

Transdermal Penetration of Topical Drugs Used in the Treatment of Acne

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Abstract

Acne vulgaris is a very common skin disease. Most patients present with mild to moderate acne comedonica or papulopustulosa grade I–II. The first-line treatment for these cases is generally via the topical route, whereas systemic medication is indicated when higher severity grades with small nodes or scarring occur. There are several topical agents available that affect at least one of the main pathogenetic factors responsible for the development of acne: hyperseborrhoea, hyperkeratosis, microbial colonisation and inflammatory and immunological reactions. Topical retinoids have a comedolytic and anticomedogenic activity, and some of them have anti-inflammatory potency. Azelaic acid and benzoyl peroxide have a moderate to strong antibacterial effect without inducing bacterial resistance, which is becoming a significant problem with the increasing use of topical

antibacterials. Topical antiandrogens may soon be available for the treatment of the pathogenetic factor hyperseborrhoea.

The transdermal penetration and the resulting systemic bioavailability of the various topical agents has not been widely considered. Apart from the retinoids, which can be associated with the risk of embryotoxicity/teratogenicity, and clindamycin, which might cause pseudomembranous colitis, information on the systemic pharmacokinetics of other topical agents is not readily available. There is still no consensus on the safe use of topical retinoids in pregnancy, and the occurrence of pseudomembranous colitis after the topical use of clindamycin does not appear to be of clinical relevance. In general, topical anti-acne agents are well tolerated and, as would be expected from their limited transdermal uptake, other significant safety concerns have not so far arisen.

Acne vulgaris is a common skin disease of the pilosebaceous unit, mainly affecting adolescents and young adults. The primary cause of acne is obstruction of the pilosebaceous canal. This is due to at least four distinct pathogenetic factors: (i) increased proliferation, cornification and shedding of follicular epithelium; (ii) increased sebum production, which seems to be under genetic control along with stimulation by androgenic hormones; (iii) colonisation of the follicle with *Propionibacterium acnes*; and (iv) induction of inflammatory responses by bacterial antigens and cell signals.^[1-5]

Topical therapy is indicated in mild to moderate acne vulgaris, whereas more severe forms with small nodules (0.5–1cm), nodes (>1cm), cysts or scarring require additional systemic therapy. The available topical agents have a direct or indirect influence on the pathogenetic factors (table I), and are selected according to the predominant type of the acne lesions. The most important ones are topical retinoids, topical antibacterials, benzoyl peroxide and azelaic acid.^[6,7]

Following topical administration, a drug can be absorbed either via the transdermal or the transfollicular route. The penetration pathway seems to depend on lipid solubility, polarity and particle size of the formulation.^[8,9] Particles between 3 and 10µm selectively penetrate the follicular ducts, whereas larger ones remain on the skin surface and smaller ones are randomly distributed in the stratum corneum and in the hair follicle.^[9]

Transdermal penetration and the resulting systemic availability of these topically applied substances has only been investigated for a few examples. The main focus has been on the retinoids and clindamycin due to their association with embryotoxicity/teratogenicity and pseudomembranous colitis, respectively. For the other agents, the otherwise scarce pharmacokinetic data are mentioned in the appropriate sections, or if systemic toxicity has been excluded that is specifically stated.^[10]

1. Topical Retinoids

The vitamin A (all-*trans* retinol) derivatives were first considered for the treatment of acne in 1962, when it became apparent that they might be useful in diseases with increased keratinisation.^[11] The first widely used retinoid was tretinoin (all-*trans* retinoic acid), followed for the topical route much later by isotretinoin (13-*cis* retinoic acid). Further chemical modification led to compounds now classified into three generations: non-aromatic, mono-aromatic and poly-aromatic (table II).^[12,13] Retinoids exert their effects on a molecular level through the nuclear receptors retinoic acid receptor (RAR) and retinoid X receptor (RXR). These ligand-dependent transcription factors bind retinoids either as homodimers (RAR/RAR, RXR/RXR) or heterodimers (RAR/RXR),^[14] which then can induce subsequent target gene expression by binding to the retinoid-responsive elements (RAREs and RXREs) in the promoter region of such genes.^[15-17] They also

Table I. Spectrum of efficacy of topical agents in acne therapy

Agent	Type of activity			
	keratolytic and/or anticomedogenic	sebosuppressive	antimicrobial	anti-inflammatory
Tretinoin	++	–	(+)	–
Isotretinoin	++	–	(+)	(+)
Adapalene	++	–	(+)	++
Tazarotene	++	–	(+)	+
Azelaic acid	++	–	++	+
Clindamycin	–	–	++	–
Erythromycin	–	–	++	–
Tetracycline	–	–	++	(+)
Benzoyl peroxide	(+)	–	+++	+
Salicylic acid	+	–	(+)	–

– = none; (+) = weak; + = moderate; ++ = strong; +++ = very strong.

