

Causality, Severity and Preventability Assessment of Adverse Cutaneous Drug Reaction: A Prospective Observational Study in a Tertiary Care Hospital

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ABSTRACT

Introduction: The number of subjects involved in a clinical trial are limited, whose findings cannot be extrapolated to the entire population. Due to the emergence of newer molecules the pattern of Adverse Cutaneous Drug Reaction (ACDR) also changes frequently. The need for this study is for early diagnosis, to reduce the morbidity and mortality due to ACDR and to ensure safety of the patients.

Material and Methods: Forty one subjects with the diagnosis of ACDR were included in the study for a period of 12 months (Jan 2009- Dec 2009). The informations such as patient demographic

details, drug history, associated comorbid conditions and pattern of the skin reaction were noted. Assessment was done for causality, severity and preventability using separate valid scales.

Results: The most common ACDR was fixed drug eruption (43.9%) and the most common causative drug for the same was surprisingly found to be paracetamol. Antimicrobials were the most common causative drug group and two significant associated risk factors were multiple drug intake and history of allergy. Among the total reactions 78% were of probable category and 59% were of moderate level severity reaction. Out of which 12% of the cases were definitely preventable.

Keywords: Fixed drug eruption, Drug alert card, Polypharmacy

INTRODUCTION

Fitzgerald emphasized that, 'the safety of drugs is of paramount importance to patients and healthcare professionals'. The repercussions of a new drug having a potentially serious side-effect profile are enormous for patients, healthcare professionals and the industry. There have been many drugs that were very successful and benefited thousands of patients, but were later found to have serious side-effects, resulting in their withdrawal [1]. Olsson S. has mentioned that, 'drug-related disease causes a considerable burden to healthcare systems around the world'. The lack of awareness in society about the magnitude of drug-related problems is a mystery. One reason is probably that drug-related injuries are not always obvious, immediate and visible. They often manifest themselves gradually and with symptoms similar to those caused by common diseases [2]. The main responsibility of any drug regulatory authority is to ensure the quality, efficacy, and safety of all marketed products. The first two criteria can be established through data obtained from preclinical and clinical trials. It is a well-established fact that pre-marketing clinical trials do not have the statistical power to detect rare Adverse Drug Reactions (ADR) nor do they have significant follow-up to identify delayed ADRs or effects from long-term exposure. In view of this, Pharmacovigilance plays a prominent role in establishing the safety profile of marketed drugs [3]. Adverse cutaneous drug reactions (ACDR) are the commonly reported type of ADR [4]. Although such cutaneous reactions are common, information regarding their incidence, severity and ultimate health effects are often not available as many go unreported [5]. Cutaneous ADR patterns and the drugs causing various reactions are changing every year, which may be due to the emergence of newer molecules and changing trends in the use of drugs [6]. The need for this study is for early diagnosis, to reduce the morbidity and mortality due to ACDR and to ensure safety of the patients.

MATERIAL AND METHODS

This prospective, descriptive, observational study was conducted in Department of Pharmacology in collaboration with Department of Dermatology, Venereology, Leprology (DVL) in a hospital at Puducherry during the time period from January 2009 to December 2009 (12 months). The study got approval from the Institutional Human Ethical Committee (IHEC) and subjects were enrolled for the study. Subjects attending Department of DVL with the diagnosis of ACDR who fulfilled the inclusion & exclusion criteria were enrolled into the study. This includes both in-patients and out-patients including those who were referred from other departments. Patients of all age group presenting with cutaneous lesions following intake of any drugs were included in the study. Patients with drug reactions without cutaneous manifestations were excluded. The diagnosis was done by the attending dermatologist. The subjects were given information about the study and written consent was taken from them. The following data were noted down in the ADR reporting form.

General History: Subject's demographic details, detailed clinical history, including pre-existing medical conditions like diabetes mellitus, hypertension etc., and relevant laboratory data were noted down.

Drug History: Drugs used during the 3 weeks preceding the adverse reaction, route of administration, dosage, concomitant medical products if any including self-medication and herbal remedies, duration of treatment, improvement after discontinuation of drug, purpose of taking the drug, whether prescribed or over-the-counter drug were noted. Past history of drug allergy, family history of drug reactions and history of any skin disease was recorded.

Drug Reaction History: Onset of reaction and its duration, morphological pattern of the reaction and drugs implicated, seriousness

of reaction and the outcomes like recovering, fatal or existing were also noted.

The subjects were given appropriate treatment by the Dermatologist and a drug alert card was provided to them to ensure patient safety in future. The entire data was entered in Excel sheet for analysis. All the documented data were analyzed for type of ADR, gender and age preponderance, common clinical pattern of the lesion, common drug and drug group involved, relationship between severity and risk factors. Suspected ACDRs were classified as TYPE-A (dose-dependent and predictable) or TYPE-B (idiosyncratic, no clear dose response relationship) according to the system introduced by Rawlins and Thompson in 1977.

