Research Paper

Application of a New "Pharmvigill©" App for the Analysis of Dermatological Adverse Drug Reaction in a Tertiary Care Hospital

Shalini Chawla, Ankur Tiwari[1], Shariq Naeem Syed[2]

Departments of Pharmacology and [1]MBBS Student, Maulana Azad Medical College, New Delhi, [2]Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh, Uttar Pradesh, India

Abstract

Aim: To assess the patterns of dermatological adverse drug reactions (ADRs) and drugs responsible to formulate a strategy for prevention and treatment using a new app. **Materials and Methods:** In the present study, 870 patients in dermatology outpatient department were screened, out of which sixty cutaneous ADRs were included in the study. The ADRs were categorized and assessed by Causality Assessment Scale and Preventability Scale using an innovative mobile software application named "Pharmvigill©-ADR analyzer App." **Results:** It was observed that rashes and acneiform eruption (25% and 16.7%, respectively) were the most common cutaneous ADRs. Nonsteroidal anti-inflammatory drugs (25%) were the most common group of drugs causing cutaneous ADRs followed by antimicrobial drugs (23.3%) and steroids (20%). Similarly, betamethasone, paracetamol, and phenytoin were the most common drugs causing ADRs. In the causality assessment, almost 81% fell into the category of "probable," whereas 58.8% of the ADRs were "probably preventable" and almost 40% were "not preventable." There was no statistically significant difference ($P > 0.05$) between scores in manual assessment and software-based assessment. **Conclusion:** Cutaneous ADRs are caused by some of the very commonly prescribed medicines. A high degree of suspicion is required to identify the "preventable" type of ADR. The ADR analysis app "Pharmvigill" is accurate and can decrease the analysis time of the ADRs in a dynamic clinical scenario.

Keywords: Adverse drug reactions, Pharmvigill© app, skin

Introduction

The World Health Organization (WHO) states adverse drug reactions (ADRs) as one of the most common causes of preventable morbidity and mortality in patients. Their occurrence imposes a huge economic and psychological burden on the society and nations.[1] The severity of the problem can be highlighted by the fact that ADRs are now the fourth leading cause of death in the USA.[2] It is, therefore, imperative to identify these ADRs as early as possible to avoid any permanent damage.[3,4] It is also a challenge for physicians to differentiate it from the normal symtomatology of the developing disease.

Skin is the most commonly affected organ by ADRs of the prescription medication. Dermatology outpatient departments (OPDs) of various hospitals deal with a large proportion of such patients. According to a study, cutaneous drug reactions are the most common ADRs (30%–45%) and are responsible for about 2% of hospital admissions in India.[5] The incidence of cutaneous ADRs in developed countries ranges from 1% to 3% among inpatients.[6] As the cutaneous ADRs are visible and can be easily detected by the patients themselves, they are often more reported than the ADRs involving other systems. Among the visible cutaneous ADRs, the most common ones are fixed drug eruptions, exanthematous drug reactions, acute urticaria, Steven–Johnson syndrome, exfoliative dermatitis, etc. These ADRs are caused by a range of drugs including antimicrobials, anticonvulsants,

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Address for correspondence: Shariq Naeem Syed, Department of Pharmacology, Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh - 202 002, Uttar Pradesh, India.
E-mail: syedshariq1@gmail.com

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anti-inflammatory drugs, and cancer chemotherapeutic agents. A meta-analysis has shown that almost 52% of the ADRs in OPD and 45% of ADRs in inpatient department patients are preventable.[7] Thus, the reporting of cutaneous ADRs not only provide valuable information for primary prevention, but also to build a consolidated data that may help plan a policy to prevent ADRs.

The analysis of data is equally important as reporting of data. These data can easily be analyzed by using information and technology tools. One such innovative tool used in the study was "Pharmvigill©-ADR analyzer" mobile app. The app is specially designed to help analyze the ADRs for causality, preventability, predictability, and severity. The data will be used for assessing the app for functional sensitivity.

