

More than skin deep. Ten year follow up of delayed cutaneous adverse drug reactions (CADR)

Linda Velta Gaudins ¹

Jennifer Ly ¹

Jason Trubiano ^{2, 3, 4, 5}

Ar Kar Aung ^{2, 6}

1. Pharmacy Department, Alfred Health, Victoria, Australia
2. Department of Infectious Diseases, Alfred Health, VIC, AUS.
3. Department of Infectious Diseases, Peter MacCallum Cancer Centre, VIC, AUS
4. Department of Infectious Diseases, Austin Health, VIC, AUS.
5. Department of Medicine, University of Melbourne, VIC, AUS.
6. Department of General Medicine, Alfred Health and Monash University, VIC, AUS.

Corresponding Author:

Linda Velta Gaudins

Pharmacy Department

The Alfred Hospital

55 Commercial Road, Melbourne, Victoria 3004 Australia

Phone: +61390763308

Email: lgraudins@alfred.org.au

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What is known about the subject

- Cutaneous adverse drug reactions (CADR) are a diverse range of delayed hypersensitivity reactions associated with high mortality and morbidity
- It is important to assign correct drug causality in CADR
- Patients should avoid the single causative agent of CADR in the future

What this study adds

- Documentation of medications involved in CADR was not universally accurate or complete
- Written information improved patient knowledge of medications to avoid after a diagnosis of CADR
- Long term follow-up is warranted in CADR patients to monitor for patient concerns, recurrence and long term sequelae

ABSTRACT

Aims

To determine the gaps in practice regarding appropriate ADR documentation and risk communication for patients diagnosed with severe cutaneous adverse drug reactions (CADR).

Methods

This was a retrospective observational cohort study conducted using hospital coding and databases to identify inpatients diagnosed with CADR from January 2004 to August 2014. Hospital discharge summaries, ADR reports and pharmacy dispensing records were reviewed for ADR documentation. Patients, who were still living in Australia and did not opt out of being contacted, were invited to be surveyed by telephone to determine their understanding of recommendations, re-exposure rates and long-term effects.

Results

Of 85 patients identified, median age was 59 (IQR 44 – 72) years and 47.1% were male. The most common diagnosis was TENS (49.4 %). Ten patients (11.8%) died as inpatients. Of the

81 patients with a drug-related causality, 47 (58%) had appropriate documentation in all three required medical record platforms. Of the 56 eligible patients, 38 (67.9 %) were surveyed; 13% had no information provided upon discharge and 26.3% patients had a mismatch in knowledge of implicated medications. No surveyed patient had a relapse of CADR, but 23.7% had a subsequent unrelated allergic reaction. Thirteen patients (34.2%) reported long term effects.

Conclusions

We found gaps in the accuracy of ADR documentation and communication of risk at discharge, which indicated risks to patient safety. Electronic systems are being developed to improve documentation. Written information about CADR is being provided at discharge to improve patient understanding and knowledge.

INTRODUCTION

Delayed cutaneous adverse drug reactions (CADR) are a heterogeneous group of T-cell mediated hypersensitivity reactions. These include life-threatening conditions which are collectively known as severe cutaneous adverse reactions (SCAR): drug rash with eosinophilia and systemic symptoms (DRESS), Steven-Johnsons syndrome (SJS), toxic epidermal necrolysis (TEN) and acute generalised exanthematous pustulosis (AGEP). Additionally, highly morbid conditions such as fixed drug eruption (FDE), erythema multiforme (EM) and linear IgA diseases (LID) are also classified under CADR [1].

The reported incidence varies according to condition, with SJS at 1-6 per 1 million person-years, TEN at 0.4-1.2 per 1 million person-years and AGEP at 1-5 per 1 million person-years [2,3]. DRESS occurs more commonly, in approximately 1 in 10,000 medication exposures

[4]. In those who develop CADR, the consequences can be significant with mortality rates of up to 10% in DRESS, 24% in AGEP, 54% in SJS, 67% in TEN [4-6]. Commonly implicated medications include antibiotics, anti-epileptics and non-steroidal anti-inflammatory drugs [7,8].

