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RESEARCH

Common adverse cutaneous drug reaction patterns and the causative drugs in Malaysia

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Background: Patients with adverse cutaneous drug reactions (ACDRs) are frequently referred from primary care to tertiary centres for further management. This causes a loss of information regarding ACDRs as these patients discontinue primary care follow-up upon referral to tertiary care. The aim of this study is to determine the prevalence and characteristics of ACDR, and to use this valuable information to enhance awareness of primary care physicians regarding this condition.
Method: A retrospective cross-sectional study on ACDR was done at the Dermatology Clinic, Kuala Lumpur General Hospital from January 2009 to December 2010.
Results: The prevalence of ACDR was 0.2%. The majority of patients (71.6%) were below 59 years of age. ACDR commonly (55.2%) occurs within hours to days of drug ingestion and is of mild to moderate severity (74.6%). About 27.6% of affected patients took 1 to 5 drugs concurrently. Common cutaneous manifestation of ACDR includes maculopapular rash (22.4%) and Stevens–Johnson syndrome (SJS, 9.7%). Antibiotics (36.6%), traditional and complementary medicine (TCM, 17.9%) and analgesics (13.4%) were the most frequent agents responsible for ACDR.
Conclusion: The prevalence of ACDR in this study is low and the majority were of mild to moderate severity. The most common cutaneous manifestation was a maculopapular reaction and Stevens–Johnson syndrome. Antibiotics were the commonest causative agent for ACDR followed by traditional and complementary medicine and analgesics. Patients presenting with cutaneous disorders in primary care should be assessed for possible ACDR. A detailed drug history, time of initiation and duration of drug consumption are all valuable information required for an accurate diagnosis and proper evaluation of ACDR. It is hoped that the findings of this study will facilitate early recognition of ACDR followed by identification and elimination of any possible offending drugs that may be prescribed in primary care practice.

Keywords: adverse drug reactions, drug eruptions, drug reactions, maculopapular drug eruptions, maculopapular exanthem

Background

Adverse cutaneous drug reaction (ACDR) is an undesirable change in the structure, function, appendages of the skin or mucous membranes and encompasses all adverse events related to drug eruption.[1] The prevalence of ACDR is about 0.16 to 1.35%.[2,3] However, this may be a deceptively low figure secondary to under-reporting. Data on ACDR are usually based on reporting by physicians and pharmacists. Mild cutaneous manifestations may be misdiagnosed or dismissed as trivial and hence unreported. Under-reporting is a common problem faced in most countries. A study in Germany showed that up to 68.2% of physician who suspected adverse drug reaction (ADR) did not actually report these events to the appropriate authorities.[4] This may be due to the tendency to report only severe ADR cases.[5] Hence more research in this area is needed to determine the characteristics of ACDR for early identification and appropriate management. Almost all patients with health problems will require medication at some point, hence it is pertinent that physicians are aware and identify ACDRs early. Primary care patients, especially those with multiple medical problems taking multiple medications, hence are at greater risk of developing ACDRs. Most patients suspected of, or presenting with, moderate or severe ACDR are usually referred to the tertiary medical or dermatology speciality for further evaluation and management. Hence, these patients are frequently lost to follow-up care at primary care and the lack of feedback after initial referral creates a gap in the knowledge regarding ACDRs. The objective of this study is to determine the prevalence and characteristics of ACDR. It is hoped that this study will reveal valuable information in order to bridge this gap, facilitate early detection using visible clinical signs, enhance management and prevent recurrence of ACDR at primary care level.

Method

This is a retrospective descriptive cross-sectional study done from January 2009 to December 2010 at the dermatology department of Kuala Lumpur General Hospital. (KLGH). A descriptive study design was selected as the researchers aimed to obtain the existing information that could be gathered to describe the characteristics of ACDR. KLGH is one of the largest tertiary hospitals with a well-established dermatology unit and serves as one of the main referral centres for dermatological cases. All cases with ACDR were identified from the clinic registry and only those labelled as definite, probable and possible ACDR based on Naranjo classification by the dermatologist were selected. Patients below the age of 12 were excluded. Epidemiology and laboratory data were collected from patients' case notes.

