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Cutaneous Adverse Drug Reactions in Hospitalized Patients in Benghazi, Libya

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Abstract

Background: Adverse drug reactions (ADRs) are a common occurrence in hospitalized patients. Few studies have examined the incidence and presentations of cutaneous ADRs in Libya.

Methods: Archival clinical and laboratory data on all inpatient dermatology consultations in a tertiary care hospital in Benghazi with a diagnosis of cutaneous adverse drug reaction between 1st May 2013 and the 30th April 2014 was retrospectively analysed.

Results: Ninety one patients were diagnosed with cutaneous adverse drug reactions. Seven reaction patterns were noted: maculopapular rash (47.3%), drug exanthems (25.3%), fixed drug eruption (15.4%), urticaria/angioedema (5.5%), erythema multiforme minor (3.3%), generalised exanthematous pustulosis (2.2%), and toxic epidermal necrolysis (1.1%). The medications responsible included antimicrobials (53.8%), non-steroidal anti-inflammatory drugs (23.1%), anticonvulsants (11.0%), chemotherapeutic agents (5.5%), intravenous contrasts (4.4%), allopurinol (1.1%), and oral contraceptives (1.1%). The total number of patients admitted to the hospital was 40,815, therefore the overall incidence was 0.22%.

Conclusion: Early identification of cutaneous ADRs and their putative medications are key in the management and prevention of more severe, and sometimes avoidable, drug reactions.

Key Words

Adverse reactions; Cutaneous; Pharmacology; Dermatology; Immunology.

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Introduction

Adverse drug reactions (ADRs) are a common occurrence in hospitalised patients, and one that all physicians will experience during their clinical practice. A meta-analysis[1] found that the incidence of serious ADRs in hospital inpatients was six point seven percent, while the incidence of fatal ADRs was 0.32%. Cutaneous ADRs are the most common, recognisable, and reported type of ADR, estimated to account for 30% of reported ADRs[2]. Although cutaneous ADRs are frequently benign and self-limiting, severe reactions, such as erythema multiforme major/Stevens-Johnson Syndrome and toxic epidermal necrolysis, are estimated to occur in one out of every 1000 hospital inpatients[3], and carry with them a high risk of morbidity and mortality. Thus, early identification of cutaneous ADRs and their putative medications are key in the management and prevention of more severe, and sometimes avoidable, drug reactions.

However, comprehensive evidence regarding the incidence of cutaneous ADRs, their severity, and the culprit medication are often not available, as although incidences are clinically noted, many cases go unreported. Few studies have examined the incidences and clinical presentation of cutaneous ADRs in hospitals in Libya, and with the introduction of new medications and changes in prescribing practice, the risk of such reactions is unclear. The aim of this paper is to report the various cutaneous ADRs, and their putative drugs, among patients managed in a tertiary care hospital in Benghazi over a one year period.

Method

Archival clinical and laboratory data kept by the dermatology department was retrospectively analysed, and data on all inpatient consultations between 1st May 2013 and the 30th April 2014 was extracted. Patients with a diagnosis of a cutaneous adverse drug reaction were noted, and the details recorded and evaluated following the STROBE guidelines.

Details of the age and gender of the patient, referring department, type of cutaneous ADR, and the putative medication were noted. Where no

putative medication has been indicated, the WHO-UMC system for standardised case causality assessment was implemented, which is based on the temporal relationship between drug ingestion and the onset of the reaction, the known latency of the clinical presentation, and epidemiological risks of the suspected drugs (based on publications and pharmacovigilance)[4]. The resulting ranking, in line with WHO criteria, may be 'certain', 'probable', 'possible', or 'unlikely'. Only those medications with a causality ranking of 'certain' or 'probable' were included in the final analysis. Cutaneous reactions due to drug abuse, errors in drug administration, and in patients with an incomplete history were excluded.

