British Journal of Clinical Pharmacology

Br J Clin Pharmacol (2017) **83** 224–226 224

COMMENTARY

Poor reporting and documentation in drug-associated Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis – Lessons for medication safety

Correspondence Dr Jason A. Trubiano, Infectious Diseases Department, Austin Hospital, 145 Studley Road, PO Box 5555, Heidelberg, VIC, Australia 3084. Tel.: +61 (3) 9496 6676; Fax: +61 (3) 9496 6677; E-mail: jason.trubiano@austin.org.au

Received 4 July 2016; **Revised** 6 August 2016; **Accepted** 21 August 2016

Caitlin Goldblatt[1], Sharmila Khumra[2,3], Jane Booth[2], Karen Urbancic[2,3], M. Lindsay Grayson[3,4] and Jason A. Trubiano[3,4,5]

[1]Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, Parkville, Australia, [2]Pharmacy Department, Austin Health, Heidelberg, VIC, Australia, [3]Infectious Diseases Department, Austin Health, Heidelberg, VIC, Australia, [4]Department of Medicine, University of Melbourne, Parkville, VIC, Australia, and [5]Infectious Diseases Department, Peter MacCallum Cancer Centre, VIC, Australia

Keywords adverse drug reactions, antibiotic allergy, severe cutaneous adverse drug reactions, T-cell mediated hypersensitivity

Tables of Links

TARGETS	
Other protein targets [2]	**Enzymes** [6]
FABP4	Acetyl CoA carboxylase
TNF-α	Adenylate cyclase
GPCRs [3]	Akt (PKB)
GLP-1 receptor	ERK1
Nuclear hormone receptors [4]	ERK2
PPARγ	FASN
Transporters [5]	Hormone sensitive lipase (HSL)
GLUT4	PKA

LIGANDS	
Adiponectin	IBMX
cAMP	IL-6
Dexamethasone	Indomethacin
Exendin-4	Insulin
Exendin-(9-39)	Liraglutide
GLP-1	Metformin

These Tables list key protein targets and ligands in this article that are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY [1], and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 [2–6].

Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) are associated with significant morbidity and mortality, therefore assigning drug causality is central to preventing reoccurrence [7]. Graudins *et al*. recently demonstrated deficiencies in the long-term labelling of patients with severe cutaneous adverse drug reactions (cADR). This

DOI:10.1111/bcp.13103

has significant ramifications, as a single prescribing error in a patient with a history of SJS or TEN has the potential to cause serious morbidity and mortality, especially when commonly employed antibiotics are implicated in up to 50% of cADR [8]. What remains unknown is whether or not ADR reporting in SJS and TEN is a widespread problem, and if such ADR reports are also conveyed to primary care physicians.

We write to share own experience with SJS and TEN over a 10-year period. The aim was to examine the aetiology of antibiotic-associated SJS and TEN (AA-SJS/TEN) in terms of drug causality, clinical characteristics, treatment and patient outcomes, subsequent ADR reporting and documentation, compared with non-antibiotic-associated SJS and TEN (NA-SJS/TEN).

We performed a retrospective observational cohort study and identified 26 cases of SJS and TEN via International Statistical Classification of Diseases and Related Health Problems (ICD-10) coding, for the period 1 January 2004 to 31 December 2015 at Austin Health (Victoria, Australia). Baseline demographic, co-morbidity, drug causality assessments (algorithm for assessment of drug causality [ALDEN] [9]), clinical characteristics, treatment/outcomes, ADR committee record, electronic medical record (EMR) and outpatient (primary care) allergy records were collated for each patient.

The median age of the cohort was 41.5 (IQR 25–52), median ALDEN score 5 (5 = probable, IQR 4–6) and 62% (16/26) male. Forty-two per cent (11/26) were AA-SJS/TEN and 58% (15/26) NA-SJS/TEN. When comparing NA-SJS/TEN and AA-SJS/TEN, a higher ALDEN score (5 [probable] *vs.* 4 [possible], $P = 0.004$) and longer drug latency (median; 21-days *vs.* 5-days, $P = 0.01$) were noted in NA-SJS/TEN patients (Table S1**)**. Seventeen antibiotics were implicated in the 11 cases of AA-SJS/TEN; aminopenicillins in 23%, sulphonamide antibiotics in 18% and glycopeptides in 12%. In NA-SJS/TEN, 46% were secondary to anticonvulsants, 20% to immunosuppressive medications (methotrexate and lefunomide) and single cases to risperidone and oxybutynin were noted.

