Topical Use of Systemic Drugs in Dermatology

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Abstract: Objective: Review the topical usage of systemic drugs in dermatological diseases. **Data Sources:** From previous Literatures, reviews and studies as well as medical websites (PubMed, MD consult, Medscape) and Scientific Journals data- bases were searched from the start date of each data- base. **Study Selection:** Selection was done by supervisors for studying new advancement in topical use of systemic drugs in dermatology and studies that addressed topical therapy in dermatology and systemic drugs used topically in dermatology. **Data Extraction:** Data from published studies were manually extracted and summarized. Study quality assessment included whether ethical approval was gained, prospective design, eligibility criteria specified, appropriate controls used, adequate follow-up achieved and defined outcome measures. **Data synthesis:** In this review the data found that several studies of the topical usage of systemic drugs in dermatological diseases to know which systemic drug can used topically. **Findings:** A total of 44 studies were included in the review as they were deemed eligible by fulfilling the inclusion criteria. Of these 44 articles, included in this review, 32 were Topical usage of systemic drugs in dermatological diseases and 12 were topical therapy. Studies indicate that some of systemic drugs can used topically in the treatment of some dermatological diseases. **Conclusion:** Extemporaneous compounding helps physicians to individualize treatment to the patient's specific needs and to create topical preparations that are not otherwise commercially available. However, comparative effectiveness studies are needed to determine whether or not topical use of systemic therapeutics is more beneficial than existing therapies.
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Introduction

The use of systemic drugs for topical use is especially attractive for dermatologists because of the potential for efficacy with relatively mild systemic adverse effects during topical application. Preparing extemporaneous formulation, many factors, such as physical and chemical properties of the drugs and excipients, stability, sterility of the products, systemic absorption, and medicolegal risks of compounding, should be considered(1). It should be noted that topical application may produce a higher chance of irritant and allergic contact dermatitis than oral forms. The development of new vehicles and delivery systems may provide greater opportunity for the topical application of systemic drugs. Topical application of systemic drugs could theoretically avoid systemic toxicities by delivering the drugs to the site of disease directly and bypass hepatic metabolism, achieving a higher local concentration in the skin (2).

Materials and methods

Search strategy

We reviewed papers on topical usage of systemic drugs in dermatological diseases from Medline databases (PubMed, Medscape, and Science Direct) and also materials available on the internet. We used systemic drugs topically in the Treatment of skin diseases searching terms. In addition, the search was performed in the electronic databases from 2003 to 2014.

Study selection

All the studies were independently assessed for inclusion criteria. They were included if they fulfilled the following criteria:

1. Published in English language.
2. Published in peer-reviewed journals.
3. Focused on topical therapy.
4. Discussed the effectiveness of topical use of systemic drugs in dermatology.
5. If a study had several publications on certain aspects, we used the latest publication giving the most relevant data.

Data extraction

Studies that did not fulfill the above criteria, such as studies on ordinary topical treatment and studies not focused on topical use of systemic drugs in skin lesions were excluded.

The publications analyzed were evaluated according to evidence-based medicine (EBM) criteria using the classification of the US Preventive Services Task Force and UK National Health Service protocol for EBM in addition to the Evidence Pyramid.

US Preventive Services Task Force:

1. *Level I*: Evidence obtained from at least one properly designed randomized controlled trial.
2. *Level II-1*: Evidence obtained from well-designed controlled trials without randomization.
3. *Level II-2*: Evidence obtained from a well-designed cohort or case- control analytic studies, preferably from more than one Center or research group.
4. *Level II-3*: Evidence obtained from multiple time series with or without intervention. Dramatic results in uncontrolled trials might also be regarded as this type of evidence.
5. *Level III*: Opinions of respected authorities, on the basis of clinical experience, descriptive studies or reports of expert committees.

Quality assessment

The quality of all the studies was assessed. Important factors included the study design, attainment of ethical approval, evidence of a power calculation, specified eligibility criteria, appropriate controls, adequate information and specified assessment measures. It was expected that confounding factors would be reported and controlled for and appropriate data analyses made in addition to an explanation of missing data.

