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Original Research Article

A rational pharmacotherapeutic study of comparative safety among topical anti-acne 1% nadifloxacin monotherapy, 0.1% adapalene monotherapy, 0.025% tretinoin monotherapy, 1% nadifloxacin and 0.1% adapalene combination therapy and 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne vulgaris, in tertiary care hospitals

Moumita Hazra*

Assistant Professor, Department of Pharmacology, K. D. Medical College, Hospital and Research Centre, Delhi-Mathura Road, Mathura, Uttar Pradesh, India

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***Correspondence to:**
Dr. Moumita Hazra,
Email:
drmoumitahazra17@gmail.com

ABSTRACT

Background: Topical adapalene and tretinoin, are comedolytic, anti-comedogenic and anti-inflammatory, on RAR (α, β, γ) receptors binding. Adapalene enables quicker follicular penetration, by lesser anti-AP-1 (c-Jun, c-Fos) and no CRBPII mRNA actions, causing chemical stability, lipophilicity and less photo-lability, producing lesser photosensitivity and no skin irritation, unlike tretinoin; wherein reducible by overnight application and combination therapy, slow-release polymers or emollients, respectively. Topical nadifloxacin is bactericidal, anti-inflammatory and comedolytic, with inhibitory effect on DNA gyrase, DNA topoisomerase IV and IL-1α, IL-6, IL-8. The Global Alliance to Improve Outcomes in Acne Guidelines recommend synergistic and additive combination therapies, which enhance therapeutic efficacy and reduce adverse effects. Due to inadequacy of data, this study was conducted, to compare the safety among topical anti-acne monotherapies and combination therapies, and to easily detect any adverse effect producing component in the topical combination therapy.

Methods: In this multi-centre, prospective, randomised, open-labelled, comparative study, groups A, B, C, D and E (20 patients each), applied topical 1% nadifloxacin monotherapy, 0.1% adapalene monotherapy, 0.025% tretinoin monotherapy, 1% nadifloxacin and 0.1% adapalene combination therapy and 1% nadifloxacin and 0.025% tretinoin combination therapy, respectively, over their facial mild to moderate acne lesions, once daily overnight; and adverse effects, like erythema, scaling, dryness, prutitus, burning, or stinging, were assessed on 0, 15, 30, 60, 90 days and follow-ups, by Local Irritation Scale.

Results: In all 5 groups, no adverse effects were observed, with no statistically significant difference among the observations.

Conclusions: The therapies were well tolerated and safe among all 5 groups.

Keywords: Nadifloxacin, Adapalene, Tretinoin, Acne, Safety, Local irritation scale

INTRODUCTION

Acne vulgaris is a self-limited, chronic inflammatory disease of the pilosebaceous unit, which causes cosmetic impairment.[1-4] The Global Alliance to Improve Outcomes in Acne Guidelines recommend a combination therapy with a topical retinoid and antimicrobial agents for the treatment of mild to moderately severe inflammatory acne.[5-8]

Adapalene, the third generation retinoid, and tretinoin, the first generation retinoid, are natural or synthetic derivatives of vitamin-A and are comedolytic, anti-comedogenic, anti-inflammatory and reduce

Propionibacterium acnes counts.[9-12] In monotherapy or combination therapy, the ability of retinoids to stimulate the growth of new cells, unclog pores and promote the normal flow of sebum is well proven. Adapalene and tretinoin have selective affinity for retinoid receptors, including retinoic acid receptors (RAR) α, β and γ, affecting cellular differentiation and proliferation. Upon binding to tretinoin, these RAR receptors form heterodimers, which subsequently bind specific DNA sequences, called retinoic acid-responsive elements (RARE), that activate transcription of genes, whose products produce the desirable pharmacological effects of retinoids.[13-17] Topical retinoids are a first-line treatment for acne vulgaris.[18,19]

Nadifloxacin, a newer topical fluoroquinolone, is bactericidal, anti-inflammatory and mildly comedolytic.[10] Nadifloxacin inhibits the enzyme DNA gyrase that is involved in bacterial DNA synthesis and replication, thus inhibiting the bacterial multiplication.[20]

Topical adapalene and topical tretinoin might rarely produce adverse effects, such as, erythema, dryness, scaling, stinging, burning, pruritus of skin and mucous membranes, photosensitivity reactions, muscle and joint pains. Topical nadifloxacin might rarely produce adverse effects, such as, pruritus, burning, irritation, erythema, peeling, flushes, papules, feeling of facial warmth, increased sweating, contact dermatitis, dryness of skin and hot flushes.[9,20,21]

Due to less data available, this study was taken up, with an objective to compare the safety among topical anti-acne 1% nadifloxacin monotherapy, 0.1% adapalene monotherapy, 0.025% tretinoin monotherapy, 1% nadifloxacin and 0.1% adapalene combination therapy and 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals; and also to easily detect the exact component in the topical combination therapy which is actually producing any adverse effect.

