Study and Evaluation of the Various Cutaneous Adverse Drug Reactions in Kasturba Hospital, Manipal

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The present study emphasizes on implementation of the adverse drug reaction reporting and monitoring system, in the Dermatology department of Kasturba Hospital, Manipal, by a clinical pharmacist, using different promotional activities. Documented adverse drug reactions were assessed and analyzed for incidence, purpose of visit, types, drug classes, individual drug causing adverse drug reactions, type of cutaneous reaction, and various predisposing factors. Management and outcome of the adverse drug reactions were also studied. Adverse drug reactions were also assessed for causality, using Naranjo's scale, severity, and preventability, using Hartwig et al. scale. Adverse drug reaction attributes to 77% of the hospital visit. Incidence of reported cutaneous adverse drug reactions, were 2.85%. Majority of the adverse drug reactions (96%) were of type B. Antibiotics (30%), were the common class of drugs, causing a cutaneous adverse drug reactions. Maximum number of adverse drug reactions were due to Acetaminophen, Amoxicillin, antitubercular drugs, and Phenytoin. Most of the adverse drug reactions were managed by withdrawal of drug (81%), and 58% patients were recovered from the reaction. Naranjos scale classifies, 29 as probable, 21 as possible, and 3 as definite adverse drug reactions. Most of the adverse drug reactions were of moderate severity, however 13 adverse drug reactions were severe. All the adverse drug reactions were probably preventable on extreme caution.

Adverse drug reactions (ADRs) are unwanted or unintended effects of drugs, which occur during proper use of a drug. The safe use of medicines is an important issue for prescribers, pharmacists, nurses, regulatory authorities, the pharmaceutical industry, and the public. Healthcare professionals have a responsibility to their patients, who themselves are increasingly aware of the problems associated with drug therapy. It is essential that the practicing pharmacist should have a thorough knowledge about the various adverse effects of the drugs, including its predictability and reversibility, frequency and severity, predisposing factors and recognition, relationship to dosage, and duration of treatment and prevention[1]. Adverse reactions are responsible for a significant number of hospital admissions, among these, cutaneous ADRs (2 to 3%) are one of the frequent reason for patients to visit the physicians[2]. Although majority of ADRs are minor reactions and are self limiting, sometimes severe and potentially life threatening situations[3] like Steven Johnson Syndrome (SJS) and Toxic epidermal necrolysis (TEN) can occur, which constitute from 2.6 to 7% of all drug reactions[7].

Drugs, no matter how safe and efficacious, are always coupled with inescapable risk of adverse reactions. ADRs are a cause of significant morbidity and mortality in patients of all areas of healthcare today. It has been estimated, that from one third to as high as one half of ADRs, are believed to be preventable[4]. The incidence and severity of ADRs can be influenced by patient-related factors like age, sex, concurrent diseases, genetic factors, and drug related factors like type of drug, route of administration, duration of therapy, and dosage. The other important risk factors associated with adverse drug reactions are gender, increased number of drug exposures, advanced age, length of hospital stay,and function of excreting organs[1,5]. Cutaneous ADRs are the most common among the various adverse reactions attributed by the drugs. Any skin disorder can be imitated, induced, or aggravated by drugs. The incidence of cutaneous drug reactions vary from 15 to 30%[6]. Studies on the epidemiology of common cutaneous ADRs have rarely been reported, since such studies can only be successfully conducted in clinics of internal medicine,

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who employ consultant dermatologists and where there is a comprehensive or intensive ADR monitoring system. Such evaluation of ADR in dermatology are yet to evolve in India.

Kasturba Hospital (KH), Manipal, a 1400 bedded tertiary care hospital, has already an established ADR reporting and monitoring system, in different medicine units. Since most of the drugs causes cutaneous ADRs, there is a need for reporting these ADRs by department of Dermatology, where cutaneous ADRs are referred and treated. The present study focuses on extending the ADR reporting and monitoring program to the dermatology department, with the objective to implement ADR reporting and monitoring system in the department of dermatology of Kasturba Hospital, Manipal; to categorize and analyze the reported cutaneous ADRs, which were reported during the study period; to evaluate the management and outcome of ADRs; and to assess the causality, severity and preventability of the reported cutaneous ADRs, using different scales.

MATERIALS AND METHODS

The present study was a prospective one, conducted in the dermatology department of KH Manipal, for a period of six months, between November 2002 and April 2003. All the inpatients and the outpatients who visited the department during the study period, were monitored for ADRs. Patient case notes/files and suspected ADR notification forms were used as main sources of data collection. For the study purpose, the following documents were used. Suspected ADR notification form, ADR reporting and documentation form, ADR alert card, Thank you card, Causality assessment scale (Naranjo's scale)[15], Severity assessment and Preventability assessment scale (Hartwig *et al.* scale)[14].

