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The Significance of Dosage Forms for Pharmacovigilance in the Case of Topical Corticosteroids

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SUMMARY

Introduction: In addition to the active pharmaceutical ingredient (API), excipients and the pharmaceutical dosage form can also affect the overall effect of pharmacotherapy. Knowledge about these effects is not important only from the aspect of drug efficacy, but also from the aspect of pharmacovigilance.

Materials and Methods: This paper presents secondary academic study results. Data on the dosage form and content of excipients were taken from SmPC documents on the official website of Medicines and Medical Devices Agency of Serbia. The presence of excipients with known effect (EKE) and their labeling was considered in accordance with the national and European regulations regarding this area.

Results: We analyzed a total of 50 medicines for topical administration that are registered in Serbia. These all contained corticosteroids as API. Thirty-five (70 %) of them had one or more EKE. Creams had the highest number of different EKE per drug (3.25). Five out of seven identified EKE have the preservative function in formulations, which could be avoided by extemporaneous drug production. The labeling of these compounds was in accordance with the regulations in most drugs.

Conclusions: The cause of an adverse drug reaction should be considered in a wider context and all the drug ingredients should be taken into account. In case of topical corticosteroids, over two third of drugs have the potential to cause adverse drug reactions that are non-API-related.

Keywords: excipient with known effect, adverse drug reactions, local use of corticosteroids

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INTRODUCTION

The definite goal of establishing a pharmacovigilance system is to prevent adverse drug reactions (ADRs), and the precondition for this is their understanding [1]. The ADRs are not only caused by the active pharmaceutical ingredient (API), but also by the excipients. Also, an important thing that can affect ADRs is the dosage form of the drug. It is well-known that the same doses of the same active pharmaceutical ingredient in different dosage forms can exhibit different effects [2-4].

Generally pharmaceutical excipients are pharmacologically inactive drug constituents. However, some of them are known to cause various effects [5,6]. For that reason regulatory bodies attribute special attention to the presence and labeling of excipients that can cause ADRs. These excipients are called excipients with known effects (EKE). 'The Rulebook on the content and manner of marking of the external and internal packaging of the medicinal product, additional marking, as well as the instruction content for the medicinal product' from 2011 stems from the Serbian drug law. The EKE list is attached to this Rulebook [7]. In the European Union, this area is under the jurisdiction of the European Medicines Agency. EU EKE list is included in the Annex to the European Commission Guidelines on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) from 2017 [8]. The significance of the excipients in topical drugs is indicated by the requirement to list all excipients on the external package of the drug, not only EKE.

Corticosteroids are an example of APIs in which the dosage form and the excipients have a proven impact on the occurrence of ADRs. Therefore, it is particularly significan to be familiar with the effects of excipients in formulations with topical corticosteroids to understand the therapeutic efficacy of these drugs. Auxiliary substances, both EKE and the ones with non-proven effects, are important in the management of ADRs of topical corticosteroid. Within their topical application, they can be found as an officinal drugs (in Serbia) for treatment of skin, eyes, ear, nose and bowel diseases. It is not uncommon for topical corticosteroids to have long-term use [9,10], which increases the chances of ADRs. This group of drugs is prescribed for children too [11], and they are a vulnerable population. In addition to officinal drugs, topical corticosteroids are also produced as magistral and galenic drugs. The common practice is diluting the products present on the market and thus adjusting the dosage for use in children. There should be additional caution regarding patients with combined therapy.

AIM

The aim of this study was to consider the influence of the excipients and the dosage forms of topical corticosteroids on their safety profile.

MATERIALS AND METHODS

This paper presents secondary academic study results. Drugs approved by Medicines and Medical Devices Agency of Serbia were chosen for this analysis. The drugs whose API should have local therapeutic effects were observed. ATC groups which contain topical corticosteroids and have registered representatives in Serbia were detected. Drugs for the treatment of inflammatory diseases were excluded from the study. A total of five ATC groups met these conditions: D07 (Corticosteroids, Dermatological preparations), R01AD (Corticosteroids), S01BA (Corticosteroids, plain), S01CA (Corticosteroids and antiinfectives in combination), S02BA (Corticosteroids).

The data about the drugs was downloaded from the official web-site of Medicines and Medical Devices Agency of Serbia. Summary of Product Characteristics, section two (Qualitative and Quantitative Composition) and subsection 6.1 (List of Excipients) were analyzed for determining the content of excipients [12]. Excipients with known effects (EKE) were separated in accordance with national and European regulations [7,8]. 'The Rulebook on the content and manner of marking of the external and internal packaging of the medicinal product, additional marking, as well as the instruction content for the medicinal product' [7] and the Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use' (SANTE-2017-11668) were used [8]. The presence of EKE and whether they were properly marked (section two of SmPC) was recorded. It was checked whether the