METHODS

Study population and place of study

This research study was conducted on the patients, suffering from mild to moderate acne on their faces, attending the out-patient departments of Dermatology and the study literature was compiled in the Departments of Pharmacology and Dermatology of K. D. Medical College, Hospital and Research Centre, Delhi-Mathura Road, Mathura, Uttar Pradesh, India and J. J. M. Medical College, Bapuji Hospital and Chigateri General Hospital, Davangere, Karnataka, India.

Study design

It was a multi-centre, prospective, open-labelled, randomized, comparative, rational pharmacotherapeutic study.

Study period

The entire research study and the compilation of the study literature were done during a period of 5 months, from December 2013 to March 2014, and December 2015 to February 2016.

Sample size: 100 patients.

Ethical approval

Before conducting the study, the clearance and the approval from the Institutional Ethics Committee were obtained. The study was conducted in accordance with the ethical principles originating from the Declaration of Helsinki and Good Clinical Practices, and in compliance with the regulatory requirements.

The patients were selected based on the inclusion and the exclusion criteria given below, and the patients fulfilling those criteria, were included in the study.

Inclusion criteria

The inclusion criteria were: (a) patients aged 12-25 years of either sex; (b) patients with mild to moderate acne (Grade– I & II) on face above the jaw line; (c) women of child bearing potential are required to have a negative urine pregnancy test result and to agree to use an effective form of contraception for the duration of study (12 weeks); (d) patients who have given consent and are willing to go for a follow-up.

Exclusion criteria

The exclusion criteria were: (a) patients with severe acne vulgaris (Grade– III & IV); (b) patients with acne lesions predominantly involving trunk (truncal acne); (c) other variants of acne: chloracne, oil acne, tropical acne, mechanical acne, severe variants like acne conglobata and acne fulminans; (d) drug induced acne; (e) if at follow-up, disease progresses and necessitates systemic therapy; (f) patients not willing to give informed consent and follow-up; (g) pregnancy and lactating mother; (h) patients with known hypersensitivity to any of the components of the drug; (i) female patients using hormonal contraceptives; (j) patients who are already on topical therapy for acne or any other topical therapy, during the previous four weeks; (k) immunocompromised and patients on medication for any chronic medical illness.

Methodology

The patients who were included in the study were assured confidentiality and an informed consent was obtained from each individual. The patients were registered and they received the treatment regimens under the direction of a treating dermatologist.

The patients underwent an antibiotic culture and sensitivity test and pre-medication dermatological topical retinoid application patch test, before the further administration of the more suitable and safer antibiotic and retinoid combination therapy, among the 5 regimens under study.

A detailed history was obtained with the proforma, giving special attention to the predisposition to acne. At first visit, the patients were interviewed for their detailed demographic profile, present and past history, obstetric and gynaecological history for female patients, family history, personal history and medication history. Complete general physical examination and systemic examination, including obstetric and gynaecological examination, were performed. Then, thorough dermatological evaluations were made.

The study was an open-labelled, randomized, comparative study. The 100 patients, suffering from mild to moderate acne on their faces, were randomly allocated into Group A, Group B, Group C, Group D and Group E of 20 patients each, for administering the 5 prescribed treatment regimens. Then, keeping in consideration of the results of the antibiotic culture and sensitivity test and the pre-medication dermatological topical retinoid application patch test, Group A (20 patients) was instructed to apply topical 1% nadifloxacin monotherapy, Group B (20 patients) was instructed to apply topical 0.1% adapalene monotherapy, Group C (20 patients) was instructed to apply topical 0.025% tretinoin monotherapy, Group D (20 patients) was instructed to apply topical 1% nadifloxacin and 0.1% adapalene combination therapy and Group E (20 patients) was instructed to apply topical 1% nadifloxacin and 0.025% tretinoin combination therapy. Before the application of the topical anti-acne agents, the patients were advised to wash the face with clean water and dry it well. Then the patients were asked to apply 1 fingertip unit (approximately 0.5 gram) of each study medication once daily in the evening, over the affected areas on the face, on the forehead, cheeks, chin and nose, with a thin film evenly spread over the entire face and it was left overnight. Special precaution was taken to avoid the periorbital, para nasal and perioral areas. According to the prescriptions, the patients in Group B and Group D applied 0.1% adapalene first, the patients in Group C and Group E applied 0.025% tretinoin first and the patients in Group A applied 1% nadifloxacin first. After half an hour, both Group D and Group E patients applied 1% nadifloxacin over that, without washing their faces.

