

Incidence of cutaneous adverse drug reactions among medical inpatients of Sultanah Aminah Hospital Johor Bahru

Latha R Selvarajah, Adv M Derm¹, Siew Eng Choon, FRCP²

¹Department of Dermatology, Hospital Sultan Ismail Johor Bahru, ²Department of Dermatology, Hospital Sultanah Aminah Johor Bahru

ABSTRACT

Introduction: Cutaneous adverse drug reactions (cADRs) are common. There are only few studies on the incidence of cADRs in Malaysia.

Objective: To determine the incidence, clinical features and risk factors of cADRs among hospitalized patients.

Methods: A prospective study was conducted among medical inpatients from July to December 2014.

Results: A total of 43 cADRs were seen among 11 017 inpatients, yielding an incidence rate of 0.4%. cADR accounted for hospitalization in 26 patients. Previous history of cADR was present in 14 patients, with 50% exposed to the same drug taken previously. Potentially life-threatening severe cutaneous adverse reactions (SCAR), namely drug reaction with eosinophilia and systemic symptoms (DRESS: 14 cases) and Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN: 6 cases) comprise almost 50% of cADRs. The commonest culprit drug group was antibiotics (37.2%), followed by anticonvulsants (18.6%). Cotrimoxazole, phenytoin and rifampicin were the main causative drugs for DRESS. Anticonvulsants were most frequently implicated in SJS/TEN (66.7%). Most cases had "probable" causality relationship with suspected drug (69.8%). The majority of cases were of moderate severity (65.1%), while 18.6% had severe reaction with 1 death recorded. Most cases were not preventable (76.7%). Older age (> 60 years) and mucosal involvement were significantly associated with a more severe reaction.

Conclusion: The incidence of cADRs was 0.4%, with most cases classified as moderate severity and not preventable. The commonest reaction pattern was DRESS, while the main culprit drug group was antibiotics. Older age and mucosal membrane involvement predicts a severe drug reaction.

KEY WORDS:

Cutaneous adverse drug reaction, inpatient, incidence, risk factors, outcome

INTRODUCTION

Cutaneous adverse drug reactions (cADRs) are common, comprising 10 to 30% of all reported adverse drug reactions.¹ Among hospitalized patients, the incidence of cADRs has been reported to be 2 to 3%.² The majority of cADRs are mild and self-limiting, especially after discontinuation of the causative drug. However, some severe cADRs, such as Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis (SJS/TEN), and drug reaction with eosinophilia and systemic symptoms (DRESS), can cause significant morbidity and mortality.³

Few studies have been done to evaluate the incidence, clinical pattern and outcome of cADRs among hospitalized patients, especially in our region. This study aims to determine the incidence, clinical pattern, severity and preventability of cADRs among hospitalized patients, and also to identify risk factors associated with developing severe cADRs.

MATERIALS AND METHODS

This was a six month prospective study, conducted from July to December 2014 at Hospital Sultanah Aminah Johor Bahru. All patients admitted to the General Medical Wards for suspected cADR, or developed cADR during hospitalization, were recruited. To ensure that no cases were missed during the study period, all the General Medical Ward physicians, medical officers, house officers and nurses in-charge were given briefing prior to study commencement, and were periodically reminded throughout the study period to notify any suspected cADR cases. Ward pharmacists were also involved in identifying and reporting any suspected cADR cases in the ward. All suspected cases were notified to the dermatology team. A complete history that included inquiry about the use of supplements, over-the counter medications and traditional medications, as well as a review of available medical records were done. Physical examination, relevant blood investigations and skin biopsy, if needed, were also performed and the clinical research form was duly completed by the attending dermatologist. Patients were followed up until discharge to determine outcome.

