Topical Acne Drugs
Review of Clinical Properties, Systemic Exposure, and Safety

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Contents

Abstract ............................................................................................................... 474
1. Introduction: Acne Prevalence, Pathogenesis, and Treatment ................................. 474
2. Factors Affecting Percutaneous Absorption ................................................................. 476
3. Topical Retinoids .................................................................................................... 477
   3.1 Tretinoin ....................................................................................................... 477
      3.1.1 Background .............................................................................................. 477
      3.1.2 Pharmacokinetics ......................................................................................... 477
      3.1.3 Drug-Related Adverse Events .............................................................................. 478
   3.2 Isotretinoin ..................................................................................................... 479
      3.2.1 Background .............................................................................................. 479
      3.2.2 Pharmacokinetics ......................................................................................... 479
      3.2.3 Drug-Related Adverse Events .............................................................................. 480
   3.3 Adapalene .................................................................................................... 480
      3.3.1 Background .............................................................................................. 480
      3.3.2 Pharmacokinetics ......................................................................................... 480
      3.3.3 Drug-Related Adverse Events .............................................................................. 481
   3.4 Tazarotene ..................................................................................................... 481
      3.4.1 Background .............................................................................................. 481
      3.4.2 Pharmacokinetics ......................................................................................... 481
      3.4.3 Drug-Related Adverse Events .............................................................................. 481
4. Topical Benzoyl Peroxide ............................................................................................. 482
   4.1 Background .................................................................................................... 482
   4.2 Pharmacokinetics ............................................................................................... 482
   4.3 Drug-Related Adverse Events ................................................................................ 482
5. Topical Antibacterials ................................................................................................ 482
   5.1 Clindamycin ................................................................................................... 482
      5.1.1 Background .............................................................................................. 482
      5.1.2 Pharmacokinetics ......................................................................................... 483
      5.1.3 Drug-Related Adverse Events .............................................................................. 483
   5.2 Erythromycin ................................................................................................... 483
      5.2.1 Background .............................................................................................. 483
      5.2.2 Pharmacokinetics ......................................................................................... 484
      5.2.3 Drug-Related Adverse Events .............................................................................. 484
6. Other Topical Agents ................................................................................................ 484
   6.1 Salicylic Acid ................................................................................................. 484
      6.1.1 Background .............................................................................................. 484
      6.1.2 Pharmacokinetics ......................................................................................... 485
      6.1.3 Drug-Related Adverse Events .............................................................................. 485
   6.2 Sulfur .......................................................................................................... 485
      6.2.1 Background .............................................................................................. 485
      6.2.2 Pharmacokinetics ......................................................................................... 486
      6.2.3 Drug-Related Adverse Events .............................................................................. 486
Abstract

This review examines the commonly available topical acne agents and factors that determine their percutaneous absorption. Reported and theoretical adverse effects from systemic exposure are detailed.

The topical retinoid class, which includes tretinoin, adapalene and tazarotene, and the topical antibacterials, clindamycin and erythromycin, are regulated by prescription in most countries. Used appropriately, the above-mentioned drugs deliver, at most, miniscule amounts of active ingredient into the circulation. Clear-cut links to systemic toxicity in humans are practically nonexistent, except in the case of topical clindamycin, which has been associated with diarrhea rarely, and there have been 2 cases of pseudomembranous colitis reported. Birth defects have occurred in two patients treated with tretinoin and one patient treated with adapalene, but causation was not proven. Another prescription drug, 20% azelaic acid, is associated with relatively high systemic exposure, which is presumed innocuous because it is a normal dietary constituent whose endogenous levels are not altered by topical use.

Benzoyl peroxide, salicylic acid, sulfur, and sodium sulfacetamide are available in concentrations of 2% or more in over-the-counter acne treatments and some prescription products. All of these agents are known to exhibit some degree of percutaneous absorption. They remain largely unregulated because, other than skin irritation, only local allergic contact dermatitis from benzoyl peroxide in about 2.5% of patients and rare local and systemic hypersensitivity reactions from sodium sulfacetamide have been reported. Salicylism has occurred using methyl salicylate ointments and high concentrations of salicylic acid on widespread areas of hyperkeratotic skin, but there are no known cases resulting from salicylic acid acne products.

Caution is advised in special circumstances, such as during childhood, pregnancy, lactation and concomitant therapy with other drugs, because relevant studies are lacking. Animal data support avoidance of many topical agents, particularly known teratogens such as retinoids and salicylic acid, in pregnant women. Salicylate avoidance is advised during lactation, because aspirin use carries the risk of bleeding disorders in nursing infants.

1. Introduction: Acne Prevalence, Pathogenesis, and Treatment

Acne is the commonest adolescent skin disorder, affecting 86% of 17-year-olds in a large government survey[1] conducted in the US. Teenage acne causes discomfort, disfigurement, emotional distress and sometimes permanent scarring.[2]

Many preadolescent children[3] and adults, mainly women,[4] also have acne. Besides diminishing the patient’s social and psychological well being,[5] acne in the pediatric age group and in pregnant and lactating women, presents therapeutic challenges, due to a paucity of drug studies in such patients.

What is known of the etiology of acne is that heredity and hormones are involved,[6-9] but neither diet nor hygiene plays a meaningful role.[10-12] The pathogenesis of acne is complex and only partially understood. Follicular occlusion with adherent keratinocytes and androgen-driven activation of sebum secretion result in the formation of microcomedones. These may enlarge to form visible non-inflammatory acne lesions referred to as open and closed comedones. Colonization of microcomedones and comedones with Propionibacterium acnes, microaerophilic Gram-positive bacteria that metabolize sebaceous triglycerides, appears to be the event that transforms these follicular impactions into inflamed acne lesions. One reasonable theory suggests that inherent hypersensitivity to P. acnes or its metabolic products is the main determinant of acne severity.[13,14]

Numerous acne medications are employed to target one or more of these processes. Topical retinoids are by far the most potent comedolytic agents.[15] Benzoyl peroxide, salicylic acid, sulfur and azelaic acid are also used to inhibit comedo formation. Topical and
oral antibacterials, benzoyl peroxide, azelaic acid, and sulfur com-
 pounds combat colonization with *P. acnes* and reduce inflam-
 mation. Hormonal agents, including contraceptives and spirono-
lactone, act as anti-androgens. Oral isotretinoin is unique in its
 ability to shrink the sebaceous gland and profoundly diminish
 sebum secretion.[16]

Clinical approaches to acne treatment may be found in com-
prehensive reviews of this topic.[17,18]

Topical therapy alone is usually preferred for mild acne. Often
a topical comedolytic agent, particularly one from the retinoid
 group, is used in a daily sequence with benzoyl peroxide, a topical
 antibacterial agent, or a fixed-combination product containing
 both. Topical therapy is also useful for moderate to severe acne,
 when combined with systemic antibacterial treatment (see figure 1) or hormonal intervention.

Oral therapy is chosen when the disease is resistant to topical
therapy, covers large areas of the body, causes significant distress
or requires rapid improvement. In suitable candidates, severe
recalcitrant acne may be treated with oral isotretinoin, generally
without concomitant topical acne therapy.

In addition to conventional medical care, there are two new
FDA-approved approaches to non-drug treatment of acne. The
first of these, used for moderate inflammatory acne, consists of
high-intensity, enhanced blue-light phototherapy (ClearLight™,
Lumenis Ltd).[19] The other is diode laser treatment (Smooth-
beam™, Candela Corporation) for back acne and atrophic facial
acne scars.[20] These modalities are promising for drug-resistant
cases, but both are costly and lack the convenience and availability
of pharmaceutical remedies.