Causality, Severity and Preventability Assessments

In order to improve the accuracy of our assessments, individual causality assessments were undertaken using the Naranjo's causality assessment scale [7] which classifies drug reactions into definite, probable, possible and doubtful ADR. Severity of the reaction was assessed using ADR Severity Assessment Scale (Modified Hartwig and Siegel) [8] – which classifies ADR into mild, moderate and severe. Preventability assessment was done by using Schumock and Thornton scale [9] which classifies the ADRs into definitely preventable, probably preventable and not preventable.

STATISTICAL ANALYSIS

Statistical analysis was done using SPSS.17.0 version. Descriptive analysis done to assess mean, median and the frequencies of multiple risk factors like age group, gender, drug group, causative drug, multiple drugs. For the purpose of analysis, the subjects were divided into 2 groups based on severity level of the reaction, i.e. mild and moderate. Binary outcomes were compared between groups using the Chi-square statistical test for assessing significance. The significant p-value was kept as < 0.05.

RESULTS

Among the 13,869 number of patients who attended the DVL OPD during the study period, 41 subjects (1.3%), either visited the hospital with already developed ACDR or developed ACDR during their stay in the hospital. Out of the total subjects 34(82.9%) were outpatients, and the remaining 7(17.1) were inpatients. The median age of our patients with cutaneous drug eruptions was 34 years, with a minimum of 7 years and maximum of 76 years. Both the genders were almost equally affected. According to Rawlins and Thompson's classification, the majority of the ADRs 38 (92.6%) was of Type B and the rest 3 (7.4%) ADRs belonged to Type A. Most common drug group which caused cutaneous drug reactions was antimicrobials in 17 (41.5%) cases, followed by NSAIDs in 11 (26.8%) cases. In 5 cases the causative drug was not known. The drugs which caused maximal ACDR were penicillin group, followed by cotrimoxazole and paracetamol.

The most common reaction observed, was Fixed Drug Eruption (FDE) with an incidence of 43.9% cases. In this study, the drug which was attributed to cause maximal number of FDE was Paracetamol. The second most common ACDR, was maculopapular rash, followed by urticaria. Interesting cases like flagellate hyperpigmentation due to Bleomycin, chloroquine induced photosensitivity in a subject with SLE, Dapsone syndrome, bullous eruptions and FDE to ofloxacin were also noted. Other reactions noted were pruritus, urticaria, exfoliative dermatitis and contact dermatitis. Of the 41 subjects, five had taken the drug earlier and all of them developed same type of reactions. A history of previous systemic illness was present in nine subjects (21.9%).

Causality Assessment

To strengthen the validity of the findings of the study, causality assessment was done for individual cases by using Naranjo's algorithm. The details of the causality assessment are given in the [Table/Fig-1].

| Causality Assessment | Types | Number of ACDR | Percentage |
|----------------------|----------|----------------|------------|
| | Possible | 9 | 22.0 |
| | Probable | 32 | 78.0 |
| | Definite | 0 | 0 |
| | Total | 41 | 100.0 |

[Table/Fig-1]: Details of causality assessment using naranjo's algorithm

Severity Assessment: On evaluation of the severity of ADRs by Hartwig et al., scale it was evident that most of the ACDR reported in the study, were of moderate severity. Details of the severity assessment are given in the [Table/Fig-2].

| Severity Assessment | Types | Number of ACDR | Percentage |
|---------------------|----------|----------------|------------|
| | Mild | 17 | 41.5 |
| | Moderate | 24 | 58.5 |
| | Severe | 0 | 0 |
| | Total | 41 | 100.0 |

[Table/Fig-2]: Details of severity assessment

Preventability Assessment

On evaluation of the chances of preventability of ADRs using modified Schumock and Thornton scale, it was evident that most of them were not preventable. Refer [Table/Fig-3] for further details.

| Preventability Assessment | Types | Number of ACDR | Percentage |
|---------------------------|------------------------|----------------|------------|
| | Definitely preventable | 5 | 12.2 |
| | Not Preventable | 36 | 87.8 |
| | Total | 41 | 100.0 |

[Table/Fig-3]: Details of Preventability Assessment

For the purpose of analysis the subjects are divided into 2 groups according to the severity level of the reaction. Then Chi-square test was applied to find out the significant risk factors. It was found that multiple drug therapy and history of allergy had a significant p value when compared with the severity level of the reaction. The [Table/Fig-4] gives the p-value for all the parameters analyzed by using Chi-square test.