inhibit the expression of genes without retinoid-responsive elements by downregulating the action of other transcription factors such as activator protein-1 (AP-1) and nuclear factor for interleukin 6 (NF-IL6), probably through competition for commonly required coactivator proteins.^[18-20] Retinoid receptors are members of the steroid-thyroid hormone superfamily and exist as α , β and γ subtypes with differential binding of the different synthesised compounds. The expression of the retinoid receptors is tissue-specific, with RAR γ being the predominant type of RAR expressed in human epidermis.^[15,18,21,22]

Intracellular concentration of retinoids is dependent on cytoplasmic binding by cellular retinoic acid binding proteins (CRABP) I and II,^[17] the latter being the dominant one in the skin.^[12]

According to their function, retinoids can be divided into three groups: (i) agonists, which stimulate the transcriptional activity of the retinoid receptors; (ii) neutral antagonists, which bind to the receptors without influencing their activity; and (iii) inverse agonists, which bind to the receptors but decrease their basal transcriptional activity.^[12,16]

All topically applied retinoids have a strong anticomedogenic and comedolytic activity, and also have an indirect antimicrobial effect due to the normalisation of the follicular environment. They modulate the altered differentiation of the infundibular keratinocytes and reduce their tendency to aggregate. Thus, the formation of comedones is sup-

pressed and the protrusion of existing comedones is accelerated.^[23-25]

Tretinoin, isotretinoin, adapalene, tazarotene and motretinide are approved for topical acne therapy, and retinoyl β -glucuronide is in clinical trials. Topical alitretinoin (9-*cis* retinoic acid), a preferential RXR ligand, has been approved for AIDS-related Kaposi's sarcoma, but was also shown to be effective in palmar hyperkeratosis. Topical bexarotene is used for cutaneous T-cell lymphoma, and retinol and retinaldehyde are used for cosmetic indications, the latter also being in clinical trials for psoriasis (table III).^[15]

Embryotoxicity/teratogenicity is the major drawback in the therapeutic use of retinoids. Exposure of the foetus during the first trimester to oral retinoids is known to produce characteristic malformations.^[26] There have also been case reports of malformations associated with retinoid embryopathy after the mother had used tretinoin topically during the first trimester of pregnancy.^[27-29] In a retrospective study, there were 1.9% major congenital abnormalities when mothers had used topical tretinoin during the first trimester of pregnancy versus 2.6% in women who were not exposed to tretinoin.^[30] Even though the daily variation of natural retinoid plasma concentrations is larger than the plasma concentrations occurring with topical retinoid application for the treatment of skin disease,^[31,32] and there is no evidence of teratogenicity from topical retinoids in animals,^[33] an individual risk of embry-

Table II. Retinoids

Agent	Administration
Endogenous	
Retinol (vitamin A)	Systemic and topical ^a
First-generation (non-aromatic)	
Tretinoin	Topical ^a and (systemic) ^b
Isotretinoin	Topical ^a and systemic ^a
Second-generation (mono-aromatic)	
Etretinate	Systemic
Acitretin	Systemic and (topical)
Motretinoid	Topical ^a
Third-generation (poly-aromatic)	
Arotinoids	(Systemic)
Adapalene	Topical ^a
Tazarotene	Topical ^a
Others	
Alitretinoin	Systemic and topical
Bexarotene	Systemic and topical
Retinaldehyde	Topical
Retinoyl β -glucuronide	Topical

a Indicated for the treatment of acne.
b () indicate route is possible but not generally used.

opathy with topical application cannot be excluded. With current knowledge, topical application of retinoids should be strictly avoided during the first trimester of pregnancy. In Germany, the administration of topical retinoids is not permitted during the entire period of pregnancy but contraception during the topical application of retinoids is not required. In the US, effective contraception during topical retinoid treatment is still recommended.

1.1 Tretinoin

Tretinoin has been a mainstay in the topical treatment of acne vulgaris for more than three decades. It has a high binding activity to all three RAR subtypes and to CRABP, and also binds (with low activity) to RXRs.^[12] Topical use of tretinoin was shown to induce the expression of epidermal CRABP II.^[34]

Tretinoin-treated skin shows stratum corneum compaction, thickening of the epidermis and granular cell layer and an increased epidermal keratinocyte mitotic index.^[15] The stimulation of keratinocyte proliferation is associated with the induction of cyclic AMP, epidermal growth factor (EGF) recep-

tor binding, protein kinase C and transforming growth factor (TGF) α .^[35,36] A direct effect on epidermal keratinocytes is shown by focal expression of intercellular adhesion molecule-1 (ICAM-1).^[37] Together with stimulation of the antigen-presenting capacity of Langerhans cells, activation of phospholipase C γ and phosphokinase C, this probably leads to immune modulating effects.^[22,38]