Drug causality, severity and preventability were further assessed using WHO and Naranjo causality assessment

This article was accepted: 31 May 2017

Corresponding Author: Latha R Selvarajah

Email: lathaselvarajah@yahoo.com

Table I: Drugs implicated in cutaneous adverse reactions (n=43)

Culprit drugs	No of cases	Percentage (%)
ANTIBIOTICS		
Sulphonamides (Cotrimoxazole)	6	13.9
Penicillin	3	7.0
Dapsone	3	7.0
Rifampicin	3	7.0
Fluoroquinolones(Ciprofloxacin)	1	2.3
ANTICONVULSANTS		
Phenytoin	4	9.3
Carbamazepine	2	4.7
Lamotrigine	1	2.3
Sodium valproate	1	2.3
ANTI-GOUT		
Allopurinol	2	4.7
NSAIDs AND ANALGESICS		
Mefenemic acid	4	9.3
Paracetamol	2	4.7
Naproxen	1	2.3
ANTI-RETROVIRAL		
Nevirapine	2	4.7
OTHERS		
Antivenom(1), cimetidine (1), omeprazole (1), pazopanib (1), hydrochlorothiazide (2), streptokinase (1), tenofovir (1)	8	18.6

NSAIDs: non-steroidal anti-inflammatory drugs

scales, Hartwig’s severity assessment scale and Schumock and Thornton preventability scale respectively. Drug causality for SJS/TEN and DRESS cases was further validated using the ALDEN and Kardaun scores respectively.

Descriptive statistics were presented as counts and percentages for categorical variables. Mean with standard deviation (SD) was used for normally distributed data while median with interquartile range (IQR) was used for data which were not normally distributed. Risk factors for developing cADRs and the severity of reaction were analysed using logistic regression models. Statistical significance was set at $p < 0.05$. SPSS version 16.0 was used for data analysis.

This study has been registered with the Malaysian National Medical Research Register (NMRR-14-279-20154) and approved by Medical Research Ethics Committee Malaysia.

RESULTS

Demographic characteristics

A total of 43 cADRs were seen among 11 017 inpatients, yielding an incidence rate of 0.4%. Among the 43 patients, 26 (60%) were admitted due to cADR, while the rest developed cADR while in ward. The commonest reason for admission among those who developed cADR while in ward was infection (52.9%). The mean length of stay was 9.7 days (range: 1-64).

Male to female ratio was 1.4:1. Most of the patients (79.1%) were below 60 years old with a median age of 45 years (IQR

33 - 58). Malays comprised 58.1% of patients, followed by Chinese (25.6%), Indians (11.6%) and other ethnicities (4.7%).

Clinical patterns and outcome

Figure 1 shows the distribution of adverse reactions seen. The majority of cADRs seen was SCAR (severe cutaneous adverse reaction: 22 cases, 51.2%).

The mean time to developing cADR following drug exposure was 14.4 days (range: 1-44). Mean onset-time of reaction for the top five reaction patterns were i) 25 days (range: 1-44) for DRESS, ii) 12 days (range: 1-31) for maculopapular eruption, iii) one day for urticaria ± angioedema, iv) 17 days (range: 12-24) for SJS/TEN and v) one day for FDE.

The majority of patients (76.7%) did not develop any complications due to the cADR. Most of them were recovering upon discharge (74.4%). There was one death (2.3%) caused by DRESS secondary to rifampicin.

Culprit drugs

Drugs implicated are shown in Table I. Antibiotics was the most commonly implicated drug group (16 cases, 37.2%) followed by anticonvulsants (8 cases, 18.6%) and non-steroidal anti-inflammatory drugs (NSAIDs: 5 cases, 11.6%). Drugs associated with the various reaction patterns are highlighted in Table II. DRESS was mainly due to antibiotics (6 of 14 cases, 42.9%), while anticonvulsants were responsible for majority of SJS/TEN (4 of 6 cases, 66.7%).

