Review paper

Status of combination drugs with betamethasone dipropionate and salicylic acid in the treatment of skin diseases

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Abstract

Combinations of topical glucocorticoids (GCs) with other substances are very often used in dermatology. One of the most common combinations is betamethasone dipropionate and salicylic acid. Betamethasone dipropionate is a potent topical glucocorticoid (belonging to class III according to the European classification) which demonstrates anti-inflammatory, anti-proliferative, immunosuppressive and vasoconstrictive properties. Salicylic acid, in turn, has a strong keratolytic and slightly antiseptic action. The use of both components in one formulation provides a significantly better GC penetration through the skin, which is crucial for the treatment of hyperkeratotic lesions. The combination ensures greater therapeutic efficacy, while maintaining good tolerability and safety profile.

Key words: betamethasone dipropionate, salicylic acid, mechanism of action, therapy.

Introduction

Topical glucocorticoids (GCs) have been used in dermatology for 60 years. The first GC applied topically was hydrocortisone, which was introduced into therapy by Sulzberger and Witten in 1952 [1]. Numerous studies undertaken in subsequent years, e.g. with a view to modifying the hydrocortisone molecule and developing advanced types of drug delivery vehicles, made it possible to enhance the anti-inflammatory and immunosuppressive properties, and improve the safety profile, of glucocorticoids [2].

Despite such a long history of therapeutic use, GCs continue to be used due to their anti-inflammatory, antiproliferative and immunosuppressive effects. The GCs are drugs of choice in a number of skin diseases including inflammatory, hyperproliferative and autoimmune dermatoses. The therapeutic effect of GCs depends on correct diagnosis, cooperation between the patient and the physician, potency of the drug, type of vehicle and application – as well as a range of genetic factors determining individual sensitivity [3].

In order to achieve better therapeutic effects, glucocorticoids are often combined with other substances such as salicylic acid. The latter has keratolytic properties and enhances GC penetration into the skin, which is of key importance for the treatment of excessively keratinized skin lesions [4].

Pharmacological properties and mechanisms of action of betamethasone dipropionate and salicylic acid

Betamethasone dipropionate

Betamethasone dipropionate (9α-fluoro-11β, 17α, 21-trihydroxy-16β-methylpregna-1,4-diene-3,20-dione 17,21-dipropionate) is a synthetic fluorinated corticosteroid for topical dermatologic use (Figure 1) [5]. According to the European classification, it belongs to potency class III. The classification utilizes a total of four classes, with class I comprising GCs of the lowest potency and class IV – the most potent GCs (Table 1). Another popular classification is the USA system which divides topical GCs into seven classes. Class I is the strongest, while class VII – the weakest (Table 2). It should be noted at this point that in the USA system the same chemical compound (depending on the pharmaceutical form of the preparation) may represent different GC classes because the clas-

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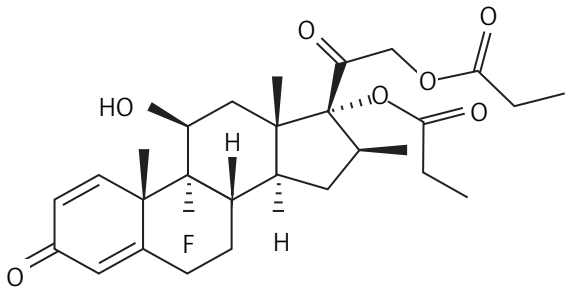
sification refers to the final product (relevant pharmacopoeial form) rather than to the properties of the glucocorticoid molecule itself [6].

Similarly to other GCs, the mechanism of action of betamethasone dipropionate has not been entirely elucidated (Figure 2). After passing through the cell membrane, GCs are known to bind to the cytoplasmic receptor (GCR) [7]. The receptor is a 777 amino acid polypeptide with three domains: A, B and C [8]. Domain A determines receptor binding to the GC molecule. Domain B, which creates the so-called zinc fingers (chemical complexes formed by cysteine residues and zinc), makes it possible for the receptor to bind to cell DNA and determines the tertiary structure of the receptor molecule. Domain C, in turn, carries immunogenicity and some biological properties of GCR. It should be stressed that an inactive receptor binds in the cell with two heat shock protein (HSP) monomers: HSP 70 and 90 [9].