In photodamaged skin, tretinoin downregulates collagen degradation by reducing collagenase amounts in tissue, stimulates collagen I and III synthesis in the dermal fibroblasts and increases the number of anchoring fibrils (collagen VII).^[39] Tretinoin has been shown to prevent UV-induced accumulation of *c-Jun* protein, which is required for matrix metalloproteinase (MMP) gene expression, thus inhibiting UV induction of MMPs, which degrade skin collagen. This might be a possible mechanism of tretinoin to protect against UV-induced collagen destruction and therefore lessen the effects of photoaging.^[40]

In cultured normal human keratinocytes, a concentration-dependent increase in retinol content was observed after exposure to tretinoin.^[41] How this might affect retinol dehydrogenases (RoDH), RoDH-4 so far being the only one known to be expressed by human epidermis,^[42] which also metabolise androgens,^[43] is still under investigation.

Apart from partial isomerisation of tretinoin to isotretinoin and alitretinoin, metabolism to its less active metabolites occurs via the cytochrome P450 enzyme retinoic acid 4-hydroxylase (CYP26)^[44] and the more recently identified cytochrome P450 CYP2S1, which apparently has a higher cutaneous expression than CYP26.^[45] The metabolites can be graded according to potency: tretinoin >3,4 didehydro-retinoic acid >4-oxo-retinoic acid >4-hydroxy-retinoic acid >5,6-epoxy-retinoic acid.^[41,46]

In a skin penetration and distribution assessment with ¹⁴C-labelled tretinoin after topical application to human skin *in vitro*, there were relatively high concentrations in the epidermis, small concentrations in the dermis and very little radioactivity in the receptor fluid. When the epidermis was analysed for

drug content, a mixture of isomers and other unidentified materials were detected.^[47]

With a topical tretinoin 0.025% gel formulation containing polyolprepolymer-2, penetration into and through human skin *in vitro* was shown to be significantly reduced, potentially enhancing epidermal deposition, compared with a commercially available gel preparation at the same concentration.^[48] Polyolprepolymer-2 helps to retain drug molecules on the skin surface and in the upper layers of the skin.^[49,50] Another new formulation is a microsp sponge delivery system consisting of macroporous beads of 10–25µm in diameter that are loaded with active ingredient. After topical application, this is gradually released depending on rubbing, temperature, pH and other factors.^[51] Tretinoin 0.1% gel microsp sponge compared with tretinoin 0.025% gel, tazarotene 0.1% gel or adapalene 0.1% gel in a split face study over 29 days showed similar facial tolerability for all retinoids.^[52] In a comparative study, a formulation of liposomally encapsulated tretinoin 0.01% was equipotent in clearing acne lesions as tretinoin 0.025% or 0.05% gel after once daily topical application to one side of the body for 10 weeks, but

showed a much better cutaneous tolerability.^[53] This was also reproducible on *in vitro* reconstructed epidermis.^[54]

With regard to systemic absorption and risk of embryotoxicity after topical application, detected faecal and plasma tretinoin concentrations were much below endogenous tretinoin levels^[55-57] and did not affect endogenous levels of tretinoin or its metabolites after single-dose or long-term treatment with topical tretinoin 0.05% cream formulations^[58] or alter plasma vitamin A levels.^[59]

1.2 Isotretinoin

Topically applied isotretinoin is effective in mild to moderate acne, but in contrast to the oral preparation is not effective in severe acne and does not reduce sebaceous gland size and suppress sebum production.^[8,60] These differential effects might be related to the induction of epidermal CRABP II expression after topical, but not oral, application of isotretinoin,^[61] whereas oral isotretinoin has been found to induce CRABP II mRNA expression in sebaceous glands.^[62] This might be due to a specific isomerisation of isotretinoin into tretinoin occurring in sebaceous glands but not in epidermis after oral application.^[41,63] The binding activity to RARs is lower than with tretinoin, and isotretinoin does not bind to RXRs or CRABP.^[64]

In a penetration study of five different formulations applied to human skin *in vitro*, substantial amounts of topically applied isotretinoin were delivered via the follicular route to the sebaceous glands, resulting in comparable concentrations to those observed after oral administration.^[8,65] After 42 days of excessive application of 0.1% isotretinoin cream to patients with photodamaged skin on a surface area of approximately 2300 cm² once daily, plasma concentrations of isotretinoin were compared with pretreatment concentrations. The results suggested systemic absorption, but to a lesser extent than that reported after the US recommended daily allowance of 5000 IU of vitamin A supplementation.^[66] The systemic availability of topical isotretinoin is negligible, and should thus not produce systemic toxicity or embryotoxicity.^[66-69]

Table III. Commercially available topical retinoids

Agent	Concentration and galenic preparation
Tretinoin	0.025, 0.01, 0.05, 0.1, 0.4% cream 0.025% gel 0.05, 0.1, 0.2% solution 0.1% lotion 0.05% ointment 0.05% in compresses 0.1% gel microsphere 0.025% polymer cream
Isotretinoin	0.05% gel 0.05, 0.1% cream
Adapalene	0.1% gel, solution, cream
Tazarotene	0.05, 0.1% gel
Motretinide	0.1% cream, solution
Alitretinoin	0.1% gel
Bexarotene	0.1% gel
Retinol	0.01–0.015%, 0.1% cream
Retinaldehyde ^a	0.05% cream, gel, lotion 0.5–1% cream
Retinoyl β-glucuronide ^a	1.2% cream

a In clinical trials.

