CUTANEOUS ADVERSE DRUG REACTION AND THEIR EONOMIC BURDEN ASSOCIATED WITH PATIENTS ADMITTED IN DERMATOLOGY DEPARTMENT OF A TERITARY CARE TEACHING HOSPITAL

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Abstract

The aim of this study was to explore the factors associated with the occurrence, subsequent prognosis and need for additional medications following cutaneous adverse drug reactions (ADRs) among inpatients and their Pharmaco economic status. To evaluate the clinical patterns of various drug induced cutaneous reactions and their economic impact on patients admitted in hospital. To evaluate the clinical patterns of various drug induced cutaneous reactions. An Ambispective observational study was conducted in a tertiary care Teaching hospital of dermatology department. The data of in-patients of 1 unit of the department of dermatology and therefore the in-patients referred from other departments thanks to cADRs were included within the study. The diagnosis of the cADR was made by the dermatologist supported on clinical and morphological grounds. The cost incurred in managing the documented cADRs was calculated supported the full total amount spent on the patients with cADR divided by total number of patients with ADRs. The outcome of this study may useful to predict and prevention of ADRs early, therefore reduces the treatment cost of Internal medicine wards which ends up with in the effective healthcare budget of the hospital.

Keywords: occurrence, Pharmaco economic status, patients, ADR, dermatology.

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Introduction

Cutaneous adverse drug reactions (CADR), also known as toxidermia, are skin manifestations resulting from systemic drug administration. These reactions range from mild erythematous skin lesions to much more severe reactions suchas Lyell's syndrome [1] [2].Cutaneous adverse drugs reactions (CADRs) are common among ADRs. They account for patients' suffering, hospitalization and economic burden, and may sometimes be fatal. [3] [4] Adverse Drug Reactions (ADR's) represent the most frequent cause of injuries due to medical care in hospitals in developed countries [5,6]. Heightened interest in ADRs was stimulated by the thalidomide tragedy in the 1960's [7].Although ADRs are a common problem in hospital and community setting, data has revealed that maximum number of patients due to adverse drug reactions usually suffer from cutaneous reactions. Cutaneous adverse drug reactions (CADRs) account for the most common and challenging type of different adverse reactions. A CADR is any unwanted harmful changes in the skin, its appendages or mucous membranes, and it includes all adverse events related to drug eruption [8].The incidence of CADRs in developed countries range from 1-3% among in-patients [9], whereas in developing countries such as ours, some studies peg it at 2-5% of the in-patients [10-13]

Awareness about the culprit drugs can help physicians to choose safer medicines [14]. The Naranjo Scale is a specific questionnaire designed for determining the likelihood of probability and is assigned through a score that is termed as definite, probable, possible, and doubtful [15]. The pattern of drug reactions and the offending drugs show changing trends with the introduction of newer drugs. The reactions can mimic viral exanthemas, neoplastic diseases, or collagen vascular diseases [16]. Although these types of cutaneous eruptions are common and complete information about their incidence, severity, complications and ultimate health effects are still unavailable because most of these cases are usually remain unreported [17].

In India, very few reports on the cost of ADRs are available. There is a need to study this aspect of health care in order to understand the economic burden imposed by ADRs. The aim of the current work was to study the cost associated with documented ADRs in a tertiary care teaching hospital.

Risk factors for ADRs

The various risk factors for ADRs are listed below.

1. Age Although relatively few data are available, adverse events are more frequently encountered at the extremes of age. In the neonate, the liver and kidney enzymes necessary for drug metabolism and elimination are not optimally functional and clearance of many drugs is less than in adults. In the elderly, changes in liver and kidney function may decrease drug elimination. [21]

2. Sex

Women are reported to have a 50 percent higher rate of adverse effects than men.[22] This is explained by the fact that there are frequent periods in a woman's life (menarche, pregnancy, lactation and menopause) when there is alteration of pharmacokinetics of drugs.[23] Also women may more frequently seek medical attention than men.

3. Past history of reactions

Reports suggest that patients with past history of ADRs are more likely to experience further ADRs. In one study 28 percent of patients who developed ADRs had a previous history of adverse drug reaction. [24]

4. Genetic factors

Genetic factors may be important. This may include polymorphism in drug metabolism and other genetic variations. The association of Stevens-Johnson syndrome toxic epidermal necrolysis (SJS-TEN) and drug hypersensitive syndrome to specific human leukocyte antigen (HLA) subtypes has been reported. [25]

5. Environmental factors

Infectious agents, sun exposure etc. may precipitate severe cutaneous drug reactions. [26]