The clinical pharmacist who was posted in the dermatology department, used to take part in the ward rounds along with other dermatologists, and actively monitor for any ADRs. To strengthen the awareness of the ADR reporting system posters were displayed, oral campaign, and formal speeches about the importance of reporting ADRs, were done. On intimation of suspected ADRs by the dermatologist, the notification form was filled up by the pharmacist, and the case was followed up for further details, and were documented in the ADR reporting and documentation forms. 'ADR alert card ' was given to the patients who exhibited hypersensitivity type of reaction, or near fatal reaction with any component of the drug. Thank you cards were issued to those dermatologists who reported ADR, so as to encourage further reporting. All the documented ADRs were analyzed for incidence, purpose of visit to the hospital, types of ADRs, drug classes, and individual drug causing cutaneous reaction, association of cutaneous reaction with drugs, predisposing factors, management and outcome of ADRs. ADRs were also assessed for causality using Naranjo's scale, severity and preventability, using Hartwig *et al.* scale. Severity of the reported ADRs were assessed at various levels, ranging between 1 and 7. Level 1 and 2 indicates mild, 3 and 4 as moderate, and level 5 and above, as severe ADRs.

RESULTS AND DISCUSSION

Implementation of ADR reporting and monitoring system in the Dermatology department was successfully done by displaying the posters, through oral campaign, and formal speeches related to importance of reporting ADRs,by the clinical pharmacist. There were 53 ADRs reported, during study period of six months.

A total number of 1859 patients visited the dermatology department, during the study period. Among these, 53(2.85%) patients, either visited the hospital with already developed ADRs, or developed ADR during their stay in the hospital. This shows a similar pattern of results, as reported by Michael Bigby[8]. Out of the total ADRs reported, 53% involved outpatients, and the remaining 47% were inpatients. Significant differences were observed in the reaction pattern, drugs involved, and severity between these two group of patients. The reason for admission in most of the in-patients, were found to be ADRs, and they were of severe category.

It was observed that 41 (77%) patients visited the hospital due to ADRs. The other reasons, were due to various diseases like epilepsy in 4 (8%) cases, 1 (2%) each of breast cancer, end-stage renal disease (ESRD), renal cell calculi, squamous cell carcinoma, and tuberculosis. Three cases could not be evaluated.

According to Rawlins and Thompson's classification,[1] ADRs were grouped into 2 types. The majority of the ADRs 51 (96%), were of Type B, since these reactions were totally aberrant effects that are not to be expected from the known pharmacological actions of a drug, when given in the usual therapeutic doses to a patient, whose

body handles the drug in the normal way. The remaining 2 (4%) ADRs belonged to Type A, since these reactions were the result of an exaggerated, but otherwise normal, pharmacological action, of a drug given in usual therapeutic doses.

Most frequently reported cutaneous drug reactions were for antibiotics in 16 (30%) cases, followed by antiepileptics in 13 (25%) cases, antitubercular drugs in 6 (11%) cases, and antipyretics in 5 (9%) cases. Some of the other drug classes involved, were steroids and ayurvedic medicines, with 2 (4%) cases each, etc. Studies conducted by Bern *et al.*, Faich *et al.* and Bigby *et al.* shows similar results, antibiotics as the most frequent cause of adverse skin reactions reported in their spontaneous surveillance[9,10], or hospital incidence system[2]. Antiepileptics have also been well known as a causative agent for a wide spectrum of dermatological ADRs[11].

It was observed, that the drugs which caused maximal undesired effects were acetaminophen, amoxicillin, anti tubercular drugs [ATT (isoniazid, rifampicin, pyrazinamide, ethambutol)] (6 each), and phenytoin (5). Studies conducted by Bigby *et al.* showed that penicillins and aminopenicillins were involved with the highest incidence of cutaneous ADRs.[2] In the study conducted by Naldi *et al.* acetaminophen was ranked 8 among common analgesics, to cause cutaneous reactions[11]. But, the present study showed more number of dermatological ADRs with acetaminophen. This may be related to the common prescribing pattern and self-medication habits among the local population. Few of the adverse reactions observed by our surveillance system, were not reported earlier in medical literature, like SJS (1), and erythematous lesion (1), induced by an ayurvedic drug (1), erythema elevatum diutinum (EED) to gatifloxacin (1), and hyperpigmentation associated with moxifloxacin (1).