Hence, this study was aimed to assess the ADRs of the patients presenting to the dermatology OPD in a tertiary care hospital and to analyze and compare the ADR profile using manual method and Pharmvigill app.

Materials and Methods

The study was designed as an observational, prospective, open-label, noninterventional study. The study was approved by the Institutional Ethics Committee of Maulana Azad Medical College and Associated Hospitals. The patients who presented to the dermatology department with suspected ADRs were enrolled in the study after obtaining a written, informed consent from them. Patients of all age groups and either gender were included in the study. The diagnosis was made by a dermatologist based on a detailed history and physical examination.

The data were collected using the Central Drugs Standard Control Organization ADR reporting form. The following details were noted in the ADR form: (1) patients' particulars, such as patients' initials, age, gender, occupation, and weight, (2) details of suspected ADRs including onset of reaction, initiation of drug therapy, description of reaction, laboratory data, and outcome of the reaction; and (3) detailed history of the drug and details of de-challenge and re-challenge.

The data were analyzed for the following parameters: (1) incidence of the cutaneous ADRs, calculated using the following formula: total number of patients with cutaneous ADRs × 100/total number of dermatology patients observed-(2), age and gender-wise distribution of the ADRs (%)-(3), nature of the cutaneous ADRs (%)-(4), major groups of the drugs responsible for the cutaneous ADRs- (5), causality assessment of the ADRs (using Naranjo ADR assessment scale); and (6) preventability of cutaneous ADRs (using Modified Schumock and Thornton criteria).

Pharmvigill-adverse drug reaction analyzer mobile app

It is an Android-based mobile app used for the analysis of ADRs. The app is a freeware and can be downloaded from the Google Play Store. The size of the apk file is 0.99 MB, while on the mobile storage, it is saved as a folder of 3.88 MB in size. It can be used on Android devices with Android 2.0 operating system and above. The language of the app is English with some screenshots from the app are shown in [Figures 1-6].

It combines five different ADR analysis scales consisting of more than 56 test items into a single questionnaire consisting of 16 questions. The scales incorporate (1) WHO-Uppsala Monitoring Center Causality Assessment Scale,[8] (2) Naranjo's Causality Assessment Scale,[9] (3) Council for International Organizations of Medical Sciences Predictability Scale, (4) Hartwig's Severity Scale,[10] and (5) Modified Schumock and Thornton's Preventability scale.[11] To scale down the question from 56 to 16 items, an algorithm was made defining 56 questions in five different scales. Similar questions were combined together in single items. Whenever any additional data set was required for a particular item, a secondary question was added as an add-on question (which would be executed once a specific response is clicked). All the questions were same as that in the respective scales, and the overall scores of scales were notchanged. The outcome of the app is precise and significantly decreases the time for the analysis of ADRs.[12]

The number of ADRs was categorized as per the causality and preventability scales using both manual method and through the Pharmvigill app. The number of ADRs in each subgroup (e.g., probable, possible, and certain) was compared using statistical analysis. If the *P* value came out to be not significant, it means that the results of the two scales were comparable.

Statistical analysis

Statistical analysis was done using SPSS 17 software (IBM corporation, Armonk, New York, USA). The values are represented as averages and percentages. The comparison of causality assessment and preventability assessment was done by using Chi-square test, and $P < 0.05$ was taken as statistically significant. Graphs were made using MS Office.

Results

A total of 870 patients who presented to the dermatology department were screened. Out of these, sixty patients with

