adrenal supression caused by topical steroid use is seen more frequently in small children because their body surface area is large relative to their total body weight [3].

Immunomodulators

Topical Calcineurin Inhibitors

It acts by binding to immunophilins (cyclophilin & macrophilin) & these complexes inhibit calcineurin, which under normal circumstances induces the transcription of IL-2.

Tacrolimus: (Tacrotec, Tacrovate)

Inhibits T – lymphocyte activation & prevents the release of inflammatory cytokines & mediators from mast cells invitro after stimulation by antigen Ig E complexes.

Available in 0.03% ointment, twice daily application

Cyclosporine - 100mg /ml may be used as mouth rinse or finger rub application using very low doses of cyclosporine 48mg/day in adhesive base was found to be effective in suppressing T cell cytokine production.

Topical agents for neuropathic pain

As neuropathic pain frequently is associated with a peripheral ectopic generator (for instance, a triggering zone near the tissue surface in trigeminal neuralgia), it is logical to use a topical anesthetic to desensitize the painful site [3].

This approach may decrease the neuronal firing and relieve the pain. Local anesthetics are prepared for topical use in several different forms, such as aqueous or viscous gels, sprays and ointments. With neuropathic conditions, the application of the anesthetic usually is limited to a small area, and in those cases, a sticky ointment or viscous gel often is preferred.

Topical anesthetics

It delivers the analgesic at the site from which the pain originates & minimizes systemic effect of the drugs.

The main type of topical anesthetic agents available for use on mucosa are benzocaine, lidocaine, tetracaine & cocaine

Benzocaine (Topical, Hurricane, Oradell, Macropain)

It reversibly stabilizes the neuronal membrane, which decreases its permeability to sodium ions. Depolarization of neuronal membrane is inhibited, which blocks the initiation & conduction of nerve impulses. It is effective on nerve endings of mucous membranes & abraded skin. It has fastest onset & short duration

Indications – mucosal pain, superficial facial pain.

Dosage – 10%, 15%, 20% gel qid

Side effects –methemoglobinemia

Lidocaine

It is amide type local anaesthesia. Its mode of action is similar to that of benzocaine [4].

Lidocaine Patch: (Lidoderm patch)

As a topical preparation, the lidocaine patch 5% is well tolerated and has an excellent safety profile.

Indications – mucosal pain, superficial facial pain.

Dosage - maximum of 3 patches per day for up to 12 hours total directly to the area of maximum pain and/or allodynia.

The patch should not be used in patients with herpes zoster or those with other types of open skin lesions as the available formulation is not sterile.

Side effects - erythema, burning, edema

Eutectic mixture of local anesthesia (EMLA)

It is a mixture of lidocaine 2.5% in 1:1 ratio.

Lidocaine & prilocaine by themselves produce a 20% anesthetic concentration to penetrate intact skin [4].

It inhibits the neuronal membrane ion refluxes.

Indications – PHN,

Trade name -AstraZeneca

Capsaicin: (Zostrix)

Active pungent ingredient in hot peppers, is used commonly as a topical medication for neuropathic pain conditions of the skin or oral mucosa.

Capsaicin exerts strong pharmacological effects on the peripheral system and the CNS.

Of particular interest is its effect on the Cfiber type of primary afferent neurons and on a specific membrane recognition site identified as an ionotropic vanilloid receptor.

Capsaicin stimulates the nociceptors to release substance P and other peptide neurotransmitters, not only at the peripheral site of application, but also centrally.

The peripheral release causes local excitation and sensitization, manifested as prolonged cutaneous pain, histamine release, erythema and thereby primary hyperalgesia and allodynia

The central release of excitatory aminoacids and neuropeptides resulting from the peripheral stimulation of the C- fiber nociceptors by capsaicin causes central sensitization that results in the phenomena of secondary hyperalgesia and an expanded skin response area for the sensitized neurons [5].

It was initially postulated that chronic application of capsaicin depleted the peripheral sensory fibers of substance P, but now it is suggested that repeated capsaicin application actually only inhibits the peripheral terminal function. It should be noted that when the capsaicin application has been discontinued, the pain typically returns.