Table 1. Analysis of the presence of excipients that can cause ADRs

Drug application	Dosage form	Number of registered medicines	Drugs with EKE	Average number of EKE per drug	Inappropriately labeled EKE	Detected EKE	ADRs caused by EKE in SmPC
Cutaneous preparations	Ointment	14	7	1	0	Propylene glycol and its esters	yes
	Cream	9	8	3.25	1	Propylene glycol Cetostearyl alcohol Chlorocresol Parahydroxybenzoates Wool fat (lanolin) Benzyl alcohol**	yes
	Cutaneous solution	3	0	0	0	/	/
	Gel	1	1	3	0	Propylene glycol Parahydroxybenzoates	yes
Eye preparations	Eye drops, suspension	4	4	1	1	Benzalkonium chloride	yes
	Eye ointment	3	1	1	0	Wool fat (lanolin)	yes
	Eye drops, solution	2	1	1	0	Benzalkonium chloride	yes
Ear preparations	Ear drops, solution	2	1	1	0	Parahydroxybenzoates	yes
Nasal preparations	Nasal spray, suspension	11	11	1	1	Benzalkonium chloride	yes
Rectal preparations	Rectal foam	1	1	2	0	Propylene glycol Cetyl alcohol	yes

ADRs of EKE was listed in subsection 4.8 (Undesirable effect) of SmPC.

RESULTS

A total of 50 drugs were analysed in this study (cutaneous preparations n=27, eye preparations n=9, ear preparations n=2, nasal preparations n=11, rectal preparations n=1). Thirty-five drugs (70.00 %) had at least one EKE. The average number of EKE per drug (refers to those which contained them) was 1.62. Creams had the most undesirable profile. Eight of nine creams had EKE with an average number of 3.25 per drug. Moreover, creams had the largest number of different EKE in their composition.

The Regulations require that all EKE are listed in subsection 2 of the SmPC. The labelling was mostly in accordance with the regulations. Only three formulations (6 %) did not have all EKE listed in the section two of SmPC.

All of the detected EKE could lead to adverse reactions which can be found among ADRs in subsection 4.8 of analysed drugs. An overview of the officinal topical corticosteroids dosage form in Serbia is given in Table 1. The characteristics of EKE detected in the analysed preparations are shown in Table 2.

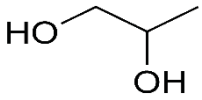
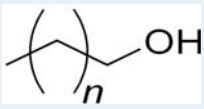
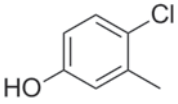
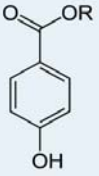
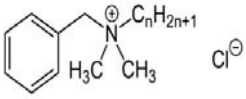
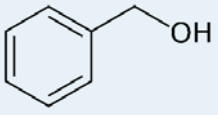
DISCUSSION

This paper gives an overview of excipients with known effect in the all authorized local corticosteroids on the Serbian market in one place. The obtained results represent a secondary source of information, which is the main limiting factor of the study.

Most of identified EKE can cause ADR in the form of local (skin) irritation or allergies. Bearing in mind that the most common ADR of dermal topical corticosteroids are exhibited primarily on the skin (18.9 % of all adverse reactions) [1], avoiding ADR caused by detected EKE can be useful.

The American Contact Dermatitis Society proclaimed propylene glycol (PG)

Table 2. Features of detected EKE

Detected EKE	Structural formula	Function of detected EKE	Effects of EKE listed in Serbian Rulebook [7]	Effects of EKE listed in EU guideline [8]	Bibliographical data about effects of EKE
Propylene glycol and its esters		Solvent, humectant	"May cause skin irritation"	"Propylene glycol may cause skin irritation"	Sensitizer, irritant, contact allergen [13-5]
Cetostearyl alcohol including Cetyl alcohol		Surfactant	"May cause local skin reactions (e.g. contact dermatitis)."	"May cause local skin reactions (e.g. contact dermatitis)."	contact allergen [16,17]
Chlorocresol		Preservative	"May cause allergic reactions."	"May cause allergic reactions."	May lead to severe ADR [18,6]
Parahydroxybenzoates		Preservative	"May cause allergic reactions, even delayed"	"May cause allergic reactions (possibly delayed)."	Contact allergen, rarely severe [19,20]
Benzalkonium chloride	 n = 8, 10, 12, 14, 16, 18	Preservative	"May cause eye irritation." "Irritant, can cause skin reactions." Does not specify anything for nasal administration.	"...Benzalkonium chloride may also cause eye irritation, especially if you have dry eyes or disorders of the cornea (the clear layer at the front of the eye)..." "Benzalkonium chloride may cause irritation or swelling inside the nose, especially if used for a long time."	Irritant, allergen, sensitizer [21-3]
Benzyl alcohol		Preservative	is stated exclusively for the parenteral route of administration	"Benzyl alcohol may cause mild local irritation."	Low acute dermal toxicity [24]
Wool fat (lanolin)	Mixture of different compounds	Base	"May cause local skin reactions (e.g. contact dermatitis)."	"May cause local skin reactions (e.g. contact dermatitis)."	Allergen [25-7]

for allergen of the year in 2018. This society found PG in 62 % (260 analysed preparations) of topical corticosteroids. This excipient appeared in 11 (22 %) drugs that were analysed in this study . In addition to allergic dermatitis, numerous cases of irritant contact dermatitis and systemic skin reactions to PG have been documented. Prevalence of allergy to PG is in

the range of 0.8 to 3.5 % [13-5].