Fig. 1. (a) A 16-year-old boy with previously untreated moderate inflammatory acne at baseline, when therapy was initiated using short-contact therapy
with 0.1% tazarotene gel once daily and 1% clindamycin lotion once daily; (b) at 1 month, showing pustular exacerbation characteristic of topical retinoid
therapy, treated with cefadroxil 500mg twice daily for 10 days while continuing topical drugs; (c) at 2 months, showing marked improvement 20 days after
stopping the oral antibacterial agent, using topical therapy alone; and (d) at 3 months, in near remission, on topical drug maintenance.

1 Use of tradenames is for product identification only and does not imply endorsement.
Table I. Safety of topical acne drugs during childhood, pregnancy and lactation[22]

<table>
<thead>
<tr>
<th>Topical acne medications</th>
<th>Safety in pediatric patients (&lt;age 12 years)</th>
<th>Safety in pregnancy/ FDA pregnancy categorya</th>
<th>Safety in nursing patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retinoids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adapalene</td>
<td>Not established</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Isotretinoin</td>
<td>Not established</td>
<td>Not established/N/A</td>
<td>Unknown</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Not established</td>
<td>contraindicated/X</td>
<td>Unknown, probably unsafe</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Not established</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Not established</td>
<td>Not established/B</td>
<td>Unknown</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Oral forms but not topical products are safe in all age groups</td>
<td>Not established/B</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic Acid</td>
<td>Not established</td>
<td>Not established/B</td>
<td>Unknown, probably safeb</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>Not established</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>Safe in children over 2 years old</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sodium- Sulfacetamide</td>
<td>Not established</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
<tr>
<td>Sulfur</td>
<td>Not established</td>
<td>Not established/C</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

a US Food and Drug Administration (FDA) Use-In-Pregnancy Rating Categories: A = Controlled studies show no risk; B = No evidence of risk in humans despite adverse findings in animals, or, human studies lacking but animal studies show no risk. The chance of fetal harm is remote, but possible; C = Risk cannot be ruled out. Data lacking in humans, animal studies positive or also lacking; D = Positive evidence of risk in humans, but benefit of use may outweigh the risk; X = Contraindicated in pregnancy.[22]

b Azelaic acid is a naturally occurring substance found in whole grain cereals and animal products.

N/A = not applicable.

Compared to oral therapy, topical drugs provide less aggressive acne intervention but also have obvious advantages. Direct application to affected skin maximizes the proportion of drug delivered to the pilosebaceous units and limits unnecessary systemic exposure,[21] thereby lessening the potential for internal adverse effects and systemic drug interactions.

The purposes of this review are to determine the extent of percutaneous absorption of various topical acne agents and to examine reported and possible consequences of such exposure. Particular attention is directed to acne treatment during childhood (under age 12 years), pregnancy, lactation, and concomitant administration of other drugs (see table I and table II).

2. Factors Affecting Percutaneous Absorption

Aside from the unique pharmacokinetic properties of each drug, certain general principals influence systemic absorption after local application.

First, the dose absorbed is proportional to the amount applied. Higher systemic absorption will result from treating larger surface areas or applying medications in an overgenerous manner. The usual amount of topical acne preparation recommended to cover the facial surface has been estimated to be approximately 0.6 grams.[23] When treatment includes the chest, shoulders and back, up to 3 additional grams may be needed, depending on the extent of body surface involved.

Secondly, frequency of application influences systemic levels. For most topical acne drugs, once-daily administration is recommended. Certain agents, particularly topical isotretinoin, benzoyl peroxide, clindamycin and erythromycin, may be used twice daily. In such cases, serial administration increases systemic exposure, particularly when a drug and/or its metabolites have slow rates of absorption or clearance.

Thirdly, the duration of application for certain drugs, including salicylic acid, is directly related to the dose absorbed.[24] While most agents are left on the surface for 8–12 hours, cleansers and masks containing benzoyl peroxide, salicylic acid, sulfur and sodium sulfacetamide are removed after a few minutes, presumably lessening absorption. A short-contact method of tazarotene application has also been described by one author (see figure 1).[25] In a clinical study of 99 patients, 0.1% tazarotene gel applied for 2–10 minutes daily produced significant acne improvement by 12 weeks.[26] To our knowledge, systemic tazarotene levels after such brief duration have not been studied.
Fourthly, inherent skin characteristics determine the rate of penetration of some topical drugs into the stratum corneum, influencing their systemic absorption. The important work of Rougier and colleagues\(^\text{27}\) in the 1980s showed that various agents penetrate forehead skin more rapidly than that of other anatomical sites tested, including postauricular, abdomen, and arm. Of note, no racial variations in topical drug absorption were observed among Asian, Black and Caucasian skin.\(^\text{28}\)

Finally, drug vehicles influence both the rate and amount of active ingredient absorbed.\(^\text{29,30}\) Generally, hydroalcoholic solutions and gels provide the most efficient drug delivery. In contrast, newer drug-delivery systems are designed to entrap active ingredients in microsponges or polymers, reducing drug penetration beyond the avascular horny layer. In acne therapy, the latter are found in commercial tretinoin formulations (see section 3.1.1).

### 3. Topical Retinoids

Topical retinoic acid was discovered for acne more than 3 decades ago.\(^\text{31}\) The term retinoids was originally used to describe chemical analogs of vitamin A.\(^\text{32}\) Starting in the late 1980s, with the discoveries of nuclear retinoic acid receptors\(^\text{33}\) and retinoid X receptors,\(^\text{34}\) the definition of retinoids evolved to include diverse molecules with the ability to bind to and activate these receptors.\(^\text{35}\)

The retinoid class contains the well known agents tretinoin, adapalene and tazarotene, which are used to treat acne and other common skin disorders, such as photoaging\(^\text{36,37}\) and psoriasis.\(^\text{38,39}\) Less familiar retinoids are alitretinoin for Kaposi’s sarcoma,\(^\text{40}\) and bexarotene for cutaneous T-cell lymphoma.\(^\text{41}\)

Several mechanisms of action are likely to be responsible for the usefulness of topical retinoid agents as acne therapy. These include modulation of keratinocyte proliferation,\(^\text{42}\) induction of orthokeratosis,\(^\text{43}\) comedolysis,\(^\text{44}\) and inhibition of inflammation.\(^\text{38}\) Oral isotretinoin also reduces sebaceous gland size and decreases sebum production.\(^\text{46}\)

Although over 5000 retinoids have been identified or synthesized,\(^\text{45}\) only 4 topical retinoids are commonly employed as acne treatment. Besides tretinoin, adapalene and tazarotene, which are approved by the US FDA, topical isotretinoin is currently available in Europe and Canada but is not FDA approved as of this writing.

While topical retinoids are the most effective anti-comedonal agents,\(^\text{15}\) their principal drawbacks are local skin irritation, gradual clinical improvement, and acne exacerbation, the so-called “retinoid flare” (see figure 1b), which occurs during the first month of treatment and may persist for several weeks.

#### 3.1 Tretinoin

##### 3.1.1 Background

Tretinoin, or all-trans retinoic acid, is a naturally occurring form of vitamin A. Typical formulations of topical tretinoin used for acne (various tradenames and generics, numerous manufacturers) include 0.025–0.1% cream, 0.01–0.025% in standard gel, and 0.025–0.1% in vehicles designed to reduce the rate of drug release, increase drug retention in the stratum corneum and inhibit deeper penetration.\(^\text{30}\) The latter include the Microsponge Delivery System\(^\text{R}\) (Enhanced Derm Technologies, division of RP Scherer Inc.) found in microsphere gel (Retin-A Micro\(^\text{R}\), Ortho Dermatological) and polyol prepolymer-2 (PP-2) found in delayed-release gel and cream formulations (Avita\(^\text{R}\), Bertek Pharmaceuticals). Tretinoin is generally applied once daily, at bedtime. The safety of tretinoin in patients aged under 12 years is not established.