- placement of a double bond between carbon C1 and C2 – increased systemic activity
- halogenation at carbon C9 – improved protection against particle disintegration and enhanced anti-inflammatory action
- addition of a hydroxyl group to carbon C17 – augmented penetration through the skin
- attachment of a methyl group to carbon C16 – reduced impact on the mineral metabolism and increased anti-inflammatory properties

Figure 1. Chemical formula of betamethasone dipropionate

Table 1. European classification of topical glucocorticoids

Class IV: very potent	Clobetasol propionate 0.05%
	Fluocinolone acetonide 0.2%
	Halcinonide 0.1%
Class III: potent	Betamethasone dipropionate 0.05%
	Mometasone furoate 0.1%
	Triamcinolone acetonide 0.1%
	Fluocinolone acetonide 0.1%
	Amcinonide 0.1%
	Betamethasone benzoate 0.25%
	Budesonide 0.025%
	Desonide 0.05%
	Fluticasone propionate 0.05%
	Betamethasone valerate 0.1% and 0.05%
Class II: moderate	Betamethasone benzoate 0.025%
	Betamethasone dipropionate 0.05%
	Flumetasone pivalate 0.02%
	Betamethasone valerate 0.025%
	Triamcinolone acetonide 0.04%
Class I: weak	Hydrocortisone 0.5% and 1.0%
	Hydrocortisone acetate 1.0%
	Dexamethasone 0.1-0.2%
	Methylprednisolone 0.25%
	Fluocinolone acetonide 0.0025%

Table 2. USA classification of topical glucocorticoids

Class I: highest potency	Clobetasol propionate 0.05% cream, ointment, liquid
	Betamethasone dipropionate 0.05% ointment
Class II: high potency	Betamethasone dipropionate 0.05% cream
	Halcinonide 0.1% cream
	Mometasone furoate 0.1% ointment
	Desoxymethasone 0.25% cream, ointment, gel
Class III: high/medium potency	Amcinonide 0.1% cream
	Fluocinonide 0.05% cream
	Fluticasone propionate 0.005% ointment
	Betamethasone valerate 0.025%
	Desoximetasone 0.05% cream
Class IV: medium potency	Mometasone furoate 0.1% cream
	Triamcinolone acetonide 0.1% cream, aerosol
	Fluocinolone acetonide 0.0025% ointment
	Hydrocortisone valerate 0.2% cream
Class V: medium/low potency	Fluticasone propionate 0.05% cream
	Betamethasone dipropionate 0.01% liquid
	Triamcinolone acetonide 0.01% liquid
	Fluocinolone acetonide 0.025% cream
	Hydrocortisone butyrate 0.1% cream
Class VI: low potency	Fluocinolone acetonide 0.01% cream, liquid
Class VII: lowest potency	Preparations containing hydrocortisone, dexamethasone, flumetasone, methylprednisolone