Following an episode of CADR, timely drug causality assessments should be undertaken to aid appropriate adverse drug reaction (ADR) “labelling”. Drug causality is usually established by the Naranjo score [9], ALgorithm of Drug causality for Epidermal Necrolysis (ALDEN) [10] or RegiSCAR criteria [10,11]. As T-cell responses can persist for extended durations post drug exposure, it is generally recommended that causative agents be avoided for an indeterminate period of time [12, 13]. Upon discharge from hospital, the patient must be provided with clear instructions, in order to prevent inadvertent re-exposure to the implicated or structurally related medications. Practice guidelines recommend communication in a written format and/or providing an “allergy” bracelet [12-14]. Moreover, medication allergies must be clearly documented in the medical record and medication charts for inpatients and in the discharge letter to patients and their general practitioners (GPs). This is pertinent, as re-exposure to the implicated or structurally related medications can cause a more severe reaction with a shorter onset, leading to more severe clinical outcomes. The recurrence rate of SJS and TEN after hospital discharge can be as high as 7% [15].

Although a crucial step, studies examining communication to patients after diagnosis of CADR remain limited. Also, little is known about patients’ knowledge of their allergies post discharge, accidental re-exposures to medications and subsequent reactions. Hence, we conducted a retrospective observational study, with the primary objectives: 1) To determine the frequency of documentation of CADR and implicated medications in (i) the hospital discharge summary, (ii) medical record and (iii) hospital pharmacy dispensing program; 2) Identify the nature and frequency of communication about the CADR at discharge ; 3)

Evaluate patients' knowledge and compliance to recommendations, factors contributing to deficiencies in patients' knowledge, and 4) To determine rates of re-exposure to implicated or structurally related medications and consequences.

METHODS

Setting

This study was conducted at Alfred Health, in Melbourne, Australia, an 800-bed university affiliated network of three teaching hospitals, providing general, surgical and psychiatric services as well as specialised units including trauma, solid organ and haematological transplants, HIV services and is the state Adult Burns Service which also is a referral centre for patients diagnosed with SCAR. This study was approved by the Alfred Health Ethics Committee as a low risk project (number: 105/15).

Hospital policy promotes voluntary reporting of ADRs to the ADR Review Committee (ADRRC). The ADRRC consists of senior clinicians and pharmacists and reviews an average of 15 reports every two weeks. Patients with ADRs evaluated as 'possible,' 'probable, or 'definite' causality by a consensus decision (based on Naranjo [9] and/or ALDEN [10] algorithms) are sent a letter with recommendations about the implicated medication/s [16].

All reports considered 'possible' causality or above are de-identified and e-mailed to the Therapeutic Goods Administration (TGA) for inclusion in the national Database of Adverse Event Notifications (DAEN) [17]. Report forms are scanned into the electronic medical records and the implicated medication/s are also entered manually into each patient's profile in the pharmacy dispensing system. ADRs must also be recorded on the patient's discharge summary which, since 2010, is entered electronically. Thus, ADR documentation is mandated at Alfred Health on three different systems.

Documentation

For this study, cases of CADR occurring, between January 1, 2004 and August 31, 2014

were identified from the hospital records using International Statistical Classification of Diseases and Related Health Problems (ICD-10). To ensure case capture we also cross-examined the Victorian Burns Registry, HIV Alfred Database and Alfred Health Adverse Drug Reaction (ADR) Committee database. To determine diagnosis and information given to the patients at discharge, patient discharge summaries, biopsy results and ADR reports were accessed by the study investigators via either paper records (before 1st April 2010) or scanned medical records from more recent admissions (1st April 2010 onwards). ADR documentation was reviewed in each patient's pharmacy dispensing record (iPharmacy®).