The effectiveness of tretinoin for acne is well documented in numerous clinical trials using concentrations of 0.01–0.1%.\(^\text{46-52}\) It is among the most effective therapies currently available for the treatment of acne. The initial response to medication may be seen at 2–3 weeks, but improvement is usually gradual. Most patients require 2–4 months to achieve notable success.\(^\text{52-56}\) Long-term adherence until spontaneous remission is necessary, because topical therapy controls rather than cures acne.

Topical tretinoin is available in emollient cream vehicle (Renova\(^\text{R}\), Ortho Dermatological), with 0.02% or 0.05% active ingredient, for palliation of signs of photodamage, including fine wrinkles, tactile roughness and mottled hyperpigmentation.\(^\text{36}\)

Oral tretinoin is used for acute promyelocytic leukemia in doses as high as 50 mg/m\(^2\)/day.\(^\text{57}\) Oral tretinoin has also been studied in clinical trials for psoriasis, using doses of 1 mg/kg/day.\(^\text{58}\) and hyperkeratotic skin diseases, using 20–60 mg/day.\(^\text{59}\)

##### 3.1.2 Pharmacokinetics

Orally, tretinoin is well absorbed, but percutaneous absorption of topical tretinoin is low, slightly less than 1% after a single dose of 0.1% tretinoin in microsphere gel and less than 2% of an emollient cream formulation.\(^\text{22}\) Following a single topical application of radiolabeled tretinoin, the blood concentration of retinoic acid was found to be unchanged from 2–48 hours.\(^\text{60}\) Percutaneous absorption after topical application does not alter systemic retinoid levels, which remain within the range of the body’s natural endogenous levels.\(^\text{61-63}\)

When taken orally, tretinoin is metabolized in the liver and excreted by the kidney. Renal excretion is 63% over 72 hours.\(^\text{22}\) The half-life of the parent compound is 0.5–2.0 hours with the major metabolites being isotretinoin, 4-oxo trans retinoic acid,
### Table II. Drug interactions from systemic and topical administration of agents found in acne products

<table>
<thead>
<tr>
<th>Agents</th>
<th>Drug interactions reported from oral or parenteral administration</th>
<th>Drug interactions reported with topical application</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Retinoids</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adapalene</td>
<td>Oral/injectable/implantable contraceptives (may decrease efficacy)</td>
<td>None known</td>
</tr>
<tr>
<td>Isotretinoin*</td>
<td>Vitamin A (additive toxic effects)</td>
<td>None known</td>
</tr>
<tr>
<td>Tazarotene</td>
<td>Tetracyclines (increased risk of pseudotumor cerebri)</td>
<td>None known</td>
</tr>
<tr>
<td>Tretinoin</td>
<td>Potential drug interaction with inducers or inhibitors of hepatic CYP 450 system although no data exists proving existence of such interactions Inducers: rifampin, corticosteroids, phenobarbital, pentobarbital Inhibitors: ketoconazole, cimetidine, erythromycin, verapamil, diltiazem, cyclosporine</td>
<td>None known</td>
</tr>
<tr>
<td><strong>Antibacterials</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clindamycin</td>
<td>Neuromuscular blocking agents (may enhance their action) Erythromycin (antagonism shown in vitro)</td>
<td>None known</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>Theophylline (theophylline toxicity)</td>
<td>None known</td>
</tr>
<tr>
<td></td>
<td>Digoxin (increased digoxin levels) Oral anticoagulants (increased anticoagulant effects, especially in elderly) Ergotamine/dihydroergotamine (peripheral vasospasm and dysesthesia from ergot toxicity) Triazolam/midazolam (decreased clearance of these benzodiazepines) Drugs metabolized by CYP 450 system such as carbamazepine, cyclosporine, tacrolimus, hexobarbital, phenytoin, alfentanil, disopyramide, lovastatin, bromocriptine, sodium valproate (elevation in serum levels of these drugs) Clindamycin (antagonism shown in vitro)</td>
<td>None known</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic Acid</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td>Benzoyl Peroxide</td>
<td>None known</td>
<td>None known</td>
</tr>
<tr>
<td>Salicylic Acid</td>
<td>Alendronate (gastrointestinal adverse effects with aspirin-containing products)</td>
<td>None known. Interaction between topical methyl salicylate and oral anticoagulants known to increase risk of bleeding</td>
</tr>
<tr>
<td></td>
<td>Oral anticoagulants, heparin and heparinoids (increased risk of bleeding)</td>
<td></td>
</tr>
<tr>
<td>Sodium Sulfacetamide</td>
<td>Varicella vaccine (increased risk of Reye’s syndrome if given within 6 weeks of vaccination)</td>
<td>None known</td>
</tr>
<tr>
<td>Sulfur</td>
<td>None known</td>
<td>None known</td>
</tr>
</tbody>
</table>

a Topical form not available in the US.

CYP = cytochrome P.

4-oxo cis retinoic acid and 4-oxo trans retinoic acid glucuronide.[22]

### 3.1.3 Drug-Related Adverse Events

Local adverse effects commonly occurring with topical application are peeling, erythema, dryness, burning and itching.[53,64] These can be minimized by decreasing exposure to sunlight, avoiding weather extremes such as cold and high wind, and using non-comedogenic moisturizers.

Systemic toxicity has not been linked with topical tretinoin, but pharmacological doses of oral tretinoin cause the typical effects of hypervitaminosis A, primarily dryness and inflammation of the...
skin and mucous membranes. Oral therapy can also lead to serious adverse reactions, including rapidly evolving leukocytosis in up to 40% of patients, hepatotoxicity, and respiratory compromise. Approximately 25% of patients with acute promyelocytic leukemia have experienced a retinoic acid-acute promyelocytic leukemia syndrome, which can occur after the first oral tretinoin dose, and is characterized by fever, dyspnea, weight gain, radiographic pulmonary infiltrates, pleural and pericardial effusions, hypotension and impaired myocardial contractility.

Oral tretinoin is an FDA Pregnancy Category D drug, signifying a high risk of fetal abnormalities if taken during pregnancy, but the topical form is Category C, meaning that the benefits must outweigh the risks. Risk assessment is a matter of medical judgment, since the teratogenic blood level of tretinoin has not been determined.

In a reported case, a female patient with acne who was using topical tretinoin gave birth to an infant born at 40 weeks gestation, weighing 2800 grams, with coarctation of the aorta, hypoplastic left hand, hypertelorism and small ear canals. She had used 0.05% topical tretinoin in an alcohol base and a 2.5% benzoyl peroxide topical preparation before conception and during the first 2 months of gestation. The patient’s family history revealed no congenital defects. There is a second case report of a congenital ear malformation in the infant of a patient with acne who applied topical tretinoin 1 month before pregnancy and during the first 11 weeks. While tretinoin was not proven to be directly related to the defects in either of these cases, they are troubling because ear malformation is typical of retinoid embryopathy.

Some experts believe that topical tretinoin is not a risk factor for congenital disorders. Nevertheless, its use during pregnancy is difficult to justify, because acne affects mainly appearance and emotional well being, which are not easily quantified.

Avoidance of the topical form is advised during lactation. Systemic exposure and adverse reactions in nursing infants cannot be ruled out, because excretion via breast milk has not been studied.

Common drugs having local adverse interactions with topical tretinoin include salicylic acid and benzoyl peroxide, which may potentiate retinoid-induced skin peeling and erythema.

