

## Original Research Article

# Comparative evaluation of adverse drug reactions in patients of acne prescribed with either topical benzyl peroxide or retinoic acid in a tertiary care teaching hospital

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## ABSTRACT

**Background:** To evaluate and compare the profile of adverse drug reaction, its causality, severity and preventability in patients of acne prescribed with either topical benzyl peroxide or topical retinoic acid in a tertiary care teaching hospital.

**Methods:** Two hundred patients attending to dermatology department with acne and prescribed with either topical benzyl peroxide or topical retinoic acid were observed for occurrence of adverse drug events (ADEs). ADEs were either spontaneously reported or elucidated from personal interviews and analyzed.

**Results:** Out of total 200 patients, 110 (55%) were given benzoyl peroxide gel (2.5%) and remaining 90 (45%) were given retinoic acid cream (0.025%). Total 54 adverse events were reported in 47 (23.5%) patients. Highest number of patients having ADR was from 16-20 years (35, 74.46%) with male predominance (59.57%). Number of adverse events reported was significantly higher ( $p < 0.05$ ) in retinoic acid group (34, 62.96%) as compare to benzyl peroxide group (20, 37.03%). Most common ADRs were exfoliation (14, 25.92%) and burning sensation (13, 24.07%). Most of the ADRs fell in category of 'probable' and 'possible' in causality assessment by both WHO-UMC method and Narenjo's scale. All the ADRs were of mild (44, 81.48%) and moderate (10, 18.52%) severity. Majority of ADRs were not preventable (24, 44.44%) followed by definitely preventable 22(40.74%) and 8 (14.81%) probably preventable.

**Conclusions:** ADRs is a common problem associated with topically used medications for acne and its occurrence is significantly higher with retinoic acid as compare to benzyl peroxide. Early diagnosis and proper education about use of topical drugs can prevent some of the ADRs.

**Keywords:** Acne vulgaris, Retinoic acid, Benzyl peroxide, Adverse drug reactions, Causality assessment of ADRs, Severity and preventability of ADRs

## INTRODUCTION

Acne vulgaris is a chronic inflammatory disorder of the pilosebaceous follicles and occurring in all races. Nearly 90% of individuals develop some degree of acne between puberty to 30 years of age.<sup>1</sup> It is one of the most common dermatologic disorders seen in dermatology outpatient

department and more than 30% appointments are for this disease, at any given time.<sup>2</sup> Despite its spontaneous regression in most patients, acne persists in 10% of those patients over the age of 25 years. It is frequently leads to emotional distress, psychosocial problems, unemployment and even depression in adolescents affecting their overall quality of life.<sup>3,4</sup>

Various factors have been implicated for development of acne like increased sebum production, sloughing of keratinocytes, bacterial growth and inflammation.<sup>3</sup> Propionibacterium acnes are the most common microorganism responsible for development of acne. Treatment of acne is usually guided by severity, lesion types, scarring, and skin discoloration, previous treatment history etc.<sup>5,6</sup> Mild to moderate acne can be effectively managed with topical therapy with benzoyl peroxide, erythromycin, clindamycin or retinoids (tretinoin, adapalene, tazarotene, isotretinoin, metretinide, retinaldehyde and b-retinoylglucuronide are currently available in India).<sup>5</sup> Other topical therapies include salicylic acid, lactic acid, azelaic acid, picolinic acid gel, dapsone gel or combination therapy with two agents. Severe acne requires systemic antimicrobials, oral contraceptive pills, retinoids etc considering the underlying cause.<sup>6</sup>

In general, all the topically used drugs are considered as safe but various studies have reported different adverse effects with these drugs. Mild erythema, itching, dryness are most common adverse events reported but they rarely may lead to severe reactions like Steven Johnson's syndrome.<sup>5</sup> Although medications used by patients can lead to improvement in acne and health related quality of life, negative outcomes due to drug-related problems are considerable.<sup>4-6</sup> Major drug related problems include adverse drug events, inappropriate use of medicines and compliance issues. Different studies have reported rate of occurrence of ADRs with topically used drugs for acne as 3% to 20%.<sup>5,6</sup> Adverse effects can decrease patient compliance and increase in use of health services, and costs of treatment.<sup>1,7</sup> However, in India, the data regarding the incidence of ADRs are limited in acne patients prescribed with topical therapy. Therefore, this study was planned to find out the baseline data regarding the occurrence of ADRs and to further assess the causative drugs, severity, and preventability in acne patients using topical drugs.