1.3 Adapalene

Adapalene is a third-generation naphthoic acid derivative of retinoic acid that binds selectively to RAR β and γ subtypes in binding assays, but activates gene expression through all three RARs. Unlike tretinoin, it does not bind to CRABP II.^[70]

Adapalene exhibits a low flux through the skin when applied once as a 0.3% alcoholic lotion to rat skin *in vitro*, and thus achieves high concentrations in the stratum corneum and in the hair follicle.^[71] As discussed in the Introduction, penetration is dependent on particle size.^[9] When an adapalene 0.1% gel was formulated as homogeneous suspension containing microcrystals of adapalene and applied topically to human skin *in vitro*, rapid penetration of adapalene into the pilosebaceous unit, the target site in acne, could be demonstrated. In a skin distribution assay with ¹⁴C-labelled adapalene in the same gel preparation applied once topically to human skin *in vitro*, the highest proportion recovered was in the epidermis and stratum corneum, and only 0.01% of the applied dose penetrated through the skin.^[72,73] When the epidermis was analysed for drug content, adapalene was essentially unchanged.^[47] After topical treatment of the entire facial area with adapalene 0.1% gel once daily for 12 weeks, no adapalene could be detected in plasma of patients, indicating a minimal degree of systemic exposure.^[74,75]

In comparison with tretinoin, adapalene is as effective in reducing acne lesions^[75-80] with an additional significant anti-inflammatory activity. This anti-inflammatory effect of adapalene is due to a greater inhibition of lipoxygenase activity and subsequent eicosatetraenoic acid (HETE) production by human leucocytes than with tretinoin, isotretinoin or etretinate.^[70,81-84] Adapalene has a significantly better cutaneous tolerability than tretinoin,^[47,76,77,85] and is far more stable under light and in the dark. In contrast to tretinoin, it is stable in combination with benzoyl peroxide.^[47,86] Comparison of adapalene with polymer formulations of tretinoin revealed the same efficacy, but better local tolerability for adapalene.^[87]

1.4 Tazarotene

Tazarotene is a recently introduced topical acetylenic retinoid. It is approved for the treatment of psoriasis in Europe and both psoriasis and acne vulgaris in the US.^[88] Tazarotene binds to all three RARs but activates gene expression effectively only through the RAR β and γ subtypes.^[16,89] Tazarotene also induces the expression of three novel genes, tazarotene-induced genes (TIG) 1, 2 and 3. TIG1 and TIG2 appear to be putative cell adhesion molecules,^[90,91] and TIG3 is an antiproliferative gene.^[92] Additionally, tazarotene inhibits AP1- and NF-IL6-dependent gene expression through all three RARs, which is probably of importance for its antiproliferative effects.^[16,93]

In a comparative trial over 12 weeks with application to the face once daily, tazarotene 0.1% gel seemed to be more efficient in reducing papules and open comedones, but similarly effective for closed comedones, than tretinoin 0.05% gel.^[94] Adapalene 0.1% gel once daily and tazarotene 0.1% gel every other day applied to the face for 15 weeks had similar efficacy in the treatment of acne,^[95,96] whereas daily application of tazarotene had significantly lower tolerability than adapalene.^[52]

In healthy volunteers, only 6% of a total dose of 2mg of tazarotene 0.1% gel applied topically under occlusion for 10 hours was distributed in the stratum corneum, and a further 2% of the dose partitioned into the epidermis and dermis. About 5% was absorbed systemically. Tazarotene is rapidly hydrolysed by esterases to its active metabolite tazarotenic acid, undergoes further metabolism and is eliminated via urinary and faecal pathways with a terminal half-life of approximately 18 hours. Percutaneous absorption is similar for healthy persons and patients with acne, leading to plasma concentrations below 1 μ g/L. The systemic bioavailability amounts to around 1% after single or multiple application to healthy skin. In patients with psoriasis, this can increase to up to 5% under steady-state conditions.^[97] After topical application of tazarotene 0.05% or 0.1% gel once daily for up to 12 weeks in patients with psoriasis, tazarotene was detectable in plasma in 2% of patients, and 61% of patients had

detectable but low plasma concentrations of the metabolite tazarotenic acid.^[98] In healthy volunteers, there was no tazarotene detectable in plasma after topical application of a 0.05% or 0.1% gel to a 20% body surface area for 10 hours, but the metabolite tazarotenic acid was detected. The maximum plasma concentration was reached after approximately 15 hours, and the mean plasma elimination half-life was about 20 hours.^[88]