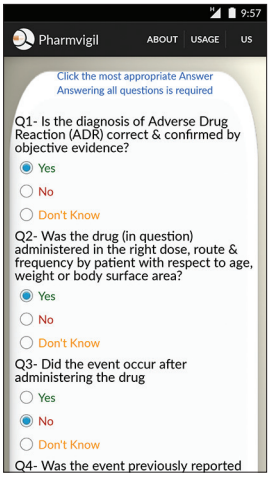

Figure 1: Pharmvigill app screenshot: Landing page and questions

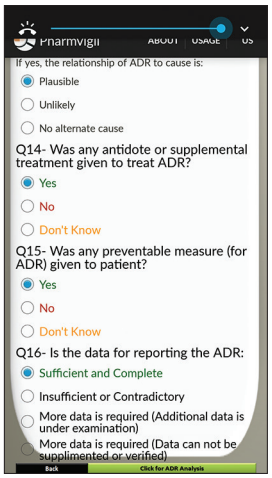

Figure 2: Pharmvigill app screenshot: Question and analysis page

Figure 3: Pharmvigill app screenshot: Scales and results' page

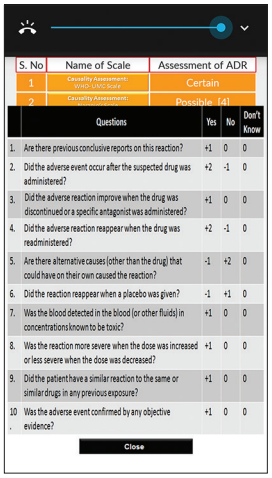

Figure 4: Pharmvigill app screenshot: Details of the scales

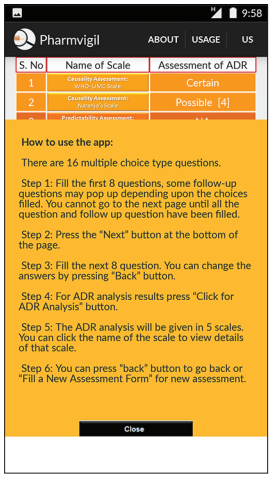

Figure 5: Pharmvigill app screenshot: User manual

suspected cutaneous ADRs were selected for the study. The incidence rate of cutaneous ADRs was calculated as 68.9 suspected ADRs/1000 dermatology patients.

The age- and gender-wise distribution of ADRs [Table 1] showed that the occurrence of ADRs has a female preponderance. There is remarkably lower number of ADRs in the age group <15 years, which might be either due to the use of much safer drug in this age group or Berkinsonian bias reflecting the number of patients presenting to the particular OPD. The number of ADRs is almost equally distributed among the age groups of 15–30 years and >30 years.

Cutaneous ADRs were more commonly reported by patients due to high visibility than the ADRs from other systems (which are often reported late when symptoms become more apparent). Among the cutaneous ADRs, rashes were the most commonly reported (25% of all cutaneous ADRs) followed by acneiform eruptions (16%) and Steven–Johnson syndrome (10%) [Table 2].

Among the drug groups, the nonsteroidal anti-inflammatory drugs (NSAIDs) had the highest incidence of cutaneous

Table 1: Age- and gender-wise distribution of adverse drug reactions

Age (years)	Male	Female	Total (%)
<15	2	3	5 (8.3)
15-30	10	15	27 (45.0)
>30	12	18	28 (46.7)
Total	24	36	60 (100.0)

ADR=Adverse drug reaction

ADRs, accounting 25% of the total ADRs, followed closely by antimicrobial agents (23.3%). Higher incidence of ADRs of these groups might be due to the higher prescription frequency of these drugs. Apart from these groups, steroids (20%), antiepileptics (16.7%), and anticancer drugs (13.3%) also had a considerable percentage of cutaneous ADRs [Table 3].

In case of drugs, betamethasone (13.3%) was the most common drug implicated in the cutaneous ADRs. The top five drugs consisting of paracetamol (10%), phenytoin (8.3%), diclofenac (6.7%), carbamazepine (5%), and metronidazole

