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Letter to the Editor

Stevens–Johnson syndrome and toxic epidermal necrolysis: The Food and Drug Administration adverse event reporting system, 2004–2013

Dear Editor

Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), which are severe cutaneous adverse reactions, are associated with fatal disorders.¹ Although many causes of SJS/TEN have been proposed, their pathogenesis is not fully understood. Hypersensitivity to medications accounts for the majority of cases of SJS/TEN.² Several research groups have presented reports on drugs implicated in SJS/TEN (selective cyclooxygenase-2 inhibitors, lamotrigine, anti-epileptic drugs, sulfonamide antibiotics, and allopurinol, etc.).^{3,4} SJS associated with *Mycoplasma pneumoniae* infection is observed mainly in children,^{5,6} while another group reported the effects of the genetic background of patients.⁷ The relationship between aging and SJS/TEN is still not clear.

Since SJS/TEN are very rare diseases,¹ the implementation phase of epidemiologic research is fraught with difficulties. The US Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS) is the largest and most well-known database worldwide, and it reflects the realities of clinical practice.⁸ FAERS, therefore, is one of the primary tools used in pharmacovigilance.

We examined the incidence of SJS/TEN in the FAERS database from January 2004 to March 2013. To extract case reports of SJS/TEN from the FAERS database, SJS/TEN were coded according to the terminology preferred by the Medical Dictionary for Regulatory Activities 16.0. We used the following three preferred terms to match SJS and TEN: SJS/PT10042033, oculomucocutaneous syndrome/PT10030081, and TEN/PT10044223. To detect SJS/TEN incidences, we calculated the reporting odds ratio (ROR), which is established for pharmacovigilance by using a disproportionality analysis.⁸ The ROR is an applicable technique that allows for adjustment through logistic regression analysis and offers the advantageous possibility of controlling for covariates.⁹ We refined the results with a dedicated correction to detect possible confounders present in the database. The reports were stratified by age as follows: ≤17 years, 18–39 years, 40–59 years, 60–79 years, and ≥80 years. The RORs were adjusted for gender, reporting year, and stratified age group. The following logistic model was used:

$$\text{Log (odds)} = \beta_0 + \beta_1 Y + \beta_2 G + \beta_3 A$$

where Y = reporting year, G = gender, and A = stratified age group.

The FAERS contains 4,746,890 reports. After excluding duplicates according to the FDA recommendation and extracting the reports completed with gender and age information, 2,257,902

reports were finally analyzed. The number of reports obtained for each preferred term was 9078 for SJS, 192 for oculomucocutaneous syndrome, and 4076 for TEN. Table 1 summarizes the scores and the reporting ratios. The breakdown of the number of case reports on valdecoxib, lamotrigine, phenytoin, acetaminophen, and furosemide was 1446 (11.0%), 1341 (3.6%), 1076 (6.1%), 834 (0.6%), and 739 (0.8%), respectively. The age-groups of patients with SJS/TEN ranged from infants to the elderly. The number of reported cases was high in the 40- to 79-year-old group. The RORs for the ≤17-year-old group indicated the highest values for both genders. We further examined the data with the adjusted RORs (Table 2). The effect of the term ≤17 years was statistically significant in the likelihood ratio test ($P < 0.0001$). The adjusted ROR of the ≤17-year-old patients in the whole data extracted from the FAERS database was 2.87 (2.67–3.07) at a 95% confidence interval (CI). The adjusted RORs (95% CI) of valdecoxib, lamotrigine, phenytoin, acetaminophen, and furosemide were 2.54 (0.40–8.98), 2.90 (2.44–3.45), 2.28 (1.79–2.88), 6.15 (4.95–7.62), and 1.58 (0.96–2.46), respectively.

To the best of our knowledge, systematic studies of SJS/TEN that are stratified by age group are very rare. In this study, we demonstrated a relatively high value for the adjusted ROR in patients aged ≤17 years. We do not have a conclusive explanation for these data. Reports of SJS due to viral infections in young patients who also received acetaminophen might be included in the data. Therefore, acetaminophen may be a causal drug and may explain the high incidence of SJS/TEN in young patients. The pharmacological actions of valdecoxib, lamotrigine, phenytoin, and furosemide are different from that of acetaminophen. Valdecoxib, lamotrigine, phenytoin, and furosemide showed high values for the adjusted RORs in the ≤17-year-old group. The numbers of reports on valdecoxib, lamotrigine, and phenytoin were higher than the number of reports on acetaminophen. We considered that mycoplasma infection could partially explain the high value of the adjusted RORs of SJS/TEN in the ≤17-year-old patients.

Another plausible reason for this might be differences in sensitivity to medication between patients aged ≤17 years and elderly patients. SJS/TEN are also believed to be partially immune-mediated, since treating patients with the same drug repeatedly can be associated with the rapid recurrence of SJS/TEN.¹⁰

On the other hand, the genetic background related to the human leukocyte antigen might have an influence on the incidence of SJS/TEN.⁷ Genetic factors that are associated with drug hypersensitivity are a complex issue. In evaluations of the true risk of medications, regional differences in drug prescriptions should be taken into account. The impact of human leukocyte antigen genotyping should

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Table 1

SJS/TEN in the FDA-adverse event reporting system database (January 2004–March 2013).