In theory, systemically absorbed tretinoin might interact with drugs that alter hepatic cytochrome P (CYP) 450 enzymes, required for tretinoin metabolism. Such drugs as cimetidine, cyclosporine, diltiazem and erythromycin may potentially increase plasma tretinoin through CYP 450 inhibition. On the other hand, pentobarbital, phenobarbital and rifampin have inducing effects on the same hepatic enzymes, thereby decreasing tretinoin levels.
3.2.3 Drug-Related Adverse Events

Local adverse events are similar to those of topical tretinoin, discussed previously. The finding that percutaneous absorption is undetectable suggests that the risk of internal effects is negligible. Topical isotretinoin has not been implicated as the cause of systemic toxicity. In one case of inflammatory bowel disease following topical application of isotretinoin, a probable relationship was not established.\(^{80}\)

Orally, isotretinoin is a potent teratogen. There have been numerous detailed reports of congenital abnormalities associated with its use.\(^{69,81-83}\) In one investigation of 154 human pregnancies with fetal exposure to oral isotretinoin, 12 patients had spontaneous abortions and 21 infants had major malformations.\(^{69}\) Among the 21 malformed infants, a characteristic pattern of malformations that involved craniofacial, cardiac, thymic and CNS structures was observed.

The FDA has designated oral isotretinoin a Pregnancy Category X drug. No dose of isotretinoin administered by mouth is considered safe. Congenital defects have occurred with its use for less than 4 days during the first trimester.\(^{84}\) For this reason, even topical application of isotretinoin should be avoided in pregnancy and used with extreme caution in women of childbearing potential. In such patients, requirements for oral isotretinoin include mandatory use of 2 forms of contraception simultaneously unless abstinence is the chosen method of birth control, 2 negative pregnancy tests prior to treatment, monthly urine pregnancy tests during therapy, oral and written warnings of birth defects, and informed consent.\(^{85}\)

Other adverse consequences of oral isotretinoin use are hyperlipidemias, most notably hypertriglyceridemia in about one-sixth of patients, and an increased ratio of low-density-lipoprotein cholesterol to high-density-lipoprotein cholesterol, known to be unfavorable toward cardiovascular disease risk.\(^{86}\) Rarer adverse effects include pseudotumor cerebri,\(^{87}\) hyperostosis,\(^{88,89}\) hepatotoxicity,\(^{90}\) premature epiphyseal closure\(^{91}\) and inflammatory bowel disease.\(^{92}\)

Depression, suicidal ideation and suicide have been reported in patients treated with oral but not topical isotretinoin\(^{93}\) and, furthermore, a causal relationship is not clear. The FDA guidelines for oral isotretinoin require that patients be warned about possible suicide risk and assessed for symptoms of mood disorders.\(^{94}\)

Because the excretion of isotretinoin in breast milk is unknown, oral isotretinoin is contraindicated during lactation.\(^{95}\) No data exist regarding topical isotretinoin use in nursing women and, therefore, avoidance is prudent.

Regarding drug interactions, topical isotretinoin can have additive local effects with other topical acne products, increasing the risk of skin irritation.

Taken concurrently with carbamazepine, oral isotretinoin has been shown to reduce levels of this commonly prescribed seizure medication.\(^{96}\) Carbamazepine levels should be monitored during treatment with oral isotretinoin. Taking isotretinoin in combination with minocycline or tetracycline is avoided due to increased risk of pseudotumor cerebri.\(^{95}\) Topical isotretinoin has not been linked with such drug interactions.

3.3 Adapalene

3.3.1 Background

One of the most commonly used topical retinoid agents, adapalene (Differin\(^{\circ}\), Galderma Laboratories), is a naphthoic acid derivative with a methoxyphenyl adamantyl side chain.

Adapalene is typically applied nightly to acne-prone skin as a 0.1% gel, solution or cream. A thin film is recommended, taking care to avoid the eyes, lips and mucous membranes. The safety and efficacy of the drug in children under the age of 12 years have not been established.

In a randomized, investigator-masked parallel European study of 268 patients with facial acne vulgaris receiving either adapalene 0.1% gel or tretinoin 0.025% gel for 12 weeks, adapalene appeared to be as effective as tretinoin.\(^{97}\) A large, multicenter clinical trial in the US showed a greater average reduction of inflammatory, non-inflammatory and total acne lesions in the adapalene-treated group compared with the tretinoin-treated group.\(^{97}\) In both studies, patients who used adapalene experienced less erythema, burning, scaling and dryness than those using tretinoin.

3.3.2 Pharmacokinetics

Because adapalene is not used as an oral drug, some aspects of its pharmacokinetics are not as well known as those of other retinoids. The adapalene microcrystal size was engineered within a range of 3–10µm, to deliver the drug preferentially into the follicular duct, with minimal penetration into the epidermis.\(^{98}\) Analyses of cryosections, radioactive tracing and fluorescence studies in human skin samples have shown that adapalene gel is found in the upper layers of the epidermis and rapidly enters the pilosebaceous units.\(^{99,101}\)

Minimal amounts (0.01% of an applied dose) of adapalene are systemically absorbed,\(^{99}\) providing evidence of limited penetration into the deep epidermis and dermis. This phenomenon may explain its relative lack of irritancy. In a pharmacokinetic study, in which 6 patients with acne were treated with 2 grams of 0.1%
Adapalene cream applied once daily for 5 days, there were no quantifiable amounts of adapalene in the plasma of any of the patients, when assayed with a limit of quantification of 0.35 μg/L.[22] Based on animal data, excretion of adapalene appears to be primarily via the biliary route.[22]

### 3.3 Drug-Related Adverse Events

Adverse effects associated with topical adapalene include erythema, scaling, dryness, pruritus and burning.[22] These effects are most common and pronounced in the first month of therapy and decrease thereafter. Exposure to sunlight and other irritating topical agents are best avoided. No serious adverse reactions have been reported.

Adapalene is an FDA Pregnancy Category C drug. Although no teratogenic effects were seen in animal studies with the drug, adequate and well-controlled studies in pregnant women are lacking. Given that adapalene binds to retinoic acid receptors and thus, may share the characteristic of teratogenicity with other compounds in the retinoid family, its use is generally avoided during pregnancy. There is a reported case of a woman treated with adapalene gel (0.3 mg/day) from the month before pregnancy until 13 weeks gestation. Therapeutically aborted at 22 weeks, the fetus was small for its gestational age and had anophthalmia and optic chiasma. It is not know whether a significant amount of the drug is excreted through breast milk. Use during lactation is therefore not recommended.

No systemic drug interactions are known to occur with adapalene use.

### 3.4 Tazarotene

#### 3.4.1 Background

Introduced in 1997, tazarotene is the newest topical agent in the retinoid class for acne. It is a synthetic acetylenic molecule that is rapidly converted to its active metabolite, tazarotenic acid, in keratinocytes. Unlike the parent compound, tazarotenic acid has the ability to bind and activate nuclear retinoic acid receptors.[103] Tazarotene gel and cream formulations (Tazorac®, Allergan Inc.) are available with 0.05% and 0.1% active ingredient. Only the more potent 0.1% products are approved by the US FDA for acne. These are typically used nightly at bedtime to treat mild or moderate facial acne. Acne therapy using tazarotene has been studied for periods as long as 15 weeks.[104] Tazarotene gel and cream formulations are also used for the treatment of plaque psoriasis,[39] and photaging,[137] but tazarotene is not approved for pediatric use.

Tazarotene gel and cream are effective in treating acne vulgaris when applied topically once daily. In a multicenter, double-blind, randomized study of 375 patients with acne, 0.1% tazarotene gel was found to be effective for acne and reasonably well tolerated by most patients.[105] In another study comparing 0.1% tazarotene gel with 0.025% tretinoin gel, tazarotene was found to be more effective in reducing noninflammatory lesions and similarly effective in reducing inflammatory lesions.[52] It is currently used mostly as an alternative to tretinoin and adapalene in refractory cases.