In preclinical studies, topically applied tazarotene gel was non-mutagenic, non-carcinogenic and non-teratogenic. In human volunteers, tazarotene gel was not sensitising, phototoxic or photosensitising.^[98,99]

1.5 Other Retinoids

Motretinide is a second-generation mono-aromatic retinoid, which is slightly less effective for the topical treatment of acne, but also causes less local irritation than tretinoin. Motretinide is available in Switzerland.^[3,100]

Retinoyl β -glucuronide is a naturally occurring biologically active metabolite of vitamin A. A 0.16% retinoyl β -glucuronide cream was shown to be effective against inflammatory and non-inflammatory acne lesions when applied once daily to the face for 18 weeks in Asian-Indian patients^[101] as well as in patients in the US, with comparable efficacy to tretinoin, but without the irritation potential or other adverse effects of tretinoin.^[102] The percutaneous absorption, metabolism and excretion of topically applied radioactive retinoyl β -glucuronide and tretinoin were similar in the rat, and thus not of relevance for the differences in local tolerability.^[103]

Retinaldehyde was shown to have significant comedolytic activity in the rhino mouse model.^[104] After topical application in acne patients of retinaldehyde 0.1% gel or its vehicle every morning and erythromycin 4% lotion every evening for 8 weeks, comedones and microcysts were significantly improved with retinaldehyde combined with erythromycin, but not with erythromycin alone. In both treatment groups, papules and pustules were re-

duced significantly. Local tolerability was very satisfactory.^[105]

2. Topical Antibacterials

Topical antibacterials are indicated in mild inflammatory acne. The most important ones used are clindamycin, erythromycin and tetracyclines.^[106] These agents reduce the population of *P. acnes* on the skin surface and in particular within the follicles, thereby reducing free fatty acids of skin surface lipids (a marker of *P. acnes* lipase activity).^[23,107,108] The antibacterials demonstrate anti-inflammatory activity by suppressing chemotaxis.^[109,110] Subsequently, an indirect comedogenic effect can be observed,^[111] which seems to be stronger with clindamycin.^[23]

The advantages of topical antibacterials in contrast with oral preparations are the reduced risk of systemic adverse effects, the avoidance of resistance selection in the gut microflora, the direct delivery at the affected area, the overall usage of less drug and the high local tolerability.^[112,113] Topical antibacterials are available in several formulations (table IV).^[114]

One of the major setbacks in the use of topical antibacterials has been the dramatic increase in bacterial drug resistance and cross-resistance over the past 20 years.^[7,106,115-117] Therefore, use of topical

Table IV. Commercially available topical antibacterials

Agent	Concentration and formulation
Single agents	
Tetracycline	3% ointment, cream
Meclocycline	1% cream
Erythromycin	1%, 2% solution 2% ointment 2%, 4% gel
Clindamycin	1% solution, gel, lotion
Fixed combinations	
Erythromycin/benzoyl peroxide	3%/5% gel
Erythromycin/tretinoin	4%/0.025% gel
Erythromycin/isotretinoin	2%/0.5% gel
Erythromycin/zinc acetate	4%/1.2% lotion
Clindamycin/benzoyl peroxide	1%/5% gel
Clindamycin/tretinoin	1%/0.025% gel
Miconazole/benzoyl peroxide	2%/5% cream

antibacterials as combination therapies, e.g. with benzoyl peroxide, either alternating or as fixed combinations (table IV)^[117-123] or alternating with azelaic acid,^[124] has been favoured, as this reduces existing resistant *P. acnes* and counteracts the selection of new resistant strains.

2.1 Clindamycin

The effectiveness of topically applied clindamycin for the treatment of acne vulgaris was first described in the late 1970s,^[125,126] and has been confirmed in various studies since.^[127-129] In an *in vitro* study on *Macaca nemestrina* monkey skin, after a single application of radiolabelled clindamycin hydrochloride 1.2% or 2.4% the percutaneous absorption varied from 0.7% to 12.9% of the applied dose in 24 hours, depending on the vehicle. The 14 vehicles studied varied up to 100-fold with respect to clindamycin bioavailability.^[130]

Topical clindamycin has been associated with the occurrence of pseudomembranous colitis. There have been case reports after application of clindamycin hydrochloride^[128,131] as well as after clindamycin phosphate,^[132] which was thought to be absorbed cutaneously to a lesser extent.^[133] Other studies differed widely with respect to bioavailability of clindamycin.^[134-136]