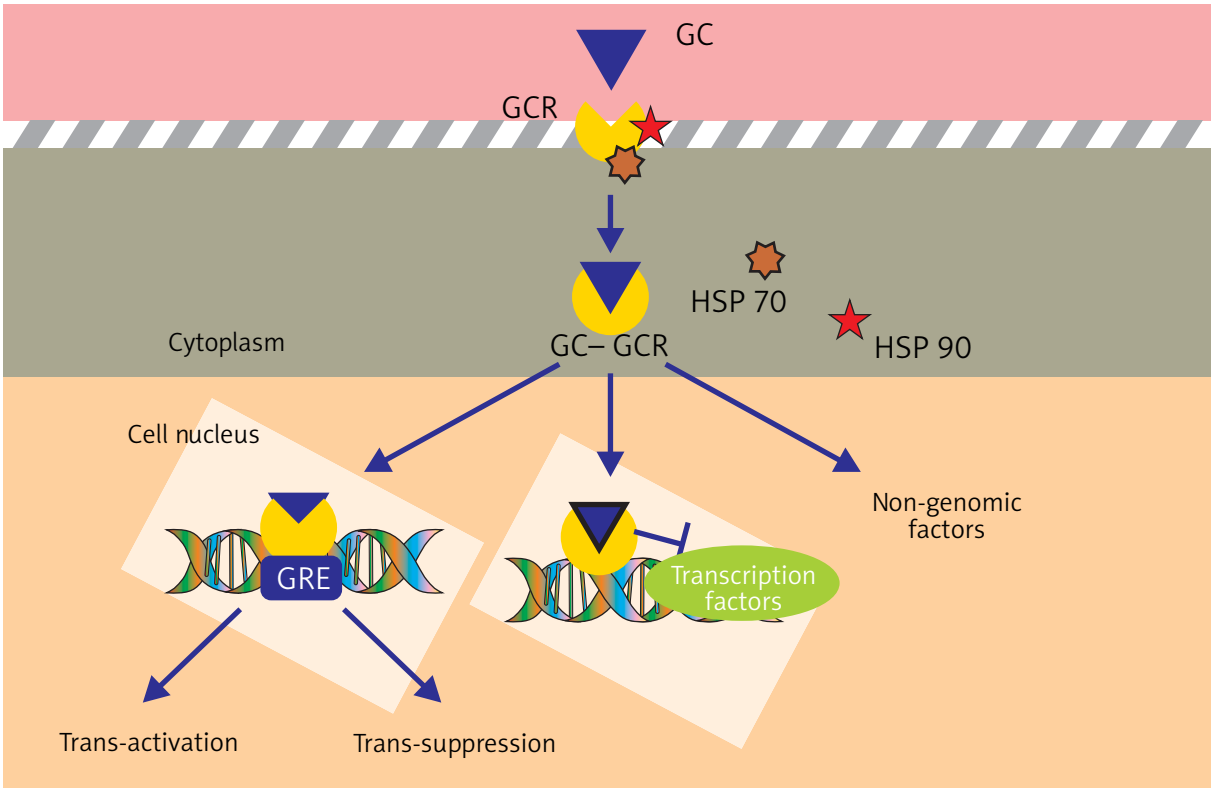


Figure 2. Mechanism of action of betamethasone dipropionate

The hormone-receptor complex thus formed moves to the cell membrane where it is bound to a specific DNA sequence called the glucocorticoid response element (GRE). The interaction results either in the stimulation (trans-activation) or suppression (trans-suppression) of transcription of specific genes [10]. An example of trans-activation is induction of the process of synthesis of anti-inflammatory proteins (e.g. lipocortin 1 or vasocortin). In turn, inhibition of gene transcription for IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, IL-11, IL-13 or TNF-α is an example of trans-suppression [11].

Recent studies indicate that gene transcription is also regulated by a process in which the GC-GCR complex directly suppresses transcription factors such as the nuclear factor NF-$\kappa\beta$, nuclear factor of activated T cells (NF-AT) or activator protein AP-1 (known modulators of genes determining the development of inflammatory responses) and affect the process of chromatin remodelling. The impact of the GC-GCR complex on the above-mentioned factors reduces the expression of adhesion molecules and, consequently, decreases leukocyte migration into the inflamed region. Suppression of the activity of proinflammatory cytokines (IL-1, IL-2, IL-6, TNF-α) and a reduction in the number of their receptors are also observed [12].

Glucocorticoids are also involved in post-transcriptional gene expression, thus affecting the transport and metabolism of mRNA, and the process of translation. The so-called fast non-genomic effects of glucocorticoids are, on the other hand, quite poorly understood, though they are presumed to play a vital role in the anti-inflammatory action exerted by this class of drugs.

As indicated above, betamethasone dipropionate applications in clinical practice stem mainly from the anti-inflammatory, immunosuppressive and anti-proliferative effects of betamethasone dipropionate. Anti-inflammatory properties exhibited by this glucocorticosteroid result from the impact of the compound on a number of processes. Betamethasone dipropionate is involved in the following mechanisms:

- constriction and decreased permeability of blood vessels;
- induction of lipocortin 1 and vasocortin synthesis processes. By binding to cell membrane phospholipids, lipocortin 1 inhibits phospholipase A2 and, as a consequence, lowers the concentration of arachidonic acid (a precursor of many mediators of inflammation). Vasocortin is another anti-inflammatory protein which reduces the rate of plasma filtration from the microcirculation into the intercellular compartment during allergic inflammatory response [13];
- decreased synthesis of many proinflammatory cytokines (e.g. IL-1, IL-3, IL-4, IL-5, IL-6, IL-8, TNF-α and GM-CSF) and reduced expression of adhesion mole-

