

Carbonic anhydrase inhibitor–induced Stevens-Johnson syndrome/toxic epidermal necrolysis leads to extensive cutaneous involvement

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Clinical Implications

- Carbonic anhydrase inhibitor–induced Stevens-Johnson syndrome/toxic epidermal necrolysis results in more extensive cutaneous manifestations and frequent ocular sequelae when compared with Stevens-Johnson syndrome/toxic epidermal necrolysis due to other drugs.

TO THE EDITOR:

Carbonic anhydrase inhibitors (CAIs) such as acetazolamide, methazolamide, ethoxzolamide, and dichlorphenamide are used to reduce intraocular pressure in glaucoma and other ocular disorders. They are also used to treat acute mountain sickness and as diuretics, antiepileptic drugs, and urinary alkalinizers.

Although CAI-induced Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported since 1989, only case series have been published, with no comprehensive studies conducted. Therefore, we investigated clinical characteristics and outcomes of CAI-induced SJS/TEN using the Korean Severe Cutaneous Adverse Reaction (SCAR) Registry database.

We retrospectively collected data on SJS/TEN and drug reaction with eosinophilia and systemic symptom from 2010 to 2015 with participation of 34 institutions nationwide. Diagnosis of SCAR was confirmed by allergists in each institution, and the inclusion criteria for SJS/TEN were (1) hospitalization and (2) widespread exanthema with 1% or more of skin detachment; more than 1 blister, not only acral involvement, with or without mucous membrane erosions. Patients with SJS/TEN were categorized into SJS, SJS/TEN overlap, or TEN according to the extent of maximal epidermal detachment: (1) SJS: epidermal detachment less than 10% of body surface area, (2) SJS/TEN overlap: detachment of 10% to 30% of body surface area, (3) TEN: detachment more than 30% of body surface area.¹ Assessment of drug causality was carried out according to the World Health Organization-Uppsala Monitoring Centre criteria, with “certain,” “probable,” or “possible” cases included in the analysis. In the SJS/TEN cases, the highest-scoring drug by algorithm of drug causality for SJS/TEN was evaluated as the likely cause when multiple drugs were involved. Clinical features of SJS/TEN caused by CAIs were compared with those caused by other drugs including nonsteroidal anti-inflammatory drugs, β -lactam antibiotics, allopurinol, anticonvulsants, and antituberculosis drugs. This

TABLE 1. Clinical characteristics of SJS/TEN according to the causative drug

Clinical parameter	CAIs (N = 15)	Non-CAIs (N = 337)	P value*
Sex, n (%)			.839
Male	8 (53.3)	159 (47.2)	
Female	7 (46.7)	178 (52.8)	
Onset age (y), median (IQR)	53.0 (33.0-60.5)	54.0 (34.5-70.0)	.462
Drug exposure duration (d), median (IQR)	7.5 (3.0-13.0)	11.0 (3.0-27.0)	.171
Latent period (d), median (IQR)	11.0 (6.5-15.5)	10.0 (2.0-24.5)	.777
Duration of disease (d), median (IQR)	36.0 (24.0-40.0)	20.0 (14.0-30.0)	.015
Hospitalization (d), median (IQR)	23.0 (16.5-30.5)	15.0 (9.0-24.0)	.037
ICU admission, n (%)	2 (13.3)	32 (9.8)	.991
Skin involvement, n (%)			<.001
SJS	3 (20.0)	240 (71.2)	
SJS/TEN overlap	4 (26.7)	31 (9.2)	
TEN	8 (53.3)	66 (19.6)	
Mucosal involvement, n (%)	15 (100.0)	253 (87.8)	.307
SCORTEN on day 1	1.0 (0.5-2.0)	1.0 (1.0-2.0)	.293
Clinical outcome, n (%)			.041
Recovery without ocular sequelae	11 (73.3)	288 (86.7)	
Ocular sequelae	3 (20.0)	16 (4.8)	
Death	1 (6.7)	28 (8.5)	

ICU, Intensive care unit; SCORTEN, severity-of-illness score for toxic epidermal necrolysis.

The Mann-Whitney *U* test and Fisher exact test were performed to compare continuous and categorical variables, respectively.

*Differences were considered to be significant if the *P* < .05.

study was approved by the institutional review board of each participating institution (approval no. H-1408-021-601).

