Review Article

A Review on a Third Generation Retinoidal Agent: Adapalene

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ABSTRACT

Adapalene, a third generation retinoid, is used to treat mild to severe acne. It is useful as monotherapy, or in combination with benzoyl peroxide. Adapalene is available in the market under the trade names Differin and Adaferin. It is also available in combination formulation with clindamycin to achieve better results. Adapalene may be an important target for pharmaceutical industries. The present work reviews the biological and pharmaceutical profile of Adapalene.

Keywords: Retinoid, Acne, Differin, Adapalene.

INTRODUCTION

Adapalene is used as a topical preparation applied to the skin and used to treat acne in people above 12 years[1-3]. It is an anti-inflammatory non steroidal agent (NSAID). Acne vulgaris, commonly known as acne is a skin disorder characterized by pimples, and greasy skin. It greatly affects skin with greater number of oil glands, like the face, back etc. Acne mostly occurs in adolescence.

The pathogenesis of Acne

Acne vulgaris is a chronic skin disorder of the pilosebaceous unit and occurs due to blockage in the skin's hair follicles[4-8].These blockages occur due to the following reasons-

1. A higher than normal amount of sebum production.
2. Excessive deposition of the protein keratin leading to comedone formation.
3. Colonization of the follicle by Propionibacterium acnes (*P. acnes*) bacteria
4. Release of pro-inflammatory chemicals in the skin.

The earliest pathologic change is the formation of a microcomedone, which is driven primarily by excessive proliferation of keratinocytes in the hair follicle.In normal skin, the skin cells that have died come up to the surface and exit the pore of the hair follicle. However, increased production of oily sebum in those with acne causes the dead skin cells to stick together. The accumulation of dead skin cell debris and oily sebum blocks the pore of the hair follicle, thus forming the microcomedone. If the microcomedone is superficial within the hair follicle, the skin pigment melanin is exposed to air, resulting in its oxidation and dark appearance (known as a blackhead or open comedone)–In contrast, if the microcomedone occurs deep within the hair follicle, this causes the formation of a whitehead (known as a closed comedone)[9-11].

Adapalene helps the skin cells rejuvenate quickly and reduces blackhead formation. It is a retinoid like compound, also used to treat keratosis pilaris. Retinoids are the forms of Vitamin A, used in medicines.

Table 1: Types of Retinoid

FIRST GENERATION	SECOND GENERATION	THIRD GENERATION
Retinol	Retinate	Adapalene
Tritinoin	Acitretin	Bexarotene
Isotretinoin	Etritretin	Tzarotene
Alitretinoin		
Retinol		

First and Second generation retinoids interact with several retinoid receptors due to flexibility of their alternate single and double bonds. However, Third generation are less flexible and thus interact with very less retinoid receptors.They can be synthesised by glucuronidation. Retinoids can decrease the chance of skin and head cancer[12-14].

Adapalene was approved in 1996 by United States FDA and manufactured by Galderma Laboratories, France. It is known as Adaferin in India. In U.S, it is available under the brand name Differin in three different preparations:- 0.1% cream, 0.1% gel and 0.3% gel. The 0.1% gel is available with benzoyl peroxide under the brand name Epiduo. The 0.1% cream and 0.1% gel are available in Europe.

TRADE NAMES: Differin (cream 0.1%, gel 0.1%, and solution 0.1%), Differin XP (Canada), Adaferin (India).

Table 2: Dugs approved by the FDA in Dermatology[15-17]

DRUGS	CLASS
Adapalene	Third generation topical retinoid
Clindamycin	Lincosamide
Doxycycline	Tetracycline antibiotics
Minocycline	Tetracycline antibiotics
Erythromycin	Macrolide antibiotics

Table 3: Product Availability

DRUG	AVAILABLE AS
Adapalene	Cream-0.1%, gel-0.1%, 0.3%, lotion-0.1%
Clindamycin	Capsules-150mg, 300mg, 75mg
Doxycycline	Capsules-50mg, 75mg, 100mg

HISTORY OF ADAPALENE[18]

The discovery of oral and topical retinoids was a major advance in the management of acne vulgaris. However, these agents were somewhat limited due to the side effects caused by these drugs. Over the last 15 years, researchers have found compounds that can provide therapeutic benefits obtained with tretinoin and isotretinoin while decreasing the potential for irritation and other untowards effects. Adapalene, a naphthoic-acid derivative, serves as an example of rational drug development