In a comparative study of clindamycin hydrochloride versus clindamycin phosphate, each in a combination gel with tretinoin 0.025% applied daily for 5 consecutive days to the faces of healthy volunteers, no clindamycin was detected in plasma after the clindamycin phosphate preparation, but clindamycin was detected in one volunteer receiving the clindamycin hydrochloride preparation. This was similar for clindamycin urinary excretion. When the penetration of the clindamycin phosphate/tretinoin gel was monitored after 4 and 12 weeks of daily treatment, in 87% of the samples there was no clindamycin detectable. The highest plasma concentration was 11 µg/L. Interestingly, there was also no demonstrable enhancing effect of tretinoin on systemic uptake of clindamycin.^[57] In a topical gel formulation stably combining 5% benzoyl peroxide and 1% clindamycin phosphate, systemic exposure

to clindamycin and degradation of clindamycin by the highly reactive benzoyl peroxide were minimal after a single application of 1g of the combination gel to the entire face.^[137]

2.2 Erythromycin

Erythromycin is well established as an effective topical antibacterial in acne therapy.^[125,138-140] In early studies, it was shown to significantly reduce *P. acnes* and Micrococcaceae in the ducts of sebaceous glands. From these results, a good penetration of erythromycin into the ducts was concluded,^[141] whereas erythromycin was not detectable in serum after extended local erythromycin treatment for eight weeks in patients with acne.^[142]

The increasing emergence of erythromycin-resistant *P. acnes* was overcome by using 4% instead of 2% erythromycin formulations. Also, the addition of zinc acetate to the erythromycin formulation was shown to enhance the bactericidal effect^[107,143,144] with an additional sebosuppressive effect.^[145,146] Topically applied 2% zinc sulfate solution over 12 weeks had no effect on acne lesions, and zinc serum levels were not elevated before, during or after treatment.^[147] When the effect of zinc on the stratum corneum penetration of erythromycin was investigated in healthy volunteers with skin surface washings and tape strippings at 6 hours after a single topical application of two different erythromycin 4%/zinc 1.2% formulations to the back, zinc was found to increase the residence time of erythromycin on the skin and decrease penetration into the stratum corneum.^[148] In a clinical trial directly comparing twice daily topical application to the face for 12 weeks of a clindamycin phosphate 1% solution with a erythromycin 4%/zinc 1.2% formulation, the latter was found to be superior.^[113]

2.3 Tetracycline

In an early study comparing oral and topical tetracycline, both reduced acne severity, but interestingly without concomitant change in surface lipids as a marker for bacterial activity.^[149] The beneficial effect of topical tetracycline on acne has been well established, but it is less used today than

in the past.^[150-152] Blood counts, blood chemistry and urinalysis in 37 patients with acne vulgaris treated with a tetracycline topical lotion for 13 weeks revealed no disturbing trends.^[153] Detectable amounts of tetracycline were found in 111 of 155 open comedones of 15 patients treated twice daily with topical 0.22% tetracycline hydrochloride. The drug content was sufficient to inhibit fully antibacterial-resistant *P. acnes*, but in 18.7% of samples the conditions were favourable for the selection and overgrowth of tetracycline-resistant strains.^[154]

2.4 Nadifloxacin

Nadifloxacin is a fluoroquinolone antimicrobial agent that has been shown in clinical trials to be effective in topical therapy for acne vulgaris. Besides its antibacterial activity, it seems to have inhibitory action on the generation of reactive oxygen species by neutrophils, leading to a reduction in oxidative tissue injury.^[155] In a recent study, all *P. acnes* isolates resistant to one or more of the commonly used antiacne antibacterials were sensitive to nadifloxacin,^[156] thus confirming previous results.^[7,157-160] Nadifloxacin resistance in *Staphylococcus aureus* strains, which were either clinically isolated^[161] or selected,^[162] was dependent on mutations in the A subunit of DNA gyrase, and did not appear to be related to mutations in the A subunit of topoisomerase IV, as is known for other quinolones.

Currently, nadifloxacin is available only in a few countries.

2.5 Chloramphenicol

Chloramphenicol is a derivative of phenylalanine, with a bacteriostatic effect against a broad spectrum of Gram-positive and Gram-negative bacteria.

Topical therapy with chloramphenicol 1% alcoholic solution led to a significant reduction in *P. acnes* compared with vehicle. Clinically relevant percutaneous absorption of chloramphenicol was ruled out, with serum concentrations averaging 25 µg/L, since therapeutic chloramphenicol concentrations after systemic administration exceed 25 mg/L. There were no adverse events or relevant changes in blood tests. Induction of resistance in *P. acnes* could

be excluded.^[163] *P. acnes* isolates resistant to one or more of the commonly used antiacne antibacterials were sensitive to chloramphenicol.^[156]

Even though percutaneous absorption is minimal, the risk of severe bone marrow depression or aplastic anaemia means that chloramphenicol should be reserved for problematic cases.^[164]