Data synthesis

A structured systematic review was performed.

Study selection and characteristics

In total, 170 potentially relevant publications were identified: 126 articles were excluded as they did not meet our inclusion criteria. A total of 44 studies were included in the review as they were deemed eligible by fulfilling the inclusion criteria. Of these 44 articles, included in this review, 32 were study topical usage of systemic drugs in skin diseases and 12 study topical drugs.

A study to discuss efficacy and side effects of systemic drugs and the topical use of these systemic drugs in some of dermatological diseases.

Anti-inflammatorydruges:

Topical aspirin for herpes zoster

Acute herpetic neuralgia (AHN) and postherpetic neuralgia (PHN) are difficult to manage, although a wide range of treatments have been proposed and applied (4). **Balakrishnan et al(3)** performed one randomized controlled trial and found topical aspirin to be more effective than oral aspirin in relieving PHN and AHN. Treatment tolerance was excellent with no adverse effects observed in these trials. The mechanism responsible for the superior analgesic properties is not clear, but it is probably a result of the pain origin of PHN and AHN being located at cutaneous free-nerve ending pain receptors. Topical aspirin seems to be a good alternative treatment for AHN and PHN in patients who cannot tolerate the adverse effects of systemic analgesic and neuroleptic agents.

Topical colchicine therapy for actinic keratosis

Actinic keratoses (aks) are the most common neoplastic skin lesions detected in individuals with Fitzpatrick skin type I or II. AKs appear as papules in a vast spectrum of sizes, shapes and colors(5). ***Akar et al* (6)** described the beneficial effects of topical colchicine for the therapy of actinic keratosis in a clinical study *using* 0.5% and 1% topical colchicine which induced complete healing of actinic keratosis in7 and 6 of 8 patients, respectively. No adverse effects of topical colchicine was observed in these studies.

TOPICAL PROSTAGLANDIN E2 FOR VITILIGO

Vitiligo is a common disorder of skin pigmentation. The prevalence rages from 0.1% to 4% and is estimated to be about 1% in white individuals **(7). Kapoor et al (8)** revealed the efficacy of PGE2 (250µg/g twice daily) in vitiligo. Patients were instructed to apply a translucent gel containing PGE2 (0.25 mg g) twice daily to the depigmented skin as a thin film sufficient to cover the affected area and then to rub it gently three to four times.Repigmentation of 75% to 100% was observed in 22 (39%) patients **(8).**

Hematopoietic Drugs

TOPICAL GRANULOCYTE-MACROPHAGE COLONY-STIMULATING FACTOR AND GRANULOCYTE COLONY-STIMULATING FACTOR FOR ULCERS :

Recurrent aphthous stomatitis is a common oral mucosal disorder. It is clinically diagnosed by painful, recurrent, yellowish white or grey, single or multiple, and round or oval ulcers with erythematous margins mainly confined to non-keratinized oral mucosa(9). Granulocyte-macrophage (GM)-colony-stimulating factor (CSF) is a cytokine that acts as a potent growth factor on the myeloid lineage of hematopoietic cells. It may also directly induce proliferation of endothelial cells and keratinocytes and thus help wound healing(1). In **Herranz et al (10)** study each patient received a daily dose of 400 µg GM-CSF diluted in 200 mL of 5% glucose, for 3 consecutive days. Patients were instructed to perform oral mouthwashes for 20 min. every 8 h. using one-third of the total solution in each session. During the 5 days, no changes to the antiviral treatment were made, and analgesics were maintained as required. The frequency and severity of oral ulcerations clearly decreased during a prolonged follow-up period after the use of topical GM-CSF. No cutaneous or systemic adverse effects were detected after the use of topical GM-CSF or granulocyte-CSF except for a burning sensation and allergic reaction in a minority of patients **(10).**

Anticonvulsive and Antipsychotic Drugs

TOPICAL PHENYTOIN FOR LICHEN PLANUS

Lichen planus (LP) is a chronic inflammatory dermatological condition usually affecting adults, but rare in children (11). **Bogaert and Sanchez** (12) performed a study involving 30 patients with lichen

planus and treated them with oral phenytoin (100-200 mg daily) for 2 to 24 weeks. Fourteen of 25 treated patients had complete resolution. In addition, 3 of 5 patients with verrucous, hypertrophic lichen planus had complete disappearance of these lesions after receiving both oral and 2% topical phenytoin for 6 months.