Indication: Stomatodynia, superficial neuropathic facial pain

Dosage – 0.025%, 0.075% cream should be applied to the affected area 3- 4 times daily.

Pain relief from topical capsaicin is usually seen in 14 to 28 days regular topical application. Maximal response may require 4 to 8 week [5].

Topical NSAIDs

Topical NSAIDs have shown effectiveness in relieving pain in acute and chronic conditions, with lower incidence of adverse gastrointestinal effects than they have when taken orally. Some of the medications used topically for pain include ketoprofen (a propionic acid derivative), diclofenac (a benzene acetic acid derivative), aspirin and ibuprofen.

Topical aspirin also has been specifically studied for dermal neuropathic pain, providing analgesia within 20 to 30 minutes.

Topical application of 5% Ibuprofen tid/day was effective in TMJ pain

Sympathomimetic agents

Sympathomimetic agents may be useful in some forms of chronic neuropathic pain.

It has been shown that injured C fibers express α1 receptors on their peripheral membranes. Sympathetic activity then would excite the C fibers, signaling pain.

Clonidine, an α2-adrenergic agonist, has been used as a topical agent for neuropathic pain because it is able to interrupt the peripheral release of norepinephrine, thereby decreasing the C-fiber stimulation

lonidine for local extraoral therapy is available as a transdermal patch. For intraoral use, it is better to have clonidine compounded into a transdermal penetrating cream and dispensed in a calibrated syringe so that the dose can be better controlled.

Anti-bacterial agents

Topical antibacterial agents may be useful in preventing infections inclean wounds

Early treatment of infected dermatoses & wounds

In reducing colonization of the nares by staphylococci,

The selection of particular antibiotic depends of course upon the diagnosis & when appropriate in vitro culture & sensitivity studies of clinical samples.

Prepacked topical antibacterial preparation that contain multiple antibiotics are available in fixed dosages well above the therapeutic thresholds.

Bacitracin ointment

It is a bacteriostatic against gram- positive and some gram-negative bacteria and may also possess some bactericidal activity at certain concentrations.

Bacitracin works by interfering with the mucopeptide transferring process and therefore prevents bacteria cell wall development

Indications: Prevention of skin and skin structure infections after a minor compromise in skin integrity such as minor burns or skin abrasion.

Neomycin & gentamicin

Neomycin and gentamicin are aminoglycoside antibiotics with gram-positive and gram-negative bactericidal activity.

It works by establishing irreversible binding to receptors present on the 30S ribosomal subunit of bacteria.

The binding prevents the initiation complex between the bacterial messenger RNA and the ribosomal subunit which results in the misreading of the bacterial DNA and formation of nonfunctional proteins.

Gentamicin 0.1% cream (Garamycin)

Indicated in treatment of minor bacterial skin infection including, folliculitis, furunculosis, impetigo, eczema, infectious eczematoid dermatitis, pustular acne, pustular psoriasis, infected seborrheic dermatitis, infected contact dermatitis.

Neomycin

Neosporin (neomycin+ bacitracin+ polymyxin B)

Prevention of skin and skin structure infections, including wound management for skin abrasion and minor burn wound infection

Metronidazole: (Metrogel)

Metrohex- metronidazole + chlorhexidine

It disrupts bacterial &protozoal DNA, inhibiting nucleic acid synthesis. Produces bactericidal, anti-inflammatory & immunosuppressive effects.

Indications: Anerobic bacterial infections such as dental abscesses, acute pericoronitis and acute ulcerative gingivitis.

Antifungal agents

Indications - Candidiasis

Cotrimazole

It inhibits the growth of pathogenic yeast by binding to phospholipids in fungal cell membrane which alters the permeability of the membrane & causes a loss of essential intracellular elements.

Dosage

Clotrimazole 1% cream (candid, canesten) 5times /day for 2 weeks

Clotrimazole 2% gel (candid V) 5 times/day for 2weeks

Side effects – nausea, vomiting, local mild burning, irritation, stinging

Nystatin (Nystat , Mycostatin)

It binds to sterol in fungal cell membrane & changes the cell wall permeability, which allows for leakage of cellular contents.