Study data collection

The required safety assessments were the detailed recorded tolerability assessments (erythema, scaling, dryness, pruritus, burning, stinging) and the reported adverse effects. All clinical medical events, whether observed by the investigator or reported by the subject and whether or not thought to be drug-related, were considered adverse effects and were thoroughly recorded on the appropriate Adverse Event Case Report Form.

Safety assessment

After enrolment in the study, on 0, 15, 30, 60, 90 days, and subsequent follow-up visits, occurrence of any adverse effect due to the study medications, like erythema, scaling, dryness, pruritus, burning, or stinging, was assessed by the Local Irritation Scale, among the 5 groups of patients. Safety assessments were conducted for all the subjects at each visit, by the scale, depicted in Table 1.[19,22] Safety assessment was graded at the baseline visit, each post-baseline visit and further follow-up visits.[21]

Statistical analysis

The data was statistically analysed, with the calculation of Z values and P values, along with the Z test.

Table 1: Scale for assessment of safety.

Grade	Score	Description
Erythema– abnormal redness of the skin		
None	0	No evidence of erythema present
Mild	1	Slight pink discoloration
Moderate	2	Definite redness
Severe	3	Marked erythema, bright red to dusky red in color
Scaling– abnormal shedding of the stratum corneum		
None	0	No scaling
Mild	1	Barely perceptible, fine scales present to limited areas of the face
Moderate	2	Fine scale generalized to all areas of the face
Severe	3	Scaling and peeling of skin over all areas of the face
Dryness– brittle and/or tight sensation		
None	0	No dryness
Mild	1	Slight but definite roughness
Moderate	2	Moderate roughness
Severe	3	Marked roughness

Continued.

Grade	Score	Description
Pruritus– scratching sensation of the skin		
None	0	No itching
Mild	1	Slight itching, not really bothersome
Moderate	2	Definite itching that is somewhat bothersome
Severe	3	Intense itching that may interrupt daily activities and / or sleep
Burning– scorching pain sensation immediately after (within 5 minutes) dosing		
None	0	No burning
Mild	1	Slight burning sensation, not really bothersome
Moderate	2	Definite warm, burning sensation that is somewhat bothersome
Severe	3	Hot burning sensation that causes definite discomfort and may interrupt daily activities and / or sleep
Stinging– prickling pain sensation immediately after (within 5 minutes) dosing		
None	0	No Stinging
Mild	1	Slight stinging sensation, not really bothersome
Moderate	2	Definite stinging sensation that is somewhat bothersome
Severe	3	Stinging sensation that causes definite discomfort and may interrupt daily activities and /or sleep

RESULTS

As depicted in Table 2, in all the 5 groups of patients, Group A, Group B, Group C, Group D and Group E, receiving topical nadifloxacin monotherapy, topical adapalene monotherapy, topical tretinoin monotherapy, topical nadifloxacin and adapalene combination therapy, and topical nadifloxacin and tretinoin combination therapy, respectively, no occurrence of any adverse effect, like, erythema, scaling, dryness, pruritus, burning or stinging, was observed due to the medications in the study; and there was no statistically significant difference among the observations. In all the 5 groups of patients, even after performing the aforesaid comparative safety assessment of topical anti-acne monotherapies and combination therapies, none of the components of the combination therapies were observed to produce any adverse effect.

Table 2: Adverse effects of the medications.

Adverse effects	Group A N (%)	Group B N (%)	Group C N (%)	Group D N (%)	Group E N (%)	Z value	P value
Erythema	0	0	0	0	0	0	0, ns
Scaling	0	0	0	0	0	0	0, ns
Dryness	0	0	0	0	0	0	0, ns
Pruritus	0	0	0	0	0	0	0, ns
Burning	0	0	0	0	0	0	0, ns
Stinging	0	0	0	0	0	0	0, ns

*Z test for proportions. ns=non-significant.