Subsequent reporting and documentation of implicated drugs in SJS and TEN cases are demonstrated in Figure 1. Compared with Graudins *et al.*, even fewer cases were referred to the ADR committee (50% *vs.* 72%) and not all implicated drugs were noted in the discharge summary (58% *vs.* 84%). Only 27% of patients had all implicated drugs noted in the outpatient (primary care) record, higher for AA-SJS/TEN than NA-SJS/TEN (55% *vs.* 7%, $P = 0.02$). For NA-SJS/TEN a larger proportion of implicated drugs were noted in the discharge summary than in the outpatient record (53% *vs.* 7%, $P = 0.01$). Two AA-SJS/TEN patients were given the same or class-related antibiotic post discharge, without reported adverse event.

Poor documentation of serious ADRs in the EMR and discharge summary is concerning, considering these form potentially the only communication to hospital clinicians and primary care physicians respectively. In cases of SJS and TEN, where mortality for antibiotic-associated severe cutaneous adverse reactions (SCAR) has been quoted at 25% [8], erroneous antibiotic prescriptions using the implicated antibiotic could have dire consequences, although the absence of cross-reactivity in T-cell mediated hypersensitivity for some beta-lactams and sulphonamides has been noted [10, 11]. This is noteworthy as antibiotics remain the causative drug in almost 50% of SJS and TEN cases, with commonly employed antibiotics such as aminopenicillins, sulphonamides and glycopeptides predominating. We focus

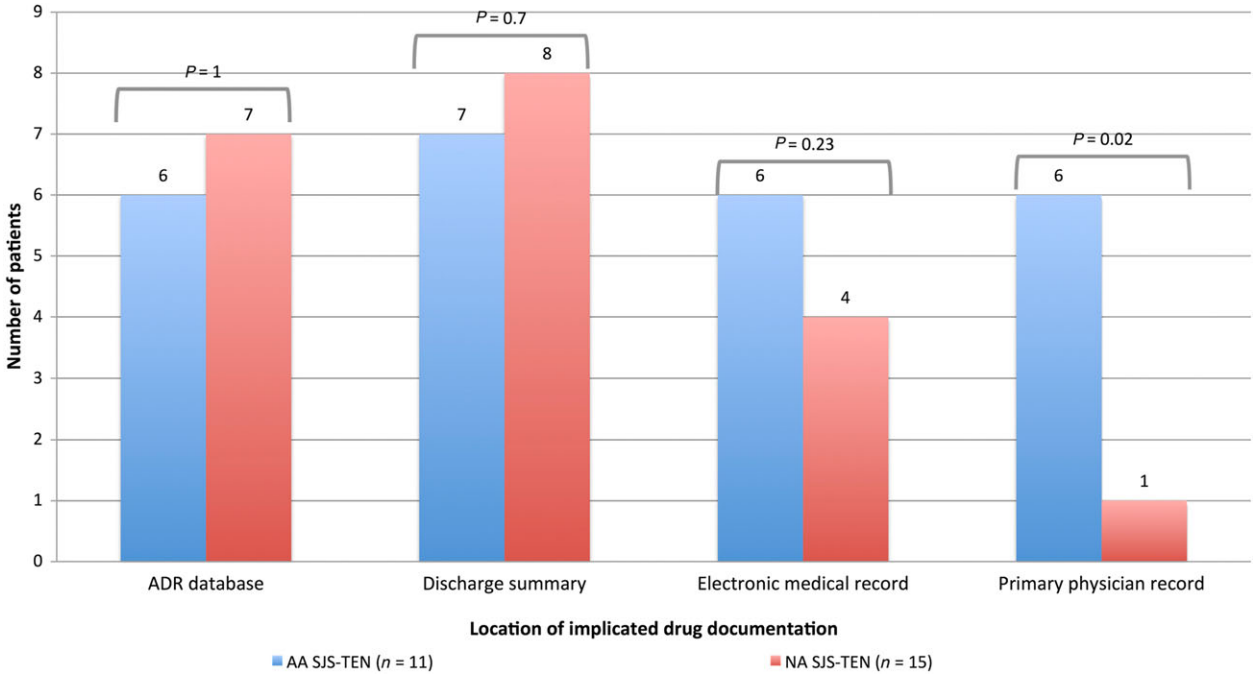

Figure 1

Documentation of implicated drugs in cases of SJS and TEN across multiple platforms

