ACTA FACULTATIS
MEDICAE NAISSENSIS

UDC: 615.262:616.5
DOI: 10.5937/afmnai37-25282

Review article

Off-Label Prescriptions in Dermatology: Challenges of New Routes of Administration for Certain Old Drugs

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SUMMARY

"Off-label drug use" refers to the prescription of medications, with reference to indications, dosage, dosage form, patient group or route of administration, which are officially unapproved. Recently, new indications for some drugs have emerged and few of them are being used off-label to treat topically a variety of dermatological conditions. Off-label use is more common in dermatology than in other medical specialties, and those drugs are basically available as compounded formulations, but the choice of a proper vehicle and safety of extemporaneous drug preparation intended for topical use are usually neglected in case of systemic drugs. Moreover, the bases commonly used as vehicles for extemporaneous dermatological preparations are stabilized with traditional surfactants known for their potential to irritate skin, while inflammatory dermatoses can worsen when exposed to irritants

In this paper, we have listed several systemic drugs which are being used in topical treatment of some frequent dermatological conditions, but not according to their officially approved indications. The choice of drugs was made according to the topical off-label dermatological prescriptions obtained from public pharmacies. The aim was also to review data related to, in our opinion, two major drawbacks of using off-label topical drugs: safety data on the use of the final dermal preparation and scientific information relevant for the choice of a proper topical vehicle for specific drug and proper stability evaluation.

Key words: **off-label drug, dermatology, compounded drugs, drug vehicle**

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INTRODUCTION

The term "off-label drug use" refers to the prescription of medications with reference to indications, dosage, dosage form, patient group or route of administration which are officially unapproved or, in other words, not in accordance with the Summary of product characteristics (SmPC) for specific drug. Off-label medications are common in the management of dermatological diseases (1). The reason probably lies in the fact that many of skin changes, which are numerous and very common in general population, are difficult to manage satisfactorily with the existing means. There is a need for developing new drugs for diseases treated by dermatologists, but just few of them were introduced in the last decade. The main reasons are weak economic potential of these drugs, hard-to-assess benefit-to–risk relationship and limitations such as inadequate surrogate end points (2). More recently, drugs are being used topically to treat some specific conditions beyond their officially approved indications and routes of administration, and there is a lack of data regarding their skin irritation potential. The skin becomes a new route of administration for those drugs, mainly because topical therapy of skin diseases allows high drug levels at the site of action and reduces systemic side effects (3, 4). Moreover, "off-label" prescriptions often relate to medications that have both well accepted therapeutic value in the medical community and proven efficacy on the basis of the results of clinical trials (5-8).

Approximately two-thirds of new drug applications submitted to the FDA relate to modifications of the existing drugs or their indications (7). In the recent years, new indications for some drugs have emerged and some of them are being used off-label to treat topically a variety of dermatological conditions (8). In fact, off-label drug use in dermatology is more common than in other medical specialties, but those drugs are basically available only as compounded formulations. Relevant studies have shown justification for newer applications and skin as an alternative route of administration only for some of those drugs. Moreover, it is obvious that the choice of a proper vehicle is often neglected here.

An unsuitable topical delivery system can decrease the efficacy of a drug while a proper one could increase its therapeutic index (9). The possibility of improving the use by employing newer vehicles is not often taken into account. Nevertheless, a major issue associated with routine use of extemporaneous preparations is the lack of stability data. The pharmacist must therefore implement stability studies according to ICH guidelines for each formulation to establish a relevant period of validity. Moreover, the bases commonly used as vehicles for extemporaneous dermatological preparations are stabilized by traditional anionic and non-ionic surfactants (10), which could have a significant potential to irritate skin and impair skin barrier function after topical use, particularly in diseased skin (11, 12). The impaired skin barrier is not able to heal properly and that could present a serious skin safety issue.

In this paper we have listed several drugs which are being used topically in the treatment of some frequent dermatological conditions, but not according to their officially approved indications and routes of administration. The choice of drugs was made according to the most frequent off-label dermatological prescriptions from public pharmacies in Niš, Serbia. The aim was also to review data related to, in our opinion, two major drawbacks of using off label topical drugs - safety data on the use of the final off-label dermal preparation and scientific information relevant for the choice of a proper topical vehicle for specific drug and proper stability evaluation.