cules. In addition, betamethasone dipropionate blocks the transcription of genes for eotaxin, endothelin 1, cyclooxygenase 2 and induced nitric oxide synthase [14];
- increased activity of endonucleases and neutral endopeptidase;
- inhibition of macrophage migration;
- inhibition of proliferation of T cells, B cells and NK cells;
- reduced degranulation of mast cells and inhibition of the process of release of histamines, kinins and other inflammatory mediators by mast cells;
- stabilization of cellular and lysosomal membranes, resulting in a blockage of lysosomal hydrolase release during the inflammatory process;
- regulation of eosinophil function (prevention of eosinophil degranulation and release of cytotoxic proteins by eosinophils; induction of eosinophil apoptosis) [15];
- impairment of Langerhans cell function through inhibiting cytokines required for their normal function;
- reduced activity of fibroblasts.

The anti-proliferative effect of betamethasone dipropionate is related to the inhibition of DNA and collagen synthesis, while immunosuppressive properties are a consequence of betamethasone dipropionate blocking T cells, B cells, Langerhans cells and mast cells (the substance reduces the severity of both immediate and delayed hypersensitivity reaction) [16].

Salicylic acid

Salicylic acid (ortho-hydroxybenzoic acid) is the most commonly used keratolytic agent (Figure 3). It also has a weak antiseptic effect.

Salicylic acid softens keratin and keratinized epidermis. By disrupting desmosomes which connect corneocytes in the corneal layer of the epidermis, it causes exfoliation of the corneal cells and facilitates the penetration of other topical drugs into the skin [17]. A significant increase in the penetration of topical glucocorticoids combined with 2-10% salicylic acid is routinely observed [18].

It should be noted, too, that salicylic acid is frequently used in combination with tars or anthralin. On the other hand, salicylic acid inactivates calcipotriol. Due to the fact that this keratolytic agent blocks the penetration of UVB, it should not be applied prior to phototherapy.

Indications for the betamethasone dipropionate and salicylic acid combination

Combination drugs containing betamethasone dipropionate and salicylic acid (in the form of ointment or liquid) are recommended in the treatment of steroid-sensitive dermatoses accompanied by excessive epidermal keratinization [19]. The combination is usually indicated for the treatment of the following dermatoses: plaque psoriasis, prurigo, various kinds of eczema (including atopic dermatitis and seborrhoeic dermatitis), lichen planus and discoid lupus erythematosus.

Efficacy of the betamethasone dipropionate and salicylic acid combination

Efficacy of the betamethasone dipropionate and salicylic acid combination has been confirmed in a range of clinical trials. Based on the trials it can be concluded that the combination is significantly superior to GCs of similar potency (such as clobetasol propionate) used in the form of single drug preparations [20]. Furthermore, the combination has higher efficacy than combinations of salicylic acid and dexamethasone acetate or flumetasone pivalate [21, 22].

Betamethasone dipropionate combined with salicylic acid has a quick onset of action. The combination makes it possible to achieve a significantly faster onset of sustained clinical improvement than the corticoid alone or a combination drug with vitamin D.

In studies by Gipa or Hevding a significant clinical improvement was already observed in the first week of application [23, 24]. In a double-blind clinical trial coordinated by Gisslen and Nordin, involving a total of 62 patients with plaque psoriasis, the onset of clinical improvement was significantly faster for the betamethasone dipropionate plus salicylic acid combination than for clobetasol in monotherapy [25]. In a 10-week clinical trial conducted in Italy an ointment containing 50 µg/g of calcipotriol was found to have superior efficacy to betamethasone dipropionate combined with salicylic acid, though the betamethasone dipropionate plus salicylic acid combination had a significantly faster onset of action [26].

The combination discussed also demonstrates a significant antipruritic effect. A significant reduction in skin itching was noted after a week-long therapy with betamethasone dipropionate plus salicylic acid in an open clinical trial of 38 patients with scalp psoriasis [27]. In another 3-week double-blind clinical trial conducted in a study group of 51 psoriasis patients a solution containing betamethasone and salicylic acid had similar efficacy to a solution with clobetasol. On the other hand, however, the betamethasone dipropionate plus salicylic acid combination was found to have a more potent antipruritic activity than clobetasol [20].

Efficacy data for combination drugs containing betamethasone dipropionate and salicylic acid are listed in Table 3.