## METHODS

A prospective observational study spread over two years was undertaken in dermatology department of a tertiary care teaching hospital in western India. The study protocol was approved by Human Research Ethics Committee of the institute prior to commencement of study. Permission from the hospital superintendent and head of the dermatology department was also obtained before conducting the study.

### Participant selection

Total 200 patients attending the dermatology outpatient department and diagnosed with acne vulgaris were included in the study. Diagnosis of acne was mainly based on clinical examination by the qualified dermatologist. Patients having cystic and nodulocystic acne, patients having acne other than acne vulgaris e. g.

oil acne, senile comedones, infantile acne and those patients who do not come for the follow up visits were excluded from the study.

### Study procedure in detail

All the patients participating in the study were explained clearly about the purpose and nature of the study in the language they understood. Written informed consent was obtained before including them in the study. All outdoor patients, new as well as old, meeting the inclusion criteria attending to dermatology department were interviewed for the first time on the day of enrollment and their case sheets were reviewed to gather necessary information -as on that day- to fill up case record forms. Detailed history and examination was carried out. Counting of lesions was done in good nature light with the help of a hand lens. Acne grading was done using lesion count: grade 1 (total number of lesions <10/100 cm<sup>2</sup>), grade 2 (10 – 20/100 cm<sup>2</sup>), grade 3 (20 – 30/100 cm<sup>2</sup>) and grade 4 (>30/100 cm<sup>2</sup>).<sup>8</sup> Patients were prescribed benzyl peroxide gel (2.5%) or retinoid acid cream (0.025%) as appropriate considering the severity, site and type of lesion. Patients were instructed to apply medication once in a day at nighttime only. All the adverse drug events reported spontaneously as well as found out during interview by investigator were recorded in the case record form with all the necessary information. The primary researcher was trained in identification and reporting and analysis of the adverse drug events. In case of conflict in analysis of the reports, the opinion of the treating physician was also obtained.

Patients were asked to come for follow up at 15 days and one month. In follow up examination, same method was employed for history and examination and ultimate response was noted as decrease in total lesion count.

### Analysis of adverse reactions

Data were analyzed to find out (i) frequency of patients developing ADE during therapy (ii) age and Sex distribution of reported ADEs (iii) causality assessment by both WHO-UMC scale and Naranjo's probability score (iv) severity of ADEs using scale of Hartwig and Siegle and (v) preventability of ADEs using criteria of Schumock and Thornton modified by Lau et al, 2003.<sup>9-12</sup>

### Statistical analysis

All data were analyzed with the help of Microsoft excel 2010. Data were represented as actual frequency, mean, percentage, standard deviation as appropriate. Chi square test was used for analysis and p value less than 0.05 was considered as significant.

## RESULTS

Out of total 200 patients, 110 (55%) were given benzoyl peroxide gel (2.5%) and remaining 90 (45%) patients

were given retinoic acid cream (0.025%). Majority was in age group of 16-20 (104, 52%) followed by age group of 10-15 years (52, 26%). Of these 200 patients, 124 (62%) were male and 76 (38%) were females. Most common

presentation of acne was with papules (100%) followed by comedones (95%). Majority of patients had grade 1 and grade 2 of acne. Baseline characteristics of the study patients are shown in Table 1.

**Table 1: Baseline characteristics of study patients with acne (n=200).**

Characteristic	No. of patients in Benzyl peroxide group (n=110)	No. of patients in Retinoic acid group (n=90)	Total	Chi-square test (p value)
Age (Mean ± SD)	18±2.1	20±3.3	-	0.62
Gender (M:F)	1:1.1	0.9:1	-	0.54
<b>Common presentation</b>				
papules	110	90	200	0.45
Pustules	25	27	52	0.68
Nodules	2	5	7	0.42
Comedones	108	82	190	0.53
<b>Grading of acne</b>				
Grade 1	53	40	93	0.08
Grade 2	24	18	42	0.06
Grade 3	25	27	52	0.68
Grade 4	8	5	13	0.53

SD = standard deviation; M:F = male to female ratio; Chi square test, P value <0.05 is considered significant.