#### 3.4.2 Pharmacokinetics

Tazarotene is converted by esterases to its active metabolite, tazarotenic acid, following topical application to the skin. Systemic absorption of the active metabolite and the parent drug is low following cutaneous application of 0.05% and 0.1% tazarotene gel formulations, at most reaching 6% of the administered dose applied under occlusion.[103,106,107] Plasma levels of tazarotene and tazarotenic acid are mostly below 0.15 μg/L and 6 μg/L, respectively.[108] There is no noticeable systemic accumulation of the drug following multiple topical applications.[109] Tazarotenic acid is further metabolized by the liver to a sulfone metabolite and a sulfoxide metabolite after it is systemically absorbed.[103] Tazarotenic acid and tazarotene are primarily excreted from the body in bile.[103] The plasma elimination half-life of the drug is 15–17 hours.[110]

#### 3.4.3 Drug-Related Adverse Events

Common adverse reactions following topical tazarotene application are similar to those of other retinoids. They include itching, burning, irritation and erythema.[22] Tazarotene is the most irritating of the topical retinoids, with local skin irritation reported in about half of patients applying it for only 2–10 minutes daily.[26] Due to increased risk of sunburn, protection from UV rays is recommended. Systemic toxicity from topical use has not been reported. An oral form is currently under investigation for psoriasis, but dosages and adverse event data are not yet available.

Topical tazarotene is designated as an FDA Pregnancy Category X drug, meaning its use is prohibited during pregnancy and in sexually active patients without reliable contraception. There are reports of inadvertent pregnancies in tazarotene-treated patients without ill effects,[111] including several female participants in psoriasis clinical trials whose infants did not have any known congenital defects. Other tazarotene clinical studies have included 6 pregnant women with uneventful outcomes,[111] but the timing and extent of exposure to tazarotene was unknown.

Because animal studies have shown high systemic levels of tazarotene to be teratogenic,[22] additional studies on the maternal/fetal plasma levels of tazarotenic acid in humans must be done before use of topical tazarotene in pregnancy can be deemed safe. Whether or not tazarotene is excreted in human breast milk is unknown. Tests in lactating rats suggest that some drug is excreted...
to the nursing offspring.\cite{22} The drug is not recommended for nursing mothers.

Topical tazarotene usage is not known to cause drug interactions.

4. Topical Benzoyl Peroxide

4.1 Background

Benzoyl peroxide is an agent with antibacterial\cite{112} and comedolytic\cite{113} action. The usefulness of benzoyl peroxide for acne is attributed primarily to its potent bactericidal effect against \emph{P. acnes}.\cite{114} The mechanism of action is thought to be degradation of bacterial proteins via release of free-radical oxygen.

Benzoyl peroxide acne products (many tradenames and generics, various manufacturers) are available in concentrations ranging from 2.5–10\%, as lotions, creams, gels, masks, and cleansers, which can be used once or twice a day. The frequency of application and concentration of active ingredient may be adjusted to control local adverse effects. Twenty percent benzoyl peroxide is a potent formulation reserved for the treatment of cutaneous ulcers. Benzoyl peroxide is not specifically FDA approved for pediatric patients, but its non-prescription status makes such use inevitable.

Benzoyl peroxide acne is attributed primarily to its potent bactericidal effect against \emph{P. acnes}.\cite{114} The mechanism of action is thought to be degradation of bacterial proteins via release of free-radical oxygen.

Benzoyl peroxide is one of the most frequently used topical preparations for acne. When compared with other topical antimicrobials, 5\% benzoyl peroxide was found to be at least as effective for acne as clindamycin\cite{115, 116} and erythromycin formulations.\cite{117}

Fixed-combination products containing benzoyl peroxide and either clindamycin (BenzaClin\textsuperscript{®}, Dermik Laboratories; Duac\textsuperscript{®}, Stiefel Laboratories) or erythromycin (Benzamycin\textsuperscript{®}, Dermik Laboratories) are more effective for acne than their individual components alone.\cite{118, 119} Further, such combinations are not associated with development of antibacterial-resistant bacteria,\cite{120} often seen with prolonged use of single-agent topical antibiotics.\cite{121}

4.2 Pharmacokinetics

Benzoyl peroxide is well absorbed into the epidermis and concentrated in pilosebaceous units. After conversion to benzoic acid in the skin, about 2\% of the applied dose enters the systemic circulation.\cite{21} It is metabolized to benzoic acid and excreted as benzoate in the urine.\cite{22}

4.3 Drug-Related Adverse Events

Common adverse effects of benzoyl peroxide include skin dryness, erythema and peeling. Contact sensitization may occur in up to 2.5\% of patients.\cite{22, 122} During use, the patient should be advised to avoid other potential sources of skin irritation such as UV radiation and topical acne medications except those recommended by the physician. Serious adverse reactions have not been reported with topical benzoyl peroxide use.

There are no known adverse effects in humans as a result of systemic exposure to benzoyl peroxide or its metabolites, but animal studies have shown carcinogenicity.\cite{22, 123}

Benzoyl peroxide is a Pregnancy Category C drug. It is not known whether the drug causes fetal harm when given to pregnant women, and it should only be used during pregnancy if clearly needed.\cite{22} Data regarding benzoyl peroxide excretion in breast milk are lacking, and its safety in nursing infants is therefore unknown.

A noteworthy drug interaction caused by benzoyl peroxide is inactivation of tretinoin when both are used simultaneously.\cite{98} In contrast, the newer retinoids adapalene and tazarotene are stable in the presence of benzoyl peroxide. Interactions between benzoyl peroxide and systemic drugs have not been reported.

5. Topical Antibacterials

5.1 Clindamycin

5.1.1 Background

Clindamycin is a lincosamide antimicrobial agent that is a semi-synthetic derivative of lincomycin.\cite{124} The antibacterial inhibits bacterial protein synthesis by attaching to the 50S subunit of the bacterial ribosome.

Topical clindamycin, used for the treatment of acne vulgaris, is available as a 1\% gel, lotion or solution (various tradenames and generics, numerous manufacturers) and in fixed-combination products. These are typically applied to affected areas once or twice daily. Oral doses of clindamycin for other conditions range from 150–450mg every 6 hours.\cite{22} Of note, oral clindamycin is FDA approved to treat infections in children under age 12 years, but appropriate monitoring is required.

Clindamycin is found in a fixed-combination acne product containing benzoyl peroxide, as described previously in section 4.1. Application of this formulation is recommended twice daily after the skin is gently washed and dried. Another fixed-combination product containing 0.025\% tretinoin and 1\% clindamycin phosphate (Velac\textsuperscript{®}, Yamanouchi Europe B.V.) is marketed in Europe and Canada\cite{125} and is currently undergoing clinical investigation in the US.

Although the phosphate compound of clindamycin is most commonly used in the treatment of acne, both the phosphate and hydrochloride salts have been shown to be effective. In an 8-week,
multicenter, placebo-controlled trial, topical clindamycin in both its phosphate and hydrochloride salts was found to produce statistically significant improvements in acne as compared with the vehicle alone.\textsuperscript{126} Clindamycin gel\textsuperscript{127} and lotion\textsuperscript{128} are less irritating than the solution formula and are equally efficacious. The fixed-combination product containing 1% clindamycin and 5% benzoyl peroxide was significantly more effective than either of the two agents applied separately, when used to treat moderate acne.\textsuperscript{129} Fixed combination clindamycin phosphate and tretinoin gel has been shown to reduce acne to a greater extent and produce a more rapid response than either agent used alone.\textsuperscript{125}

5.1.2 Pharmacokinetics

Topically administered 1% clindamycin has been found to have low bioavailability, with values differing considerably in different studies, including values from 4–5\%\textsuperscript{130} to less than 1\%.\textsuperscript{22}

In one study, 2ml of 1% clindamycin solution applied to the entire face twice daily for 4 weeks did not achieve detectable serum concentrations in an assay sensitive to 0.4 \(\mu\)g/ml, but the drug was observed in the urine of 10 of 13 patients.\textsuperscript{130} There was a wide range of urinary recovery of the drug between participants, suggesting that different patients may absorb clindamycin to varying extents. In clinical trials evaluating topical clindamycin, detectable urine levels were noted following the application of topical clindamycin hydrochloride, but not following topical clindamycin phosphate.\textsuperscript{131} In another study, there was no detectable serum level of clindamycin hydrochloride following the topical application of a 1% hydroalcoholic solution.\textsuperscript{122}