Dosage – 100,000 U/g cream & ointment, apply to affected area 4-5 times/day

Side effects – nausea, vomiting, diarrhea, stomach pain, contact dermatitis.

Ketoconazole (Nizoral)

It is broad spectrum synthetic antifungal agent functions by altering the permeability of the cell membrane of the organism by way of the drug impairing the synthesis of ergosterol, a vital component of fungal cell membrane.

Dosage – 2% cream: rub gently into the affected area 1-2 times daily.

Side effects – irritation, pruritus, stinging

Miconazole

It inhibits the growth of the common dermatophytes Epidermophyton floccosum & the yeast-like fungus C. albicans. The drug has no contraindications.

Indications: angular stomatitis, various forms of candidiasis, and antiviral agents.

The viral conditions that the oral & maxillofacial surgeon most likely encounters are herpes labialis. The agents that are used topically for this condition are penciclovir & zovirax ointment.

Acyclovir: (Acivir, Cyclovir, Herperax, Herpex)

It interferes with herpes simplex virus DNA polymerase &inhibit viral DNA replication. It is also effective against other viruses.

It seems to shorten the course of the herpetic eruptions & produces a slight decrease in pain.

Dosage: 5% cream,topical application to lesion 4times daily for 4 days

Side effects – pain, burning, stinging.

Penciclovir Cream 1% (Denavir Cream)

It is active against herpes viruses. It selectively inhibits herpes virus DNA synthesis & prevents viral replication.

Indicated in herpes labialis.

Dosage – the cream should be applied to the lesion every 2 hours during waking hours for a period of 4 days . Treatment should be started as soon as possible during the prodrome or as soon as the pateint become aware of lesion.

Side effects – mild erythema, occasionally headache

Docosanol: (Abreva)

It is saturated 22-carbon aliphatic alcohol that inhibits HSV replication intracellular events surrounding viral entry into target cells. Its mechanism of action is still poorly understood.

It is high lipophilic compound & targets viruses with lipid containing envelope such as HSV.

It probably inhibits fusion of the HSV envelope with the plasma membrane& therefore blocks subsequent viral replicative events.

Dosage – 10% cream is available, thin film is applied 4 times daily until healed. It reduces the healing time by 1.6 to 4.6 days

Side effects – tingling at application site [6].

Topical opiates

Are increasingly applied for the relief of pain. Mu receptor agonists are the most potent topical opiod analgesics delta &k being effective.

Opiod receptor are present on the peripheral terminals of thinly myelinated & unmyelinated cutaneous sensory fibers.

However peripheral opiods actions are not prominent in normal tissue & appear after the induction of inflammation due to enhanced opiod receptor expression.

According to a study topical morphine was used in pateints of head & neck cancer receiving chemotherapy, it decreased the severity of pain & duration of pain & duration of functional impairment

(Advanced studies in medicine 2003)

Amlexanox:(lexanox)

Potent anti-allergic, anti-inflammatory effect.

It inhibits the release of histamine and leukotrienes from mast cells, basophils and neutrophils in in vitro settings, possibly through increasing intracellular cyclic AMP content in inflammatory cells, a membrane-stabilising effect or inhibition of calcium.

Indication – aphtous ulcers

Dosage – 5% paste, 4 times /day until ulcer heals

Side effect- Transient pain, stinging or burning, contact mucositis, nausea and diarrhea.

Mouth rinses

Chlorhexidine 0.2% (Clohex, Nitrahex, Rexidine,peridex)

It is potent, chemoprophylactic agent. It has a broad-spectrum action & effective against G+ve than G-ve bacteria. It acts by binding readily to negatively charged bacterial cell wall thereby disrupting membrane integrity &affecting its functions. In high concentration it is bactericidal.