Spironolactone

Spironolactone (SP) is a synthetic steroidal diuretic. Due to its structure it is an anti-androgen drug, some clinical studies have shown its potential to block the DHT receptors and reduce the sebum secretion in sebaceous glands in skin after oral use, which can be crucial for acne therapy (13-16). At the same time, spironolactone is used in the form of off-label topical acne therapy in order to avoid systemic side effects. In most cases, it is prescribed by dermatologist in a form of extemporaneous preparation with 5% of SP in a vehicle. According to relevant legislation, the choice of a proper vehicle should be made by pharmacist, and amphiphilic pharmaceutical bases are usually used in that purpose. Yamamoto and Ito (14) applied spironolactone 5% gel to healthy male individuals without acne and a significant reduction of the sebum secretion rate was observed. However, there are no comprehensive

studies to demonstrate the suitability of the most commonly *ex-tempore* used pharmaceutical bases to serve as vehicles for topical spironolactone in terms of physicochemical stability. Also, ten cases of allergic contact dermatitis caused by 2% or 5% topical spironolactone have been reported in the literature (15). Apart from that, there are no safety data obtained in comprehensive studies on the use of the final dermal preparation of spironolactone, the same as for many off-label topical dermatological drugs on skin.

We investigated the potential of emulsions based on alkyl polyglucosides (APGs), a newer "green" FDA certified class of polyethylene glycol-free surfactants to serve as vehicles for topical SP. Emulsions with 5% spironolactone showed acceptable skin irritation profiles and significant potential for skin hydration, which is important in acne treatment. Good physical stability was also obtained showing that moisturizing APG-based emulsions could be promoted as safe and stable vehicles for off-label topical spironolactone (16).

Other types of vehicles should be investigated as potential topical spironolactone carriers. Data obtained from future comprehensive studies should give a pharmacist an insight into the proper use of this drug in alternative pharmaceutical form and its alternative route of administration, beyond the officially approved. Special needs of skin with acne should be taken into consideration during the choice of the vehicle, with an emphasis on applicative characteristic of the preparation which can affect the patient adherence to therapy.

Propranolol

Propranolol is a nonselective, competitive antagonist beta adrenergic receptors. It exerts its effects primarily by blocking the action of the endogenous catecholamines, epinephrine and norepinephrine. Propranolol is widely used to treat cardiovascular disorders (hypertension, angina, arrhythmias, myocardial infarction) and non-cardiovascular conditions such as hyperthyroidism, pheochromocytoma, migraine, anxiety (17).

Infantile haemangiomas are the most common tumor of infancy (18). In many cases they are left untreated to involute spontaneously, but residual skin changes commonly occur. Oral propranolol is currently the first line treatment for infantile haemangiomas, but due to the risk of systemic adverse effects, the use of off-label topical preparations has recently been investigated (17).

The 2015 recommendations from the European expert group state that as there is insufficient information regarding the safety and efficacy of off-label topical beta-blockers, they cannot be recommended as standard treatment. Their potential for the future is focused on use in small, superficial haemangiomas (19). It has been suggested that topical propranolol suppress haemangioma proliferation by reducing the levels of vascular endothelial growth factor (VEGF). According to some studies, 90% of lesions improve following the initiation of topical propranolol (20). Due to the availability of topical timolol, as ophthalmic solution, there are more studies on the use of topical timolol instead of topical propranolol. However, topical timolol is much less represented in compounding practice compared to topical propranolol.

In Serbia, as well as in the whole of Europe, topical propranolol preparations are usually prepared as extemporaneous creams, ointments and gels by local pharmacies according to doctor prescription. The concentration of propranolol is usually from 0.5% to 5%; there are no scientific data which could help pharmacist with the choice of a proper vehicle for topical propranolol. However, the optimal formulation, dosage and duration of use of both topical timolol and propranolol are currently unknown. Kunzi-Rapp (21) confirmed the efficacy of local application of 1% propranolol hydrophilic ointment in superficial hemangiomas of the skin, but the safety aspect was not investigated.

Another study did not identify a significant difference between the topical effects of 2.5% and 5% propranolol gel on the skin (22). The fact that 2.5% and 5% samples have the same "efficacy" is a sign that the protocol is probably not adapted to the test samples or indicate that this kind of vehicle is not suitable for topical propranolol. The absence of dose-response effects is always suspicious.

Eleven studies (600 patients) documented adverse effects, but no systemic effects attributable to topical propranolol were recorded (23-26). Minor localized side effects, such as itching and erythema, were seen and they could indicated the problematic skin safety profile of this drug, but the choice of a vehicle was not taken into account. Kobayashi et al. (22) demonstrated increased skin irritation with increasing topical propranolol concentration and application times. In these studies, propranolol was

administered under adhesive patches, and the development of erythema was considered to be mainly due to physical factors such as peeling (22). However, no comprehensive study was conducted in order to clarify this concern (23-27).

Oxymetazoline

Oxymetazoline is a selective α1 adrenergic receptor agonist and α2 adrenergic receptor partial agonist. In the form of oxymetazoline hydrochloride, it has been used as a nasal spray, a local decongestant. Besides, oxymetazoline has been used off-label for a decade, as topical treatment of the symptoms of rosacea (28). Persistent facial erythema is a bothersome, therapeutically challenging feature of rosacea. It was shown that 1% topical oxymetazoline improved moderate to severe erythema of rosacea on the first day of application, reducing erythema within 1 hour and maintaining efficacy through 12 hours (29). The benefit of topical oxymetazoline for long-term management of persistent facial erythema of rosacea was also confirmed (30). Regarding a lack of proper commercial pharmaceutical forms with oxymetazoline intended for topical use, besides compounded preparations, nasal spray containing a lower concentration of oxymetazoline HCl was even used for topical rosacea treatment.