Cetostearyl alcohol including Cetyl alcohol were detected in nine drugs (18 %). These excipients very rarely lead to irritant and allergic reactions, but there are case reports in the literature showing evidence of their harmful effects. Hence, care should be taken when using the preparations containing them [16-7].

Chlorocresol (detected in three drugs, 6 %) can cause contact dermatitis and contact urticaria. The case of life-threatening immediate hypersensitivity with anaphylaxis to chlorocresol was also documented. This fact makes chlorocresol an excipient with the potential for the most severe side effects [18].

The presence of parabens was observed in 6 drugs (12 %). Parahydroxybenzoates (Parabens) have attracted a lot of attention from the general and professional public recently, due to certain claims that they have a hormonal effect on estrogen receptors, and consequently a carcinogenic effect. There is still no solid evidence for these claims. Studies have shown that the toxicological potential increases with the increase of the side chain length and with benzoic ring presence [19, 20]. As methyl and propyl derivatives have been detected in this study, side effects are expected to be exclusively local irritation.

Fifteen drugs (30 %) contained benzalkonium chloride. It is a preservative that can act as an irritant or allergen. Skin sensitization is low and appears to occur in 0.02 % to 0.7 %. Hypersensitivity reactions type 1 and type 4 may occur with ophthalmic, cutaneous, ear and inhalation applications [21-3]. A high proportion (83.33 %, 5/6) of preparations with benzalkonium chloride was observed in eye drops (suspension and solution). This excipient can be incorporated into contact lenses, therefore a caution is necessary for the people who wear them [7, 8]. Benzalkonium chloride was also present in all ear preparations. Although these drugs are intended for topical use, due to anatomical closeness to the lungs, caution is necessary. It is known that inhalation of benzalkonium chloride can lead to serious side effects such as bronchospasm, especially in asthma patients [7, 8].

Benzyl alcohol is generally safe excipient. However, studies have shown irritation potential on the skin [24]. It was found in just one drug (2 %).

Lanolin was present in five analysed drugs (10 %). Different components of lanolin can be responsible for allergic reactions, but most frequently used is lanolin alcohol. The prevalence of this allergy is relatively high and varies from 1.2 % to 6.9 %. The allergy is expressed as allergic contact dermatitis, especially with prolonged use on damaged skin [25-7].

CONCLUSION

The study has shown that a significant number of topical corticosteroids contain EKE. Over two thirds of analyzed drugs (70 %) have the potential to cause non-API-related adverse drug reactions in a particular group of patients. Magistral preparations may be the possible solution for this problem. Most frequently detected excipients have the preservative function and they can be completely removed from the formulations in this way.

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CONFLICTS OF INTEREST

All authors declare no conflict of interest.

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Značaj farmaceutskih formulacija za farmakovigilancu na primeru topikalnih kortikosteroida

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KRATAK SADRŽAJ

Uvod: Pored aktivnog famaceutskog sastojka (API), ekscipijensi i sam farmaceutski oblik doziranja mogu uticati na ukupni efekat farmakoterapije. Poznavanje ovih efekata važno je ne samo sa aspekta efikasnosti lekova, već i njihove farmakovigilance.
Materijal i metode: Podaci o farmaceutskom obliku i sadržaju ekscipijenasa preuzeti su iz SmPC dokumenata koji se nalaze na zvaničnom veb sajtu Agencije za lekove i medicinska sredstva Srbije. Prisustvo ekscipijenasa sa poznatim delovanjem (EKE) i njihovo obeležavanje razmatrano je u skladu sa nacionalnom i evropskom regulativom ove oblasti.
Rezultati: Analizirano je ukupno 50 lekova namenjenih za lokalnu primenu koji su registrovani u Srbiji i kao API sadrže kortikosteroide. Njih 35 (70 %) je u svom sastavu imalo jedan ili više EKE. Najveći broj različitih EKE po leku su imali kremovi (3,25). Pet, od ukupno sedam identifikovanih EKE, ima funkciju konzervansa u formulacijama i oni mogu biti izbegnuti ekstemporalnom izradom lekova. Obeležavanje ovih jedinjenja je u većini lekova bilo u skladu sa propisima.
Zaključak: Uzrok pojave neželjenih reakcija na lekove treba posmatrati u širem kontekstu i u obzir uzimati sve komponente leka. Na primeru topikalnih kortikosteroida preko dve trećine lekova ima potencijal da prouzrokuje neželjene reakcije na lek koje nisu povezane sa API.

Ključne reči: ekscipijensi sa potvrđenim delovanjem, neželjena reakcija na lek, kortikosteroidi za lokalnu primenu

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