Recognizing adverse drug reactions

For estimating the probability that a specific drug is responsible for an ADR, several scales have been developed.[27-29] The most widely used is the Naranjo algorithm.[27] It has good internal reliability and assessment can be carried out quickly; it consists of ten questions about the probability that the reported ADR is due to a particular drug. A score of 1 to 4 points indicates that an ADR is considered possible, 5 to 8 probable, and 9 or more definite. The criteria to be considered in diagnosing severe cutaneous adverse reactions and their causes are as follows.2

1. Alternative causes should be excluded, especially infections, since many infectious illness are difficult to distinguish clinically from the adverse effects of drugs.
2. The interval between the introduction of a drug and the onset of a reaction should be examined.
3. Any improvement after drug withdrawal should be noted.
4. The physician should determine whether similar reactions have been reported with the same compounds.
5. Any reactions on re-administration of the drug should be noted.

Types of ADRs

ADRs may be due to immunological or non-immunological mechanisms, the latter being more common. ADRs may be predictable (type A) or unpredictable (type B). [31-33]

Type-A (Predictable reactions)

These are due to known pharmacological actions of the drugs, are usually dose related and occur in otherwise normal individuals. Predictable reactions include toxicity or overdose, side effects, drug interactions and secondary effects.

Type-B (Unpredictable reactions)

These are dose independent, not related to pharmacological actions of the drug and may have a genetic basis. These reactions are divided into three categories: intolerance idiosyncratic reaction and hypersensitivity reaction.

Type C reactions include those associated with chronic therapy.

Type D reactions consist of delayed reactions e.g. carcinogenesis and teratogens.

Economic status:

Cost analysis of ADRs raises important issues, like which perspective to adopt in analyzing ADRs. A social perspective is preferred in a Pharmacoeconomic evaluation, since it includes all the relevant costs. [18] Cost of ADRs includes hospital costs, in particular those arising from an increase in length of stay caused by an ADR. Usually, the cost of excessive hospital stays is used to calculate the additional cost of ADR management for insurance companies or the health care system.[19] [20].

Many studies have documented risk factors, including age, gender, comorbidities, polypharmacy, inappropriate use of drugs, poor cognitive function, alcohol intake, length of stay and depression, as associated with ADRs. [34-38]. However, lifestyle, food style, medical-seeking behaviours and healthcare systems in Asian countries are quite different from western countries. In this sense, the genetic characteristics and susceptibility to drugs, and prescription behaviors were also different in various ethnic groups. For example, the study setting is under a compulsory national health insurance system in which patients are usually seeking multiple medical assistances including western medicine, herbal medicine and food supplements at an affordable cost. Therefore, the characteristics and factors associated with ADRs and the subsequent medical and economic impacts are anticipated to be different.

ADRs contribute to lengthened hospital stays, increased medical expenses and, most importantly, decreased care quality and safety.[35] [36] [37-40]. Because older inpatients are more likely to have multiple conditions and chances for ADRs, ADR issues in older individuals are worthy of attention. Although many studies have documented risk factors of ADR occurrence, most of the study samples were from western populations.[41] [42] Due to the differences in ethnicity and healthcare systems, an investigation of Asian ethnicities with a large series of cases is warranted. This study aimed to examine factors associated with ADRs, and the impacts of these factors on prognosis and medical expenses among older inpatients in an Asian population.

METHODS:

The data of in-patients of 1 unit of the department of dermatology and therefore the in-patients referred from other departments thanks to cADRs were included within the study. The diagnosis of the cADR was made by the dermatologist supported on clinical and morphological grounds. The identification of cADR, causality assessment, management, documentation of outcome and screening for predisposing factors was allotted out using standard operating procedure.

The cost incurred in managing the documented cADRs was calculated supported the full total amount spent on the patients with cADR divided by total number of patients with ADRs. Within the cases where the offending drug was stopped and where the treatment was continued with none change, the value of treatment was considered as nil. All the cases which involved expenditure on drugs, laboratory tests, consultation, hospital stay etc., were considered for the calculation of the

price incurred for the hospital. If the patient was shifted to the intensive care unit from the ward to which he/she was admitted in order to manage cADRs, this additional price of care was added to the total value. Only direct price were included for the value calculation.

RESULTS:

Case records of all patients managed by the specific unit of the dermatology department during the study period were included for the review. The cases included patients admitted to the study unit directly and patients referred by / transferred from other treating departments. Totally 132 cADRs were identified in such patients. Median age (in years) of the patients was 38 (Range 10-72). The number of males with ADRs was higher than number of females in the documented records.