Communication at discharge and patient outcomes

Alfred Health patients identified with a CADR diagnosis were invited by a letter to participate in a telephone survey. Participation was voluntary with an opt-out option provided. Patients known to be deceased, who did not have a medication-related reaction, living overseas or did not give consent, were excluded. Patients were contacted by a trained pharmacy intern (JL) or pharmacist (LG) by telephone. If the patient could not be contacted by telephone after three attempts, no further attempt was made. Four patients requested the survey by email, but then did not respond, despite an email reminder. Questions in the survey form were designed to assess; frequency and methods of risk communication to the patients upon discharge, allergy specialist follow-up, patient's knowledge of their allergy and medication/s involved, any further ADRs or inadvertent re-exposure to implicated or related medications. (Appendix 1) Patients' understanding was matched with hospital documentation. Comments regarding outcomes were noted.

Definitions

CADR diagnosis was taken from the discharge summary and/or biopsy comments. CADR was defined as; erythema multiforme (EM) fixed drug eruption (FDE), acute generalised

erythematous pustulosis (AGEP), drug reaction with eosinophilia and systemic symptoms (DRESS), drug-associated linear IgA disease (LID), Stevens-Johnsons syndrome (SJS) and toxic epidermal necrolysis (TEN). SJS was defined as widespread macules or blisters with skin detachment of <10% of body surface area (BSA), TEN if skin detachment was >30% BSA. DRESS was defined as per regiSCAR criteria [4]. Drug-induced maculopapular exanthems, IgE-mediated urticarial reactions and angioedema were not included in the study.

A 'mismatch' in patient's knowledge was defined as non-concordance between patient's recall of their own medication allergies and documented description on any of the medical record platforms (ADR reports, discharge summaries and pharmacy dispensing records). Factors that could potentially influence such 'mismatch' were pre-determined as: 1) number of implicated medications (1 vs. >1), 2) patient's age (≥ 65 vs. <65 years), 3) time from index reaction (≥ 5 vs. <5 years) and 4) receipt of written information (yes vs. no). These factors were selected on assumption that a mismatch may be more likely: if multiple medications were involved in the index reaction; with older age due to age-related cognitive factors; with longer time elapsed from the index reaction; and if no written information was provided upon discharge. Patients' comments were defined as pertaining to 'psychological' issues if related to the mental and emotional state of a person or 'physiological' if affecting health or normal functioning.

Statistical analysis

Data were collated for analysis. Deceased patients were excluded from the surveyed cohort, but included in the overall statistical analysis regarding documentation, except where indicated. All categorical data were presented as counts and proportions whilst numerical data were presented as median and interquartile ranges. Chi-square and Fisher's exact tests were employed to detect statistical significance between categorical variables whilst Mann-

Whitney U test was used to detect differences between numerical variables. For surveyed patients, pre-determined factors that could potentially influence 'mismatch' were analysed with bivariate models using 2x2 tables (for example, matched vs. mismatched and one medication vs > one medication) and presented as odds ratios. For all analyses, a two-sided p value of <0.05 was considered statistically significant.

RESULTS

A total of 85 patients were recruited; 61 from ICD-10 coding data, including 20 patients also in the Burns Registry, and an additional 24 from ADR Committee database. Fifty four of the 85 (63.5%) patients were admitted since 1st April 2010, when electronic medical records were introduced. The median age of patients was 59 (IQR 44-72) years, with 40 (47.1%) being male (Table 1). TENS/SJS in 57 (67%) patients was the most common diagnosis.

Four cases were not related to medications (1 mycoplasma infection, 3 unclear precipitant).

Amongst 81 patients with medication-related CADR, 35 (43.2%) had more than one medication implicated. Of the 135 implicated medications, 54% were antibiotics, the most common classes were penicillins and cephalosporins, comprising 22.2% of all implicated medications. The next class commonly implicated was anticonvulsants, which comprised 10.4% of all medications (Table 1). Ten patients (11.8%) died during the index admission; nine patients were diagnosed with TENS and one with AGEP. A further four died by the time of survey (Figure 1). Later deaths were not directly attributable to CADR. Of the patients who survived to discharge ($n = 71$), none died within 60 days after discharge.

Documentation

For the 81 patients with a medication-related CADR, 71.6% had the ADR reported to the hospital ADR Committee. (Table 2) Eighty-four per cent of discharge summaries noted the CADR and possible causes; only 9.9 % had a specific recommendation regarding medication/s to avoid. The majority (82.7%) of ADRs were documented in the pharmacy

dispensing system. Only forty-seven (58%) CADR patients had documentation in all required areas as mandated by our organisation: discharge summary, ADR report and pharmacy dispensing system.