Table II: Drugs implicated in various cutaneous adverse drug reactions (n=43)

Reaction pattern	Culprit drug	Number of patients
DRESS (n=14)	Cotrimoxazole	2
	Phenytoin	2
	Rifampicin	2
	Penicillin	1
	Dapsone	1
	Hydrochlorothiazide	1
	Nevirapine	1
	Mefenemic acid	1
	Allopurinol	1
	Pazopanib	1
	Sodium valproate	1
Maculopapular eruption (n=9)	Cotrimoxazole	3
	Dapsone	2
	Penicillin	1
	Rifampicin	1
	Omeprazole	1
	Nevirapine	1
Urticaria + angioedema (n=7)	Mefenemic acid	1
	Naproxen	1
	Paracetamol	1
	Penicillin	1
	Cimetidine	1
	Streptokinase	1
	Anti-venom	1
SJS / TEN (n=6)	Phenytoin	2
	Allopurinol	1
	Cotrimoxazole	1
	Carbamazepine	1
	Lamotrigine	1
Fixed drug eruption (n=3)	Mefenemic acid	2
	Paracetamol	1
Cutaneous vasculitis (n=3)	Carbamazepine	1
	Ciprofloxacin	1
	Tenofovir	1
Photodermatitis (n=1)	Hydrochlorothiazide	1

DRESS: drug rash with eosinophilia and systemic symptoms; SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis;

The mean number of concurrent drugs patients took was 3 (range 0-10). Polypharmacy, with intake of at least five drugs concurrently, was mainly noted among the elderly patients (> 60 years, 44.4%) as compared to the younger age group (< 60 years, 14.7%).

Drug causality, severity and preventability

The assessment by WHO and Naranjo’s scales revealed that most cases (30 cases, 69.8%) were classified as probable causality, 5 cases (11.6%) had definite drug causality, and the remaining 8 cases (18.6%) showed possible drug causality.

Figure 2 illustrates the severity and preventability assessment among the patients. The majority of cases was classified as moderate severity (28 cases, 65.1%), and were not preventable (33 cases, 76.7%). Seven out of eight of the definitely preventable cases had previous history of cADR to the same causative drug. The main culprit drug identified in the preventable reactions was mefenemic acid (37.5%).

Risk factors

Factors such as age, gender and ethnicity were evaluated, but they did not show any significant association with increased risk of developing cADRs. A further analysis was conducted to identify the risk factors associated with severity of cADRs. Multivariate analysis showed that older age (≥ 60 years old) and presence of mucosal involvement were independently associated with increased risk of developing severe cADR (Table III).

DISCUSSION

Previous studies showed that the prevalence of cADRs among inpatients range between 0.36% and 12.2%,^{2,4,5,6} while its incidence is reported to be between 2 to 3%.² The low incidence of cADRs in our study may be attributed to the inclusion of only medical inpatients. Under-reporting by attending medical personnel could be contributory in spite of our best effort to recruit all patients with ADRs during the study period.

Table III: Risk factors associated with severe cutaneous adverse drug reactions

Risk factors	Non severe cADR (%) [n=35]	Severe cADR (%) [n=8]	Univariate analysis		p value	Multivariate analysis p value
			Crude OR ^a	95% CI ^b		
Age (years)						
< 60	30 (85.7)	4 (50.0)	1	-	-	-
> 60	5 (14.3)	4 (50.0)	6.00	1.12,32.14	0.036	0.033
Gender						
Male	19 (54.3)	6 (75.0)	1	-	-	-
Female	16 (45.7)	2 (25.0)	0.63	0.19,2.13	0.295	-
Ethnicity						
Malay	19 (54.3)	6 (75.0)	1	-	-	-
Chinese	9 (25.7)	0 (0)	0.70	0.12,4.20	0.700	-
Indian	5 (14.3)	0 (0)	NA	NA	NA	-
Others	2 (5.7)	1	NA	NA	NA	-
Comorbidity						
No	5 (14.3)	2 (25.0)	1	-	-	-
Yes	30 (85.7)	6 (75.0)	1.49	0.29,7.63	0.465	-
HIV co-infection						
No	24 (68.6)	7 (87.5)	1	-	-	-
Yes	11 (31.4)	1 (12.5)	1.09	0.28,4.05	0.302	-
Previous drug allergy						
No	24 (68.6)	5 (62.5)	1	-	-	-
Yes	11 (31.4)	3 (37.5)	1.64	0.45,5.94	0.741	-
Underlying atopy						
No	28 (80.0)	7 (87.5)	1	-	-	-
Yes	7 (20.0)	1 (12.5)	1.98	0.41,9.59	0.626	-
Concurrent drugs						
0 – 4	28 (80.0)	6 (75.0)	1	-	-	-
5 – 9	6 (17.1)	2 (25.0)	3.38	0.60,19.16	0.636	-
> 10	1 (2.9)	0 (0)	NA	NA	NA	-
Mucosal involvement						
No	30 (85.7)	4 (50.0)	1	-	-	-
Yes	5 (14.3)	4 (50.0)	6.00	1.12,32.14	0.036	0.036