This study was approved by the Ministry of Health Medical Research Ethics Committee and Universiti Kebangsaan Malaysia ethical committee.

ACDRs are classified as severe and non-severe reactions. In this study, severe ACDRs are defined as reactions causing permanent damage or requiring intensive care or haemodialysis.[6] Acute life-threatening events such as Stevens–Johnson syndrome (SJS),

toxic epidermal necrolysis (TEN), exfoliative dermatitis (ED) and drug rash with eosinophilia and systemic symptoms (DRESS) were included in this category.[7] Non-severe ACDR consist of mild and moderate reactions. Mild ACDRs are those that did not require hospitalisation or specific therapy while moderate ACDRs are defined as ACDR requiring hospital admission, a change in therapy, or requiring specific interventional treatment.[6] The non-severe ACDRs include all other diagnoses that do not fulfil the criteria for severe ACDR (mild and moderate reactions). Patients' files with incomplete data entry were excluded from analysis. Data were analysed with descriptive statistical methods using the Statistical Package for the Social Sciences (SPSS 17.0, IBM, New York, USA).

Results

A total of 69 849 patients were seen at the dermatology clinic and ward during the study period. The prevalence of ACDR was 0.2% (n = 134). The mean age for the study population was 47.0 ± 17.5 years, the youngest being 14 and the oldest 91 years. The majority (71.6%) were 59 years and below. There were no patients below the age of 12 years. Males and females were equally affected (1.1:1) The majority (61.9%, n = 83) of patients with ACDR belong to the Malay ethnic group, followed by Chinese (19.4%, n = 26), Indians (11.2%, n = 15) and others (7.5, n = 10) (see Table 1).

Table 1: Demographic characteristics of ACDR in general

Characteristics	Percentage (n)
Age, mean (±SD)	47 (±17.5)
Age groups	
≤ 59 years	71.6 (96)
60 to 74 years	22.4(30)
≥ 75 years	6.0 (8)
Gender	
Female	48.5 (65)
Male	51.5 (69)
Ethnicity	
Malay	61.9 (83)
Chinese	19.4 (26)
Indian	11.2 (15)
Others	7.5 (10)
Total	**100 (134)**

Table 2: ACDR onset, severity and number of concurrent drugs consumed

Characteristics	Percentage (n)
Onset	
Hours to days	55.2 (74)
Weeks	18.0 (24)
Months to years	22.4 (30)
Unknown	4.4 (6)
Severity	
Mild	24.6 (33)
Moderate	50.0 (67)
Severe	25.4 (34)
Number of concurrent drugs	
1–5	27.6 (37)
6 or more	11.2 (15)
Unknown	61.2 (82)

Table 3: Manifestations of ACDR

Cutaneous manifestations	Percentage (n)
Maculopapular rash	22.4 (30)
Stevens–Johnson syndrome (SJS)	9.7 (13)
Others	9.7 (13)
Fixed drug eruptions (FDE)	8.9 (12)
Photodermatitis	8.2 (11)
Exfoliative dermatitis	8.2 (11)
Urticaria	6.0 (8)
Erythema multiforme	5.3 (7)
Toxic epidermal necrolysis (TEN)	4.5 (6)
Angioedema	4.5 (6)
Drug rash with eosinophilia and systemic symptoms (DRESS)	3.7 (5)
Vasculitis	3.7 (5)
Acute generalised exanthematous pustulosis (AGEP)	3.7 (5)
Drug induced bullous pemphigoid	1.5 (2)
Total	**100 (134)**

Table 4: Common drugs responsible for ACDR

Drug group	Percentage (n)
Antibiotics	36.6 (49)
TCM	17.9 (24)
Analgesics	13.4 (18)
Anti-hypertensives	10.4 (14)
Others	7.4 (10)
Anti-gout	6.7 (9)
Anti-epileptics	5.3 (7)
Anti-fungals	2.3 (3)
Total	**100(134)**

More than half (55.2%, n = 74) of the ACDRs occurred within hours to days of drug ingestion. ACDRs mostly belong to the mild and moderate category of severity (74.6%, n = 100). Less than one-third of the patients (27.6%, n = 37) took 1 to 5 drugs concurrently (see Table 2).