A topical cream containing the vasoconstrictor oxymetazoline has been approved by the Food and Drug Administration to treat symptoms of rosacea in 2017. It is marketed as Rhofade® by Allergan, indicated for the treatment of "persistent facial erythema associated with rosacea in adults" (31, 32). However, regarding that Rhofade is not available in all European countries, 1% oxymetazoline is being prescribed in a form of extemporaneous preparations although there are no comprehensive studies dealing with the choice of a proper topical vehicle for this drug.

Recently, a number of studies have demonstrated sustained safety, tolerability, and efficacy of oxymetazoline for moderate-to-severe persistent erythema of rosacea. The cream was used as a vehicle in almost all cases, but without any specific data about the type of the cream, emulsifiers etc. Moreover, the importance of a vehicles choice was clearly neglected in those studies, since a vehicle-control group was not included in most of them.

CONCLUSION

Topical use of off-label systemic drugs in dermatology is very common, since application to the skin could theoretically avoid systemic toxicities by delivering the drug directly to the site of the disease. A higher local concentration of the drug on the skin is supposed to be achieved. However, systemic drugs for off-label topical use are almost exclusively and inevitably available as extemporaneous preparations, that is, in the form of compounded topical preparations such as creams or gels.

Spironolactone, oxymetazoline and propranolol in the form of extemporaneous creams and gels are the most prescribed systemic drugs for off-label topical use. On the other hand, topical application may produce a higher chance of irritation and allergic reactions than in the case of oral drug delivery, and it seems that this aspect is not sufficiently investigated in most of the relevant studies.

Moreover, bases commonly used as vehicles for extemporaneous dermatological preparations are stabilized by traditional anionic and non-ionic surfactants, which could additionally present a skin safety issue. Or, in some cases, compounding often involve the use of old fashioned ointment bases, with unacceptable applicative characteristics which can affect the patient adherence to therapy, particularly in a case of patients with acne and other skin inflammations.

In this article, we provided a review summarizing published data on the topical use of some off-label systemic drugs, with special emphasis on their safety and suitability of a vehicle. However, it seems that that the issue of vehicle is being taken for granted. The possibility of improving topical off-label use by employing newer vehicle is not often taken into account.

There is a need for more comprehensive studies on safety of systemic drugs for off-label topical use, alongside the suitability of different types of vehicles to serve as carriers for those topical drugs.

Acknowledgement

This research was supported by the Faculty of Medicine University of Niš Internal Scientific Project titled: "Investigation of selected synthetic and herbal medicinal substances for off-label skin application.".

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"Off-label" primena lekova u dermatologiji – izazovi novih puteva primene određenih starih lekova

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SAŽETAK

"Off-label" upotreba lekova, tj. upotreba lekova bez dozvole, podrazumeva propisivanje lekova, u smislu doze, indikacija, farmaceutskog oblika i puta primene ili ciljne grupe bolesnika, za koje ne postoji zvanično odobrenje. U poslednje vreme ističu se nove indikacije za određene lekove. "Off-label" upotreba lekova češća je u dermatologiji u odnosu na druge specijalnosti. Ti lekovi uglavnom su dostupni u obliku magistralno izrađenih preparata za lokalnu upotrebu na koži; u tom slučaju obično se ne poklanja dovoljno pažnje izboru nosača i bezbednosti lokalno primenjenog leka, koji je inače indikovan za sistemsku primenu. Štaviše, podloge (baze) koje se tradicionalno koriste kao nosači za magistralno izrađene lekove obično su stabilizovane surfaktantima koji mogu da iritiraju kožu. To svakako nije povoljno imajući u vidu da se stanje inflamatornih dermatoza može pogoršati kada se iste izlažu iritansima.

U ovom radu dat je prikaz nekoliko starijih sistemskih lekova, koji se u poslednje vreme upotrebljavaju u lokalnom tretmanu čestih dermatoloških oboljenja i to van zvanično odobrene indikacije. Izbor lekova napravljen je na osnovu informacija o najčešćim magistralnim preparatima ovog tipa, izrađenih prema receptu lekara u apotekama. Cilj rada bio je i prikaz dostupnih naučnih informacija koje se tiču dva, po našem mišljenju, najveća nedostatka "off-label" lokalne upotrebe lekova u dermatologiji: bezbednosti primene finalnih formulacija na kožu i izbora nosača za određene lekove, u smislu njihove stabilnosti i bezbednosti primene.

Ključne reči: **"off-label" primena lekova, dermatologija, magistralni lekovi, nosači za lekove**