**Table 2: ADRs distribution in patients of acne (n=54 events).**

Sr.no.	Reported reaction	No. of events in Benzyl peroxide group	No. of events in retinoic acid group	Total
1	Exfoliation	2	12	14
2	Burning sensation	8	5	13
3	Erythema	4	6	10
4	Itching	2	4	6
5	Photosensitivity	2	2	4
6	Hyperpigmentation /skin darkening	1	2	3
7	Dry skin	1	2	3
8	Skin maculopapular rash	0	1	1
	Total	20 (37.03%)	34 (62.96%)*	54 (100%)

\*chi-square test, p value <0.05: total number of adverse events reported was significantly higher in retinoic acid group as compare to benzyl peroxide group.

**Table 3: Causality assessments of ADRs.**

Causality category	WHO-UMC scale Number of ADRs (%)	Naranjo scale Number of ADRs (%)	Chi-square test (p value)
<b>Certain/definite</b>	3 (5.56)	0	0.07
<b>Probable</b>	35 (64.81)	37 (68.52)	0.51
<b>Possible</b>	16 (29.63)	17 (31.48)	0.82
<b>Unlikely/doubtful</b>	0	0	-
<b>Conditional/unclassifiable</b>	0	NA	-
<b>Total</b>	54(100)	54(100)	-

Chi square test, P value <0.05 is considered significant.

Out of 200 patients, 47(23.5%) developed some or other adverse drug events. Total number of events reported was 54 as few patients had developed more than one adverse drug reactions. Most of the patients fell within the age range of 16-20 years (35, 74.46%) followed by that of 10-15 years (11, 23.4%). Only one patient (2.12%) above the age of 25 had developed ADR. Of 47 patients who

developed ADRs, 28 (59.57%) were men and 19 (40.42%) were women.

Total number of adverse events reported was significantly higher (p <0.05) in retinoic acid group (34, 62.96%) as compare to benzyl peroxide group (20, 37.03%). All the adverse drug reaction affected the skin

system as all the prescribed were applied topically. Most common ADRs were exfoliation (14, 25.92%) and burning sensation (13, 24.07%). Frequencies of individual events are shown in Table 2.

The causality assessment of the ADRs was carried out using both the WHO – UMC criteria and Naranjo’s scale. The analysis using WHO – UMC scale showed that in majority of the cases, a causality association was falling in the category of ‘probable’ (35, 64.81%) and ‘possible’ (16, 29.63%) while in 3 (5.56%) cases it was found to be ‘certain’. No case fell in the category of unlikely/doubtful and conditional/unclassifiable (Table 3). Causality was also assessed using Naranjo’s algorithm. This is an objective questionnaire based method of evaluation. The common association was of probable (37, 68.52%) and possible (17, 31.48%) categories by this method. No statistically significant difference was found in causality analyses by both the methods (p >0.05).

On evaluating severity assessment by Hartwig scale, out of 54 adverse drug reactions, 44 (81.48%) were mild and 10 (18.52%) were moderate. None of the patient developed serious ADR (Table 4).

**Table 4: Severity of adverse drug reactions (Hartwig scale).**

Severity	Severity Level	No. of events (%)	Total (%)
Mild	1	32 (59.26)	44 (81.48)
	2	12 (22.22)	
	3	8 (14.81)	
Moderate	4a	1 (1.85)	10 (18.52)
	4b	1 (1.85)	
Severe	5	0	0
	6	0	
	7	0	
<b>Total</b>		54 (100)	54 (100)

**Table 5: Preventability of ADRs**

S. no.	Categories according to modified Schumock and Thornton scale	Type of ADRs	No. of events (%)
1	A	Definitely preventable	22 (40.74)
2	B	Probably preventable	8 (14.81)
3	C	Not preventable	24 (44.44)
<b>Total</b>			54 (100)

The preventability assessment of ADRs was carried out using modified Schumock and Thornton scale. As shown in Table 5, majority of ADRs were not preventable (24, 44.44%) followed by definitely preventable 22 (40.74%) and 8 (14.81%) probably preventable.

## DISCUSSION

Acne is a one of the most common disease encountered in dermatology department all over the world. Majority of times it is self-limiting in adolescent age group, but around 20-30% of patients requires therapy. Topical agents such as clindamycin, erythromycin, benzoyl peroxide and retinoic acid have been mainstays in the treatment of acne vulgaris for the past two decades.<sup>3-6</sup> Previous studies have demonstrated that the benzyl peroxide and retinoic acid can be very effective in treatment with fewer side effects. This study was aimed at Comparative evaluation of adverse drug reactions in patients of acne prescribed with either topical benzyl peroxide or retinoic acid in a tertiary care teaching hospital.