Topical Chlorpromazine ForVasculitis

Cutaneous vasculitis is defined as a pathological process characterized by inflammation of the skin blood vessel wall; the disease process causes an alteration of the blood flow, ischemia, and damage to the neighboring tissue (13).

Chlorpromazine is one of the oldest antipsychotic drugs and the therapeutic effects of topical chlorpromazine had been reported in a patient with leukocytoclasticvasculitis. The effect of chlorpromazine may be caused by its complement-inhibiting property. Chlorpromazin in 1% concentration as gel has demonstrated its efficacy in patients with generalized non thrombocytopenic purpura. These findings are in agreement with the complement-inhibiting action of the drug. Having in mind the risk of patient photosensitization due to the drug, authers recommend short duration of the treatment(1).

Chemotherapy of Neoplastic Diseases

Topical Methotrexate For LymphomatoidPapulosis

Lymphomatoidpapulosis (LyP) is a lymphoproliferative disorder that affects middle-aged patients in the form of recurrent outbreaks of papules or papulonecrotic lesions. It runs a benign course and usually resolves spontaneously in 4 to 6 weeks(14**). Bergstrom and Jaworsky(15)** study, their patient moistened a 2.5-mg tablet of methotrexate with tap water and rubbed it onto a bandage until the gauze turned orange. Patient then applied this bandage daily on newly formed papules. He used approximately one third of a tablet (0.83 mg) per lesion per day. With this regimen, his lesions regressed within 2 to 3 days, and rarely took up to a week to resolve. The papules were smaller (5-10mm) and rarely ulcerated. Lesions not treated in this manner grew larger, up to 2 cm, and persisted for more than 3 weeks. However, he was able to control the extent of these lesions and prevent scar formation with the topical application of methotrexate to new lesions (15).

Topical Methotrexate for Psoriasis

In Eskicirak et al (16) study use 0.2% methotrexate in aqueous cream under occlusion for 24hr was applied daily to nine patients with psoriasis vulgaris. Forty-eight hours after the start of treatment, clinical and histopathologic improvement was seen, and, at the end of week 2, complete improvement in three patients and partial improvement in four patients was reported (16).

Topical BleomycinFor Oral Leukoplakia:

The term leukoplakia clinical refers to a white patch or plaque that cannot be characterized clinically or histologically as any other disease (17). **Epstein et al** (18) evaluated the use of topical 1% Neomycin in dimethyl sulfoxide for the treatment of dysplastic oral lesions. Bleomycin was applied once daily for 14 consecutive days to lesions of the oral mucosa in 19 patients. Immediate post treatment biopsies and the clinical response were evaluated and clinical follow-up was conducted for as long as possible. Topical bleomycin prevent the potential progression of leukoplakia from dysplasia to carcinoma. Topical bleomycin is well tolerated and only a transient minor mucosa reaction was noted (18).

Topical thalidomide gel in oral chronic Graft Versus Host Disease (cGVHD)

Oral cGVHD-related pain is reported frequently, and oral dryness has been associated with inferior health-related quality of life. A preliminary data for topical thalidomide gel in the management of oral ulcerative cGVHD was reported(19). The response to thalidomide was measured by evaluating clinical performance and biological characteristics, including the healing rate of oral ulcers, pain intensity (sensory and affective pain) and concentration of cytokines in oral fluids the result found improvement in all cases with no advers effect of topical thalidomide reported in this study (19).