Fifteen (1.9%) of the 783 cases of SCAR included in the final analysis were caused by CAIs (methazolamide = 13, acetazolamide = 2). All the cases related with CAI were SJS/TEN, and there was no case of drug reaction with eosinophilia and systemic symptom. The clinical features of patients with CAI-induced SJS/TEN are summarized in Table E1 in this article's Online Repository at www.jaci-inpractice.org.

In comparing clinical characteristics between SJS/TEN induced by CAI and non-CAI drugs, the sex ratio and onset age of SJS/TEN induced by CAIs were not different (Table 1). There were no significant differences in drug exposure duration and latent period between SJS/TEN induced by CAIs and non-CAI drugs. However, subgroup analysis showed that CAI-induced SJS/TEN was associated with significantly shorter duration of drug exposure or latency compared with SJS/TEN induced by certain drugs including allopurinol, anticonvulsants, or antituberculosis drugs (*P* < .001) (Figure 1, A).

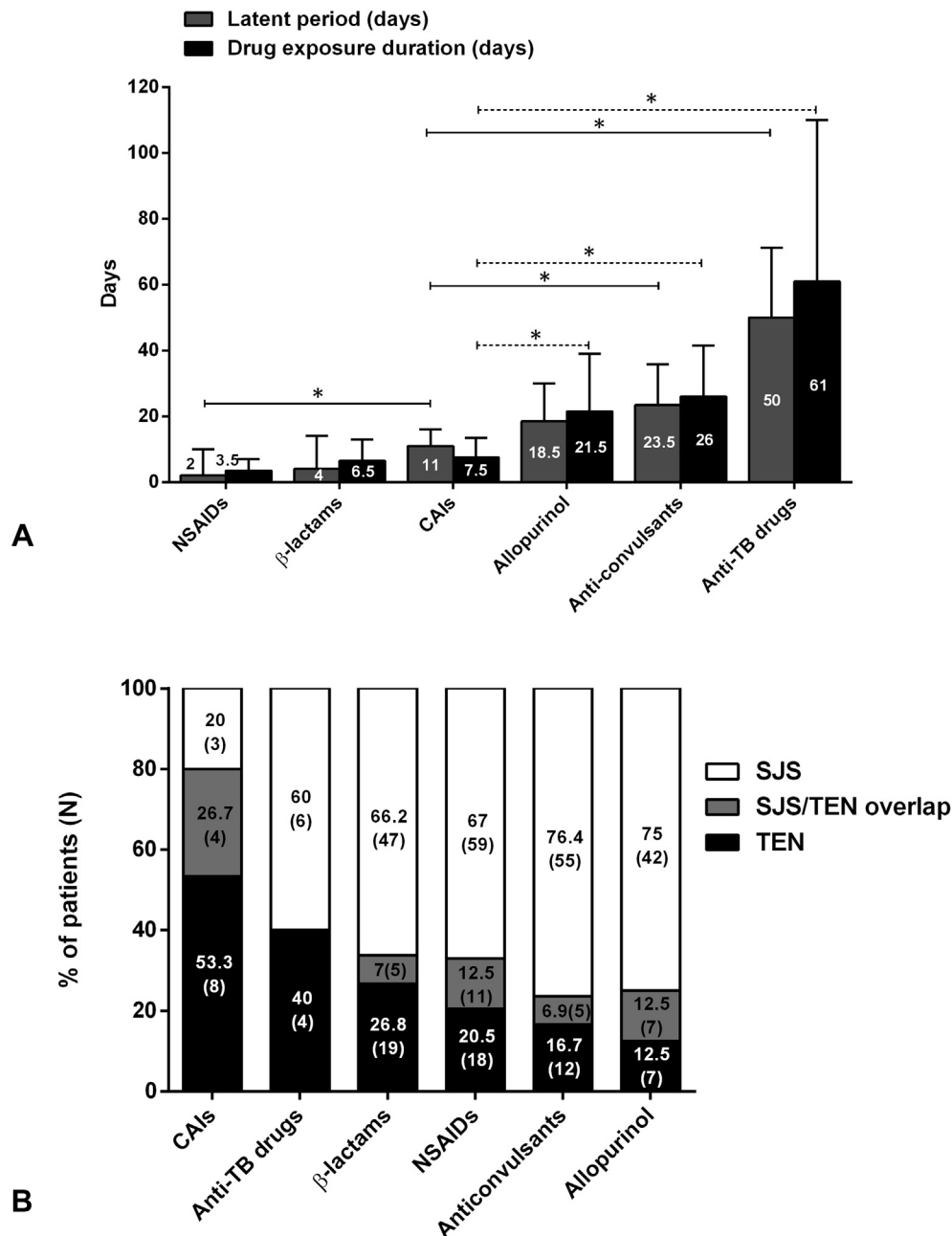


FIGURE 1. Comparison of clinical characteristics of patients with SJS/TEN by each causative drug. **A**, Drug exposure duration and latent period (* $P < .05$ at the pairwise comparisons of the Kruskal-Wallis test). **B**, Extent of skin involvement. *NSAID*, Nonsteroidal anti-inflammatory drug; *TB*, tuberculosis.

Cases of SJS/TEN caused by CAIs had significantly longer duration of illness than those caused by non-CAIs at 36 (24-40) days versus 20 (14-30) days, respectively ($P = .015$). Duration of hospitalization was also significantly longer, at 23 (16.5-30.5) versus 15 (9-24) days ($P = .037$), although intensive care unit admission rates were comparable (13.3% vs 9.8%; $P = .991$). In terms of skin involvement, the proportion of TEN or SJS/TEN overlap was notably higher in cases caused by CAIs than by non-CAI drugs (80% vs 28.8%; $P < .001$) (Figure 1, B), but severity-of-illness score for TEN (SCORTEN) was not higher than that of non-CAI cases. Although the mortality rate related with SJS/TEN was not different,

the incidence of ocular sequelae such as conjunctivochalasis, trichiasis, and severe dry eye was significantly higher in the CAI-related cases compared with the non-CAI cases (20% vs 4.8%; $P = .041$).

This is the first description of the unique clinical features of CAI-induced SJS/TEN compared with SJS/TEN caused by other drugs. In this study, SJS/TEN overlap or TEN caused by CAI accounted for 80% (12 of 15). Chinese data also showed that TEN developed in 81% (9 of 11) since 2015 when the first Chinese CAI-related case report was made.²⁻⁴ This suggests that CAI may induce rapid progression involving larger skin areas over a short latent period.