| Comparison between mild & moderate groups of drug eruptions | | | |
|---|--------|----------|---------|
| Parameters Studied | Mild | Moderate | p-Value |
| Mean age | 38.05 | 38.62 | 0.667 |
| Gender (M:F) | 0.5:1 | 1:0.7 | 0.146 |
| History of allergy | 4.80% | 24% | 0.039 * |
| Multiple drugs | 14.50% | 46% | 0.006 * |

[Table/Fig-4]: p-value for all the parameters analyzed by using Chi-square test
*Significant p-value (p < 0.05)

DISCUSSION

In this prospective study we have found that Fixed Drug Eruptions are the most common reaction pattern and the most common causative drug for the same was surprisingly found to be paracetamol. Antimicrobials were the most common causative drug group of ACDR and two risk factors; multiple drug intake and history of allergy have been found to be significantly associated with the severity level of the reaction. Nearly 20% of the reactions were due to self-medication. There was no influence of gender on the occurrence rate of ACDR in this study. ACDR was almost

equally distributed between the genders (Male: Female ratio is 0.9:1). It is in contrast to literature which says that ACDR are more common in females. The incidence of ACDR was more common in the age group 21-40 years which contradicts literature showing more ACDR in the geriatric population. But in this study the incidence was only 12% in the age group of more than 60 years. According to Rawlins and Thompson classification the majority of the ADRs were of Type B (92.6%) and the remaining 7.4% were Type A. Chatterjee S et al., [10] have also observed 96% of Type B and 4% of Type A reaction. Antimicrobials were the most common cause of ACDR and this finding was well correlated to other studies. The most common offending agent was penicillin group. But in a study conducted by Bharat Tank et al., [11] the common offenders were analgesics mostly due to self-medication. In a study conducted by Jhaj R. et al., [12] they have observed that beta-lactum group was involved with the highest incidence of cutaneous ADRs. But, the present study showed more number of ADRs with paracetamol. This may be related to the common prescribing pattern and self-medication habits among the local population. The most common reaction observed was fixed drug eruption. This finding was similar to the study done by Pudukadan David et al., [13] In our study, the drug which was attributed to cause maximal number of FDE was Paracetamol. But in many studies the common offending agent which produced FDE was Co-trimoxazole. In this study it was interesting to note that two cases of FDE were due to quinolones which may be due to increased use of quinolones over Co-trimoxazole. In our study 20% of subjects developed ACDR due to self-medication. This shows that proper instruction and increasing the awareness is a must to all the subjects and prevention of the adverse reaction in future. When we assessed for severity with self-medication it was not a significant risk factor. On statistical analysis it showed that the significant risk factors were multiple drug therapy and history of allergy. Out of the 41 ACDRs reported, 32 were probable, 9 were possible and no definite/doubtful cases. Since rechallenge was not done in any subjects due to ethical issues, we couldn't get any definite relationship cases. On evaluation of the severity of ADRs by Hartwig et al., scale it was evident that most of the ACDR reported in the study were of moderate severity. Most of the subjects with history of allergy and on multiple drug therapy developed more number of moderate level severity reaction than others. This finding was statistically significant. On evaluation of the chances of preventability of ADRs using modified Schumock and Thornton scale, it was evident that 87% were not preventable but 13% were definitely preventable. Those definitely preventable cases have a previous history of similar reaction following same drug intake; which shows the lack of awareness. This would have been prevented by educating the patient and by issuing a drug alert card. Hence we have issued a drug alert card to the subjects which will benefit them in at least two ways; by preventing adverse reaction in future and to reduce their economic burden due to ADR. Gor A P et al., [14] have applied both the prospective analysis and retrospective analysis in their study to find the incidence of ADR; they were 3% and 1% respectively. In view of the demerits

of retrospective analysis, prospective analysis has been taken up in the present study.

LIMITATION

Limitation of the study is small sample size and hence these results cannot be extrapolated to the rest of the population. There are more variations when compared with other study population. This may be due to changes in common disease pattern, use of newer drugs and dietary factors interfering with drugs action. Rechallenge test was not done due to patient concern and ethical issues.

CONCLUSION

Our study showed that 20% of ACDR are definitely avoidable and steps were taken to reduce their impact by distributing drug alert card. Polypharmacy and history of allergy are noted as significant risk factors which can be prevented by taking proper history, prescribing appropriate drugs, educating the patients about the risk of self-medication and by issuing a drug alert card when allergy to a drug is suspected.

All the medical institutes and hospitals can carry out special projects on drug safety, causality analysis of all the ADR on a monthly basis and maintain a database of all ADR and notifications.

To conclude, remember "Primum non nocere" which means "First of all be sure you do no harm" Hippocrates (460-370BC).

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