ADVERSE CUTANEOUS DRUG REACTION— BURDEN IN A RURAL TEACHING HOSPITAL IN EASTERN INDIA

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ABSTRACT

BACKGROUND: Patient safety has become a leading topic in the national level. An ADR can lead to significant morbidity, mortality and financial costs. People in every country of the world are affected by adverse drug reactions (ADRs) and it is estimated that at least 60% of ADRs are preventable (WHO fact sheet). Almost any medicine can induce skin reaction, certain drug classes such as NSAIDS, antibiotics and antiepileptics have drug eruption rates approaching 1-5%. Cutaneous adverse drug reactions are defined as noxious, unintended, morphologic skin changes with or without systemic involvement that develop after local or systemic administration of drugs in dosage commonly used for prevention, diagnosis or treatment of disease or modification of physiologic function.

OBJECTIVES: To study clinical patterns, causality, preventability and severity of ACDRs(Adverse Cutaneous Drug Reactions) among patients attending Skin & Venereal Disease Department in a tertiary care hospital. METHODS: Cross-sectional descriptive observational study involving 1500 patients attending Skin OPD will be scrutinized for 2 months irrespective of age, sex and diagnosis. Only patients with suspected drug-related cutaneous reactions will be included. Relevant details including adverse events and medications will be recorded in a predesigned case report form. Causality Assessment carried out as per Naranjo’s algorithm whereas Preventability & Severity as per Schumock and Thornton Scale & WHO-guidelines, respectively. RESULT AND DATA ANALYSIS: Appropriate statistical methods will be used for analysis of result. DISCUSSION: Study will be discussed according to the result.
Keywords: ACDRs, NSAIDS, ADRs, Naranjo’s algorithm.

INTRODUCTION
WHO defined Adverse Drug Reaction (ADR) as – “a response to a drug that is noxious and unintended and occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function”\(^1\). There is a Chinese proverb “The gem cannot be polished without friction, nor medicines perfected without trials”\(^2\). Hence pharmaco therapeutics without ADR monitoring cannot be completed. ADR Monitoring centers worldwide had been established after an infamous incident of Thalidomide disaster (1961) reported by Dr. McBride (Australia)\(^2\). Monitoring in India started in 1982, with five nodal centres under the Drug Controller General of India. It is a collaborative activity of both clinicians and pharmacologists. Patient safety has emerged as a leading topic in the national level\(^2\). An ADR can lead to significant morbidity, mortality and financial costs\(^3\). People of different countries of the world are affected by ADRs and it is estimated that at least 60% of ADRs are preventable (WHO fact sheet)\(^3\). Almost any medicines can affect different organs of which skin reactions are the majority, certain drug classes such as NSAID, antibiotics and antiepileptics have cutaneous drug eruption rates approaching 1-5%\(^4\). According to WHO data base adverse drug reactions like rash, pruritus, urticaria are reported respectively from 4.2%, 2.7% and 2.6% of patients receiving drugs\(^4\). Adverse cutaneous drug reactions [ACDRs] are defined as noxious, unintended, morphologic skin changes with or without systemic involvement that develop after local or systemic administration of drugs in dosage commonly used for prevention, diagnosis or treatment of disease or modification of physiologic function\(^5\). Majority of the study on ADR has been done in urban population, hence we have planned to assess the burden, clinical patterns, causality, preventability and severity of ACDRs among rural patients attending Department of Skin & Venereal Disease in a rural teaching hospital.

METHODS
Cross-sectional descriptive observational study involving 1500 patients attending Skin OPD of a tertiary care hospital, were scrutinized for 2 months irrespective of age, sex and diagnosis. The above mentioned 1500 patient has been divided into average 30 patients each day for 50 working days within the above mentioned period. Only patients with suspected drug-related cutaneous reactions were included. Relevant details including adverse events and medications were recorded in a predesigned case report form (CRF). Analysis was done
in the Department of Pharmacology. Causality assessment was carried out as per Naranjo’s algorithm\[1\]. Preventability & Severity were measured as per “Schumock and Thornton Scale” \[1\]& WHO-guidelines respectively.

**RESULTS**

Among 1500 patients ACDRs was reported in 1.49% (65.21% males, median age 27 years) (depicted in Fig 1).Age incidence of ACDRs shown in Fig 2.Majority of ACDRs were found in patients previously treated by private practitioners (69.56%). ACDRs between 3rd &10th days of drug administration were 47.82%. Fig 3 depicts different presentations of cutaneous reactions, among which erythematous rashes were found in 39.13% and 17.39% presented with hyperpigmentation. Offending drugs causing ACDRs were shown in Fig 4, antimicrobials represented the major (30.43%) cause of ACDRs. Severity assessment shows, 14 in Grade-I, 08 in Grade-II, and 01 in Grade-IV, given in Fig 5.