Systemically absorbed clindamycin has been determined to have a total protein binding of 60–95\%.\textsuperscript{133,134} After oral use, the drug is widely distributed throughout the body and is partially metabolized in the liver to clindamycin sulfoxide and N-dimethyl clindamycin, and excreted by the kidney,\textsuperscript{135} as well as through the biliary route and feces.\textsuperscript{136}

5.1.3 Drug-Related Adverse Events

Application-site erythema and dry skin are the most common local events reported with topical clindamycin products.\textsuperscript{22} Serious adverse effects of orally administered clindamycin include leucopenia,\textsuperscript{137} thrombocytopenia,\textsuperscript{138} diarrhea,\textsuperscript{139} pseudomembranous colitis and hepatotoxicity.\textsuperscript{140} Topical use is contraindicated in patients with a history of regional enteritis, ulcerative colitis or antibacterial-associated colitis. During a multicenter, controlled study of 358 patients using topical clindamycin versus vehicle for acne, 12 episodes of diarrhea occurred in patients given active therapy, with at least one episode thought to be treatment-related.\textsuperscript{126}

Besides its association with simple diarrhea, systemic exposure to clindamycin may cause pseudomembranous colitis, a serious illness that results from the eradication of normal intestinal flora, allowing overgrowth of \textit{Clostridium difficile}. This microbe produces two toxins that damage the intestinal wall, which in severe cases may be life-threatening.\textsuperscript{141} Pseudomembranous colitis is readily induced in hamsters with topical clindamycin application\textsuperscript{142} and has been documented in two patients with acne exposed to clindamycin topically.\textsuperscript{143,144} In one case, pseudomembranous colitis developed in a patient applying topical 1% clindamycin phosphate to facial acne intermittently over a 6-month period.\textsuperscript{143} The patient’s stool assay was positive for \textit{C. difficile}. After successful colitis treatment, the patient resumed topical clindamycin, leading to recurrent stool-positive \textit{C. difficile} infection. Following a second course of treatment and complete cessation of clindamycin use, the patient remained symptom free over an 18-month follow-up period.

Topical clindamycin is an FDA Pregnancy Category B drug. Chances of harm to the fetus are remote, especially with the low level of systemic exposure when the drug is applied topically.

Systemically absorbed clindamycin from topical application may be excreted in breast milk, although studies are lacking. Orally administered clindamycin has been reported in human breast milk in the range of 0.7–3.8 \(\mu\)g/ml.\textsuperscript{22} There are no clinical reports of adverse effects in infants whose mothers were breastfeeding while using topical clindamycin.\textsuperscript{145} It should be noted that loose stools and diarrhea are common during infancy, allowing a possible association with maternal clindamycin use to be overlooked.

Reported drug interactions with oral clindamycin include those with non-depolarizing neuromuscular blockers, whose effects may be potentiated, prolonging neuromuscular blockade.\textsuperscript{146} This effect is more common at higher doses of clindamycin and would be unlikely from percutaneous absorption. A laboratory observation with possible clinical ramifications is that clindamycin and erythromycin have been shown to be antagonistic \textit{in vitro}.\textsuperscript{22,147} The antibacterials are believed to compete for the same protein-binding sites. It is therefore advisable to avoid concurrent use of the two agents, either topically or by mouth.

5.2 Erythromycin

5.2.1 Background

Erythromycin is a macrolide antibacterial that attaches to the 50S subunit of bacterial ribosomes. It prevents the effective progression of the translocation reaction necessary for bacterial protein synthesis.\textsuperscript{22}

Erythromycin is available in topical formulations for acne treatment as a 2% gel, solution, or ointment (various tradenames and generics, numerous manufacturers). A fixed combination gel
containing erythromycin and benzoyl peroxide (see section 4.1) is available in the US. An erythromycin-isotretinoin combination gel (Isotrexin®, Steifel Germany) is marketed elsewhere but is not currently US FDA approved. Patients apply the medication to skin twice daily following thorough washing and drying of skin.

Oral doses of erythromycin for adults range from 250mg every 6 hours to a maximum dose of 4 grams daily, reserved for serious infections.[22] Systemic therapy is used for a variety of infectious diseases, including otitis media, Campylobacter enteritis, neonatal conjunctivitis, Legionnaires disease, preoperative bowel preparation, and infections caused by gram-positive organisms, mycoplasma, and chlamydia.

Efficacy of topical erythromycin for acne has been demonstrated in numerous randomized studies. Both gel[148] and solution[149] forms of 2% erythromycin were superior to placebo in controlled trials of populations exceeding 150 patients. A study using 1% erythromycin showed the drug to significantly reduce *P. acnes* in the ducts of sebaceous glands in placebo-controlled tests.[150] In a more recent study of the anti-propionibacterium activity of the drug, the addition of 5% benzoyl peroxide to 3% erythromycin gel had greater effect than erythromycin alone in patients with acne with resistant strains of cutaneous propionibacterium.[120] In another study, the combination of 3% erythromycin and 5% benzoyl peroxide was found to be comparable in efficacy to the combination of 1% clindamycin and 5% benzoyl peroxide, with both of these formulations proving more efficacious than 5% benzoyl peroxide alone for acne.[151] And finally, a recent, randomized, multicenter, double-blind study of 157 patients showed a topical solution containing 2.3% erythromycin and 1% bifonazole applied once daily was more effective for acne treatment than 2.3% erythromycin solution applied twice daily.[152]

Topical acne preparations containing erythromycin are not specifically approved for pediatric patients, but oral erythromycin suspensions are FDA approved in all age groups, including infancy.

**5.2.2 Pharmacokinetics**

Percutaneous absorption of erythromycin is very low after topical application. In 2-month studies of topical 2% erythromycin use, no serum levels were detected.[152,153]

After oral administration, the drug is widely distributed in body tissues. Metabolism occurs in the liver by demethylation. Erythromycin is concentrated and excreted in its unchanged form in urine, bile and feces.

**5.2.3 Drug-Related Adverse Events**

Topical erythromycin use is associated with occasional burning, peeling, dryness, pruritus and erythema. Oily skin has also been reported from erythromycin in certain vehicles.[22] Systemic reactions have not been reported with topical administration, most likely due to its low systemic absorption.

With oral erythromycin use, abdominal cramping, nausea, and vomiting are commonly reported.[22] Less common adverse effects include cholestatic jaundice,[154] hepatitis,[155] ototoxicity,[156] and hypersensitivity.[157] Pseudomembranous colitis may occur rarely.

Both oral and topical erythromycin formulations are designated as FDA Pregnancy Category B. Animal reproductive studies with erythromycin have demonstrated no evidence of teratogenicity, but there are no well-controlled studies in pregnant women. As animal teratogenicity studies are not always predictive of effects in humans, the drug should be considered during pregnancy only if the potential benefits outweigh the risks.

Oral erythromycin, even in moderate doses, is excreted in the breast milk of lactating women,[22] and there are reports of a possible link between erythromycin administration during pregnancy and nursing with hypertrophic pyloric stenosis in infants.[158] It is not known whether topical erythromycin is excreted in breast milk. Because its safety in nursing women has not been established, caution is advised.

As mentioned in section 5.1.3, erythromycin has been shown to antagonize clindamycin in vitro, a finding to consider when selecting a topical acne regimen.[22,147] In the past, oral erythromycin was known to potentiate life-threatening ventricular arrhythmias and QT prolongation when combined with several drugs that are no longer marketed. These include the non-sedating antihistamines astemizole and terfenadine and the gastrointestinal agent cisapride.[22] No such interactions have been reported in patients with acne using topical erythromycin. The low absorption of erythromycin makes systemic effects unlikely.