Communication at discharge and patient outcomes

Of the 67 patients with drug-induced CADR known to have survived to survey date, 38 (56.7%) were able to be contacted. (Figure 1) The median age of surveyed patients on admission was 59 years (IQR 48 - 71). On analysis regarding the representativeness of the sample, there was no statistically significant difference in characteristics between surveyed and non-surveyed patient groups (Table 1)

For surveyed patients, we further examined if an individual's current knowledge of implicated medications matched the discharge summary in the medical records, and found that 26.3% had a mismatch. In examining factors that could contribute to mismatch, we found that only receipt of written information at discharge was significantly associated with a match in knowledge ($p=0.04$) (Table 3).

Of the 38 patients surveyed, three (7.9%) had been re-exposed to a beta- lactam antibiotic after discharge, with one patient having a reaction (non-CADR). A further nine (23.7%) patients experience ADRs to unrelated medications or substances since the CADR admission. Only four (10.5%) patients had been referred to allergist or immunologist for follow-up. Although no surveyed patients had a relapse of their CADR, 13 of the 38 surveyed patients (34.2%) volunteered comments about the negative sequelae post discharge (Table 4). Physiological and psychological effects were reported up to ten years after SCAR admission.

DISCUSSION

Although the epidemiology, associations and treatment of severe dermatological ADRs are well-described, medical documentation and risk communication to patients are important

management aspects that can be overlooked. There is little published research in patient experiences with adverse events [18] and there are only a few studies involving long-term follow-up of CADR patients [19]. This study is one of the few to highlight aspects of CADR documentation and risk communication, from both health system and patient perspectives. Documentation of implicated medications after hospital discharge to prevent inadvertent re-exposure and development of severe clinical consequences is recommended by the National Institute for Health and Care Excellence (NICE) [13]. The benchmark for accurate allergy recording and communication should be close to 100%, especially for conditions with high mortality and morbidity such as CADR. Our research highlighted that, like many institutions [20, 21], we fell short of this benchmark. It is of concern that in at least 15% of patients, the information about the reaction was lacking in pharmacy records and/or discharge summaries. Moreover, only ten per cent of discharge summaries, which are usually given to both GP and the patient, had explicit recommendations for further management of the reaction and avoidance of medications. Furthermore, a quarter of patients were identified as having a knowledge gap regarding implicated medications. Similar to findings in a recent study [22], we also found that written information about the CADR significantly improved patients' knowledge. Moreover, patients' experiences were not always adequately addressed and followed up.

Although having three different systems to record the same allergy information may provide a safety net, we found that almost half of the patient documents were incomplete and not always accurate, sometimes even providing conflicting and confusing information to patients and health practitioners. These discrepancies may arise due to variable reporting and documentation practices, compounded by deficiencies in treating clinicians' knowledge of ADRs and patients' understanding of the medications involved. We found that although a majority of CADR reactions were reported to the ADRRC, which plays an important role in

ensuring that patients received accurate written information after discharge, this information was often processed retrospectively and highly dependent on the accuracy of input by the treating teams. From November 2014, pharmacist involvement in completing the medication management in discharge summaries was implemented, which has improved the accuracy and completeness of ADR documentation [23]. In response to the risks to patient safety resulting from incomplete ADR documentation, the implementation of an electronic ADR documentation and risk mitigation package, as the one 'source of truth' for ADR information, has been proposed for implementation as part of our network's medical record system, so that a complete set of information can be communicated to patients and their carers.

The retrospective nature of the study meant that ADR-related data may have been less complete in pre-2010 paper-based records. All eligible patients were not able to be contacted; however the surveyed and non-surveyed patient cohorts were not statistically different. Some patients were contacted up to ten years after their diagnosis, so reliance on memory may not have led to accurate information, but testing due to time from diagnosis showed no significant difference in patient recall of information. As specific medication avoidance after a CADR may be life-long, the results are indicative of patient retention of information. A recall bias may have been introduced by sending out an invitation letter prior to commencement of the study. We attempted to minimise this bias by wording the invitation letter as generic as possible without outlining specific outcomes we were attempting to measure. The letter may have improved patient's knowledge, as they had the opportunity to refer to written information provided by the hospital before answering the survey. This would have over-estimated the effect size of patient knowledge.