PHYSICO CHEMICAL PROPERTIES[19, 20]

Adapalene is chemically 6-[3-(1-adamantyl)-4-methoxyphenyl] naphthalene-2-carboxylic acid, having empirical formula $C_{28}H_{28}O_3$ and molecular weight 412.52012 g/mol. It has melting point between 319-322˚C and boiling point 606.3˚C at 760 mmHg. The density and refractive index is around 1.2 g/cm^3 and 1.66 respectively. pKa value of adapalene is 4.23. It is white to off- white crystalline powder, which is practically insoluble in water but soluble in tetrahydrofuran and sparingly soluble in ethanol. The solubility of Adapalene in different solvent system varies greatly. Solubility profile of different solvents are given in the below table.

Table 4: Solubility profile at 25˚C

S.No	Solvents	Solubility
1.	Water	<1mg/ml
2.	DMSO	>10mg/ml
3.	Ethanol	<1mg/ml
4.	DMF	Approx 5mg/ml

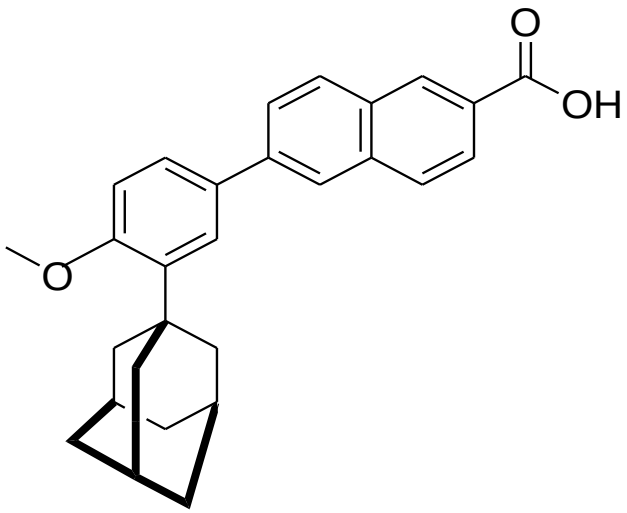
Adapalene is similar to tretinoin but is chemically and phytochemically stable under ordinary conditions. It has adamantine group attached to it. It is stable under light and oxidative conditions.

Table 5: TAXANOMY

Description	It belongs to the class of organic compounds known as retinoids.
Kingdom	Organic compounds
Super class	Lipids
Class	Prenol lipids
Sub class	Retinoids
Substituent	Phenylnaphtalene, benzoyl, anisole, benzenoid

Table 6: Predicted properties

Property	Values
Hydrogen acceptor count	3
Hydrogen donor count	1
Rotatable bond count	4
LogP	8.6
Bioavaibility	1



Chemical structure of Adapalene

MECHANISM OF ACTION[21-29]

Adapalene belongs to third generation retinoid class, which inhibits keratinocyte differentiation. Keratinocyte is found in the outermost layer of the skin, epidermis. It has exfoliating and anti-inflammatory effects. Retinoids bind and activate RAR (retinoic acid receptor) or RXR (retinoic X receptor). RXR is activated by 9-cis retinoic acid. It includes RXR- alpha, RXR-beta, and RXR gamma. RAR is activated by all- trans-retinoic acid and 9-cis retinoic acid. It includes RAR-alpha, RAR- Beta, and RAR- gamma.

RAR and RXR are homologous to glucocorticoids, vitamin D3, and thyroid hormone receptors. Adapalene binds to RAR- beta and gamma, or the RXR- subtypes. RAR forms a heterodimer with RXR. RXR may also form a homodimer. These dimmers then bind to retinoic acid response elements (RAREs), which causes transcription of genes involved in normalization of keratinisation. Moreover, retinoids also block activator protein-1 (AP-1). Adapalene causes down regulation of Toll- like receptors (TLR-2). It is highly lipophilic and do not bind to Crabp. It is a group D medicine in pregnancy.