**6. Other Topical Agents**

### 6.1 Salicylic Acid

**6.1.1 Background**

Salicylic acid is a topical keratolytic agent that works by dissolving the intercellular cement that holds epithelial cells together.[159] It is a component of a variety of over-the-counter acne remedies.

Concentrations of salicylic acid ranging from 0.5–10% (various tradenames and generics, numerous manufacturers) have been recommended for acne,[160,161] but 2% is the maximum strength allowed in non-prescription acne products in the US. This active ingredient is commonly found in acne cleansers. It is also used in concentrations of 3–6% as a keratolytic agent to treat hyperkeratotic skin disorders such as psoriasis, ichthyoses, palmoplantar keratosis, keratosis pilaris and pityriasis rubra pilaris,[162] and in
concentrations of 5–40% for wart and corn removal. Salicylic acid is approved for use in pediatric acne.

Salicylic acid is not given orally because it causes severe stomach irritation. Salicylate analgesia is given by mouth in the form of acetylsalicylic acid (aspirin). The standard dose of aspirin for pain relief is 650mg, which can be given every 4 hours. One 650mg dose of aspirin is equivalent to 500mg of salicylic acid.

### 6.1.2 Pharmacokinetics

Percutaneous absorption of salicylic acid is quite efficient compared with that of most topical agents. The bioavailability of topical salicylic acid application varies widely according to the duration of contact and the vehicle. Prolonged application of Kerasal® Ointment (polyethylene glycol, glycerol, petrolatum and 10% urea) led to absorption of approximately 9% of the active ingredient, whereas application of 5% and 10% salicylic acid ointment (mineral oil and petrolatum) led to absorption of 25% and 20%, respectively. The time to peak concentration following topical application with occlusion is 5 hours. In a study of topical methyl salicylate analgesic (2–6 mg/L), salicylic acid serum concentrations ranged from 0.3–0.9 mg/L one hour after application.

Salicylate toxicity is associated with serum levels of 200–400 µg/ml. Systemic toxicity is therefore unlikely with topical use of the drug, although toxicity is possible if the drug is applied to a large surface area of the body for prolonged periods of time. Systemically absorbed salicylic acid is 50–80% albumin-bound in serum, and it is excreted mostly by the kidney.

### 6.1.3 Drug-Related Adverse Events

At concentrations of 2% or greater, salicylic acid is likely to cause some degree of local skin peeling and discomfort. Adverse reactions resulting from systemic exposure to the drug are possible if it is used for prolonged periods over large areas of the body. Possible adverse effects include salicylate toxicity, toxic inner ear damage, and hypersensitivity.

Signs and symptoms that should alert the physician to the possibility of salicylate toxicity include increased respiratory rate, dizziness, loss of hearing, lethargy, and symptoms of gastrointestinal disturbance, including nausea, vomiting and diarrhea. There are numerous reports of acute salicylate intoxication as a result of topical salicylic acid use. In one case, systemic salicylate toxicity was seen in a man who had used a methyl salicylate ointment analgesic on this thigh twice daily for several weeks. He presented with a 3-day history of blurred vision, tinnitus, shortness of breath and was found to have a salicylate concentration of 518 mg/L, with a mixed metabolic acidosis/respiratory alkalosis. He had not taken any oral medications containing salicylate. There is also a report of a patient who developed toxic inner ear damage after receiving salicylic acid treatment for psoriasis.

Salicylic acid can cause hypoglycemia by increasing glucose metabolism while impairing gluconeogenesis. Refractory hypoglycemia has been reported in a man with end-stage renal failure applying 10% salicylic acid cream to 80% of his body surface area. His serum salicylate level was 3.2 mmol/L. Following hemodialysis and glucose infusions, the patient recovered and remained euglycemic.

Salicylic acid is an FDA Pregnancy Category C drug. There are no human studies of topical salicylic acid use during pregnancy, but systemic salicylic acid and aspirin are known to induce malformations in rat embryos.

The excretion of salicylic acid in breast milk and its safety if consumed by nursing infants are unknown. Of interest, it is recommended that aspirin use be avoided by nursing mothers, because salicylate is excreted in breast milk and may lead to rashes, platelet abnormalities and bleeding in nursing infants.

With significant systemic exposure to salicylic acid, as can occur following oral ingestion of aspirin, there is a risk of adverse drug reactions with oral anticoagulants and low-molecular-weight heparins, both of which increase risk of bleeding. In patients with diabetes mellitus treated with hypoglycemic drugs, aspirin use may increase the effectiveness of the latter, leading to hypoglycemia. Cases of Reye’s syndrome have occurred following the use of oral salicylates during varicella infection (chickenpox). Salicylates should be avoided for at least 6 weeks after recovery from chickenpox or receiving the varicella vaccine. Although systemic toxicity has not been associated with topical acne products containing salicylic acid, the rapid and efficient percutaneous absorption of the drug dictates a cautious approach.

### 6.2 Sulfur

#### 6.2.1 Background

The chemical element sulfur is considered a mild keratolytic and bacteriostatic agent. In keratinocytes, sulfur is reduced to hydrogen sulfide by an unknown mechanism. The hydrogen sulfide formed from sulfur is thought to break down keratin. Sulfur is also believed to have activity against P. acnes.

Topical sulfur is available in lotions, creams, soaps and ointments. Preparations containing 1–10% sulfur have been used as acne treatment for many decades. This element is more efficacious when used in combination with other drugs, including benzoyl peroxide and sodium sulfacetamide. Sulfur is also found in over-the-counter and prescription acne products combined with...
resorcinol or salicylic acid. Such topical preparations may be applied to acne-prone sites up to 3 times daily for several days, decreasing frequency as symptoms improve.

6.2.2 Pharmacokinetics

The bioavailability of topically applied sulfur is believed to be about 1%.\[175\] In the skin, it is converted to hydrogen sulfide through a reaction between the sulfur element and keratinocytes.\[175\]

6.2.3 Drug-Related Adverse Events

Adverse effects from topical administration of sulfur are rare and are mainly limited to dryness and malodor of the skin.\[175\] Sulfhemoglobinemia\[179\] and metabolic acidosis\[180\] are among the more serious adverse reactions that can occur with oral ingestion of sulfur, but these have not been reported with topical use.

Sulfur is an FDA Pregnancy Category C drug, meaning its use in pregnant women should be reserved for cases where the benefits of use clearly outweigh the potential harm to the fetus. The excretion of sulfur in breast milk is unknown.

There are no known drug interactions with sulfur. Of note, patients with sulfonamide sensitivity may generally use elemental sulfur without untoward effect.

6.3 Sodium Sulfacetamide

6.3.1 Background

Sodium sulfacetamide is a bacteriostatic antibacterial in the sulfonamide group. It displays activity against several gram-negative and gram-positive organisms.\[124\] Sulfonamides act through competitive antagonism of para-aminobenzoic acid (PABA), halting bacterial DNA synthesis.\[124\]

Sodium sulfacetamide 10%, usually combined with 5% sulfur, is found in topical acne suspensions, lotions and creams (various tradenames and generics, numerous manufacturers). This combination has been found to be synergistic in acne treatment.\[181\]

Sodium sulfacetamide is also available as an ophthalmic formulation for acute bacterial conjunctivitis and chronic blepharitis, and it is found in intravaginal preparations for chlamydial and bacterial vaginitis.

6.3.2 Pharmacokinetics

While the absorption of sodium sulfacetamide through intact skin has not been determined, in vitro studies using human cadaver skin found percutaneous absorption to be about 4%.\[22\] Systemically administered sulfonamides are rapidly excreted in the urine.\[22\]

6.3.3 Drug-Related Adverse Events

Adverse reactions associated with the topical use of sodium sulfacetamide are infrequent and generally restricted to local events such as itching, erythema and discomfort.\[22\] Local contact sensitization has occurred. Very rare reactions reported include erythema multiforme\[182\] from topical use and its more severe form, Stevens-Johnson syndrome,\[183,184\] from ophthalmic use. It is important to remember that hypersensitivity reactions may occur whenever a sulfonamide is re-administered, regardless of the route of administration. Topical sodium sulfacetamide is contraindicated in any patient with a history of sensitivity to 'sulfa' drugs.