Indicated in gingivitis

Dosage – 10ml swish & expectorate, bid

Side effects – teeth staining, taste change, tongue discoloration

Povidone-iodine

Indications

Used as an aid to oral hygiene

Presentations: As a 1% mouthwash.

Dose: 10 ml undiluted or diluted to 20 ml with water as a rinse 4 times daily.

Desensitizing agents

Definition. Desensitizing agents are defined as drugs that alleviate painful sensations that sometimes occur in exposed dentin and cementum.

Types of Desensitizing Agents.

Fluoride. (in the form of sodium fluoride, stannous fluoride, acidulated- phosphate fluoride, and so forth) it decrease the permeability of dentin in vitro, possibly by precipitation of insoluble calcium fluoride within the tubules.

Oxalates: In 1981, Greenhill and Pashley reported that 30 percent potassium oxalate caused a 98 percent reduction in dentin permeability in vitro. Oxalate products reduce dentin permeability and occlude tubules more consistently in laboratory studies

Calcium phosphates. Calcium phosphates may reduce dentin sensitivity effectively. Calcium phosphates occlude dentinal tubules in vitro and decrease in vitro dentin permeability.

Potassium nitrate. Potassium nitrate, which usually is applied via a desensitizing toothpaste, also can reduce dentin sensitivity when applied topically in an aqueous solution or an adhesive gel.

Potassium nitrate does not reduce dentin permeability in vitro, but potassium ions do reduce nerve excitability in animal models

Bonding resins and dentin adhesives. With the newer systems becoming more adherent to dentin, these materials have become very popular. Resins and adhesives are now designed to flow into dentin tubules to seal the dentin surface when they are set [7].

Desensitizing toothpastes/dentifrices ensiform, Sensodyne)

Most desensitizing toothpastes contain a potassium salt such as potassium nitrate, potassium chloride or potassium citrate.

Vitamin A (retinoic acid 0.01% to 0.5%)

Retinoids have been noted to have ant keratinizing and immuno-modulating effects; they stimulate macrophage activation and antibody dependent cell- mediated cytotoxicity.

Moreover, retinoids may reduce CD4 lymphocyte infiltration and increase the macrophages in OLP lesions, thus accelerating the healing process.

Used in treatment of leucoplakia, chronic hyperplastic candidiasis

Trade name – Retin-A [8].

Table 1: Results of state anxiety based on intenet addiction level

TOPICAL MEDICATIONS.

MEDICATIONS	EXAMPLES OF TOPICAL PREPARATIONS FOR ORAL AND PERIORAL USE	MECHANISM OF ACTION
Topical Anesthetics	Benzocaine in Orabase (Bristol-Meyers Squibb) cream (20%)* (for intraoral use only) Lidocaine gel, viscous solution, ointment, spray and adhesive patch† (for intraoral use only) Eutectic mixture of local anesthetic (EMLA cream, Astra/Zeneca)† (lidocaine and prilocaine) (for intraoral and extraoral use)	Sodium channel blockade
Neuropeptides: Capsaicin	Cream in 0.025%* and 0.075%* strengths (for intraoral and extraoral use)	Inhibition of peripheral nociceptor terminal function
Nonsteroidal Anti-inflammatory Drugs	Ketoprofen (10-20%) in a pluronic lecithin organogel, or PLO, base† (for extraoral use only) Diclofenac (10-20%) in PLO base† (for extraoral use only)	Blocks prostaglandin production through cyclooxygenase inhibition
Sympathomimetic Agents: Clonidine	Patch† (for extraoral use only) 0.01% in PLO base† (for intraoral use only)	Influences peripheral alpha adrenergic activity
NMDA§-Blocking Agents: Ketamine	0.5% in PLO base or in Orabase† (for intraoral use only)	Antagonist to NMDA receptor
Anticonvulsants	Carbamazepine (2%) in a PLO base† (for extraoral use only)	Blocks use-dependent sodium channel activity
Tricyclic Medications: Amitriptyline	2% in PLO base† (for extraoral use only)	Blocks sodium channels
Antispasmodics: Baclofen	2% in PLO base (for extraoral use only)	Gamma-aminobutyric acid

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