Recommendations for Prevention of Drug Re-Exposure in Toxic Epidermal Necrolysis

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ABSTRACT

Drug re-exposure resulting in Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN) is a rare phenomenon and has scarcely been reported. With an aging population, polypharmacy, and a lack of a unified electronic medical record, standard recommendations to prevent or minimize the risk of re-exposure are necessary. We identified five patients, with diagnosis confirmed SJS/TEN, and determined the clinical characteristics and contributing risk factors leading to re-exposure. Polypharmacy, multiple prescribers, advanced age, medical illiteracy, retention of discontinued medications and self-prescribing all contributed to re-exposure in this cohort of patients. This case series demonstrates the potentially deadly effect of drug re-exposure, and the need for both streamlined and integrated medication allergy documentation systems.

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INTRODUCTION

Adverse drug events (ADEs), or injury resulting from a medical intervention related to a drug, can happen in the outpatient setting. Specifically, in the outpatient setting, ADEs accounts for over 2.5 million physician office visits and approximately 125,000 hospital admissions each year.[1] A specific form of ADE is drug re-exposure. Drug re-exposure can result from both patient and prescriber factors. Patient factors include polypharmacy, medical illiteracy,[2] living alone, and older age. Retention of discontinued medications and self-prescribing practices also play a role.[3] As it pertains to prescribers, relying on the electronic medical records (EMR) or pharmacies to accurately detect and catalog allergies at the time of dispensing is not realistic as 43% of patients use multiple pharmacies.[4]

Severe cutaneous adverse drug reactions, such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), can be a rare, but life-threatening result of medication re-exposure. SJS/TEN span the continuum of epidermolytic cutaneous reactions, and mortality ranges from less than 10 percent in SJS to over 30 percent with TEN. Patients who recover from a severe adverse reaction to a medication may be at risk for SJS/TEN upon re-exposure as they maintain a long-term cytotoxic memory response to the inciting drug.[5] In SJS/TEN re-exposure has an incidence of up to 18%,[6,7] and leads to severe acute SJS/TEN, especially in instances of multiple recurrences.[8]

CASES

In this series, we report a single-center experience of TEN as a result of drug re-exposure. Five patients were evaluated by an inpatient dermatology consult service and found to have drug re-exposure-induced TEN (Table 1). Diagnosis was made based on clinical findings[9] and supporting cutaneous histopathology, when available. Initial drug exposure resulted in sensitization that presented with a variety of severe reactions including SJS, but also pancytopenia, facial swelling, and a painful rash with fever.

Upon re-exposure, a single dose of the offending drug class was sufficient to induce TEN. Distinct temporal relationships with re-exposure to the offending agents was noted to be within 14 days for sulfadiazine, within 72 hours for TMP-SMX, and within a few hours for aromatic anti-epileptic class drugs. Average SCORTEN[9] score on arrival was 2.6. Average body surface area (BSA) involved was 73%. Failure to recognize the offending agent (Patient 1), failure to reconcile allergies (Patients 2 and 4), and self-medicating (Patients 3 and 5), contributed to re-exposure (Table 1).

All five patients were admitted to the burn intensive care unit and received supportive care; and additionally, received systemic corticosteroids, intravenous immunoglobulin or both. Two patients succumbed to TEN within 10 days of hospitalization and one was discharged to hospice.

TABLE 1.

Drug Re-Exposure												
Patient	Age, y / Race / Sex / Comorbidities	Initial Drug, Reason	Initial Diagnosis	Re-Exposure Drug, Reason	SCORTEN	Signs and Symptom(s)	Drug to Symptoms (time)	Time Between Drug Exposures	Histopathology	Final Diagnosis	Outcome	Risk Factor for Re-Exposure
1	52, Black, M, HIV	TMP-SMX, cerebral toxoplasmosis	Drug-induced pancytopenia	Sulfadiazine, cerebral toxoplasmosis	4	Nikolsky + erythematous bullous rash covering 90% BSA Ano-genital oropharyngeal, and ocular, mucosal involvement	14 days	18 days	Intraepidermal necrotic keratinocytes and subepidermal bullae formation, supports SJS as clinically suspected.	TEN	Death on day 8 of hospital	Failure to recognize offending agent
2	100, Caucasian, F	TMP-SMX, UTI	Diffuse erythematous rash and skin pain	TMP-SMX, UTI	2	Nikolsky + erythematous bullous rash covering 40% BSA Genital and oroph aryngeal mucosal involvement	< 1 hour	3 years	None obtained	TEN	Discharged to home hospice on day 7 of hospital ization	Failure of allergy reconciliation
3	66, Black, M, HIV, HTN	TMP-SMX, UTI	Nikolsky +, diffuse dusky skin eruption, mucosal involvement, skin biopsy c/w SJS.	TMP-SMX, UTI	4	Pruritus and hand swelling, Febrile, Diffuse erythema covering 40% BSA Ano-genital, oropharyngeal, and ocular, mucosal involvement	< 1 hour	6 months	Near complete epidermal necrosis, specificial mixed perivascular inflammation. Clinical correlation supports SJS/TEN	TEN	Death on day 10 of hospitalization	Self-medicating
4a[a]	21, Black, M, HTN, seizure disorder, mental illness	Carbamazepine, seizure disorder	Rash and facial swelling	Oxcarbamazepine, seizure disorder[c]	1	Eye soreness, dysuria, sores on lips, erythroderma of extremities with flaccid bullae covering 80% BSA Ano-genital, oropharyngeal, ocular, mucosal involvement	< 1 hour	Unknown	None obtained	TEN	Discharged to inpatient psychiatry on day 3 of hospitalization, then wth skilled nursing on day 6.	Failure of allergy reconciliation
4b[a]	22, Black, M, HTN, seizure disorder, mental illness	Aripiprazole, seizure disorder	Nikolsky's +, diffuse dusky skin eruption with vesicles, mucosal involvement, skin biopsy c/w SJS/TEN	Aripiprazole, seizure disorder	2	Nikolsky+ diffuse skin duskiness with bullae covering BSA 80% Ano-genital, Oropharyngeal ocular mucosal involvement	< 1 hour	2 months	Full thickness epidermal necrosis	TEN	Discharged with skilled nursing on day 11 of hospitalization	Failure of allergy reconciliation