The commonest manifestations of ACDR include maculopapular rash (22.4%, n = 30) followed by Stevens–Johnson syndrome (SJS, 9.7%, n = 13). Other cutaneous manifestations are shown in Table 3.

Among the medications responsible for ACDR were antibiotics (36.6%, n = 49), traditional and complementary medicine (TCM), 17.9%, n = 24) and analgesics (13.4%, n = 18) (see Table 4).

Discussion

The prevalence of ACDR in this study was 0.2% (n = 134). This is roughly similar to studies from other parts of the world.[2,8] Previous local studies have reported an incidence of 0.86%.[9] The low prevalence in this study may be attributed to the possibility that mild cases of ACDR not requiring dermatology consultation may not have been referred and hence not captured in this study.

The mean age of patients in this study is 47 years, which is similar to a study in Mexico. An earlier study in Malaysia showed a lower mean age.[9] This is probably because the paediatric population was excluded from the present study. The relationship between

age and ACDR remains debatable as studies have shown controversial results.[4,10] It appears that males are more susceptible to ACDRs in general.[10,11] However, the exact reason for this phenomenon is yet to be determined.[3] In this study, the Malay ethnic group contributed the highest number of ACDRs as they form the ethnic majority. Most patients with ACDR to took 1 to 5 concurrent drugs (27.6%) while about 11.2% took more than 6 drugs. Polypharmacy has been shown to increase the risk for ACDR. A 13% risk was found with the use of 2 drugs and increases up to 82% with 7 or more medications possibly due to drug–drug interaction.[12] This raises a concern of ACDRs among the elderly population as many of them are on multiple concurrent medications.[13]

Maculopapular rash is the most common cutaneous manifestation (22.4%) of ACDR in the present study followed by SJS (9.7%). This is quite similar to both local studies and those from different parts of the world.[2,9] Skin reactions are the most common clinical manifestations of ACDR due to high immunogenic activity in the skin.[14]

There are not many previous studies that looked at the relationship between duration of drug intake and onset of ACDR. A recent study in Turkey showed that the mean lag time between drug consumption and initial reaction was 2 weeks with a wide range between 5 minutes and 120 days.[14] The onset of reaction is determined by drug and host factors. The chemical compound, physical form, half-life and the immune response triggered by the drug influences the onset of adverse reactions.[15]

Severe ACDR accounts for of 24.5% of drug reactions in this study. Earlier local studies show a higher range at 40.6%.[9] Hospital-based studies are expected to detect more cases of severe ACDR compared with primary care, as they are referral centres to which patients are referred for close monitoring and management as severe reactions can cause fatalities. Antibiotics are the most common group of drugs responsible for ACDR in the present study (74.6%). Other studies have also found similar results.[9,16] A local study by Ding found that clotrimoxazole was the commonest antibiotic to cause ACDR.[9] Hence the decision to initiate antibiotic treatment should be justified to prevent unnecessary morbidity.

Limitations of this study include the drawback due to the retrospective nature, and that information pertaining to underlying disorders such as HIV or connective tissue disease, which renders an individual more susceptible to ACDRs, could not be established. Incomplete documentation in the case notes also resulted in loss of valuable data. The data-collection form was designed is such a way that only the drug group was identified but the particular drug, i.e. the specific antibiotic responsible for the reaction, was not captured.

Conclusion

In this study, the prevalence of ACDRs is low (0.2%.). Most reactions were of mild to moderate severity and commonly occur among those younger than 60 years of age. The most frequent cutaneous manifestation was maculopapular reaction and Stevens–Johnson syndrome. Antibiotics were the commonest causative agent for ACDR followed by traditional and complementary medicine and analgesics. ACDR usually occurred early, within hours to days of drug ingestion. For patients presenting with dermatological disorders a detailed drug history, time of drug consumption and chronology of events should be investigated so as to be able to exclude ACDRs as the possible underlying cause. Recent consumption of antibiotics and the possibility of polypharmacy should also be probed. Knowledge of the common morphology of skin reactions and a suggestive drug history would be useful to primary care physicians to identify ACDR with ease. Lastly, physicians should be proactive in detecting and reporting all ADRs as this would provide a valuable database of information for monitoring the safety profile of drugs in the future.

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