Meanwhile, the SCORTEN of patients with SJS/TEN caused by allopurinol or antituberculosis drugs was higher than that of patients with SJS/TEN caused by other drugs including CAI. This difference is likely due to higher proportion of older age or those with chronic kidney disease in the former group. The mortality rate was dependent on the SCORTEN rather than the type of causative drug (see Table E2 in this article's Online Repository at www.jaci-inpractice.org).

The genetic susceptibility of SCARs in association with certain culprit drugs has been reported, and HLA-B*59:01 has been suggested as a risk marker of CAI-induced SJS/TEN.^{5,6} The HLA genotypes were identified in 5 patients with CAI-induced SJS/TEN in this study and they also had HLA-B*59:01 allele. Including this study, all the literature about CAI-related SJS/TEN was studied in Korean, Japanese, or Chinese descendants.^{2-4,6,7} The occurrence confined to Asian descent of CAI-induced SJS/TEN probably originates from ethnic differences in the frequency of the risk HLA allele, B*59:01, which occurs in 2.1% of Koreans, 1.8% of Japanese, and 0.1% to 0.2% of Han Chinese, but almost never seen in whites.⁸ Summarizing the cases of literature and this study, HLA-B*59:01 allele (B*59:01 is the only subtype of B59 in the above 3 countries) was positive in 94.4% (34 of 36) of patients with HLA-B information and there was a linkage disequilibrium with HLA-A*24:02 and HLA-C*01:02 (see Table E3 in this article's Online Repository at www.jaci-inpractice.org). When the frequency of HLA-B*59:01 in Korean patients (21 of 22) was compared with that in the general Korean population (20 of 485),⁹ there was a strong association with the development of CAI-induced SJS/TEN (odds ratio, 488.3; 95% CI, 62.5-3813.4; $P < .0001$).

However, our study is limited by retrospective design, small number of patients caused by CAI, and HLA data unavailability for some patients, and our results might not be applicable to non-Asians.

Nonetheless, our findings highlight the importance of studying each drug-induced SCAR as a unique condition despite similar clinical manifestations. CAI exclusively caused SJS/TEN and resulted in more extensive skin involvement and higher rate of ocular sequelae despite shorter drug exposure and latent period. Clinicians should pay particular attention to these characteristics of CAI-induced SJS/TEN.