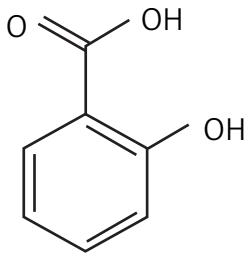


Figure 3. Chemical formula of salicylic acid

Table 3. Clinical trials assessing the efficacy of combination drugs containing betamethasone dipropionate and salicylic acid

Reference	Trial design and duration	Study population	Frequency of drug application and pharmacopoeial form of drug	Results
Gip [23]	Open, 3 weeks	30 patients: 18 with plaque psoriasis (PP) and 12 with seborrh-oeic dermatitis (SD)	0.05% betamethasone dipropionate + 2% salicylic acid; liquid; twice daily	Rapid onset of action: marked improvement in all PP patients and in 7 SD patients during the first week of therapy; complete regression of skin lesions in 5 SD patients (42%). Complete remission in 10 out of 18 PP patients (56%) and 12 SD patients (100%) after 3 weeks of therapy. Marked improvement in the remaining 8 PP patients
Landi [22]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. flumetasone pivalate + salicylic acid); 3 weeks	60 patients: 17 with plaque psoriasis (PP), 9 with eczema, 1 with chronic lupus erythematosus, 1 with parapsoriasis, 1 with lichen planus	0.05% betamethasone dipropionate + 3% salicylic acid (ointment) vs. 0.02% flumetasone pivalate + 3% salicylic acid (ointment); twice daily	Significantly superior efficacy of the combination drug with betamethasone dipropionate and salicylic acid in the elimination of skin scaling, infiltration, erythema and pruritus. Group treated with combination drug: complete remission in 10 PP patients (63%) and 8 patients with other dermatoses (57%). Group treated with flumetasone pivalate: complete remission in just 6 PP patients (30%). No adverse reactions in either of the study groups
Chattopadhyay *et al*. [21]	Partially-blind, comparative (betamethasone dipropionate + salicylic acid vs. dexamethasone acetate + salicylic acid); 4 weeks of drug application, follow-up period – 12 weeks	110 patients: 76 with plaque psoriasis (PP) and 34 with chronic eczema (CE)	0.05% betamethasone dipropionate + 3% salicylic acid (ointment) vs. 0.1% dexamethasone acetate + 4% salicylic acid (ointment)	Markedly higher efficacy of the betamethasone dipropionate + salicylic acid combination in the elimination of pruritus, skin redness and infiltration after 4 weeks of treatment. Recurrence of skin lesions in 7% of PP patients and 16% of CE patients in the group treated with betamethasone dipropionate + salicylic acid after 12 weeks of treatment. Recurrence of skin lesions in 33% of PP patients and 27% of CE patients in the group treated with dexamethasone acetate
Fredriksson [30]	Open, 3 weeks	50 patients with various dermatoses accompanied by excessive epidermal shedding 90 patients	0.05% betamethasone dipropionate + 3% salicylic acid (ointment)	Markedly higher efficacy of the combination drug containing betamethasone dipropionate and salicylic acid than betamethasone dipropionate alone; higher efficacy of both betamethasone dipropionate preparations than 3% salicylic acid.
	Double-blind, 4 weeks		0.05% betamethasone dipropionate (ointment), 3% salicylic acid (ointment)	Marked improvement in 22 patients using the combination drug and in 7 patients using betamethasone dipropionate, lack of improvement in patients treated with 3% salicylic acid, after 2 weeks of treatment
Eriksson [31]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. flumetasone pivalate + salicylic acid)	62 patients with plaque psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (ointment); 0.02 % flumetasone pivalate + 3% salicylic acid (ointment); twice daily	Markedly higher efficacy of the preparation containing betamethasone dipropionate (significant improvement in 71% of study patients) relative to the flumetasone pivalate preparation. No side effects in the betamethasone dipropionate group; 2 cases in the flumetasone pivalate group
Malfitan [32]	Open, between 14 and 21 days; assessment of efficacy and safety	86 patients with plaque psoriasis or other dermatoses responding to GCs	0.05% betamethasone dipropionate + 2% salicylic acid (solution)	Complete regression of skin lesions or marked improvement in 91% of patients; partial clinical improvement – 8%; no improvement – 1%; adverse reactions – 3 cases

Table 3. cont.