Results

During the study period, a total of 91 patients were diagnosed with cutaneous ADRs. As the total number of patients admitted to the hospital during this period was 40,815, the overall incidence of cutaneous ADRs was 0.22%. The patients' age ranged from seven to 76 years, with a mean age of 38 years. Forty eight (52.8%) of these patients were female and 43 (47.2%) were male. This gives a male : female ratio of 0.9 to one. A detailed breakdown according to age group is shown in **Table 1**, and according to referral department is shown in **Table 2.**

Age range (years)	No. (%)
≤10	2 (2.2)
11-20	8 (8.8)
21-30	16 (17.6)
31-40	31 (34.0)
41-50	19 (20.9)
51-60	8 (8.8)
61-70	4 (4.4)
>70	3 (3.3)
Total	91 (100)

Table 1: *Breakdown of patients according to age group*

Regarding the clinical nature of the reactions noted, seven different clinical reaction patterns were observed. These were maculopapular rash (47.3%), drug exanthems (25.3%), fixed drug eruption (15.4%), urticaria/angioedema (5.5%), erythema multiforme major (3.3%), generalised exanthematous pustulosis (2.2%), and toxic epidermal necrolysis (1.1%).

Referral Department	No. (%)
Pediatrics	3 (3.3)
Cardiology	12 (13.2)
Nephrology	10 (11.0)
Oncology	11 (12.1)
Neurology	9 (9.9)
Ear, nose, throat	6 (6.6)
Orthopaedics	8 (8.8)
Respiratory	9 (9.9)
Gastroenterology	10 (11.0)
Hematology	5 (5.5)
Obstetrics and gynecology	8 (8.8)
Total	91 (100)

Table 2: *Referral pattern according to medical specialty*

Antimicrobials were the most common putative medications, accounting for 53.8% of incidences, followed by non-steroidal anti-inflammatory drugs (23.1%), anticonvulsants (11.0%), chemotherapeutics agents (5.5%), intravenous contrast (4.4%), allopurinol (1.1%), and oral contraceptives (1.1%). A detailed breakdown of the causative drugs and their corresponding clinical reactions patterns are shown in **Table 3**.

Discussion

This study has highlighted the various clinical reaction patterns and putative medications seen in an inpatient setting. A wide range of various cutaneous ADRs were seen, ranging from maculopapular rash to toxic epidermal necrolysis. While many of these reactions may be seen as mild and self-limiting by many physicians, there were several cases of more severe ADRs seen in this study, most notably two cases of generalised exanthematous pustulosis, and one case of toxic epidermal necrolysis. These conditions are associated with high morbidity and mortality, with toxic epidermal necrolysis having a reported mortality rate of approximately 30%[3]. It is therefore of upmost importance that physicians recognise these severe ADRs promptly, and make treatment immediately available to the patient.

A total of 91 cutaneous ADRs were seen in this

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	MR	DE	FDE	U/A	EMM	GEP	TEN	Total no. (%)
Antimicrobials								49 (53.8%)
Amoxicillin	4	1	1	1				7
Ciprofloxacin	4	1	1					6
Erythromycin	1		1					2
Flucloxacillin	2	1						3
Co-trimoxazole	11	3		1	1	1		17
Ceftriaxone	2		1					3
Clarithromycin		1			1			2
Fluconazole	1	2						3
IV penicillin	3	2					1	6
NSAIDs								21 (23.1%)
Diclofenac	4	1	2	2				9
Ibuprofen	3	2	2	1				8
Aspirin	1	3						4
Anticonvulsants								10 (11.0%)
Phenytoin	2	1	1					4
Carbamazepine	3		1			1		5
Lorazepam		1						1
Chemotherapeutic agents								5 (5.5%)
Methotrexate		1	2					3
Fluorouracil		1	1					2
IV contrast	1	2	1					4 (4.4%)
Allopurinol					1			1 (1.1%)
Oral contraceptives	1							1 (1.1%)
Total	43	23	14	5	3	2	1	91

MR: maculopapular rash; DE: drug exanthems; FDE: fixed drug eruption; U/A: urticaria/angioedema; EMM: erythema multiforme major; GEP: generalized exanthematous pustulosis; TEN: toxic epidermal necrolysis; NSAIDs: non-steroidal anti-inflammatory drugs; IV: intravenous