Safety pharmacology: 90-day minipig study (0.0, 0.2, 0.6, and 1.2mg adapalene/kg/day) with 0.1% lotion was performed. No changes in electrocardiograms and blood pressure were observed during the treatment . The safety pharmacology studies with adapalene had also been conducted at much higher dose levels. Thus, the gavage doses (10, 30, 100mg/kg) of adapalene did not affect the behaviour, physical health, spontaneous loco motor activity, hexobarbital sleeping time, pain response, basal tone of ileum, and gastrointestinal motility in CD-1 mice. However, in 2-5 post-dose hours at the mid- and high dose levels, drug caused a moderate decrease in body temperature. The oral doses at the same levels did not affect the functioning of the cardiovascular, respiratory, and central nervous systems in beagle dogs, and urine volume and electrolyte excretion in Wistar rats

NON CLINICAL TOXICOLOGY[30]

The following studies have been performed to assess the toxicity of adapalene:

General toxicology: In adult minipigs, a four-week study (0.0, 0.2, 0.6, and 2.0mg adapalene/kg/day) with 0.1% lotion was followed by a 3-month dermal study. In the main study (0.0, 0.2, 0.6, and 1.2mg/kg/day), no systemic toxicity was seen at the highest dose level. On day 1, the plasma drug level was below the detection limit . However, the repeated topical applications resulted in some drug accumulation which did not translate into any systemic toxicity. The minimal skin irritation developed at all dose levels was much reduced during the one-month recovery period. The acute oral LD50 for adapalene in both sexes of S-D rats and CD-1 mice was greater than 5,000mg/kg. The acute LD50 of adapalene applied as 0.3% solution was greater than 10mL/kg (30mg/kg) in Iffa Credo OF1 male and female mice. In acute rat dermal study, 2grams/kg of 0.3% adapalene

(6mg/kg/day) gel did not produce any toxicity. In two separate studies where Iffa credo OF1 mice received gavage (110, 300, and 500mg /kg) and intraperitoneal doses (30, 60, and 80mg/kg) of adapalene for two weeks (10 doses), loss of hair, body weight, spontaneous long bone fractures and skeletal resorption were observed. The topical applications of 0.3% adapalene gel in rats at the dose of 2 mL/kg (6mg adapalene/kg/day) for 4-26 weeks did not cause any systemic toxicity. The dose-related lesions (scabs and acanthosis) disappeared during 8 weeks . In a 26-week gavage study (0.15, 1.5, and 15.0mg adapalene/kg/day) in CD rats, the drug related toxicity was restricted to a slight decrease in the number of erythrocytes in high dose females and an increase in the plasma alkaline phosphatase at the highest dose level in both sexes. Irrespective of the high plasma drug levels (7.6, 50.2, and 113.4 in males and 9.4, 46.0, 148.6ng/mL in females) after the last dose, no biological effects of any significance were observed. Dogs treated orally (1mg/kg/day) and topically (6mg/kg/day) for 26 weeks, did not exhibit any bone-related systemic toxicity, however, epidermal hyperplasia and superficial dermal inflammation on the application sites were observed. In another 26-week oral (1-20mg/kg/day) dog study, the changes in bones due to increased osteoclastic activity and resorption resembled hypervitaminosis A syndrome. It was inferred that 1mg oral adapalene/kg/day is close to the threshold dose that causes cranial bone changes in dogs.

Genetic toxicology: Adapalene do not show mutagenic effects in vitro (ames test, Chinese hamster ovary cell assay) and in vivo (mouse micronucleus test).

Carcinogenicity: a combined chronic toxicity dietary admix study in CD rats and one dermal oncogenicity study in CD-1 mice was performed. In the topical study, mice received one daily application of 0.03, 0.1, and 0.3% aqueous gel for 19 weeks. Due to the severity of dermal lesions, the frequency of application was reduced to five times a week, and for the same reason was further reduced to three times per week from week 63. A number of animals were sacrificed on humane ground due to severe local reactions. Gross pathological examination revealed thickening of the skin. The histopathologic examination indicated acanthosis, hyperkeratosis, scabs, ulcers, diffused subcutaneous inflammation, collagen deposition, atrophy of glandular and follicular structures, and increased superficial follicles in the drug treated skin. Most of these incidences were dose related. No drug related neoplastic changes were observed.

Reproductive toxicology: In rat oral reproductive and fertility study where F0 female were treated with daily doses of 1.5, 5, or 20mg adapalene/kg for 15 days, no effects on reproductive performance and fertility, F1 litter size, growth, development to weaning, and subsequent reproductive performance of the offspring, were observed.
In dermal teratology studies with adapalene gels (0.03, 0.1, and 0.3%), the number of ribs in rats and rabbits at the highest dose level were increased. In the rat oral teratogenicity study (5, 25, and 60mg/kg/day), based on significant skeletal and visceral malformations, both mid and high doses were established as teratogenic. At the low dose, only minimal skeletal variations (additional ribs) were observed. This dose was considered to be non-teratogenic. In segment 3 oral rat study (0.15, 1.5, and 15mg/kg/day), the highest dose of adapalene had no effect on the litter parameters of F0 and F1 generations, and on F2 fetuses.