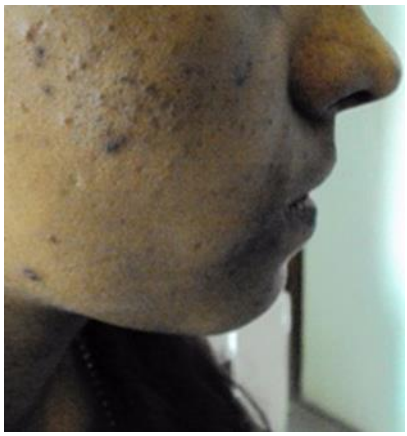

Figure 1: Lesions of acne vulgaris on the face, before treatment.

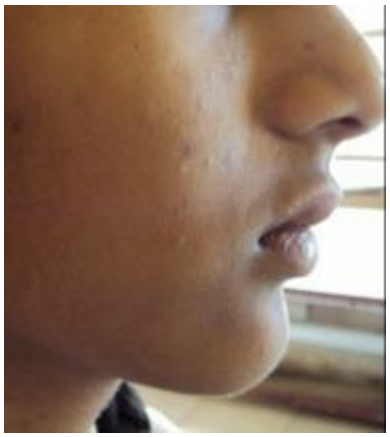

Figure 2: Face, after treatment, with no adverse effects.

Figure 1 shows the lesions of acne vulgaris on the face of a patient in the study, before treatment.

Figure 2 shows the reduced lesion counts on the face of the patient in the study, with no occurrence of adverse effects, after treatment.

DISCUSSION

Acne vulgaris is a common skin disease characterized by non-inflammatory follicular papules or comedones and by inflammatory papules, pustules and nodules in its more severe forms. The pathogenesis of acne vulgaris is multifactorial. Four main key factors responsible for the development of acne lesions are follicular epidermal hyperproliferation with subsequent plugging of the follicle, excess sebum production, the presence and activity of *Propionibacterium acnes* and inflammation.[1-4]

Topical combination anti-acne therapy is patient compliant and cost-effective, as it has synergistic and additive actions on multi-pathogenetic factors, enhances therapeutic efficacy as greater comedolytic, better anti-inflammatory with more reduction in lesion counts, minimises bacterial resistance and minimises adverse effects, unlike topical anti-acne monotherapy.[5-8]

Topical retinoids are safe and efficacious for the treatment of acne vulgaris.[18]

Adapalene, is more stable chemically, less photo-labile, and more lipophilic, which enables it to penetrate follicles quickly. Fluorescence microscopic studies have shown that adapalene microcrystals penetrate follicular openings to the level of sebaceous gland within 5 minutes of application.[15] The selective uptake by follicles is thought to be due to its lipophilicity and may contribute to adapalene's success in the treatment of acne. Adapalene loaded tristearin, soya lecithin based solid lipid nanoparticles (SLNs-A) has salient features like controlled release, target ability, potential of penetration, improved physical stability, low cost compared to phospholipids, and ease of scaling-up that make solid lipid nanoparticles (SLNs) better than liposomes for effective drug delivery of adapalene.[16] As it also has anti-inflammatory action and only a trace of drug is absorbed systemically, it is preferred.

Topical retinoids, like adapalene or tretinoin, through a thinning effect on stratum corneum, facilitate percutaneous penetration of topical antibiotics, and help to achieve higher concentrations of the antimicrobial agent in the pilosebaceous canal which *Propionibacterium acnes* inhabits and this combination is also helpful to prevent or reduce bacterial resistance.[17]

Tretinoin stabilizes lysosomes, increases ribonucleic acid polymerase activity, increases prostaglandin E2, cAMP and cGMP levels, and increases the incorporation of thymidine into DNA. It acts in acne by its decreased cohesion between epidermal cells and increased epidermal cell turnover, resulting in the expulsion of open comedones into open ones.[21] It fades post-acne pigmented spots and leathery post-acne skin surface.[12] In the epidermis, retinoids induce epidermal hyperplasia in atrophic skin and reduce keratinocyte atypia. Topical Tretinoin is relatively photo-labile and thus should be applied once every night. The significant functions of retinoids include acne vulgaris, photoaging, roles in vision, regulation of cell proliferation and differentiation and bone growth, immune defense and tumour suppression.[9,21]