Reference	Trial design and duration	Study population	Frequency of drug application and pharmacopoeial form of drug	Results
Gisslen and Nordin [25]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. clobetasol); 3 weeks	62 patients with plaque psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (ointment); 0.05% clobetasol (ointment); once daily	Comparable efficacy of both drugs; more rapid onset of therapeutic effect for 0.05% betamethasone dipropionate + 3% salicylic acid
Scarpa [27]	Double-blind, comparative (0.05% betamethasone dipropionate + 3% salicylic acid vs. calcipotriol); 6 weeks	160 patients with plaque psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (ointment); calcipotriol 50 µg/g (ointment); twice daily	Comparable PASI reduction
Kuokkanen and Zador [28]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. budesonide); 3 weeks	24 patients with plaque psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (ointment); 0.025% budesonide (ointment); twice daily	Markedly faster onset of action for the drug containing 0.05% betamethasone dipropionate + 3% salicylic acid; superior efficacy of the drug in weeks 2 and 3 of therapy
Elie *et al*. [29]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. betamethasone dipropionate vs. salicylic acid); 3 weeks	40 patients with erythematous/ exfoliative lesions within the scalp	0.05% betamethasone dipropionate + 3% salicylic acid (liquid); 0.05% betamethasone dipropionate; 3% salicylic acid; twice daily	Greater efficacy of the combination drug than betamethasone dipropionate alone in the elimination of scaling and redness, and reduction of pruritus. No side effects in either of the study groups
Hœvding [24]	Open, 4 weeks	38 patients with scalp psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (solution); twice daily	Marked regression of symptoms after the first week of therapy, clinical improvement after 2 weeks; good tolerance and cosmetic properties of the products
Hillström *et al.* [20]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. clobetasol); 3 weeks	51 patients with scalp psoriasis	0.05% betamethasone dipropionate + 3% salicylic acid (liquid); 0.05% clobetasol (liquid)	High efficacy of both drugs; markedly superior antipruritic effect of the betamethasone dipropionate plus salicylic acid combination
Nolting and Hagermeier [33]	Double-blind, comparative (betamethasone dipropionate + 3% salicylic acid vs. 0.05% betamethasone dipropionate); 3 weeks	100 patients with scalp psoriasis and other dermatoses responding to GCs	0.05% betamethasone dipropionate + 3% salicylic acid (solution); 0.05% clobetasol (solution)	Markedly faster onset of action for the combination product containing 0.05% betamethasone dipropionate and 3% salicylic acid

Table 3. cont.

Reference	Trial design and duration	Study population	Frequency of drug application and pharmacopoeial form of drug	Results
Tosti *et al.* [34]	Double-blind, comparative (betamethasone dipropionate + salicylic acid vs. calcipotriol); 10 weeks	58 patients with nail psoriasis	64 mg/g betamethasone dipropionate + 0.03 mg/g salicylic acid (ointment); 50 µg/g calcipotriol (ointment)	Superior efficacy of calcipotriol, however markedly faster onset of action for the betamethasone dipropionate plus salicylic acid combination

Contraindications for the betamethasone dipropionate and salicylic acid combination

Prior to initiating treatment with combination drugs containing betamethasone dipropionate and salicylic acid, attention should be given to contraindications to these agents (Table 4) and the risk of adverse reactions (both local and systemic) [35].

Betamethasone dipropionate and salicylic acid should not be applied to extensive skin areas, damaged skin or for prolonged periods (in excess of 14 days). If occlusive dressings are used, it should be noted that they markedly increase drug penetration. Glucocorticosteroid penetration through the skin is the most pronounced in the genital area, in skin folds, in the eyelid region and on the face. On the other hand, drug absorption is poorer through the skin on the back of the hands and feet, and on the soles. Therefore, the drugs discussed should not be applied to the face, to the genital area or skin folds [36].

Use of betamethasone dipropionate and salicylic acid during pregnancy and lactation

Medical literature contains no reports of randomized controlled clinical trials investigating topical use of betamethasone dipropionate and salicylic acid combinations in women during pregnancy and lactation. Consequently, due to the lack of data, combination drugs can only be used if benefits to the mother outweigh risks to the foetus or baby. In this case, however, they should not be applied over large areas of the skin and the duration of therapy should be as short as possible.