SAFETY AND TOLERABILITY[31-33]

Nursing mothers- it is not known if Differin is excreted in human milk. However, caution should be exercised when the cream is administered to a nursing mother.

Pediatric use- effectiveness in pediatric patients who are below 12 years has not been established.

Geriatric use- clinical studies of Adapalene were conducted in patients who were 12-30 years of age with acne vulgaris and therefore did not include subjects who were 65 years and older.

PHARMACOKINETICS AND PHARMACODYNAMICS[37-40]

A 3-month minipig dermal study (0.0, 0.2, 0.6, and 1.2mg/kg/day) with 0.1% lotion was carried out. No drug was detected in the plasma on day 1. The systemic drug exposure in both sexes increased with time in a non-linear fashion. The value of Tmax in both sexes increased with the dose; however, in females it was 3.4 times greater. Also, the average topical absorption of adapalene did not exceed 5 percent. The

systemic absorption in rabbits was higher (14%). Adapalene is mostly restricted to stratum corrneum, which acts as a reservoir for drug release. However, only a small amount is released to the epidermal layers. Adapalene and metabolites were mainly distributed in tissues and organs involved in metabolism and excretion. Adapalene did not exhibit any affinity for lipid-rich or melanin-containing tissues or organs. Adapalene is metabolized in animals and humans, however, its metabolic pathways and metabolites have not been properly characterized.

Absorption- Single topical dose of 0.6mg/kg [14C]-adapalene, the detectable (minimum level of detection 0.15ng/mL) amounts of the parent drug were found in the plasma of mouse, rat, rabbit, and dog. A single dose topical mass balance study with 0.6mg/kg [14C]-adapalene 0.1% solution under occlusion indicated absorption of 2.5 to 8% in hairless nu-ICO rats. However, the repeated daily applications of the same dose increased the absorption up to 12 percent. The absorption in rabbits was greater (up to 14%) than that of mice, rats and dogs. The bioavailability via the dermal route was also greater (4%) in rabbits than rats (2%). In rats, the absolute bioavailability after a single oral dose of 14C-adapalene was less than 10 percent. In a 26-week gavage study in rats, with a Tmax of 2-3 hours, approximate bio availabilities at dose levels of 0.15, 1.5, and 15mg/kg/day, were 75%, 17%, and 3%, respectively. In a rat teratology study with 0.1% aqueous topical gel (0.6, 2.0, and 6.0mg adapalene/kg), the bioavailability on day 10 was about 10%. In a repeated dose study (25mg adapalene/kg/day) in rabbit, the absolute bioavailability was about 1%. In a single dose oral study in beagle dogs, the systemic bioavailability of 4-5% was achieved. Following the oral radioactive doses (0.1 and 1.0mg/kg) of adapalene to pregnant rats, the peak drug levels in the mother and fetus were achieved at 3 and 4 hours, respectively. The amount of radioactivity in the plasma of fetus at 1 hour accounted for 4% of the maternal plasma radioactivity. The t1/2 in the mother was about 14 hours at both dose levels, while in fetus; the values were 29 and 40 hours for the low and high levels, respectively. In the sub-chronic dermal study in minipigs (0.0, 0.2, 0.6, and 1.2mg/kg/day) with the proposed lotion formulation, the systemic absorption (Cmax) in females was 21 times greater than males; the value for AUC0-24hr.in females was 16.5 times greater. No drug was detected in the plasma of women treated topically with 2g of 0.1% adapalene gel per day for 3 months. The absorption studies with excised human skin or cultured keratinocytes revealed a slightly higher absorption (never exceeding 10%) than in majority of the intact animals.

Distribution- In single and multiple-dose [14C]-adapalene studies in Sprague Dawley (S-D) rats, irrespective of the dose (0.12-0.5mg/kg), vehicle (PEG-400, CMC, or gel) or route (intravenous, oral, topical) more radioactivity was found in the plasma of females.

In the single topical application of 0.3% adapalene in male S-D rats, it was found that only 7% of the dose was found in the skin, out of which 3% was seen in stratum corneum. The amount was reduced to 0.1% after 7 days.