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TABLE E1. Clinical features of patients with CAI-induced SJS/TEN

Case no.	Age/sex	Causative drug*	Drug exposure/ latency (d)	Duration of disease/ hospitalization (d)	Phenotype	Treatment outcome	Ophthalmologic condition	Underlying disease
1	38/M	Methazolamide	8/11	27/23	TEN	Ocular sequelae	Glaucoma	None
2	26/F	Methazolamide	2/11	30/26	TEN	Recovery	Not described	Atopic eczema
3	47/M	Methazolamide	8/11	28/28	TEN	Ocular sequelae	Glaucoma	None
4	53/M	Methazolamide	9/5	50/19	TEN	Death	Glaucoma	None
5	60/F	Methazolamide	2/5	40/32	TEN	Recovery	Glaucoma	None
6	57/M	Methazolamide	4/8	72/64	TEN	Recovery	Cataract	HTN, DM
7	56/M	Acetazolamide	13/5	37/30	TEN	Ocular sequelae	Not described	None
8	64/M	Methazolamide	31/16	48/34	TEN	Recovery	Not described	None
9	33/F	Methazolamide	1/15	21/18	SJS/TEN overlap	Recovery	ICL operation	None
10	76/F	Methazolamide	2/18	40/15	SJS/TEN overlap	Recovery	Cataract	HTN, OA
11	22/M	Acetazolamide	18/13	11/7	SJS/TEN overlap	Recovery	ICL operation	None
12	24/F	Methazolamide	5/16	15/15	SJS/TEN overlap	Recovery	Not described	None
13	75/F	Methazolamide	7/3	28/22	SJS	Recovery	Glaucoma	None
14	33/M	Methazolamide	15/9	9/4	SJS	Recovery	Uveitis	None
15	61/F	Methazolamide	15/23	36/31	SJS	Recovery	Macular cyst	HTN

DM, Diabetes mellitus; F, female; HTN, hypertension; M, male; OA, osteoarthritis.

*All causative agents were administered orally.

TABLE E2. SCORTEN and mortality of SJS/TEN according to the causative drugs

Clinical parameter	CAIs (N = 15)	NSAIDs (N = 88)	Anticonvulsants (N = 72)	β -Lactams (N = 71)	Allopurinol (N = 56)	Anti-TB drugs (N = 10)	P value*
Mortality, n (%)	1 (6.7)	2 (2.3)	4 (5.6)	6 (8.7)	9 (16.1)	3 (30.0)	.007
SCORTEN on day 1	1.0 (0.5- 2.0)	1.0 (1.0- 2.0)	1.0 (1.0-2.0)	1.0 (1.0- 2.0)	2.0 (2.0- 3.0)	2.0 (1.0- 3.0)	<.001
Age >40 y, n (%)	9 (60.0)	54 (61.4)	58 (80.6)	40 (56.3)	52 (92.9)	10 (100.0)	<.001
BUN >10 mmol/L, n (%)	2 (15.4)	10 (12.2)	6 (9.4)	8 (12.7)	37 (71.2)	2 (20.0)	<.001

 β -Lactams, Beta-lactam antibiotics; BUN, blood urea nitrogen; NSAID, Nonsteroidal anti-inflammatory drug; SCORTEN, severity-of-illness score for toxic epidermal necrolysis; TB, tuberculosis.

*The Kruskal-Wallis test and Fisher exact test were performed to compare continuous and categorical variables, respectively.