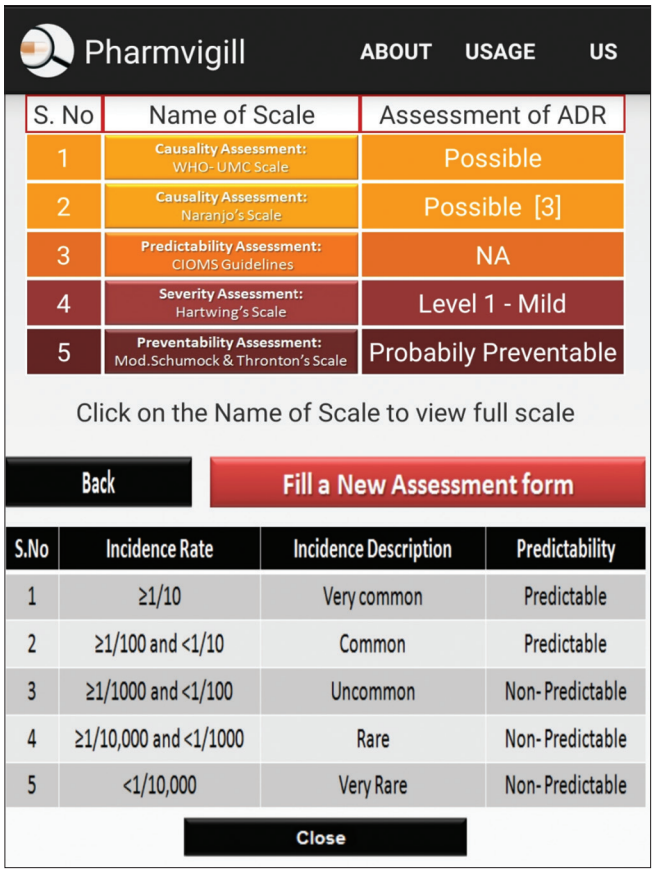

Figure 6: Preventability assessment of cutaneous adverse drug reactions

(5%) with betamethasone consisted almost 48% of the reported ADRs in the skin [Table 4].

Using the manual assessment, causality assessment showed that almost 81% of the cutaneous ADRs fell in the "probable" range, whereas 13.3% belonged to "possible" category. Similar results can be seen with the app where almost 80% of the ADRs came under the "probable" category. The "definite" category came at a dismal third with only 5% of the total cutaneous ADRs as calculated manually as well as through the mobile app. The difference in values in causality assessment done manually and through mobile app was not statistically significant ($P > 0.05$) [Table 5].

Preventability assessment was done using the Modified Schumock and Thornton criteria. The assessment showed 58.3% of the ADRs as "probably preventable," whereas 40% were categorized as "not preventable." The assessment through the mobile app showed similar results [Table 6].

Discussion

Cutaneous ADRs are the most commonly reported ADRs. The visibility of the skin ADRs makes the patients report them earlier than other ADRs. Second, the diagnosis of skin ADRs is much more definitive and easier than ADRs involving other systems. Cutaneous ADRs range from mild rashes, exanthematous eruption, or fixed drug eruption to markedly severe forms such as toxic epidermal necrolysis.

Table 2: Types of cutaneous adverse drug reactions

Cutaneous ADR	Frequency (%)
Rash	15 (25.0)
Acneiform eruption	10 (16.7)
Steven-Johnson syndrome	6 (10.0)
Exanthematous eruption	4 (6.7)
Fixed drug eruption	4 (6.7)
Erythema and erythema multiforme	3 (5.0)
Urticaria	3 (5.0)
DRESS syndrome	3 (5.0)
Alopecia	2 (3.3)
Hand and foot syndrome	2 (3.3)
Striae and cushingoid habitus	2 (3.3)
Pruritis	2 (3.3)
Rosacea	1 (1.7)
Erythroderma	1 (1.7)
Toxic epidermal necrolysis	1 (1.7)
Hypopigmentation and atrophy	1 (1.7)
Total	60 (100.0)

ADR=Adverse drug reaction, DRESS=Drug rash with eosinophilia and systemic symptoms

Table 3: Major groups of drugs causing cutaneous adverse drug reactions

Drug group	ADR	Percentage
Steroids	12	20.0
Antimicrobials	14	23.3
Antiepileptics	10	16.7
NSAIDs	15	25.0
Anticancer	8	13.3
Others	1	1.7