The most common reaction observed, was maculopapular rashes with an incidence of 11 (21%) cases. These findings were similar to studies carried out by Kushwaha *et al.* and Naina *et al.*, to evaluate the incidence of dermatological ADRs[12,13]. In this study, the drug which was attributed to cause maximal number of maculopapular rashes, was amoxicillin (6). amoxicillin, which induced maculopapular rash, is well documented in medical literature, and there were very high reported incidences (5%)[2]. The second most common ADR, was erythematous skin lesion (8). This was more among patients treated with roxithromycin (2), and antiepileptics like phenytoin (1) and carbamazepine (1). The other most common skin reactions were fixed drug eruption (5), urticaria (5), SJS (4), hyperpigmentation (3), pruritis (2), angioedema (2), and acne (2).

Out of 53 ADRs, 20 reported cases had predisposing factors. Among these, the most common was history of allergy of the patient (7). Other risk factors involved, were inconcurrent disease (3), pharmacokinetic variables (3), multiple drug therapy (4), and pharmaceutical factors (1). Whenever the patient had severe ADR to the particular drug, 'ADR alert card ' was given to the patient, and they were asked to produce the same, while visiting the physician or pharmacist in the future.

Most of the ADRs were managed by the withdrawal of the drug in 43 (81%) cases. The remaining 10 patients continued on the same drug, without any major changes. However, in these cases, reaction may or may not be continuing. It was the dermatologist's discretion, whether the benefit of the drug overweighed the existing ADR. The final outcome of the dermatological ADRs were that, 58% of patients recovered from the reaction, and 17% had it continuing on them. The fate of 23% of patient were not known, while there was one death reported, either due to the direct or indirect effect of the drug,during the study.

To strengthen and further emphasize the validity of the findings of the study, causality assessment was done by using Naranjo's scale. Out of the 53 ADRs reported, 29 ADR's were probable, 21 ADR's were possible, and 3 ADR's were definite. It was emphasized that most of the reported ADRs were caused by the accused drug, and not otherwise. Results are tabulated in Table 1.

On evaluation of the severity of ADRs by Hartwig *et al.*,[14] it was evident that most of the dermatological ADRs reported in the study, were of moderate severity. A total of 13 ADRs came under the level 3, while 7 ADRs came under level 4 (a), and 8 ADRs under level 4 (b). These results demonstrate that most of the ADRs were moderate in terms of severity. The dermatological patients were also exposed to higher rates of severity, with 13 ADRs

TABLE 1: CAUSALITY ASSESSMENT

Probability scale	Definite	Probable	Possible	Unlikely
Naranjo's scale	3	29	21	0

As per the Naranjo's scale of causality assessment, ADRs were classified as definite, probable, possible and unlikely.

TABLE 2: SEVERITY ASSESSMENT

Severity levels	Level 1	Level 2	Level 3	Level 4 (a)	Level 4 (b)	Level 5	Level 6	Level 7
No. of ADRs	3	8	13	7	8	13	0	1
Percentage of ADRs	6	15	24	13	15	25	0	2

As per the Hartwig *et al*. ADR severity assessment scale, level of severity of ADRs classified as level 1 to 7. Level 1 and 2 indicates mild, level 3, 4 (a) and 4 (b) as moderate, level 5, 6 and 7 as severe.

coming under level 5 category. The ADR, which came under this category, were mostly skin reactions like SJS, EM, and urticaria. The study also reported one death, which was probably caused by ATT-induced erythma multiforme (Major). Even though various incidences support the finding that the most common ADRs are skin reactions, there has been very less effort to curtail its severity. Reactions like SJS have a very high incidence of occurrence, and pose a significant risk to patient's life. It further emphasizes the importance of monitoring ADRs. Results are tabulated in Table 2.

On evaluation of the chances of preventability (Hartwig *et al.*) of the ADRs, it was evident that all the ADRs may have probably been preventable, if proper precautions were taken.

This study shows that ADRs attribute to a significant percentage of hospital visits, in the dermatological population. The mechanism behind most of the dermatological ADRs was hypersensitivity reaction, and was most commonly associated with antibiotics, analgesics, and antiepileptics. Maculopapular rash was the most common type of ADRs. Most of the reactions were of moderate severity, and could be managed by the withdrawal of the drug.

By implementing the ADR reporting and monitoring system, the pharmacist can promote drug safety and better patient care, among health care professionals. Involvement of a pharmacist in patient care, can help in prevention and early detection of ADRs.

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