TABLE E3. Published cases of CAI-related SJS/TEN with HLA information

Race	Sex	Onset age	Causative drug	Phenotype	HLA type	Reference
Korean	F	74	Methazolamide	SJS	A2, Cw1†	Kim et al ^{E1}
Korean	M	53	Methazolamide	SJS	A2, B59 , Cw1	Kim et al ^{E1}
Korean	F	33	Methazolamide	SJS	A2, B59 †	Kim et al ^{E1}
Korean	M	35	Methazolamide	SJS	A2, B59 , Cw1	Kim et al ^{E1}
Korean	F	30	Methazolamide	SJS	A2, B59 , Cw1	Kim et al ^{E1}
Korean	M	64	Methazolamide	SJS	A2, B59 , Cw16	Kim et al ^{E1}
Korean	M	37	Methazolamide	TEN	A2/24, B59 /46, Cw1/3	Kim et al ^{E1}
Korean	M	59	Methazolamide	SJS	A2/26, B59 /61, Cw1/8	Kim et al ^{E1}
Korean	F	66	Methazolamide	SJS	A24/26, B59 /35, Cw1/3	Kim et al ^{E1}
Korean	F	40	Methazolamide	TEN	A*24:02/30:04, B*59:01 /14:01, C*01:02/08:02	Kim et al ^{E1}
Korean	F	47	Methazolamide	TEN	A*24:02/26:02, B*59:01 /55:07, C*01:02/01:02	Kim et al ^{E1}
Korean	M	47	Methazolamide	TEN	A*24:02/33:03, B*59:01 /07:05, C*01:02/15:05	Kim et al ^{E1}
Korean	M	29	Methazolamide	SJS	A*24:02/24:02, B*59:01 /54:01, C*01:02/01:02	Kim et al ^{E1}
Korean	M	43	Methazolamide	TEN	A*02:01/11:01, B*59:01 /40:01, C*01:02/15:02	Kim et al ^{E1}
Korean	M	38	Methazolamide	TEN	A*24:02/11:01, B*59:01 /40:02, C*01:02/03:04	‡
Korean	F	33	Methazolamide	SJS/TEN	A*02:01/24:02, B*59:01 /35:01, C*01:02/04:01	‡
Korean	M	47	Methazolamide	TEN	A*24:02/24:02, B*59:01 /15:01, C*01:02/03:03	‡
Korean	M	57	Methazolamide	TEN	A*02:01/24:02, B*59:01 /44:03, C*01:02/07:06	‡
Korean	F	76	Methazolamide	SJS/TEN	A*02:01/24:02, B*59:01 /40:02, C*01:02/03:04	‡
Chinese-Korean	M	42	Methazolamide	TEN	B*59:01	Jiang et al ^{E2}
Korean	M	53	Acetazolamide	SJS	A2/24, B59 /48, C*01:02/08	Kim et al ^{E1}
Korean	F	31	Acetazolamide	SJS	A24/26, B59 /62, Cw3	Yang et al ^{E3}
Japanese	F	47	Methazolamide	SJS	A11/26, B59 /62, Cw1/4	Shirato et al ^{E4}
Japanese	F	40	Methazolamide	SJS	A24/26, B59 /46, Cw1	Shirato et al ^{E4}
Japanese	F	30	Methazolamide	SJS	A2/24, B59 /54, Cw1	Shirato et al ^{E4}
Chinese	F	56	Methazolamide	TEN	B*59:01	Zhu et al ^{E5}
Chinese	F	51	Methazolamide	TEN	A*02:01/24:02, B*59:01 /15:27, C*01:02/04:01	Yang et al ^{E3}
Chinese	F	59	Methazolamide	TEN	A*11:01/11:02, B*59:01 /27:04, C*01:02/12:02	Yang et al ^{E3}
Chinese	F	58	Methazolamide	TEN	A*31:01/69:01, B*52:01 /55:02, C*01:06/12:02	Yang et al ^{E3}
Chinese	M	38	Methazolamide	TEN	A*03:01/11:01, B*59:01 /44:02, C*01:02/05:01	Yang et al ^{E3}
Chinese	M	51	Methazolamide	TEN	A*02:06/24:02, B*59:01 /48:03, C*01:02/08:01	Yang et al ^{E3}
Chinese	M	49	Methazolamide	TEN	A*02:06/11:01, B*59:01 /15:01, C*01:02/01:02	Yang et al ^{E3}
Chinese	M	33	Methazolamide	SJS	A*33:03/11:01, B*59:01 /58:01, C*01:02/03:02	Yang et al ^{E3}
Chinese	M	67	Methazolamide	SJS	A*11:01/11:01, B*59:01 /45:01, C*01:02/06:02	Yang et al ^{E3}
Chinese	F	57	Methazolamide	TEN	B*59:01	Zhu et al ^{E5}
Chinese	M	36	Methazolamide	TEN	B*59:01	Jiang et al ^{E2}

F, Female; M, male.

Bold indicates that HLA-B59 (**B*59:01**) is a strong risk allele of CAI-induced SJS/TEN.

†HLA typing for A, B, C was performed but HLA B or C result was not shown when B59 or Cw1 was negative.

‡From the current study.

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