Our study found, that having written information is pertinent in improving patient's understanding. A patient information leaflet has been developed with input from the hospital consumer group, the hospital's Burns unit and ADR Committee members (Appendix 2). This

is to be given to patients at discharge, by the team pharmacist, nurse or doctor, with personalised information, agreed upon by the treating team and consistent with the discharge diagnosis. An alert bracelet is another form of written information. As we do not routinely provide these to our patients, we did not evaluate their use.

As CADR patients may be inpatients under various teams, a coordinated approach is being discussed at our hospital network, to facilitate CADR patient follow-up after discharge. The question about allergy referral was posed to ascertain whether further testing for causality determination was carried out for this high risk patient group. Referral for antibiotic reactions is of importance, so as not to unnecessarily incorrectly 'label' a patient allergic, leading to restrictions in future choice of antibiotics [24].

Where available, we suggest ADR review committees in healthcare institutions should form an integral part in risk communication, so that allergic events are systematically reviewed and written information conveyed to both healthcare practitioners (hospitalists and GPs) and patients in a timely, comprehensive and actionable manner. Formalising ADR management has been recognised an essential component to health service quality as Medication Safety, including ADR management, is one of the ten components of the Australian National Safety and Quality Health Service accreditation standards [25].

CONCLUSION:

We found that, although there were many opportunities for documentation of ADRs, appropriate and accurate documentation was far from universal. Therefore, there was no agreed upon "source of truth" for ADRs. Both accurate documentation of implicated medications and timely determination of causality are essential to formulate recommendations for both patients and their health care workers. An electronic documentation system has been proposed to address this gap. As written information given to

patients increases patients' knowledge, improving the accuracy of the discharge summary and a specific information leaflet was developed. The provision of on-going follow-up after discharge is essential to mitigate risk and address patients' concerns.

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COMPETING INTERESTS

There are no competing interests. This study was undertaken within existing hospital resources. All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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Table 1: Documentation of medication-related SCAR

Figure 1: Cutaneous Adverse Drug Reaction (CADR) patient selection

Table 2: Surveyed and non-surveyed cohort comparison

Table 3: Risk communication provided to patients with cutaneous adverse drug reactions

Table 4: Comments from surveyed patients

Appendix 1: Survey

Appendix 2: Patient information leaflet

Table 1: Documentation of medication-related SCAR

Documentation	N	%
	n =81	
Discharge summary	68	84.0
ADR report in medical record	58	71.6
Pharmacy dispensing records	67	82.7
Complete allergy documentation: (Discharge summary+ ADR report + Pharmacy)	47	58.0
Non-deceased patients	n =71	
Specific recommendation documented	7	9.9

Table 2: Surveyed and non-surveyed cohort comparison

	Surveyed n= 38	Not surveyed n=47	Total n =85	P-value
Median age years, (IQR)	59 (48 -71)	57(44 - 72)	59 (44-72)	0.97
Male (%)	15 (36.9)	25 (53.2)	40 (47.1)	0.28
Diagnosis			N (%)	
TENS	14	27	41 (49.4)	0.09
SJS	10	7	17 (17.6)	
AGEP	6	5	11 (12.9)	
DRESS	7	4	11 (12.9)	
EM	1	3	4 (4.7)	
Linear IgA	0	2	2 (2.3)	
Time since admission				
Greater than 5 years	13 (34.2)	22 (46.8)	35 (41.2)	0.27
Less or equal to 5 years	25 (65.8)	25 (53.2)	50 (58.8)	
ADR reported	29 (76.3)	30 (63.8)	59 (69.4)	0.24
Type of medication	57	78	n = 135	
Antimicrobials	25	48	73	0.054
Penicillins	7	12	19	
Cephalosporin's	5	6	11	
Glycopeptides	2	8	10	
TMP-SMX	3	5	8	
Macrolides	1	5	6	
Quinolones	0	4	4	
Nevirapine	3	0	3	
Fluconazole	0	3	3	
Other#	4	5	9	

Non-antimicrobials	32	30	62	0.054
NSAID	4	3	7	
Phenytoin	2	3	5	
Carbamazepine	3	1	4	
Lamotrigine	2	2	4	
Allopurinol	2	2	4	
Chinese/herbal products	1	3	4	
PPI	2	1	3	
Sulphasalazine	3	0	3	
Other #	18	9	27	

The sum exceeds the total of 81 cases, because in 35 patients, more than one medication was implicated.