Table 1. Demographic characteristic of patients

Characteristics	Number of patients with cADR (n=132)	Number of patients related hospitalization due to cADR (n=39)	Number of patients developed with cADR during hospital stay (n=93)
Male	69	15	39
Female	63	24	54
< 21	10	2	12
21-30	17	6	17
31-40	41	3	26
41-50	32	10	18
51-60	12	6	7
>60	20	12	16

The number of cADRs observed in age groups of 31 to 40 and 41 to 50 years was higher than other age groups (Table 1). The median length of stay of study population was 17 days (Range 7-26). Type B reactions accounted for 43 of the cADRs followed by Type A reactions 89 Twenty five patients had more than one cADRs (Range: 2-4) (Table 2).

Table.2 Classification and Assessment of ADRs

Parameters	Number of ADRs(n=157)
Type A	89
Type B	43
Causality	
Definite	5
Probable	79
Possible	48
Onset of ADRs	
Acute (< 1 h)	28
Sub-acute (1 to 24 h)	61
Latent (> 48 hrs)	43
Severity	
Mild	45
Moderate	82
Severe	5
Preventable	
Definitely preventable	28
Probably preventable	92
Not preventable	12
Predisposing Factors	
Age	24
Gender (Female)	**34**
Multiple and inter-current disease	**74**
Polypharmacy	**182**
Minor	**27**
Moderate	**56**
Severe	**98**

The most frequently reported reaction was Maculopapular rash (54) followed by acne (18) and Urticaria (18). In 18 cases the cADR was responsible for hospitalization [(12 angioedema, 12Stevens Johnson Syndrome (SJS), 5 Toxic Epidermal Necrolysis (TEN)] (Table3).

Table 3 Cutaneous ADRs and drugs involved.

ADRs	No of cases n=183	Drugs involved
Acne	18	Navirapine (3), Phenytoin (4), carbazapine (3), amoxapine (3), isoniazide (4), lithum (2)
Angioedema	12	Azithromycin (2), Ceftriaxone(3), Ciprofloxacin(4), Lopromide (1), Piperacillin+tazobactum (2),Prednisolone (1)
Dermographia	4	Nimesulide (1), cefotaxime(2), erythromyscin(1)
Epidermal necrolysis	8	Amoxycillin+clavulanate (3), Diclofenac (2), Fluconazole (1), Levofloxacin (1), Phenytoin (1)
Erythema multiforme	4	Azithromycin (2), Fluconazole (1), Lamivudine (1)
Hypertrichosis	4	Cefotaxime (1), phenytoin(2), cyclosporine(1)
Pruritus	9	Amoxycillin+clavulanate (4), Ceftriaxone (3), Cefuroxime (1), Ciprofloxacin (1), Diclofenac (1)
Rash erythematous	14	Azithromycin (4), Cefixime (3), Ciprofloxacin (1), Levofloxacin (2), Piperacillin+tazobactum (2),Zidovudine (3)
Rash maculopapular	54	Acylovir (4), Amlodipine (4), Amoxycillin+clavulanate (6), Ampicillin (2), Azithromycin (3), Betadine(3), Carbamazepine (3), Cefotaxime (1), Ceftriaxone (8), Cefuroxime (1), Ciprofloxacin (6),Clindamycin(1),Co-trimoxazole (2), Diclofanac+ paracetamol (1), Diclofenac (3), Etoricoxib(1),Gentamycin(1),Hydroxy urea (1), Ibuprofen (2), Isoniazid+Rifampin+Pyrazinamide+ Ethambutol (1).
Skin discolouration	9	Betadine (1), amiodarone(3), tetracycline(2), chloroquine(3)
Stevens Johnson Syndrome	12	Carbamazepine (1), Ciprofloxacin (2), Indomethacin (3), lamivudine (2), Phenytoin(2),furosemide (2)
Urticaravessicuiosa	12	Amoxycillin+clavulanate (1), Carbamazepine (1), Ceftriaxone (1), Derriphylline (1), Glipizide (1), Levofloxacin (1), Paracetamol (1)
Urticaria	18	Ampicillin (4), Atorvastatin (2), Cefixime (2), Ciprofloxacin (4), Diclofenac (3), Paracetamol (1),Phenytoin (1), Tramadol (1)
TEN	5	Phynetoin(2), fluconazole(3).

The cost incurred in managing the documented cADRs was calculated based on the total amount spent on the patients with cADR divided by total number of patients with ADRs. In the cases where the offending drug was stopped and where the treatment was continued without any change, the cost of treatment was considered as nil. All the cases which involved expenditure on drugs, laboratory tests, consultation, hospital stay etc., were considered for the calculation of the cost incurred for the hospital. If the patient was transferred to the intensive careunit from the ward to which he/she was admitted in order to manage cADRs, this additional cost of care was added to the total cost. Only direct costs were included for the cost calculation. (Table 4).

