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Mini Review

Cutaneous Adverse Drug Reaction: A Review of a Four-year Experience in a Tertiary Referral Hospital in Malaysia

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Introduction: There are many types of cutaneous adverse drug reactions (CADRs), from transient erythema to severe life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with significant morbidity and mortality. Awareness of the local epidemiology of CADR may play a vital role in future clinical management protocols.
Methods: A retrospective review of all patients referred to the Department of Dermatology of Hospital Tengku Ampuan Afzan, Kuantan, Pahang, Malaysia, with confirmed CADR from 2013 to 2016 was carried out to determine the epidemiology of CADR in the local population.
Results: A total of 62 reactions involving 59 patients were seen among 7,353 new patients, yielding an incident rate of 0.8% (yearly CADR rate range: 0.16 – 1.89%), with the highest rate seen among indigenous peoples (2.53%). SJS (15 cases) was the most frequent CADR, followed by maculopapular eruption (13) and TEN (6) among others. Severe CADRs (SJS, TEN, drug-related eosinophilia with systemic symptoms – DRESS, and acute generalized exanthematous pustulosis – AGEP) accounted for 40.3% of all reactions. Two-thirds of patients were aged between 21 and 60 years, while the mean age was 47.2 years (range: 3 – 92). More females (80.0%) had SJS than males (20.0%), but TEN showed a reverse pattern (83.3% males vs 16.7% females). Overall, the male:female ratio was 1.68:1. Allopurinol was the most common culprit drug causing SJS (7/15) and TEN (2/6). Cotrimoxazole and Cloxacillin were the two most common antimicrobials implicated in CADR, while the most common analgesic was Celecoxib. One-third of our patients took only a single drug, while the average number of drugs taken by a patient was three. Two patients died, one each from dapsone hypersensitivity syndrome and TEN, resulting in a mortality rate of 3.39%.
Conclusion: SJS was the most common CADR encountered in our center, while the most common culprit drug was allopurinol. Antibiotics as a group caused the most CADR.
Keywords: Malaysia; Dermatology; Allopurinol; Anti-Infective Agents
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Introduction

Drug reactions are unwanted reactions of the body following the administration of drugs that are uncharacteristic of the expected pharmacodynamic effects.[1] These include cutaneous adverse drug reactions (CADR), which range from mild pruritus and transient erythema to severe life-threatening conditions such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), with significant morbidity and mortality. Sadly, drug reactions are often under-reported, and CADR are often misdiagnosed as viral exanthems or attributed to collagen vascular diseases. This in turn may be due to insufficient awareness by healthcare providers, given the emergence of newer classes of drugs with yet unclassified adverse effects as well as evolving prescription profiles.[2, 3] Hence, it is hoped that this clinical audit and review of literature will create the much needed awareness of the epidemiology of CADR, and subsequently influence future, more judicious prescribing practices of healthcare providers.

Methods

A retrospective review of all patients referred to the Department of Dermatology of Hospital Tengku Ampuan Afzan (HTAA), Kuantan, Pahang, Malaysia, with CADR from 2013 to 2016 was carried out to determine the epidemiology of CADR in the local population.

Results

A total of 62 CADR involving 59 patients were seen among 7,353 new patients, yielding an incidence rate of 0.80% (yearly CADR rate range: 0.16 – 1.89%). The highest CADR rate was seen among indigenous peoples (Table 1).

Table 1. Rates of CADR between both genders and various ethnic groups

	No. of new patients N (%)	No. with CADRN (%)	CADR rate (%)
Gender			
Male	3567(48.5)	37(62.7)	1.04
Female	3786(51.5)	22(37.3)	0.58
Ethnicity			
Malay	5697 (77.5)	41(69.5)	0.72
Chinese	1176(16.0)	11(69.5)	0.94
Indian	322(4.4)	3(5.1)	0.93
Indigenous	158(2.1)	4(6.8)	2.53
Total	7353	59	0.80

CADR: cutaneous adverse drug reaction

Two-thirds of patients with CADR were between 21 and 60 years old, with a mean age of 47.3 years (range: 3 – 92). Two patients died, one each from dapsone hypersensitivity syndrome and TEN, resulting in a mortality rate of 3.39%. More females (80.0%) had SJS than males (20.0%), while TEN showed a reverse pattern (83.3% males vs 16.7% females). Fig 1 illustrates the various CADR reported in our cohort, while fig 2 highlights the culprit groups of drugs.

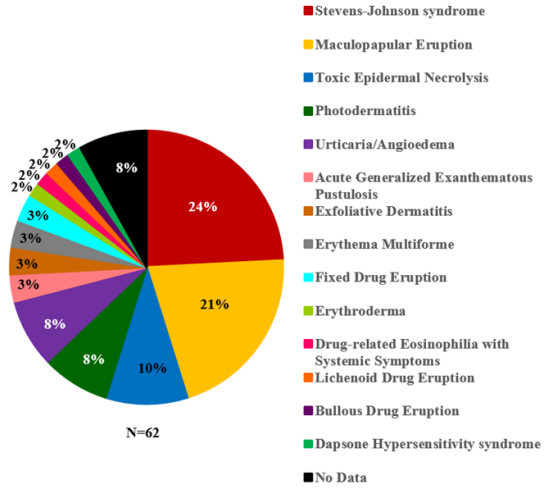

Figure 1. Type of CADR

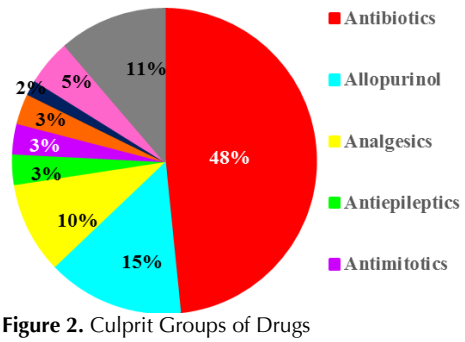

Figure 2. Culprit Groups of Drugs

Allopurinol was the most common culprit drug causing SJS (7/15) and TEN (2/6). Cotrimoxazole and Cloxacillin were the two most common antimicrobials implicated in CADR, while the most common analgesic was Celecoxib. One-third of our patients took only a single drug, while the average number of drugs taken by a patient was three.