In the same study, the micro-autographic analysis showed that the maximum amount of radioactivity was present in the stratum corneum followed by epidermal layer. No radioactivity was found in dermis and hypodermis. It is suggested that the stratum corneum acts as a reservoir for drug release. A 28-day rat topical study (0.1mg/site) with 0.1% adapalene solution was conducted. It was found that 2% of the total dose was present in the skin. The amount of radioactivity found in the tissue was 0.06-0.08% of the administered dose. Seven days after the intravenous dose in male rats, rabbits and dogs, adrenals, liver, bile and spleen contained more radioactivity than the plasma. Each species exhibited a characteristic pattern of distribution, whereas in rat the highest amount of radioactivity was found in the adrenals. The tissue distribution data obtained from a rat dermal whole body autoradiography study revealed accumulation of drug-related radioactivity mainly in organs and tissues involved in the metabolism and excretion. In vitro study with human blood, 26% of the 3 H-adapalene was bound to erythrocytes and the total binding in blood was more than 99%, mostly to lipoproteins and albumin.

Metabolism- Adapalene cannot be metabolised by human epidermis, or after topical exposure in a rat study. It further caused low percutaneous penetration and systemic toxicity. However, the drug was metabolized by cultured hepatocytes from human, mouse, rat, rabbit, and dog. The metabolism in dogs was very similar to men. The data from several studies had indicated that

metabolism probably affects only the methoxybenzene moiety. However, out of 7 fecal metabolites, only one has been identified. In vitro studies showed that the major metabolite in rabbit and mouse was a glucuronide.
In 14-day rat topical (0.15-50mg/kg/day) study, adapalene did not exhibit any potential to induce or inhibit any drug metabolizing enzymes including CYP 1A, 2B, 3A, 2E, 4A, and UDP glucuronyltransferase. It confirms the findings that the drug interaction with adapalene is minimal.

Excretion- intravenous dose of [14C]-adapalene to rats, glucuronides, a sulfo-conjugate, and the parent drug showed 63.2, 17.1, and 19.1% of the radioactive pool in the bile. In an enterohepatic circulation study, 3-6 hours after the intravenous dose of radioactive drug into the rat duodenum, 75% of the metabolic pool was due to parent drug, while 24.1% had undergone glucuronidation; sulfonation was almost negligible. After reabsorption, the compounds were once again eliminated via the fecal route, indicating the existence of a considerable enterohepatic circulation of adapalene and its metabolites. In rats, the bile contained 79% of the administered dose, and the enterohepatic circulation was approximately 50 percent. In all species, irrespective of route of administration, adapalene is eliminated mainly in the feces, and greater than 80% of the excretion is complete in seven days. In lactating rats, radioactivity was also excreted in the milk. In four volunteers, the total amount of radioactivity found in the feces following a topical application of 0.1% adapalene solution amounted to 0.02-0.06% of the applied dose. No significant amount of radioactivity was found in the urine. Comparison of Pharmacokinetic and Pharmacodynamic Parameters of different drugs given in Table 7.

Pharmacodynamic parameters- The pharmacodynamic studies conducted have showed that topical adapalene normalized the differentiation of follicular epithelial cells causing decreased microcomedone. In cultured human keratinocytes, adapalene inhibited the activity of transglutaminase I, a membrane bound enzyme involved in terminal differentiation of keratinocytes. The data of both in vivo and in vitro studies had revealed that the drug also blocked the chemotactic (directional) and chemokinetic (random) responses of human polymorphonuclear leukocytes and inhibited the oxidation of arachidonic acid to inflammatory mediators[41-43].
Adapalene gel was effective in treating the signs of UVB- induced photodamage on the skin of hairless mice. It induced a significant increase in the number and size of repair zones.

EFFICACY

The safety and efficacy of Adapalene gel (0.3%) in acne was performed with 653 volunteers of 12-52 years of age. All females were required to have a negative urine pregnancy test at the beginning of the study. An equal no of males and females were involved.