3. Benzoyl Peroxide

Benzoyl peroxide has been one of the most important agents in the topical acne therapy for a long time. It has strong antimicrobial, slight anti-inflammatory (possibly due to a reduction of reactive oxygen species) but only mild anticomedogenic effects. It has no effect on sebum production.^[24,165,166] Available benzoyl peroxide preparations include 2.5%, 3%, 5% and 10% gels, 2.5%, 4% and 5% creams, 4% solution and 5% lotion. Additionally, there are fixed combinations with topical antibacterials (table IV).^[117-123,167,168]

Micromolar concentrations of benzoyl peroxide were found to inhibit the release of reactive oxygen species from human neutrophils, but were associated with marked drug-induced cytotoxicity. In cell-free assays investigating the effects of benzoyl peroxide on protein kinase C and calmodulin, regulators of the release of reactive oxygen species, there was only marginal inhibition of protein kinase C and no inhibition of calmodulin. Thus the anti-inflammatory activity of benzoyl peroxide is unlikely to be mediated by protein kinase C or calmodulin.^[169]

In one study, the sebum excretion rate was shown to increase by 22.5% after 1 or 2 months of treatment with 5% benzoyl peroxide. This was thought to be due to comedolytic activity, thus influencing the pooling of sebum in the upper parts of the pilosebaceous duct.^[170] Nevertheless, present evidence excludes any effect on sebaceous gland activity and direct comedolytic activity.

The common induction of irritant dermatitis can be avoided by less frequent application, and the incidence of true contact sensitivity is low.^[171] A water-based benzoyl peroxide preparation was found to cause significantly less skin irritation than

an alcohol-based preparation.^[172] In a comparison of 2.5%, 5% and 10% gel formulations of benzoyl peroxide, 2.5% was equivalent to the other two concentrations in reducing inflammatory lesions and significantly reduced *P. acnes* after 2 weeks of topical application. Local adverse effects were less frequent with the 2.5% gel than with the 10% preparation, but similar to those with the 5% gel.^[173]

An assessment of percutaneous penetration of benzoyl peroxide *in vitro* on human skin and *in vivo* on five patients with leg ulcers showed conversion of the absorbed benzoyl peroxide to benzoic acid, preferably in the dermis. Only benzoic acid penetrated through the skin, and no benzoyl peroxide could be detected in the serum of treated patients. Therefore, systemic toxicity during local therapy with benzoyl peroxide can be excluded.^[174]

One of the great advantages of benzoyl peroxide is that it does not cause bacterial resistance, and is thus well established for combination therapy with topical antibacterials.^[175-179]

4. Azelaic Acid

Azelaic acid is a naturally occurring saturated C₉ dicarboxylic acid. Its effect on acne lesions was a coincidental finding in a study evaluating the use of azelaic acid for chloasma.^[180] Since then, its efficacy on comedonal and inflammatory acne lesions has been confirmed in a series of different studies, with an effectiveness equal to that of other topical medications.^[181-184] Azelaic acid modifies epidermal keratinisation, has antibacterial properties against both aerobic and anaerobic bacteria, and possesses anti-inflammatory activity. The last effect is due to scavenging activity on reactive oxygen species, as has been shown for human neutrophils and in cell-free systems.^[185,186] Changes in sebum composition, sebum secretion or sebaceous gland size were not detectable.^[181,187-190] Interestingly, there is an antiproliferative and cytotoxic effect on human malignant melanocytes,^[191] which is related to the inhibition of mitochondrial oxidoreductase activity and DNA synthesis by azelaic acid.^[192]

The concentration of azelaic acid in follicular casts after a single topical application of azelaic acid

20% cream to the forehead and back was shown to be comparable with the concentration required to inhibit the *in vitro* growth of *P. acnes* and *Staphylococcus epidermidis*.^[193] Percutaneous absorption of azelaic acid was investigated in six healthy volunteers after a single topical treatment with 5g of azelaic acid 20% cream on the face, the chest and the upper back, followed 1 week later by an oral dose of azelaic acid 1g as an aqueous microcrystalline suspension. After both treatments, renal excretion of the unchanged compound was measured. The percutaneous absorption of azelaic acid from a cream was assessed as 3.6% of the dermally applied dose.^[194]

At the moment only a 20% cream formulation is on the market, but a new formulation of a 15% gel with better acceptance for greasy skin is starting to become marketed.