Discussion

Where do we stand against other Asian centers? Table 2 below compares our findings with clinico-epidemiological studies on CADR in Malaysia and various Asian countries. Severe CADR, namely SJS and TEN, were among the most common CADRs observed in the Malaysian hospitals listed above, including ours. This could be due to a referral bias, being dermatology referral centers accepting serious CADRs. This could also explain the lower CADR rate in our cohort compared to 1.38% and 1.5% of dermatology referrals in Denmark[4] and Tunisi[5], respectively. We now know that there are specific genetic markers for carbamazepine- and phenytoin-induced CADRs, namely the HLA-B*15:02 allele predicting the risk of carbamazepine[6-9] as well as phenytoin[10-13] induced SJS/TEN in South-East Asian populations, HLA-A*31:01 allele for carbamazepine-induced hypersensitivity reactions in European populations[14], and HLA-B*15:13 for phenytoin-induced SJS/TEN among Malays in Malaysia[10], and that these allelic markers occur with varying frequency in different ethnic populations. Likewise, HLA-B*13:01 has been reported to be a predictor for dapsone-induced, drug-hypersensitivity syndromes among patients with leprosy.[15] HLA-B*13:01 has also been found among the three main indigenous groups in Peninsular Malaysia, namely the Temuan, Jehai, and Kensiu, with the Kensiu peoples having the highest allele frequency.[16] Whether this holds true for the indigenous peoples of the state of Pahang, resulting in higher CADR rates among them, requires further pharmacogenomic studies. Antimicrobials being the predominant culprit group in almost all of the studies above not only reflects the high infectious diseases burden in tropical and subtropical Asia, but also serves to remind us of more judicious prescriptions of these agents in the future.

Conclusion

SJS was the most common CADR encountered in our center, while the most common culprit drug was allopurinol. Antimicrobials as a group caused the most CADR, and indigenous peoples have a high rate of developing CADR.

Table 2. A comparison of Clinico-Epidemiological Studies on CADR in Malaysia and Various Asian Countries

	Huang HY, et al.[17] (2004-2008) Shanghai, China N=734	Choon SE, et al.[18] (2001-2010) Johor Bahru, MalaysiaN=362	Talib NH, et al.[19] (2009-2010) Kuala Lumpur, MalaysiaN=134	Garg HK, et al.[20] (2010-2012) Ajman, UAE N=43	Mokhtari F, et al.[21] (2006-2013) Isfahan, Iran N=282	Janardhan B, et al.[22] (2013-2014) Hyderabad, India N=481	Our Study (2013-2016) Kuantan, Malaysia N=62
Male:Female ratio	1:1.97	1:1.14	1:1.1	1:1.15	1:1.55	1:1.78	1:1.67
Mean age (years)	43.90(8-93)	39.60(1-98)	47(14-91)	30.0	29.48(0.4-90)	42(1-64)	47.2(3-92)
Median latency (days)	7.64±8.32	NA	NA	5.63±0.5	NA	4(1-120)	6
Incidence/Prevalence (%)	NA	Incidence: 0.86	Prevalence: 0.2	NA	NA	Prevalence: 1.08	Incidence: 0.8
Most common CADR (%)	1.0 EM (34.7) 2.0 Urticaria (26.2) 3.0 MPE (21.7)	MPE (42.3) SJS (24.3) DRESS (9.4)	MPE (22.4) SJS (9.7) FDE (8.9)	MPE (48.8) Erythroderma (18.6) Urticaria (11.7)	SJS (31.9) MPE (24.5) TEN (11.0)	MPE (35.6) Urticaria (26.2) FDE (17.9)	SJS (24.2) MPE (21.0) TEN (9.7)
Most common groups of culprit drugs	1.0 Antimicrobials (48.3) 2.0 Allopurinol (6.0)	1.0 Antimicrobials (40.3) 2.0 AEDs (22.4) 3.0 Allopurinol (13.8)	1.0 Antimicrobials (36.6) 2.0 TCM (17.9) 3.0 Analgesics (13.4)	1.0 Antimicrobials (48.8) 2.0 Analgesics (32.5) 3.0 TCM (4.6)	1.0 AEDs (51.8) 2.0 Antimicrobials (33.7) 3.0 Analgesics (5.7)	1.0 Antimicrobials (56.3) 2.0 NSAIDs (19.5) 3.0 AEDs (16.6)	1.0 Antimicrobials (48.4) 2.0 Allopurinol (14.5) 3.0 Analgesics (9.7)

EM: Erythema Multiforme; MPE: Maculopapular Exanthem; SJS: Stevens-Johnson Syndrome; DRESS: Drug-Related Eosinophilia with Systemic Symptoms; FDE: Fixed Drug Eruption; TEN: Toxic Epidermal Necrolysis; AEDs: Anti-Epileptic Drugs; TCM: Traditional and Complementary Medicine; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; NA: Not Available

Ethical Approval

Not applicable.

Conflicts of Interests Disclosure

None.

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