Table 7: Comparison of Pharmacokinetic and Pharmacodynamic Parameters of different drugs

	Brand name	Biological half life	Protein binding %	Bioavaibility %
Adapalene	Differin	13 hrs	>99	5
Clindamycin	Cleocin	2.4-3.2 hrs	>90	4.5
Doxycycline	Doryx	18 hrs	82-93	>80
erythromycin	Eryc	1.5-2 hrs	73-81	30-65

Table 8: Safety and efficacy of Adaplene gels

	Adapalene gel 0.3% N=258	Adapalene gel 0.1% N=261	Vehicle gel N=134
Success rate	53.0	41.0	12.0
Inflammatory lesions	27.7	28.1	27.8
Non inflammatory lesions	39.4	41.0	40.0

CLINICAL STUDIES

Over the past few years, numerous clinical trials have been conducted to study the efficacy and tolerability of Adapalene in the treatment of acne vulgaris. A comparison study was performed on Adapalene and All-Trans Retinoic acid in human skin[44]. Adapalene which is relatively selective for retinoic acid receptor, was found to be an effective comeodolytic agent in the rhino mouse model. In this observation, the effects of CD271 on the development of erythema, spongiosis, and epidermal hyperplasia were studied.

A multi centre study[45] to compare the safety and efficacy of adapalene 0.1% solution and tretinoin 0.025% gel, in a once-daily dosage regimen for 12 weeks. 297 patients were involved by eight investigators in this randomized, investigator-masked study in a parallel group design. An open label period using adapalene followed this study to assess the long-term safety of adapalene solution. Adapalene and tretinoin proved to be clinically and statistically effective in treating acne by reducing inflammatory (47% and 50%, respectively) and non-inflammatory lesions (57% and 54%) as compared to baseline. Adapalene was more effective than tretinoin in patients who had greater improvement in open comedones. No serious adverse event was reported during this study.

In an another study[46], Adapalene 0.1% gel has been studied in 80 patients against isotretinoin 0.05% gel, which is the cis-isomer of retinoic acid, to compare their effectiveness and tolerance. Both lesion counts and global assessment showed a better degree of efficacy with adapalene than isotretinoin.

In a study[47], isolatation of the impurities present in adapalene was done. Three impurities were isolated and characterised during the optimisation of a synthetic procedure to adapalene. First impurity was a by-product of the Friedel–Crafts reaction of adamantanol with 4-bromoanisole. The others were due to side reactions of the final Negishi coupling.

A study[48] on 253 subjects to assess the maintenance effect of adapalene 0.1% gel and gel vehicle in subjects successfully treated in a previous 12 week study of adapalene-doxycycline combination. The study demonstrated a clinical benefit of continued treatment with adapalene 0.1% gel as a maintenance therapy. In another study by Zhang et al (2004), a total of 300 acne subjects entered the multicentre, randomized, investigator-blinded study comparing the efficacy and safety of adapalene 0.1% gel plus clindamycin 1% solution versus clindamycin 1% solution alone. In the second part of the study (weeks 12–24) completed by 241 subjects, the efficacy and safety of adapalene 0.1% gel alone as a maintenance therapy were investigated. This study confirmed the importance of a maintenance therapy after a successful initial treatment and underlined the benefit of a combination therapy with a topical retinoid such as adapalane and a topical antibiotic in the treatment of inflammatory acne.

The assessment[49] of adapalene gel for the treatment of actinic keratoses and lentigines was done. 90 patients with actinic keratoses and solar lentigines were treated daily with either adapalene gel (0.1% or 0.3%) or its vehicle gel for 4 weeks, followed by twice-daily applications for 9 months. Out of the 90 patients (69 male, 21 female; mean age 63.1 years) who were involved in the the study, 83 patients completed 9 months of treatment. With adapalene gel 0.1% and 0.3%, the mean number of actinic keratoses was reduced by 0.5 ± 0.9 (mean ± SE) and 2.5 ± 0.9, respectively. Whereas, with the vehicle gel, there was an increase of 1.5 ± 1.3 . After 1 month of treatment, the patients who received adapalene had lightening of solar lentigines as compared with the patients who were treated with vehicle gel. After 9 months, 57% and 59% of the patients had lighter lesions in the adapalene 0.1% and 0.3% groups, respectively, in comparison with only 36% in the vehicle group ($P < .05$). [49]

USES[50-52]

This medication is used to treat acne. It may decrease the number and severity of acne pimples and promote quick healing of pimples that do develop. Adapalene belongs to a class of medications called retinoids. It works by affecting the growth of cells and decreasing swelling and inflammation.

DOSAGE AND ADMINISTRATION

Usual adult dose for acne- Adapalene topical 0.1% gel, 0.3% gels

It should be applied to the affected area once a day at bedtime after washing. A thin film should be applied avoiding eyes, lips, angles of the nose, and mucous membranes. Lotion- apply a thin film of lotion to the entire face and other affected areas of the skin once daily, after washing gently with a mild cleanser.