Other (implicated in <3 cases). *Antimicrobials*: clindamycin, daptomycin, doxycycline, lincomycin, meropenem, metronidazole, pentamidine, telaprevir. *Non-antimicrobials*: amitriptyline, amphetamine, aspirin, benzimidine, codeine, combination 'cold' tablet, diazepam, diltiazem, ferrous sulphate, frusemide, hydroxychloroquine, influenza vaccine, leflunomide, loratidine, norgestrel, oral contraceptive pill, penicillamine, pholcodine, pseudoephedrine, quetiapine, sodium valproate, venlafaxine.

ADR= adverse drug reaction, NSAIDs = non-steroidal anti-inflammatory drug; Penicillin= amoxicillin, amoxicillin + clavulanic acid, ampicillin, benzylpenicillin, flucloxacillin, piperacillin; PPI= proton pump inhibitor; TMP-SMX= trimethoprim + sulphamethoxazole;

AGEP = Acute generalised exanthematous pustulosis, DRESS= drug rash with eosinophilia and systemic symptoms; EM= erythema multiforme, SJS= Steven-Johnson's syndrome, TEN= toxic-epidermal necrolysis

Table 3: Risk communication provided to patients with cutaneous adverse drug reactions

Communication		Number n = 38		%	
No information given		5		13.2	
Information given		33		86.8	
Written only		15			
Written and verbal		11			
Verbal only		7			
Given by					
Doctor		16			
Pharmacist		7			
Nurse		1			
Doctor + pharmacist		1			
Doctor + Nurse + Pharmacist		2			
Can't recall		6			
Patient knowledge and discharge diagnosis		Matched (n = 28)	Mismatched (n = 10)	Odds ratio (95% CI)	p-value*
Implicated medications	1 drug	11 (39.3)	2 (20.0)	0.38	0.28
	>1 drug	17 (60.7)	8 (80.0)	(0.07 – 2.2)	
Patient's age	≥65 years	12 (42.9)	3 (30.0)	0.57	0.48
	<65 years	16 (57.1)	7 (70.0)	(0.12 – 2.7)	
Time from index reaction	≥5 years	8 (28.6)	3 (30.0)	1.07	0.93
	<5 years	20 (71.4)	7 (70.0)	(0.22 – 5.2)	
Received written information	Yes	22 (78.6)	4 (40.0)	0.18	0.03
	No	6 (21.4)	6 (60.0)	(0.04 – 0.86)	

* 2-tailed Fisher's exact test for interaction

Table 4: Comments from surveyed patients

Descriptions	TENS	AGEP	DRESS	Patients* n =13
<i>Physiological</i>	Eyesight hasn't returned to normal; Nail changes remain; Mucosa , lips still inflamed; Body took months to settle after discharge	Voice changes remain; Skin tears easily	Inadequate pain relief; Constant headache	6
<i>Psychological</i>	Concerned about being given antibiotics without being asked about allergies	Avoids all over the counter medicines; Traumatic experience		2
<i>Communication</i>	Frustrated due to lack of medical practitioner knowledge about diagnosis; GP now avoids prescribing all antibiotics (for patient)	Piperacillin was the causative agent, but patients states not allergic to penicillins	Diagnosis took a long time to figure out; Wasn't informed about the diagnosis; wanted better follow-up; not informed about prednisolone therapy effects	5

*Note that the 13 patients 17 comments

TEN= toxic epidermal necrolysis, AGEP = Acute generalised exanthematous pustulosis, DRESS= drug rash with eosinophilia and systemic symptoms