*NA: not available (figures not computable)

^aOdds Ratio ^bConfidence Interval

^cForward Stepwise Likelihood Ratio was applied for multivariate analysis for all the variables considered in the univariate analysis. There were no interactions amongst independent variables.

cADR: cutaneous adverse drug reaction; HIV: human immunodeficiency virus

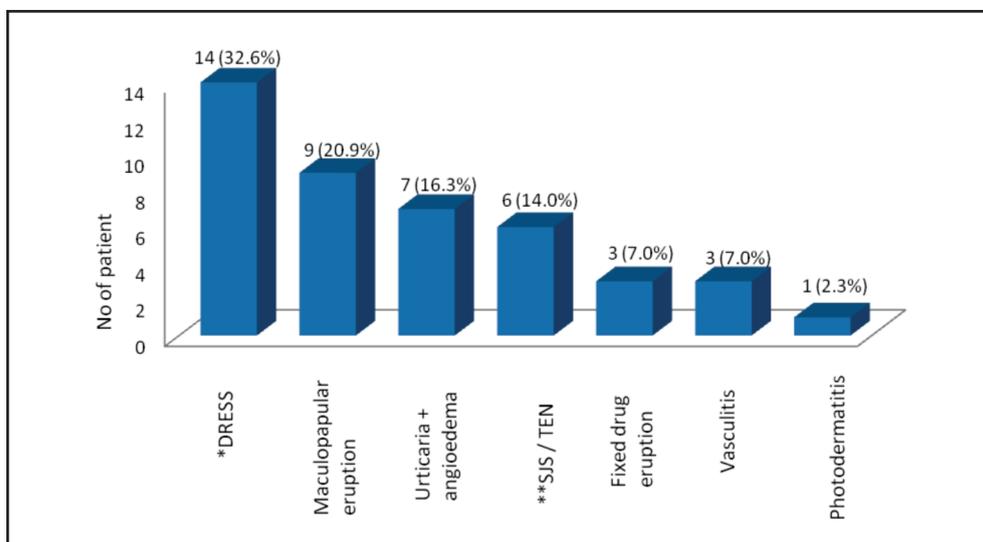
The age and gender distribution in our study was similar to the distribution among the total admissions in the general medical wards during the study period. Unlike previous studies^{7,8,9} which identified older age and female gender as risk factors for developing cADRs, we did not find similar significant associations in our study. A previous study of 362 cADRs seen in our department of Dermatology identified a significantly lower cADR rate among Indian patients.³ We failed to identify similar risk factors in our study, likely due to our small sample size and inclusion of only inpatients.

In contrast to other inpatient studies for cADRs which identified maculopapular eruption and urticaria as the main reaction patterns seen,^{5,9,10} our study showed that SCAR was the commonest reaction encountered. This discrepancy could be due to referral bias as our hospital is the main tertiary referral centre, and thus receive more serious and

complicated cases. Mild cADRs are also usually not admitted. Underreporting of mild and self-limiting symptoms could also be a contributory factor.

The main culprit drug groups identified in our study were antibiotics and anticonvulsants, in-keeping with the results of other studies.^{3,9,10} Antibiotics were the most frequently implicated drug group in our study, consistent with the fact that the commonest reason for admission was infection.