Table 4 Management and outcome of the cADR

ADRs	FREQUENCY
Acne	18
Angioedema	12
Dermographia	4
Epidermal necrolysis	8
Erythema multiforme	4
Hypertrichosis	4
Pruritus	9
Rash erythematous	14
Rash maculopapular	54
Skin discolouration	9
Stevens Johnson Syndrome	12
Urticaravessicuiosa	12
Urticaria	18
TEN	5

The minimum cost incurred for managing cADRs was Rs.82 and the maximum cost incurred was Rs. average cost of Rs.3, 78,748 (US$ 5112) each. (Table 5). Type B reactions accounted for 43 of the cADRs followed by Type A reactions 89 Twenty five patients had more than one cADRs. The most frequently reported reaction was Maculopapular rash (54) followed by acne (18) and Urticaria (18). In 18 cases the cADR was responsible for hospitalization [(12 angioedema, 12Stevens Johnson Syndrome (SJS), 5 Toxic Epidermal Necrolysis (TEN)]. The total cost incurred in managing all cADRs reported was Rs 895281.3. (US$ 12083.7) The minimum cost incurred for managing cADRs was Rs.82 and the maximum cost incurred was Rs. 31,562 (US$ 426). Five patients had severe reactions and incurred the highest expenditure, with an average cost of Rs.3, 78,748 (US$ 5112) each (Table 5).

Table 5 Cost involved in the management of cADRs

ADRs	Frequency	Total Cost in US$.	Average case Cost per US $
Acne	18	289.39	16.07
Angioedema	12	3210.1	267.5
Dermographia	4	14.3	3.575
Epidermal necrolysis	8	17.35	2.16
Erythema multiforme	4	16.13	4.03
Hypertrichosis	4	19.25	4.81
Pruritus	9	29.87	3.318
Rash erythematous	14	23.12	1.65
Rash maculopapular	54	1205.89	22.33
Skin discolouration	9	2107.12	234.1
Stevens Johnson Syndrome	12	5112.1	426.0
Urticara vessicuiosa	12	19.24	1.60
Urticaria	18	19.87	1.10
TEN	5	458.69	91.73

DISCUSSION:

Totally 132 cADRs were identified in such patients. Median age (in years) of the patients was 38 (Range 10-72). The number of males with ADRs was higher than number of females in the documented records.

The number of cADRs observed in age groups of 31 to 40 and 41 to 50 years was higher than other age groups (Table 1). The median length of stay of study population was 17 days (Range 7-26). Type B reactions accounted for 43 of the cADRs followed by Type A reactions 89 Twenty five patients had more than one cADRs (Range: 2-4) (Table 2).

The most frequently reported reaction was Maculopapular rash (54) followed by acne (18) and Urticaria (18). In 18 cases the cADR was responsible for hospitalization [(12 angioedema, 12Stevens Johnson Syndrome (SJS), 5 Toxic Epidermal Necrolysis (TEN)] (Table3).

The cost incurred in managing the documented cADRs was calculated based on the total amount spent on the patients with cADR divided by total number of patients with ADRs. In the cases where the offending drug was stopped and where the treatment was continued without any change, the cost of treatment was considered as nil. All the cases which involved expenditure on drugs, laboratory tests, consultation, hospital stay etc., were considered for the calculation of the cost incurred for the hospital.

The total cost incurred in managing all cADRs reported was Rs 895281.3. (US$ 12083.7) The minimum cost incurred for managing cADRs was Rs.82 and the maximum cost incurred was Rs. 31,562 (US$ 426). Five patients had severe reactions and incurred the highest expenditure, with an average cost of Rs.3, 78,748 (US$ 5112) each.

LIMITATIONS OF THE STUDY:

Rechallenge was not performed for many ADR cases and this might alter the causality if such information is available for all the cases. While polypharmacy was found to be a significant risk factor for ADR, the therapeutic rationale of individual prescriptions were not assessed thus any underlying problems with the prescriptions were not identified.

CONCLUSION

CADRs have discovered to be a widespread hassle in healthcare and maximum of those reactions can be iatrogenic. Hence its miles of maximum significance that clinicians should have complete expertise of suspected damaging drug

reactions with all older and more modern medicines.

Along with this, early reporting and prevention of damaging drug reactions with the aid of using medical doctor will honestly lessen the frequency and severity of ADRs and sooner or later the affected person protection can be enhanced.

Hence, the clinicians ought to be recommended for the reporting of ADRs, due to the fact on this exercise they may genuinely early apprehend and reply to the response and enhance the affected person protection with the aid of using prevention of those reactions in future.

The final results of this take a look at may also beneficial to be expecting and prevention of ADRs early, consequently reduces the remedy fee of trendy medicinal drug wards which ends up withinside the powerful healthcare finances of the hospital.

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