Pharmacotherapy of gastric acidity and peptic ulcer:

Topical cimetidine for acne and periodontitis

Acne is a chronic inflammatory disease of pilosebaceous unit. Prevalence being 56% in boys and 45% in girls between 14 to 16 years of age group (20)**. Schmidt and Spona**(21) showed a reduction of facial comedones in 10 patients using 2% lotion of topical cimetidine. The proposed mechanism may be mediated through its antiandrogenic and immunomodulative effects, such as interfering with chemotaxis, phagocytosis, and suppressor T-cell and natural killer cell activity (22)**.**

Hormones and Hormone Antagonists:

Topical methimazole in treatment of hydroquinone-resistant melisma

Melasma is an acquired hyperpigmentation disorder of the skin in sun-exposed areas. Topical methimazole(MMI) safety was also tested in vivo in melasma patients. A study by **Kasraee et al** (23) involving 20 patients with melasma showed nochange in serum TSH, free thyroxine, and free triiodothyronine levels after a 6-week period of once daily application. MMI was shown to reduce ultraviolet-induced erythema in the skin, adding to its depigmenting effect a potential sun protective action. The authors hence report the successful management of two HQ-resistant patients with MMI. The efficacy of MMI for the

treatment of melasma and its advantages over other known depigmenting compounds suggest that topical MMI should be added to the available armamentarium of anti-melasma treatments (14).

Immunomodulator Drugs

Topical Cyclosporine For Treatment Of Psoriatic Nails

Cannavò et al (25) do a prospective randomized placebo-controlled study in order to analyze the effectiveness and tolerability of topical oil-dissolved 70% CsA solution in nail psoriasis. **Cannavò et al** (25) study show that topical therapy with oral CsA solution is a safe, effective and cosmetically highly acceptable treatment modality for nail psoriasis. The ability of CsA to influence keratinocyte proliferation and T-cell lymphokine release, reducing the cornification of the upper layers of the epidermis, may prevent the typical alterations observed in nail psoriasis.

Chemotherapy of Microbial Diseases

Topical Cidofovir For The Treatment Of Dermatologic Conditions:

Zabawski et al (26) used topical cidofovir to treat two patients with verruca vulgaris. In subsequent case reports, the effectiveness of topical cidofovir for verruca, either in immunocompetent or immunocompromised patients, has been reported (27). Similarly, 3 RDBPCTs demonstrated its efficacy for the treatment of mucocutaneous herpes simplex infection, cervical intraepithelial neoplasia, and anogenital warts (28). Many case reports have also suggested topical cidofovir as a promising, efficacious treatment for various dermatologic conditions, including anogenital squamous cell carcinoma in situ, vulvar intraepithelial neoplasia, Bowenoidpapulosis, and molluscumcontagiosum (27).

Vasoactive Drugs

Topical spironolactone for acne vulgaris

Clinical pilot studies with topical spironolactone have demonstrated beneficial effects in patients with acne and idiopathic hirsutism (29)**. Berardesca et al (30)**showed that 5% topical spironolactone cream acts as an anti-androgen in human sebaceous glands, competing with dihydrotestosterone (DHT) receptors and producing a decrease of labelled DHT. At the concentrations used the effect has been only local. No side effects were recorded during the study (30).

Topical atropine for multiple hidrocystomas

Eccrinehidrocystomas are benign cystic lesions which originate from eccrine glands duct predominantly located on the face - eyelid and cheek regions. These lesions are more frequent in females than males (31). In a study, topical 1% atropine sulfate in aqueous solution demonstrated a significant mean reduction of lesions (70%) in 5 women treated for 15 days, and only a few adverse effects such as symptomatic mydriasis and a slight decrease of accommodation amplitude were observed (32).In anther study authors use lower concentration of atropine (0.03%) the result is reduction of lesion and with no ocular side effects or dryness of oral mucosa (31).

Drugs Acting At Synaptic and Neuroeffector Junctional Sites

Topical glycopyrrolate for cranio facial hyperhidrosis and Eccrinehidrocytomas

Hyperhidrosis, a condition characterized by excessive sweating, can be generalized or focal. Generalized hyperhidrosis involves the entire body and is usually part of an underlying condition, most often an infectious, endocrine, or neurologic disorder (33). **Saucedo et al(34)** show successful treatment of multiple eccrinehidrocystomas with Topical glycopyrrolate because of its effectiveness (about 77–100% in cases report), safety, scarcity of adverse effects reported, its deference to bodily resistance, and the lack of discomfort to the skin.