According to the Food and Drug Administration (FDA), both betamethasone dipropionate and salicylic acid are designated pregnancy category C.

Table 4. Contraindications to using combination drugs containing betamethasone dipropionate and salicylic acid

- Hypersensitivity to betamethasone dipropionate, salicylic acid or any excipients in the formulation
- Skin infections (caused by viruses, bacteria, fungi or parasites)
- Post-vaccination skin reactions
- Common acne, acne rosacea
- Perioral dermatitis
- Diaper dermatitis
- Skin cancer, precancerous skin lesions
- Delayed wound healing

Adverse reactions

Combination drugs with betamethasone dipropionate and salicylic acid are generally well tolerated by patients [37]. Data from clinical trials suggest that the betamethasone dipropionate plus salicylic acid combination rarely provokes adverse reactions. Whenever any adverse reactions occur, they are typically localized, mild and transient, such as erythema or a burning sensation. Gip and Hamfelt have also shown that betamethasone dipropionate combined with salicylic acid does not increase the degree of GC penetration into the circulation and has no impact on the risk of systemic adverse effects [38].

Nevertheless it should be noted that the application of betamethasone dipropionate plus salicylic acid combination to large areas of the body, to damaged skin, under occlusive dressing, for prolonged periods or in small children can lead to both local and systemic adverse reactions [39].

Local and systemic adverse effects associated with betamethasone dipropionate therapy are listed in Table 5. Table 6 includes symptoms of salicylic acid poisoning.

Use of combined drugs with betamethasone dipropionate and salicylic acid in children

Betamethasone dipropionate and salicylic acid combinations should not be used in children below 12 years of age. The combination is contraindicated because of the risk of systemic adverse reactions due to the fact that the skin structure in children is different from that

Table 5. Adverse reactions associated with topical GCs

Local adverse reactions	Systemic adverse reactions
• Thinning of the epidermis and dermis	• Hyperglycaemia
• Stretch marks	• Cushing's syndrome
• Atrophy of subcutaneous tissue	• Increase in blood pressure
• Steroid acne and exacerbation of common acne and acne rosacea	• Adrenal failure
• Perioral dermatitis	• Osteoporosis
• Folliculitis	• Peptic ulcers
• Skin discoloration and depigmentation	• Inhibition of the hypothalamic–pituitary–adrenal axis
• Excessive hair growth	
• Telangiectasias	
• Chronic erythema	
• Increased susceptibility to bacterial, viral, fungal and parasitic skin diseases	
• Impaired wound and ulceration healing	
• Granuloma gluteale infantum	
• Contact allergy to GCs	
• More severe relapse of the disease following attempted discontinuation of GCs	
• Glaucoma, cataract	

Table 6. Clinical symptoms accompanying salicylic acid poisoning classified by salicylic acid concentration in blood

Salicylic acid poisoning	Blood concentration of salicylic acid [mg%]	Clinical symptoms
Mild	45–65	Dizziness, tinnitus, impaired hearing, headaches
Moderate	65–95	Vomiting, excessive sweating, diarrhoea, hyperventilation, confusion, agitation, electrolyte disorders, elevated liver test results, disorders of the acid-base balance
Severe	95–120	Hyperthermia, pulmonary oedema, hallucinations, convulsions, increased prothrombin time
Critical	> 120	Coma, death

in adults. The epidermal layer in children is thin, while the cornified (hydrophilic), granular and spinous layers are poorly developed. Also, the amount of collagen and elastic fibers in the dermis is much smaller in children than in adults. Sweat glands are not fully developed, whereas sebaceous glands are already active before birth. In addition, children's skin has multiple dilated blood vessels. What also needs to be considered is the fact that children have a high ratio of body surface area to weight, which entails a greater area for the absorption of topical steroids and salicylic acid via the skin [40].

Conclusions

Combination drugs containing betamethasone dipropionate and salicylic acid are effective and well tolerated topical medications, which has been proven in a number of clinical trials. Betamethasone dipropionate used in combination with salicylic acid provides better GC penetration into the skin. This is crucial in the treatment of focal lesions with excessively keratinized surface. The combination is recommended in the therapy of a range of skin diseases including plaque psoriasis, prurigo, various kinds of eczema (including atopic dermatitis and seborrhoeic dermatitis), lichen planus and discoid lupus erythematosus.

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