Usual pediatric dose for acne-Adapalene topical 0.1% cream, 0.1%gel and 0.3%gel
11 years or less-safety and efficacy have not been studied. 12 to 18 years-apply to the affected area once a day at bed time after washing. Safety and effectiveness of the lotion formulation in pediatric under the age of 12 have not been established.

OVERDOSE
Differin cream is intended for cutaneous use only. If the cream is applied excessively, better results will not be obtained and marked redness, scaling or skin discomfort may occur. The acute oral toxicity in mice and rats is found to be greater then 10ml/kg. Adapalene lotion may be harmful if swallowed.

ADVERSE EFFECTS[53]
The main side effect is retinoid reaction which is due to free carboxylic group present in the structure of Adapalene. The other commonly reported side effects are skin redness, scaling, dry skin, and contact dermatitis, skin irritation, stinging and burning. Other infrequent cutaneous adverse events reported which may be related to the application of adapalene included vesiculobullous eruption, sunburn, herpes labialis, acne flare and eyelid oedema.

Incidence of Local Cutaneous Irritation with DIFFERIN Gel, 0.3% from Controlled Clinical Study (N=253)

DRUG INTERACTIONS
Adapalene has been shown to enhance the efficacy of topical clindamycin, although adverse effects are also increased. Application of adapalene gel to the skin 3–5 minutes before application of clindamycin enhances penetration of clindamycin into the skin, which may enhance the overall efficacy of the treatment as compared to clindamycin alone.
Unlike tretinoin (Retin-A), adapalene has also been shown to retain its efficacy when applied at the same time as benzoyl peroxide due to its more stable chemical structure.
Use of other irritating topical products should be used with caution. Caution should be exercised in using preparations containing sulphur, resorcinol, or salicylic acid in combination with DIFFERIN gel. If these products have been used, it is advised not to start therapy with Differin gel until the effects of such preparations in the skin have reduced.

COMPARISON WITH OTHER MEDICATIONS
Adapalene exhibit retinoid effects. However, it also shows some anti-inflammatory properties. Pharmacodynamic differences separate adapalene from tretinoin. First, although adapalene binds to specific retinoic acid nuclear receptors (RARα, RARß, and RARγ), the affinity of adapalene for RARα is much lower than tretinoin. Second, unlike tretinoin, adapalene does not bind to cellular retinoid binding protein II (CRAB II). Animal studies have showed that adapalene is a potent modulator of cellular differentiation, keratinisation, and inflammatory processes, all of which represent important features in the pathology of acne vulgaris. Thus, topical adapalene normalized the differentiation of follicular epithelial cells resulting in decreased microcomedone formation. It also inhibited the lipoxidation of arachidonic acid to inflammatory mediators. Adapalene is chemically and phytochemically more stable than tretinoin. In conclusion, from the non-clinical safety view point, DIIFERIN (adapalene) Lotion 0.1% was well tolerated.

STORAGE
Store Adapalene at room temperature, between 68 and 77 degrees F. Brief storage at temperature between 59 and 86 degrees F is permitted. Store away from heat and light. Donot freeze or refrigerate. Keep Differin lotion away from children and pets.

Table 9: Maximum Severity Scores Higher Than Baseline

	Mild	Moderate	Severe
Erythema	66 (26.1%)	33 (13.0%)	1 (0.4%)
Scaling	110 (43.5%)	47 (18.6%)	3 (1.2%)
Dryness	113 (44.7%)	43 (17.0%)	2 (0.8%)
Burning/stinging	72 (28.5%)	36 (14.2%)	9 (3.6%)

Table 10: Patient reported local cutaneous adverse events with Differin Gel

	Differin Gel, 0.3% N=258	Vehicle Gel N=134
Related adverse events	57 (22.1%)	6 (4.5%)
Dry skin	36(14%)	2 (1.5%)
Skin discomfort	15 (5.8%)	0 (0.0%)
Desquamation	4 (1.6%)	0 (0.0%)

CONCLUSION

Adapalene is a napthoic acid derivative with retinoid like activity. It binds to the retinoic acid receptor and is more active and chemically stable than tretinoin. It also exhibit anti-inflammatory property and is better tolerated. This drug represents a useful therapeutic option in the management of patients with mild to moderate acne vulgaris. It could be an attractive target for pharmaceutical industries. Its other effects may also be explored by research units.

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