TABLE 1. CONTINUED

Drug Re-Exposure												
Patient	Age, y / Race / Sex / Comorbidities	Initial Drug, Reason	Initial Diagnosis	Re-Exposure Drug, Reason	SCORTEN	Signs and Symptom(s)	Drug to Symptoms (time)	Time Between Drug Exposures	Histopathology	Final Diagnosis	Outcome	Risk Factor for Re-Exposure
4c[a]	23, Black, M, HTN, seizure disorder, mental illness	Oxcarbamazepine, seizure disorder[b]	Nikolsky+, diffuse dusky skin eruption with vesicles, mucosal involvement, Skin biopsy c/w TEN	Oxcarbamazepine, seizure disorder	2	Nikolsky + dusky bullous rash covering >70% BSA Oropharyngeal and ocular mucosal involvement	< 1 hour	1 year	Full thickness epidermal necrosis	TEN	Discharged with skilled nursing on day 9 of hospitalization	Failure of allergy reconciliation
5	63, Black, M	TMP-SMX, UTI	Fevers, and burning of skin	TMP-SMX, UTI	3	Pruritus and burning of skin, painful blisters on extremities, Nikolsky +, covering 40% BSA Oropharyngeal and ocular mucosal involvement	72 hours[c]	1 month	Marked epidermal necrosis and reepithelialization	TEN	Discharged to skilled nursing unit on day 6	Self-medicating

[a]Same patient, three re-exposures
[b]Same exposure
[c]Patient was concurrently on high dose intravenous steroids
Acronyms: y, year, M, male, F, female, HIV, human immunodeficiency virus, HTN, hypertension, UTI, urinary tract infection, SJS, Stevens Johnson Syndrome, TEN, toxic epidermal necrolysis, TMP-SMX, trimethoprim-sulfamethoxazole, Nikolsky +, Nikolsky sign positive, BSA, body surface area, c/w, consistent with

DISCUSSION

In the United States, an aging population, polypharmacy, multiple prescribers, and use of various medical record systems that don't integrate allergy data increase the risk of re-exposure. This case series documents that self-medicating, failure to recognize the offending agent, and/or reconcile allergies all contributed to drug re-exposure. Additionally, it documents that in those patients diagnosed with drug re-exposure induced TEN, re-exposure to the sensitizing drugs led to high mortality, greater BSA and mucosal surface involvement, and higher SCORTEN scores.

Currently, there are no standard recommendations to prevent or minimize the risk of re-exposure in patients diagnosed with SJS/TEN. At our institution, we have made multiple efforts to reduce the risk. When a diagnosis of SJS/TEN is made, the allergies section of the EMR is updated by the dermatologist, severity categorized as critical, and a note made to reference the date of dermatology's consult to make the details readily available. In some cases, medications known to cross-react with the allergen are also preemptively added to the allergy list.

Prior to discharge, we discuss the diagnosis, implicated drugs and classes, as well as a plan to prevent re-exposure. We ask that families to complete an inventory of all medication in patients' homes and inform any prescribing pharmacies and physicians of the SJS/TEN diagnosis. Patients are sent home wearing their allergy alert bracelet from their hospitalization, and we recommend that they obtain medical identification jewelry listing both generic and brand names of the allergen. At follow up, we review medication allergies, and ask if all discontinued medications have been removed from the home. Ideally, national registries for sharing of allergy data for pharmacists will be developed in the near future.

Limitations to this study include small sample size, our reliance on patients' recollection of initial drug reaction in some cases, and the possibility of a confounding diagnosis, such as generalized bullous fixed drug eruption.[10] This case series demonstrates the potentially deadly effect of drug re-exposure, and the need for both streamlined and integrated medication allergy documentation systems.

DISCLOSURE

The authors have no conflicts.

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