ADR=Adverse drug reaction, NSAIDs=Nonsteroidal anti-inflammatory drugs

Table 4: Most common drugs causing cutaneous adverse drug reactions

Drug	ADR	Percentage (%)
Betamethasone	8	13.3
Paracetamol	6	10.0
Phenytoin	5	8.3
Diclofenac	4	6.7
Metronidazole	3	5.0
Carbamazepine	3	5.0
Carboplatin	2	3.3
Ethambutol	2	3.3
Co-trimoxazole	2	3.3
Clobetasol	2	3.3
Aspirin	2	3.3
Ibuprofen	2	3.3
Others	19	31.7

ADR=Adverse drug reaction

Table 5: Causality assessment of cutaneous adverse drug reactions (Naranjo's Scale)

Causality assessment	Manually	Using mobile app Pharmvigill-ADR analyzer	Statistical difference (*P*)
Definite	3	3	>0.05
Probable	49	48	>0.05
Possible	8	9	>0.05

ADR=Adverse drug reaction

Table 6: Preventability assessment of cutaneous adverse drug reactions

Preventability	Manually	Using mobile app Pharmvigill-ADR analyzer	Statistical difference (*P*)
Definitely preventable	1	1	>0.05
Probably preventable	35	35	>0.05
Not preventable	24	24	>0.05

ADR=Adverse drug reaction

In the present study, the incidence of cutaneous ADRs was found to be 68.9/1000 patients (6.89%). Different studies have quoted diverse incidence of cutaneous ADRs ranging from 1% to 8%.[13] It is observed that there is a large variation in the incidence rate between outdoor and admitted patients with a high prevalence of 11.2% as reported in the intensive care unit patients.[14] These studies only take into account the reported ADRs which are merely the tip of the iceberg. A significantly large proportion of the patients with milder ADRs do not report, leading to the underreporting of the actual incidence of ADRs.

The incidence of a specific ADR also depends on the type of the medication commonly prescribed to the patients. For example, a tertiary care neurology center has a reasonably high footfall, with high phenytoin prescription rates, which can explain the higher number of Steven–Johnson syndrome reports in the study. Similarly, the acneiform eruption points toward more widespread use of steroids and hormonal drugs.

NSAIDs and antimicrobials are the major groups implicated in the occurrence of cutaneous ADRs, which is consistent with previous studies. These groups comprise almost 48% of the total cutaneous ADRs reported. The higher incidence with these groups can be explained by the fact that they are the most prescribed groups of medications in India, and they are also available as over-the-counter medications.

Assessment of ADRs is an important issue in clinical medicine. The scales of causality, preventability, and severity assessment are tools in the comprehensive analysis of ADRs. The scales are long and cumbersome when used manually. To simplify the process, Pharmvigill-ADR analyzer App was used. The results indicated that there was no statistically significant difference between the results of app and manual calculation, but the time consumed in the process was markedly lower with the app. In causality assessment, most of the ADRs were categorized into the "probable" category." Only 5% of the ADRs were grouped under the "definite category." It may be due to the stringent criterion of de-challenge and re-challenge of the drugs which, in clinical practice, is seldom done. The study also reveals that a large proportion of the ADRs are preventable, which is in agreement with the previous similar studies.[15]

There are a few limitations of the study. The duration of the study was less, and further studies with more patients are required to obtain a more comprehensive view of the cutaneous ADR spectrum. The patients referred from the radiotherapy department were also included, which led to a slight increase in ADRs reported in anticancer drugs.

Conclusion

Cutaneous ADRs are the most common type of ADRs reported. As a group, NSAIDs are the most common drug group, and beclomethasone is the most common drug implicated for cutaneous ADRs in dermatology OPD. The ADR analysis app "Pharmvigill" is as accurate as manual analysis method for assessing ADRs in a dynamic clinical scenario.

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Conflicts of interest

There are no conflicts of interest.

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