In rare cases, oral sulfonamides and sulfonyleureas are associated with life-threatening events, including agranulocytosis, Stevens-Johnson syndrome, toxic epidermal necrolysis, fulminant hepatic necrosis and aplastic anemia.\[22\] These have not been reported due to acne products that contain sodium sulfacetamide.

Although no problems associated with topical use of sodium sulfacetamide during pregnancy have been reported, the drug is an FDA Pregnancy Category C drug. Neonatal jaundice can occur in newborn infants of women given oral sulfonamides during pregnancy.\[22\]

It is not known whether topical application of sodium sulfacetamide is excreted in breast milk.\[22\] Systemically absorbed sulfonamide antibacterials are typically excreted through lactation, and are capable of producing kernicterus in the nursing infant.\[22\]

There are no reported drug interactions due to topical sodium sulfacetamide, but oral sulfonamides participate in several drug interactions. It has been reported that administration of sulfonamides may increase the prothrombin time in patients receiving warfarin.\[22\] There is also a potential interaction with cyclosporine, resulting in decreased cyclosporine concentrations.\[185\] Some sulfonamides have also been shown to decrease hepatic clearance of phenytoin.\[186\]

6.4 Azelaic Acid

6.4.1 Background

Azelaic acid is a naturally occurring, saturated, straight-chained dicarboxylic acid found as a dietary constituent in whole grain cereals and animal products.\[22\] For acne treatment, its mechanisms of action are believed to be related to its mild antibacterial and anti-keratinizing effects.\[22,187\]

Azelaic acid is available as a 20% topical cream (Azelex®, Allergan Inc.), which is applied twice daily according to package labeling. Improvement of symptoms are typically seen within 4 weeks of starting azelaic acid therapy.\[187,190\] Safety and efficacy have not been established in pediatric patients. It has also been shown to be effective for melasma, reducing pigment intensity and
Table III. Estimated absorbed doses of topical acne drugs versus orally administered comparable agents

<table>
<thead>
<tr>
<th>Topical acne therapy</th>
<th>Topical application, typical dose (mg)</th>
<th>Estimated % of topical dose absorbed</th>
<th>Estimated dose of topical drug absorbed (mg)</th>
<th>Single oral dose of same or comparable drug (mg)</th>
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<td>face + upper trunk&lt;sup&gt;b&lt;/sup&gt;</td>
<td>face only&lt;sup&gt;a&lt;/sup&gt;</td>
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</tr>
<tr>
<td>Erythromycin</td>
<td>2–3</td>
<td>12–18</td>
<td>72–108</td>
<td>Undetectable</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>20</td>
<td>120</td>
<td>720</td>
<td>4&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Salicylic acid</td>
<td>0.5–2</td>
<td>3–12</td>
<td>18–72</td>
<td>9–25</td>
</tr>
<tr>
<td>Sodium sulfacetamide</td>
<td>5–10</td>
<td>30–60</td>
<td>180–360</td>
<td>4&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Sulfur</td>
<td>2–10</td>
<td>12–60</td>
<td>72–360</td>
<td>1</td>
</tr>
</tbody>
</table>

<sup>a</sup> Based on 0.6g per application, the estimated amount to cover the face.<sup>[23]</sup>

<sup>b</sup> Based on 3.6g per application, the estimated amount to cover the face, chest, shoulders and back.<sup>[23]</sup>

<sup>c</sup> Oral tazarotene is under investigation. Dosage data are unavailable at this time.

<sup>d</sup> Based on commercial 20% azelaic acid cream. Percent absorbed may be 8% with gel vehicle.<sup>[187]</sup>

<sup>e</sup> Oral acetyl salicylic acid dose of 650mg.

<sup>f</sup> Based on studies in cadaver skin.<sup>[23]</sup>

<sup>g</sup> Oral sulfamethoxazole dose of 400–800mg.

NA = Not applicable; no comparable agent.
lesion size.\textsuperscript{187,191} Of interest, hypopigmentation has occasionally been reported as an adverse effect of the drug.\textsuperscript{22}

Azelaic acid is a useful adjunct to more conventional topical acne therapies, particularly when there has been dissatisfaction with standard regimens due to local irritation. The adverse effect profile of azelaic acid, from both local and systemic administration, compares favorably with other more widely used acne therapies. Twelve-week placebo-controlled studies of the efficacy of topical 20\% azelaic acid cream applied twice daily have shown it to be successful in improving mild-to-moderate acne.\textsuperscript{190,192}

6.4.2 Pharmacokinetics

After application of a single topical dose of azelaic acid cream, 3–5\% is retained in the stratum corneum, and up to 10\% penetrates into the epidermis and dermis.\textsuperscript{22} Approximately 4\% of the cutaneously applied dose is absorbed systemically.\textsuperscript{22} This percutaneous absorption is increased to 8\% when gel formulations are used.\textsuperscript{187} Some of the systemically absorbed drug is metabolized in the liver to glutaric acid and pimERIC acid;\textsuperscript{187,193} however, the drug is eliminated mainly unchanged through renal excretion. The elimination half-life is 45 minutes after oral administration and 12 hours after topical application, indicating a slower rate of systemic absorption and/or clearance with topical compared with oral administration.\textsuperscript{22}

Normal endogenous levels of azelaic acid are determined by dietary intake. Baseline serum and urine levels in humans have not been found to be altered with topical 20\% azelaic acid treatment.\textsuperscript{22}

6.4.3 Drug-Related Adverse Events

Common adverse effects of topical azelaic acid include pruritus, burning, stinging and tingling.\textsuperscript{22} Erythema, dryness, peeling, hypopigmentation and hypertrichosis have also been reported.\textsuperscript{22} Despite its relatively high concentration of active ingredient and moderate degree of percutaneous absorption, topical azelaic acid has not been linked with systemic effects.\textsuperscript{187} Hypokalemia was reported in one patient treated, experimentally, with high-dose oral azelaic acid for malignant melanoma.\textsuperscript{194}

Azelaic acid is an FDA Pregnancy Category B drug. Studies using high oral doses in animals do not result in teratogenic effects in the offspring, but controlled studies are lacking in humans.\textsuperscript{22}

Passage of azelaic acid into milk has been demonstrated using an in vitro equilibrium dialysis technique.\textsuperscript{22} Since only about 4\% of the applied dose is absorbed, normal endogenous levels are not expected to be altered in human breast milk. Caution is advised in nursing mothers.

Azelaic acid has not been associated with drug interactions. Similarly to other acne products, it might be expected to enhance the irritating potential of concomitant topical therapy.

7. Conclusions

Given the extraordinary prevalence of acne and the availability of products to treat it, a reasonable assumption is that at least a hundred million patients worldwide have used such drugs over the past half-century. Although local adverse effects are commonplace, systemic toxicity appears to be remarkably low, based on the handful of reported incidents.

Aside from the obvious explanation that absorbed doses are too small to cause internal effects (see table III), there are other likely reasons for the rarity of such cases.

First, patients are often unaware of systemic risks, particularly with non-prescription products. Second, physicians may be unacquainted with certain drug interactions and systemic events that are theoretically possible. Finally, data in children and pregnant women are lacking for most acne agents. Acne is rarely a threat to general health and, therefore, clinical studies in these vulnerable populations are seldom undertaken.

The favorable historical safety record of topical agents does not excuse drug makers and prescribers from their duties to minimize potential risks. Every drug regimen requires vigilance, regardless of the route of administration.

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492

Akhavan & Bershad


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