The objective of this rational pharmacotherapeutic study was to do a comparative assessment of the safety of topical 1% nadifloxacin monotherapy, topical 0.1% adapalene monotherapy, topical 0.025% tretinoin monotherapy, topical 1% nadifloxacin and 0.1% adapalene combination therapy and topical 1% nadifloxacin and 0.025% tretinoin combination therapy, in mild to moderate acne, in tertiary care hospitals. A total of 100 patients participated in the study. All the patients completed the study. In the 5 groups receiving topical nadifloxacin monotherapy, topical adapalene monotherapy, topical tretinoin monotherapy, topical nadifloxacin and adapalene combination therapy and topical nadifloxacin and tretinoin combination therapy, no adverse effects due to the study medications, like, erythema, scaling, dryness, pruritus, burning or stinging, were observed in the study; and there was no statistically significant difference among the observations. The objective of this study was also to perform a comparative study of topical anti-acne monotherapies and combination therapies which would easily detect the exact component in the topical anti-acne combination therapy which is actually producing any adverse effect. In this study, even after performing the aforesaid comparative safety assessment of topical anti-acne monotherapies and combination therapies, none of the components of the combination therapies were observed to produce any adverse effect on the patients. These study observations corroborate the study observations in similar previous studies of safety assessment of topical anti-acne monotherapies or combination therapies.[3,5-8,11,12,22]

Being RAR-selective retinoids, adapalene and tretinoin are more associated with occasional mucocutaneous and musculoskeletal adverse effects, mild in nature, unlike retinoid X receptors (RXR)-selective retinoids, which induce physiochemical adverse effects, moderate to severe in nature. Topical application of retinoids is rarely associated with mild adverse effects, unlike systemic retinoids, which are comparatively more associated with moderate to severe adverse effects. Adapalene and Tretinoin, improve dyspigmentation through anti-AP-1 (activator protein) mechanism, which is a transcription factor composed of c-Jun and c-Fos, regulate the expression of vascular endothelial growth factors and activate the synthesis of metalloproteinases on UV irradiation. They think the stratum corneum by decreasing

the number of cell layers, which leads to mild photosensitivity. Adapalene does not bind to cytosolic receptor protein, hence it has no affinity for cellular (cytosolic) retinol binding protein, and does not induce cytosolic retinol binding protein II messenger ribonucleic acid and thus it is very rarely associated with skin irritation, but it induces CRBP II messenger ribonucleic acid when applied under occlusion for 4 days to human skin; unlike tretinoin, which has the capacity to bind cytosolic retinoid-activating binding proteins associated with mild skin irritation, occasionally. Available formulations with co-polymer microspheres or prepolyolprepolymer-2 for slow release of tretinoin and concomitant use of emollients or combination therapy decrease skin irritation.[9,14,21,23] Topical nadifloxacin very rarely causes mild cutaneous adverse effects.[20,24-26]

Studies also suggest that the effectiveness of nadifloxacin in inflammatory acne lesions may be attributed to its inhibitory effect on pro-inflammatory cytokines like interleukin (IL)-1α, IL-6 and IL-8, which play an important role in acne pathogenesis. Nadifloxacin also inhibits the enzyme DNA topoisomerase IV, which enhances its anti-bacterial spectrum to Gram-positive, Gram-negative as well as anaerobic bacteria such as *Propionibacterium acnes* as well as against methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Staphylococcus epidermidis*, among others.[20]

Therefore, on comparative safety assessment, topical 1% nadifloxacin monotherapy, topical 0.1% adapalene monotherapy, topical 0.025% tretinoin monotherapy, topical 1% nadifloxacin and 0.1% adapalene combination therapy and topical 1% nadifloxacin and 0.025% tretinoin combination therapy were all well tolerated and safe, in the treatment of mild to moderate acne vulgaris.

This study would be a helpful step for developing newer dermatological anti-microbial, anti-inflammatory and anti-neoplastic diagnostics and therapeutics; for developing faster, more efficacious, safer, more precise and cost-effective therapeutics in patients suffering from acne vulgaris; and for enhancing dermatological health and cure.

CONCLUSION

Topical 1% nadifloxacin monotherapy, topical 0.1% adapalene monotherapy, topical 0.025% tretinoin monotherapy, topical 1% nadifloxacin and 0.1% adapalene combination therapy and topical 1% nadifloxacin and 0.025% tretinoin combination therapy were all well tolerated and safe, in the treatment of mild to moderate acne vulgaris.

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