New Promising and Potential Compounding

Topical tumor necrosis factor-alfa in the treatment of chronic ulcers

Infliximab, a chimeric immunoglobulin (IgG1) monoclonal antibody that binds to soluble and transmembrane tumor necrosis factor-alfa, has been approved for the treatment of psoriasis, inflammatory bowel disease, ankylosing spondylitis, psoriatic arthritis, rheumatoid arthritis, and sarcoidosis (36). **Streit et al (35)** reported that topical infliximab, either as a solution (10 mg/mL) or gel formulation (0.45, 1,or 4.5 mg/g) produced complete healing in 5 of 14therapy-resistant ulcers and at least a 75% reduction in size in another 4 ulcers within 8 weeks in a case series study. This case series did not report any systemic or local adverse effects**.**

2.Topical activated protein C for chronic ulcers

Activated protein C (APC) is a serine protease that plays a central role in physiologic anticoagulation, and is commonly used in coagulation and inflammatory-related disorders. The mechanism of action may depend on inhibition of inflammation, stimulation of angiogenesis, and reepithelialization and antiapoptotic properties (37).In a case series reported by **Whitmont et al(38)** 4 patients with refractory leg ulcers undergoing topical APC treatment (200 µg/mL in distilled water) showed a rapid and positive response. These preliminary data indicate that the topical administration of APC fortherapy of refractory wounds was safe and effective.

Topical thiosulfate for dystrophic calcinosis

Sodium thiosulfate is an antidote to cyanide poisoning and has been used to prevent kidney stones and to treat tumoral calcification and calciphylaxis in patients with end-stage renal disease. Its effectiveness may act through chelation of calcium thiosulfate salts,

which are 250- to 100,000-foldmore soluble than other calcium salts. **Wolf et al (39)** reported a patient with systemic lupus erythematosus and dystrophic calcification successfully treated with topical sodium thiosulfate and suggested topical thiosulfate as a well-tolerated treatment for dystrophic calcinosis.

Discussion

Topical therapy is the use of medicaments directly on surface of skin or mucosa. Topical treatment offers the potential to achieve high concentration of a drug in the skin with minimal exposure of other organs, which can greatly increase efficacy and also safety relative to systemic administration(2). The main advantage of is to bypass first pass metabolism. Topical application of systemic drugs could theoretically avoid systemic toxicities by delivering the drugs to the site of disease directly and bypass hepatic metabolism, achieving a higher local concentration in the skin. For examples the traditional cornerstones of analgesic therapy for patients with acute pain topical agents offer an alternative to oral modalities and can effectively treat patients with acute pain while offering lower systemic absorption and conferring little risk of systemic toxicity. There are sufficient data supporting the use of various topical formulations of nonsteroidal anti-inflammatory drugs (NSAIDs) for herpetic pain and demonstrating markedly less patient risk of systemic toxicity than is associated with oral NSAID therapy. Use of topical NSAID therapy has been useful in reducing acute-phase herpes zoster pain. Topical analgesics represent an alternative treatment modality for patients experiencing acute pain who cannot or choose not to take oral therapies (1). Topical colchicine therapy for psoriasis and actinickeratosisauthers reported complete clearing of recalcitrant psoriasis patients treated topical colchicine solution under occlusive application(40).

Conclusion

Topical application of systemic drugs could theoretically avoid systemic toxicities by delivering the drugs to the site of disease directly and bypass hepatic metabolism, achieving a higher local concentration in the skin. However, given the high cost of new drug development, many innovative topical preparations of systemic drugs will not become commercialized in the near future. Therefore, off-label use of extemporaneous compounding of systemic drugs for topical use is often inevitable, although there are legal considerations and unpredictable stability and safety of these preparations. It should be noted that topical application may produce a higher chance of irritant and allergic contact dermatitis than oral forms. The development of new vehicles and delivery systems may provide greater opportunity for the topical application of systemic drugs, however, comparative effectiveness research is needed to determine if these new formulations translate to better outcomes.

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