Out of 200 patients, 47 (23.5%) developed some or other adverse drug events. Total number of events reported was 54 as few patients had developed more than one adverse drug reactions. The findings are falling in the broad range of ADRs occurring with topical drugs according to different literature.<sup>5,6</sup> However, this prevalence rate is higher than that described for reported incidence of ADRs of 3-6% in general population with systemic medication use.<sup>13</sup> Highest prevalence of ADRs was in the adolescent age group with male preponderance (59.57% as compare to female 40.4%). These findings are also well correlated with the other studies done from Pakistan and other literature.<sup>5,6,14</sup> Several factors – genetic, ethnic, dietary, environmental, or simply ADRs reporting patterns may account for this relatively small difference in rate of ADRs among Indian patients.

Patients in the retinoic acid developed significantly more ADRs than benzyl peroxide group in this study (P <0.05). The most common ADR reported in both the groups was exfoliation (25.93%). Burning sensation was reported more in benzylperoxide group as compare to retinoic acid group. Rest all other ADRs like erythema, itching, photosensitivity, hyperpigmentation, drying of skin and rash were found more common in retinoic acid group. These findings are similar to other studies.<sup>14,15</sup> Few patients reported that they could not follow the advice given by doctors like avoiding sunlight, application of sunscreen and calamine lotions at the day time for ADRs which may be possible reason for development of some of the ADRs.

Causality analysis of ADRs is done by using either WHO-UMC criteria or Naranjo’s scale. However, there are very few studies wherein causality analysis of ADRs in acne patients has been carried out by both methods used concurrently. In our study, we carried out causality assessment using both the methods with the view to find whether there is any difference in assessment outcome by both methods. We found that there was no significant difference (P >0.05, Table 3) in the assessment outcome by both methods and thus both methods measure the causality assessment similarly. In earlier studies by Shah

et al and Sharma et al, compared the causality assessment using both methods in spontaneously reported events showed that there was no difference between the two methods in grading ADRs but Naranjo's scale is more time consuming.<sup>16,17</sup> Thus our study is in line with these two studies by Shah et al and Sharma et al.<sup>16,17</sup> Further, we also experienced that due to insufficient data on dechallenge or rechallenge, it became very difficult to assign the category of 'certain' or 'definite' to any ADR. Thus, both methods are effective in analysis of causality for a given ADR and any of them can be used.

One of the important parameters of ADRs analysis is to evaluate its severity. For this purpose the most commonly and best used scale is Hartwig's scale. We observed that 81.48% of adverse events were of mild severity suggesting no discontinuation of the offending drug required or withholding the causative drug without any other intervention was sufficient to treat the ADR. Only 10 (18.52%) adverse events were at level 3 or 4 meaning that they required admission to the hospital for management of ADR, or prolongation of hospital stay by at least one day in case of already hospitalized patients and required either an antidote or interventional treatment. None of the patient developed severe ADRs. The carry home message would be that we need to exercise caution and restrain in prescribing for acne as it lead to frequent mild ADRs. The physician should be able to identify occurrence of ADRs at the earliest and be ready to gear up for meeting the situation effectively.

Preventability analysis of ADRs in our study showed that around half of the ADRs (30, 55.15%) were 'definitely' or 'probably' preventable, which is consistent with the broad range of figures (30-70%) suggested in literature.<sup>18,19</sup> It is not possible to prevent all the ADRs but some ADRs (type A – Augmented – dose related) can be predicted considering the pharmacological actions of a drug. Considering the burden of ADR, related morbidity and cost involved in its treatment, it is desirable to take measures for prevention of ADRs. Though all the preventive measures are difficult to execute, but simple measures like previous history of allergy, avoiding sunlight after drug application, application of sunscreen lotions and moisturizers can easily be practiced. Enhance education of patient about prescribing can also help in reducing medication errors and ADRs.<sup>20</sup>

## CONCLUSION

Acne is a common dermatological condition and widely treated with topical antimicrobial agents, benzyl peroxide and retinoic acid. Rate of occurrence of ADRs was reported as around 23%. Significantly higher number of ADRs was reported in retinoic acid group as compare to benzyl peroxide group. Though all the ADRs were mild and moderate in severity, nearly half of them were preventable. It is very prudent to timely identify and diagnosis these ADRs and take appropriate steps for treatment and prevention.

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