Table 3: *Causative medications and their corresponding clinical reaction patterns*

study. As the total number of patients admitted to the hospital during this period was 40,815, the overall incidence of cutaneous ADRs was 0.22%. This is slightly greater than a similar study done in Singapore[5], which noted an overall incidence of 0.1%, yet significantly less than a previously reported figure of two percent[2]. These differences may be explained through several factors: firstly, this study only included cases that were referred to the dermatology department for consultation. It is highly likely that many cases of cutaneous ADR, especially relatively mild ones, were instead treated by the presiding physician. Secondly, there is a possibility that many incidences may go unreported, as indicated by anecdotal reports of record-keeping errors in Libyan hospitals[6]. Lastly, patients with a shorter duration of stay are more likely to develop any cutaneous ADRs following their discharge from the hospital, and as such are more likely to have been treated as outpatients. Because of this, the actual incidence of cutaneous ADRs may actually be significantly higher than the incidence found in this study, and further prospective studies may clarify the true figure.

In a previous study conducted in Singapore[7], Fong *et al* discovered that the most common causative medications in cutaneous ADRs were antimicrobials (51.4%) and anti-inflammatory/analgesics (17.8%). These findings have been reflected in this study, where the two most common causative medications found were antimicrobials (53.8%) and non-steroidal anti-inflammatory drugs (23.1%). Of individual medications, the antimicrobial co-trimoxazole was most often to blame, accounting for 17 occurrences, followed by the non-steroidal anti-inflammatory drugs diclofenac (with nine occurrences), and ibuprofen (with eight occurrences).

The age of the patients seen in this study ranged from seven to 76, with a mean age of 38. The most commonly affected age group was 31-40, with 34.0% of patients falling into this category. This is in line with a similar study conducted in India in 2011[8], which noted that patients in the 21-40 age group accounted for approximately half of all incidences of cutaneous ADR. Male patients accounted for 47.2% of all cutaneous ADRs seen in the study, with female patients accounting for 52.8%. This is a finding reflected in other studies[5,8], that found that cutaneous ADRs affect female patients more than male patients.

In addition to the risk of morbidity and mortality, ADRs also contribute to a growing healthcare cost, with ADRs estimated to constitute between one point six and four billion dollars in direct hospital costs per year in the United States alone[9], as well as being reported to be responsible for approximately five to nine percent of hospital expenditure in the United Kingdom[10]. This increased financial burden from the development of ADRs places greater pressure on the already underfunded healthcare sector, and may negatively affect patient care.

The treatment of ADRs presents a challenge in hospitalised patients; namely, the accurate diagnosis of the ADR and the identification of the causative medication, as well as the treatment by cessation of the offending drug (or drugs). This latter issue is especially challenging when the patient is in an acute setting, where they are often on multiple medications concurrently, many of which may be essential to treatment, and the cessation of which may be life-threatening for the patient. Under-recognition and diagnosis of adverse drugs reactions by physicians, as well as incorrect identification of the putative medication, may lead to increased morbidity and mortality among patients experiencing adverse drug reactions. Similarly, over-diagnosis of an adverse drug reaction, or incorrectly identifying a drug as the cause, may lead to the patient being deprived of essential medication, potentially leading to either less effective treatment, or an increase in expense due to the use of more costly alternative medications. Therefore, accurate diagnosis of the reaction, and prompt identification of the causative medication, are essential in timely and effective treatment of ADRs.

In summary, cutaneous ADRs are relatively common occurrences in hospitalised patients, and constitute a major clinical problem in terms of morbidity, mortality, and increased healthcare expenditure. This study has demonstrated for the first time the typical cutaneous ADRs seen in hospitalised patients in a Libyan city. The clinical presentation of cutaneous ADRs ranges from somewhat benign reaction patterns, to those that may be life threatening. With the number of drugs being available for use in hospitals increasing each year, it is essential that all physicians have an understanding of potential ADRs and common putative medications, to recognise and treat them promptly and accurately, and to reliably report all instances of ADRs. This will help all clinicians to treat these iatrogenic events as effectively and efficiently as possible.

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