Azelaic acid does not appear to induce bacterial resistance. It is well tolerated, non-teratogenic and not associated with systemic adverse events or photodynamic reactions.^[181]

5. Other Agents

5.1 Salicylic Acid

Salicylic acid has mainly a keratolytic effect. Additionally, it increases penetration of other substances, has a slight anti-inflammatory effect, and is bacteriostatic and fungistatic in low concentrations as a result of competitive inhibition of pantothenic acid, which is important for microorganisms. Salicylic acid can be supportive during maintenance therapy when used as a 1–3% alcoholic solution.^[195]

Salicylic acid is transdermally absorbed to an extent dependent on skin hydration, with highest absorption in children. The percutaneous absorption of salicylic acid can lead to systemic intoxication, especially in children and in patients with renal insufficiency who have increased accumulation. Symptoms occur from 300 mg/L in serum, and are characterised by hearing loss, tinnitus, epistaxis, nausea and vomiting and dryness of the mucosae. Increasing concentrations lead to respiratory alkalosis and via compensation subsequently to metabolic acidosis. Disturbances of haemostasis and renal dis-

ease can also occur. Plasma concentrations above 400 mg/L are lethal.^[196-198]

5.2 Antiandrogens

Serum androgen levels and acne are not closely correlated. In more than 98% of cases the individual end organ response is the main pathogenetic factor.^[3] Androgens increase the activity of the sebaceous gland and may also induce hyperkeratosis of the pilosebaceous duct.^[199]

Oral contraceptives have been used successfully in the treatment of acne for decades, but initially topical anti-androgens could not be shown to have effects on sebocytes.^[200] More recently, topical in-coterone acetate, a nonsteroidal antiandrogen, as a 10% solution produced a significant reduction in the number of inflammatory acne lesions, but without changes in comedo counts or sebum excretion rates after 12 weeks of twice-daily facial treatment.^[201] Topical cyproterone acetate, a steroidal anti-androgen with progestational activity, had an effect on acne lesions comparable with that of the oral preparation after 3 months of therapy when a total dose of 20mg was applied once daily to the face in a liposomal formulation to enhance transdermal penetration. Serum cyproterone acetate concentrations were 10 times lower after topical application than after oral intake.^[202] However, confirmation of these study results is still lacking.

One study demonstrated a beneficial effect of 2% spironolactone in a cream base on acne lesions,^[203]

which could not be confirmed by other investigations.^[204,205]

A promising new concept is inhibition of 5 α -reductase. This enzyme metabolises testosterone into 5 α -dihydrotestosterone in androgen-regulated target tissues, and exists in two isoforms. The type 1 isoenzyme occurs in the skin, located mainly in the sebocytes, epidermal and follicular keratinocytes, hair dermal papilla cells, melanocytes and sweat glands, whereas type 2 isoenzyme exists in the prostate. Antagonists selectively binding to the type 1 isoenzyme might be candidates for the treatment of seborrhoea and acne.^[206,207]

The main limitation of anti-androgen therapy is the obvious fact that it cannot be used for male patients under normal conditions.

5.3 α -Hydroxy Acids

α -Hydroxy acids are naturally occurring carboxylic acids that are known to facilitate desquamation of the stratum corneum.^[208,209] Of dermatological importance are glycolic acid, lactic acid and gluconic acid. So far, well-controlled trials are lacking.^[210]

5.4 Sulfur

The efficacy of topical sulfur-containing preparations in acne therapy is controversial; some authors have demonstrated keratolytic effects,^[211] whereas others have shown a comedogenic effect.^[212]

Table V. Adverse drug reactions of topical therapies for acne

Agent	Erythema	Scaling	Burning	Flare-up	Bacterial resistance	Photosensitivity	Other
Tretinoin	+++	+++	++	++	-	++	-
Isotretinoin	++	++	+	+	-	(+)	-
Adapalene	+	+	+	+	-	-	-
Tazarotene	+	+	+	+	-	-	-
Azelaic acid	+	+	+++	-	-	-	-
Benzoyl peroxide	++	++	+	+	-	+	Bleaches hair and clothes; rarely contact sensitivity
Topical antibacterials-	-	-	-	-	+++	Tetracycline	Rarely contact sensitivity

- = none; (+) = weak; + = moderate; ++ = strong; +++ = very strong.

5.5 Tea Tree Oil

Tea tree oil has been shown *in vitro* to possess antibacterial activity. It has thus been suggested to be effective in topical therapy for acne. So far, evidence for its usefulness in acne therapy is lacking. Adverse effects of tea tree oil are usually mild and transient, consisting mainly of allergic reactions.^[213,214]

6. Conclusions

Topical anti-acne treatment should be determined by the type of the predominant lesion, according to a recent consensus conference.^[215] Use of a topical treatment is mainly limited by local adverse effects, which may necessitate a switch to another agent (table V). In general, combination therapy with different topical agents improves efficacy and reduces toxicity. There is very little data available as to whether topical agents might enhance transdermal penetration of each other when used either as fixed combinations or as alternate treatment regimens. So far, there is also still no final consensus on the safe use of topical retinoids in pregnancy.

New preparations like liposome encapsulation,^[53,216,217] polymeric microspheres^[218-220] or the microsphere delivery system^[51,52] have been developed to increase the transdermal penetration and thus the efficacy of topically applied drugs. This might also enhance transdermal uptake and systemic absorption, leading to an increased risk of systemic adverse effects.^[7]

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