Our study showed a wide number of drugs causing cADRs, with cotrimoxazole identified as the most frequently implicated drug. Predominance of sulphonamides as a causative agent for cADRs has been reported in many other previous studies,^{9,10,11} thus raising the need for higher vigilance when using this drug and consideration of prescribing other safer alternatives.



*DRESS: drug rash with eosinophilia and systemic symptoms;
 **SJS: Stevens-Johnson syndrome; TEN: toxic epidermal necrolysis;
Fig. 1: Distribution of cutaneous adverse drug reactions patterns (n=43).

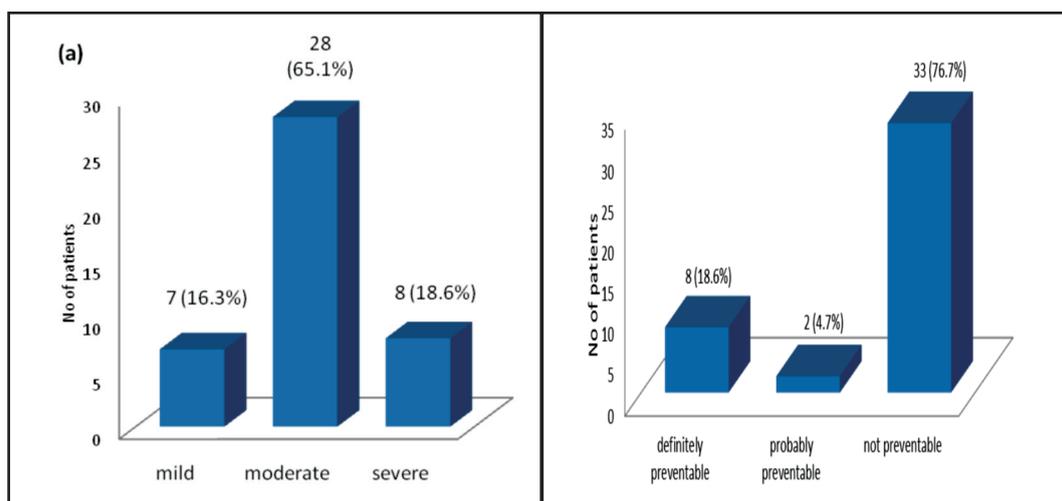


Fig. 2: Severity and preventability assessment of 43 patients with cutaneous adverse drug reactions.

As compared to a previous cADR study done in our department of Dermatology,³ where carbamazepine and allopurinol were identified as the commonest causative drugs, our study showed a lower proportion of cases associated with these drugs. This change in drug pattern could be due to a more judicious use of allopurinol currently, and also the availability of newer anti-epileptic drugs. In Malaysia, allopurinol has been consistently reported as one of the commonest causative drug for cADRs, especially SCAR.^{3,12} This has led to the implementation of various risk minimization strategies by the relevant authorities, including stricter prescription regulations and compulsory cautionary labels on product inserts for allopurinol, thus resulting in fewer allopurinol-induced cADRs.

Previous studies have identified older age, female gender, presence of comorbid illness, concomitant HIV infection and polypharmacy as risk factors for cADRs.^{7,13} We failed to identify similar factors in our study, likely due to our small sample size. However, we found that older age (≥ 60 years) and mucosal membrane involvement were significantly associated with a more severe reaction ($p=0.04$). Older age has consistently been advocated as a significant risk factor for ADRs in many studies and meta-analyses, likely owing to the increased potential for drug-drug interactions, and altered drug handling by the body in the elderly.^{7,8} Lesions in the mucosa take longer time to heal, thus explaining its association with a poorer prognosis.

Assessment of preventability of cADRs is an integral part of pharmacovigilance, and may guide towards policy changes to reduce cADRs. In our study, we had about 23% of preventable cases, a higher number as compared to previous reported figures of between 12 to 16%.^{14,15} These preventable reactions were associated with the intake of the same culprit drug taken previously, mainly mefenemic acid. Mefenemic acid is a commonly prescribed analgesia, and easily obtained over the counter. A repeat intake of this drug despite having previous adverse reaction to the same drug indicates a serious lack of awareness among our patients regarding cADRs and its potential harm. Regular education regarding cADRs, as well as stricter prescription regulations may help to reduce these preventable reactions.