Fig 6 provides causality assessment result which is comprised of 18 (78.26%) "probable" and rest "possible" cases. All of them were probably preventable. None was labeled "certain". Only one ACDR was found severe, leading to death [metronidazole induced Steven Johnson’s Syndrome]. Suspected drug(s) was discontinued as a remedial measure in 91.30% cases and during follow-up it has been shown that 76.19% patients recovered after drug discontinuation. During evaluation of prescriptions polypharmacy was found in 60.87% cases. Oral and parenteral routes are involved in 73.91% and 26.09% cases respectively.
ANNEXURE-1

PRE-DESIGNED CASE REPORTING FORM FOR ADVERSE DRUG REACTION

PATIENT INFORMATION

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<th>Patient name</th>
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<tbody>
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<td>Age</td>
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<td>Weight (Kg)</td>
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<td>Place where admitted</td>
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SUSPECTED MEDICATIONS USED BY PATIENT INCLUDING SELF MEDICATION AND HERBAL PRODUCTS

<table>
<thead>
<tr>
<th>SL NO</th>
<th>NAME (brand/generic)</th>
<th>Manufacturer</th>
<th>Batch No/Lot No.</th>
<th>Exp date</th>
<th>Dose used</th>
<th>Route used</th>
<th>Frequency</th>
<th>Used for how many days</th>
<th>Reason for prescribing</th>
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Reported By with Designation

Figure 1: ACDRs case load (%) in our setting
Figure 2: Age incidences [%] of ACDRs

Figure 3: Presentations of ACDRs (%) in our settings

Figure 4: Offending drugs [%]
DISCUSSION

A cross-sectional descriptive observational study was carried out to assess the burden, clinical patterns, causality, preventability and severity of ACDRs among patients attending Skin & Venereal Disease OPD in a tertiary care hospital which is situated in a sub-urban area and received majority patients from rural agricultural belt. As ACDRs is quite annoying to patients and the most common one, so we have done this study to analyze the burden and pattern of reported ACDRs in our hospital setting. The particular department for ADR monitoring has been chosen as because maximum reportings are done by Skin OPD, as per Pharmacovigilance and ADR monitoring cell of our college.
Reporting and causality assessment has been done on the basis of dechallenge. Rechallenging were not done as it is against humanitarian ground, hence none was labeled certain. Interestingly there was male predominance. Logically we can expect approximately equal number of patients for both the sexes. The inference of our observation could be that either the males suffer more from illnesses or there is a bias in favor of males for providing health care. Since both the sexes are at equal risk of suffering from illnesses, the second reason seems to be more acceptable. Probably males being bread earner of the family in rural India therefore they get more attention. Also the recent 2011 census data have shown 945 females for 1000 males (0.93:1) in Burdwan, which may partly be the reason for this difference. As per the above census data male literacy rate is higher than female [ male : 82.42% ; female : 69.63% ], which may be one of the reason for that.

Antibiotics were the main causative agents followed by NSAIDs and antiepileptics depicted in Raut et al study, which is at per with our study \[^3\]. Antimicrobials such as metronidazole, ornidazole, ofloxacin, ceftriaxone, piperacillin, tazobactum etc. are the most common offending drugs here as they are the most common prescribed medicine in our setup. Erythematous rashes and hyperpigmentation usually were the most common presentation of ACDRs and it also corroborates with our results. Fixed drug eruption, Maculopapular rashes, Bullous rashes, Erythema multiforme were also found in our study. Fatal reactions to drugs are uncommon, but reactions such as Stevens-Johnson’s syndrome and toxic epidermal necrolysis (SJS-TEN) and exfoliative dermatitis may result in death even if the eruption is the only manifestation\[^6\]. In our study there was only one case(4.34%) report of fatal death or fatal adverse drug reactions (FADR) due to metronidazole (Steven Johnson’s syndrome) as per our assessment and information obtained from skin OPD, most probably as we dealt with ACDRs only and/or due to early reporting by patients. Medical burden due to FADR is quite significant as we know FADR are estimated to be the seventh most common cause of death in Sweden\[^7\].

As the management protocol insists on withdrawal of offending drugs as early as possible hence the suspected drugs were withdrawn in more than 90% cases and recovery (76.19%) were quite satisfactory. Remaining 23.81% had not recovered after dechallenging may be due to polypharmacy. Raut et al study showed incidence of ACDRs in medicine inpatients was found to be 2.3% \[^3\]. Our study showed incidence to be 1.49%, most probably as we had dealt only with patients attending Skin OPD.
CONCLUSIONS
Medical burden due to fatal adverse drug reaction though 04.34% in our study, it is quite significant. Our assessment showed ACDRs are quite high as it was an outdoor based observational study involving a single department with 2 month period. Some ACDRs has life threatening potential as our study showed Mortality due to ACDRs, though less, can occur and was quite significant. Proper awareness & responsibility regarding drug use, education about ADR, rational drug utilization and evidence based prescription to avoid polypharmacy should be done. Timely generation and early recognition of signals can prevent morbidity and mortality due to ACDRs. Thus medical error can be avoided.

ACKNOWLEDGEMENTS
To all technical staffs of Department of Pharmacology and Skin and Venereal Diseases of our institution.

REFERENCES