on AA-SJS/TEN, as antimicrobials are frequently prescribed in hospital and community settings post ADR. Our study, in addition to that by Trubiano *et al.*, demonstrates that AA-SJS/TEN potentially presents more acutely than NA-SJS/TEN, reflected by the significantly shorter drug latency [8].

There are a number of limitations to this study, including the retrospective nature, small study numbers and potential for patients to have changed primary care providers post discharge. Nonetheless, it highlights that commonly employed antibiotics are often implicated in the acute onset of SJS and TEN, and further supports claims by Graudins *et al.* and others for the need to address recording of serious ADRs, especially antibiotics, to ensure medication safety [12]. Overall, greater vigilance is required to engage physicians and pharmacists to report to the ADR committee, ensuring accuracy of allergy documentation in the EMR and that appropriate information is conveyed to both patients and primary care physicians.

Competing interests

There are no competing interests to declare.

References

1 Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SP, *et al.* The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl Acids Res 2016; 44: D1054–68.

2 Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, *et al.* CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: Overview. Br J Pharmacol 2015; 172: 5729–43.

3 Alexander SPH, Davenport AP, Kelly E, Marrion N, Peters JA, Benson HE, *et al.* CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: G protein coupled receptors. Br J Pharmacol 2015; 172: 5744–869.

4 Alexander SPH, Cidlowski JA, Kelly E, Marrion N, Peters JA, Benson HE, *et al.* CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: Nuclear hormone receptors. Br J Pharmacol 2015; 172: 5956–78.

5 Alexander SPH, Kelly E, Marrion N, Peters JA, Benson HE, Faccenda E, *et al.* CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: Transporters. Br J Pharmacol 2015; 172: 6110–202.

6 Alexander SPH, Fabbro D, Kelly E, Marrion N, Peters JA, Benson HE, *et al.* CGTP Collaborators. The Concise Guide to PHARMACOLOGY 2015/16: Enzymes. Br J Pharmacol 2015; 172: 6024–109.

7 Sekula P, Dunant A, Mockenhaupt M, Naldi L, Bouwes Bavinck JN, Halevy S, *et al.* Comprehensive survival analysis of a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis. J Invest Dermatol 2013; 133: 1197–204.

8 Trubiano JA, Aung AK, Nguyen M, Fehily SR, Graudins L, Cleland H, *et al.* A comparative analysis between antibiotic- and nonantibiotic-associated delayed cutaneous adverse drug reactions. J Allergy Clin Immunol Pract 2016; doi: 10.1016/j.jaip.2016.04.026.

9 Sassolas B, Haddad C, Mockenhaupt M, Dunant A, Liss Y, Bork K, *et al.* ALDEN, an algorithm for assessment of drug causality in Stevens-Johnson Syndrome and toxic epidermal necrolysis: comparison with case–control analysis. Clin Pharmacol Ther 2010; 88: 60–8.

10 Buonomo A, Nucera E, Pecora V, Rizzi A, Aruanno A, Pascolini L, *et al.* Cross-reactivity and tolerability of cephalosporins in patients with cell-mediated allergy to penicillins. J Investig Allergol Clin Immunol 2014; 24: 331–7.

11 Strom BL, Schinnar R, Apter AJ, Margolis DJ, Lautenbach E, Hennessy S, *et al.* Absence of cross-reactivity between sulfonamide antibiotics and sulfonamide nonantibiotics. N Engl J Med 2003; 349: 1628–35.

12 Moskow JM, Cook N, Champion-Lippmann C, Amofah SA, Garcia AS. Identifying opportunities in HER to improve the quality of antibiotic allergy data. J Am Med Inform Assoc 2016; 23: e108–12.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13103/suppinfo

Table S1 Differences in baseline demographics and clinical features in patients with antibiotic associated SJS/TEN and non antibiotic associated SJS/TEN