CONCLUSIONS

The incidence of cADRs among inpatients in this study was 0.4%. The commonest reaction seen was DRESS, while the most frequently implicated drug group was antibiotics, mainly cotrimoxazole. The majority of cADRs had moderate severity, and mostly was not preventable. Older age (≥ 60 years) and mucosal membrane involvement were significantly associated with a more severe adverse reaction.

REFERENCES

1. Arulmani R, Rajendran SD, Suresh B. Adverse drug reaction monitoring in a secondary care hospital in South India. *Br J Clin Pharmacol* 2008; 65(2): 210-6.
2. Bigby M, Jick S, Jick H, Arndt K. Drug-induced cutaneous reactions: a report from the Boston Collaborative Drug Surveillance Program on 15 438 consecutive inpatients, 1975 to 1982. *J Am Med Assoc* 1986; 256(24): 3358-63.
3. Choon SE, Lai NM. An epidemiological and clinical analysis of cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. *Indian J Dermatol Venereol* 2012; 78(6): 734-9.
4. Lee HY, Tay LK, Thirumoorthy T, Pang SM. Cutaneous adverse drug reactions in hospitalised patients. *Singapore Med J* 2010; 51(10): 767.
5. Fiszenson-Albala F, Auzerie V, Mahe E, Farinotti R, Durand-Stocco C, Crickx B, Descamps V. A 6-month prospective survey of cutaneous drug reactions in a hospital setting. *Br J Dermatol* 2003; 149(5): 1018-22.
6. Borch JE, Andersen KE, Bindslev-Jensen C. The prevalence of acute cutaneous drug reactions in a Scandinavian university hospital. *Acta Derm Venereol* 2006; 86(6): 518-22.
7. Pedrós C, Quintana B, Rebolledo M, Porta N, Vallano A, Arnau JM. Prevalence, risk factors and main features of adverse drug reactions leading to hospital admission. *Eur J Clin Pharmacol* 2014; 70(3): 361-7.
8. Kongkaew C, Noyce PR, Ashcroft DM. Hospital admissions associated with adverse drug reactions: a systematic review of prospective observational studies. *Ann Pharmacother* 2008; 42(7-8): 1017-25.
9. Sharma VK, Sethuraman G, Kumar B. Cutaneous adverse drug reactions: clinical pattern and causative agents--a 6 year series from Chandigarh, India. *J Postgrad Med* 2001;47(2):95-9
10. Nandha R, Gupta A, Hashmi A. Cutaneous adverse drug reactions in a tertiary care teaching hospital: A North Indian perspective. *Int J Appl Basic Med Res* 2011; 1(1): 50-53.
11. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, et al. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999; 48: 839-46.
12. Ding WY, Lee CK, Choon SE. Cutaneous adverse drug reactions seen in a tertiary hospital in Johor, Malaysia. *Int J Dermatol* 2010; 49(7): 834-41.
13. Alexopoulou A, Dourakis SP, Mantzoukis D, Pitsariotis T, Kandyli A, Deutsch M, Archimandritis AJ. Adverse drug reactions as a cause of hospital admissions: a 6-month experience in a single center in Greece. *Eur J Intern Med* 2008; 19(7): 505-10.
14. Al-Tajir GK, Kelly WN. Epidemiology, comparative methods of detection, and preventability of adverse drug events. *Ann Pharmacother* 2005; 39(7-8): 1169-74.
15. Padmavathi S, Manimekalai K, Ambujam S. Causality, Severity and Preventability Assessment of Adverse Cutaneous Drug Reaction: A Prospective Observational Study in a Tertiary Care Hospital. *J Clin Diagn Res* 2013; 7(12): 2765.