	Gender	Total			Valdecoxib			Lamotrigine			Phenytoin			Acetaminophen			Furosemide		
		Reported cases		Reporting ratio (%)	Reported cases		Reporting ratio (%)	Reported cases		Reporting ratio (%)	Reported cases		Reporting ratio (%)	Reported cases		Reporting ratio (%)	Reported cases		Reporting ratio (%)
		SJS or TEN	Total		SJS or TEN	Total		SJS or TEN	Total		SJS or TEN	Total		SJS or TEN	Total		SJS or TEN	Total	
Total		12,279	3,522,995	0.3	1446	13,105	11.0	1341	36,817	3.6	1076	17,510	6.1	834	137,968	0.6	739	96,686	0.8
<i>Stratified by age[†]</i>																			
≤17 years	M	620	65,307	0.9	1	4	25.0	111	1460	7.6	67	548	12.2	85	2347	3.6	16	761	2.1
	F	563	56,120	1.0	1	16	6.3	149	1639	9.1	45	417	10.8	67	2576	2.6	4	643	0.6
18–39 years	M	697	127,899	0.5	12	186	6.5	92	2693	3.4	49	1106	4.4	73	6410	1.1	23	1117	2.1
	F	1231	286,740	0.4	25	329	7.6	310	6992	4.4	96	1321	7.3	80	14,295	0.6	25	1975	1.3
40–59 years	M	1096	296,747	0.4	40	1087	3.7	89	3013	3.0	91	2214	4.1	90	14,281	0.6	90	7729	1.2
	F	1443	491,273	0.3	64	1426	4.5	208	6621	3.1	155	2310	6.7	102	24,254	0.4	67	9664	0.7
60–79 years	M	1139	328,040	0.3	41	938	4.4	32	1139	2.8	69	1687	4.1	80	14,109	0.6	150	19,915	0.8
	F	1307	429,293	0.3	54	1544	3.5	58	1988	2.9	106	1809	5.9	110	19,877	0.6	194	20,774	0.9
80≤ years	M	234	69,164	0.3	6	123	4.9	4	144	2.8	6	340	1.8	8	3348	0.2	31	7508	0.4
	F	377	107,319	0.4	16	376	4.3	8	236	3.4	22	446	4.9	36	6238	0.6	71	10,879	0.7
Subtotal		8707	2,257,902	0.4	260	6029	4.3	1061	25,925	4.1	706	12,198	5.8	731	107,735	0.7	671	80,965	0.8

[†] Completed with age and gender.**Table 2**

Adjusted reporting odds ratio of SJS/TEN stratified by age.

	Total		Valdecoxib		Lamotrigine		Phenytoin		Acetaminophen		Furosemide	
	Adjusted ROR	(95%CI)	Adjusted ROR	(95%CI)	Adjusted ROR	(95%CI)	Adjusted ROR	(95%CI)	Adjusted ROR	(95%CI)	Adjusted ROR	(95%CI)
Reporting year	0.92	(0.91–0.92)	0.98	(0.91–1.05)	0.96	(0.94–0.98)	1.12	(1.09–1.16)	0.96	(0.93–0.98)	0.93	(0.90–0.95)
Gender female	0.87	(0.84–0.91)	0.99	(0.77–1.29)	1.16	(1.01–1.33)	1.46	(1.25–1.71)	0.74	(0.64–0.86)	1.00	(0.86–1.16)
<i>Age</i>												
≤17 years	2.87	(2.67–3.07)	2.54	(0.40–8.98)	2.90	(2.44–3.45)	2.28	(1.79–2.88)	6.15	(4.95–7.62)	1.58	(0.96–2.46)
18–39 years	1.46	(1.37–1.55)	1.79	(1.20–2.62)	1.35	(1.16–1.57)	1.08	(0.87–1.34)	1.54	(1.24–1.90)	1.76	(1.26–2.41)
40–59 years [†]	1.00		1.00		1.00		1.00		1.00		1.00	
60–79 years	0.99	(0.93–1.04)	0.91	(0.69–1.22)	0.95	(0.74–1.20)	0.92	(0.76–1.13)	1.10	(0.90–1.35)	0.94	(0.78–1.14)
80≤ years	1.06	(0.97–1.16)	1.05	(0.63–1.65)	1.03	(0.54–1.78)	0.65	(0.43–0.95)	0.92	(0.66–1.27)	0.62	(0.48–0.79)

[†] As reference.

be evaluated with respect to a variety of ethnic backgrounds by using well-organized epidemiologic studies, the FAERS database, or both.

The FAERS database is subject to many biases such as under-reporting, over-reporting, and confounding by comorbidities.⁸ In general, the crude ROR is inapplicable to inferences of comparative strengths of causality and only offers a rough indication of the signal strength.⁸ The FAERS database is a spontaneous reporting database system and detailed patient information is not included. Therefore, the definition of SJS/TEN in the FAERS database is not stringent. We must highlight this profound limitation in the FAERS database. Despite such limitations that are inherent to spontaneous reporting, it may be acceptable to compare the adjusted RORs of a particular event that are derived from stratified analysis within a particular context.

This study was the first to evaluate the relationship between SJS/TEN and aging by using the FAERS database. We hope that these data will update the information available to clinicians and be potentially useful for improving the management of SJS/TEN.

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Conflict of interest

JA is an employee of Medical Database. The rest of the authors have no conflict of interest.

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