

Chronic ocular complications of Stevens-Johnson syndrome associated with causative medications in Korea



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Clinical Implications

- Nonsteroidal anti-inflammatory drugs, including cold medicine, might be associated with severe chronic ocular complications in Korean patients with Stevens-Johnson syndrome and/or toxic epidermal necrolysis.

TO THE EDITOR:

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are hypersensitivity reactions that cause inflammation of the skin and mucous membranes.¹ The ocular surface is one of the main sites involved in SJS/TEN, and chronic ocular complications (COCs) lead to visual impairment.

Previous studies evaluated the correlation between causative medications and the severity of COCs in SJS/TEN.^{2,3} However, no consensus has been reached. A report suggested that ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs) is associated with severe COCs in Japanese with SJS/TEN.⁴ Therefore, we investigated whether NSAIDs are associated with the severity of COCs in Korean with SJS/TEN.

The study was approved by the Institutional Review Board of Seoul National University Hospital (No. 1610-101-801). Medical records of 77 patients (154 eyes) who visited the Department of Ophthalmology at 3 tertiary hospitals (Seoul National University Hospital, $n = 138$ eyes; Chonnam National University Hospital, $n = 10$ eyes; and Yonsei University Hospital, $n = 6$ eyes) with diagnosis of SJS/TEN between December 2003 and March 2014 were retrospectively reviewed.

The diagnosis of SJS/TEN was made by the physician based on the criteria established in a previous report.¹ The date of onset was determined based on the appearance of skin eruptions and/or mucosal involvement.^{1,5,6} Drug history was taken after exclusion of analgesics or cold medicine that had been administered within 1 to 3 days before the onset of skin eruptions to determine causative drugs. The criterion of the time interval of 4 to 28 days between the beginning of drug use and the onset of the skin eruptions is applied as suggested in previous studies.^{3,7} Medical records of the causative drugs were retrospectively collected. The study included patients diagnosed with SJS/TEN with identified causative drug who were followed up for more than a year. To exclude long-term effects due to mechanical trauma of the lids, we evaluated a chronic ocular surface complication score (COCs) during a follow-up period of 1 to 3 years. The mean follow-up period between the evaluation time and the onset of disease was 19.1 months.

COCs includes conjunctival hyperemia, decreased tear volume, lid or corneal involvement, limbal deficiency, and

TABLE 1. Causes of Stevens-Johnson syndrome and toxic epidermal necrolysis

Cause	No. of patients (%)
NSAID	42 (27.27)
Cold medicine	14 (9.09)
Acetaminophen	12 (7.79)
Loxoprofen	4 (2.60)
Ibuprofen	2 (1.30)
Unidentified NSAID	10 (6.49)
Antibiotics	56 (36.36)
Antibiotics only	36 (23.38)
NSAID and antibiotics	20 (12.99)
Anticonvulsant and antibiotics	
Allopurinol	12 (7.79)
Anticonvulsant	40 (25.97)
Anticonvulsant only	36 (23.38)
NSAID and anticonvulsant	4 (2.60)
Sulfasalazine	8 (5.19)
Others	20 (12.99)
Total	154

NSAID, Nonsteroidal anti-inflammatory drug.

symblepharon, ranging from 0 to 15 points.⁸ A high COCS was defined as 8 or higher.⁸ The odds ratio (OR) of the proportion of high COCS was compared between patients who received each medication and those who did not receive any medication among all the patients. The OR of the proportion of high COCS was compared between patients who received NSAIDs ($n = 42$) and those who received antibiotics ($n = 36$), allopurinol ($n = 12$), anticonvulsants ($n = 36$), or sulfasalazine ($n = 8$). The OR of the proportion of high COCS was compared between patients who received antibiotics ($n = 56$) and those who received allopurinol ($n = 12$), anticonvulsants ($n = 40$), or sulfasalazine ($n = 8$). Because we wanted to know the effect of NSAIDs on COCs, patients who took NSAIDs combined with other medication were included in the NSAID group. Statistical analysis was performed using GraphPad prism version 5.0 (Graphpad Software, San Diego, Calif). Fisher's exact test was used to compare the proportions of high COCS between groups.

The causes of SJS/TEN are shown in Table 1. Most of the cold medicines that are commonly available in South Korea contain acetaminophen (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

Patients with SJS/TEN who took NSAIDs showed a significantly higher rate (28.57%) of high COCS than those who did not take NSAIDs (5.36%) (OR: 7.067; $P < .001$; Table II). However, other medications such as antibiotics, allopurinol, anticonvulsants, and sulfasalazine were not related to severe COCs. COCS was lower than 8 in all patients who received allopurinol or anticonvulsants. Based on subgroup analysis, the NSAID group was significantly associated with high COCS when compared with other groups. Only 4 patients received NSAIDs and anticonvulsants simultaneously (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org). However, all patients who took anticonvulsants or allopurinol,

TABLE II. Evaluation of the proportion of high COCS in groups depending on causative medications in Korean patients with SJS/TEN

Causative medication	Low COCS (%)	High COCS (%)	P value*	OR (95% CI)
NSAID†				
Receiving	30 (71.43)	12 (28.57)	.0002	7.07 (2.45-20.41)
Not receiving	106 (94.64)	6 (5.36)		
Antibiotics†				
Receiving	46 (82.14)	10 (17.86)	.1153	2.45 (0.90-6.62)
Not receiving	90 (91.84)	8 (8.16)		
Allopurinol†				
Receiving	12 (100)	0	.3620	
Not receiving	124 (87.32)	18 (12.68)		
Anticonvulsant†				
Receiving	40 (100)	0	.0039	
Not receiving	96 (84.21)	18 (15.79)		
Sulfasalazine†				
Receiving	6 (75)	2 (25)	.2364	2.71 (0.50-14.57)
Not receiving	130 (89.04)	16 (10.96)		
NSAID (n = 42) vs antibiotics (n = 36)‡			.0902	3.20 (0.93-11.02)
NSAID (n = 42) vs allopurinol (n = 12)‡§¶			.0485	
NSAID (n = 42) vs anticonvulsant (n = 36)‡§¶			.0003	
NSAID (n = 42) vs sulfasalazine (n = 8)‡			1.0000	1.20 (0.21-6.80)
Antibiotics (n = 56) vs allopurinol (n = 12)‡¶			.1894	
Antibiotics (n = 56) vs anticonvulsant (n = 40)‡¶			.0046	
Antibiotics (n = 56) vs sulfasalazine (n = 8)‡			.6373	0.65 (0.11-3.72)

CI, Confidence interval; COCS, chronic ocular surface complication score; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis.

We did not compare the proportion of high COCS between the groups of allopurinol, anticonvulsant, and sulfasalazine because there were no patients with high COCS in allopurinol or anticonvulsant groups and in sulfasalazine group there was only 1 patient who showed high COCS. Bold indicates statistical significance ($P < .05$).

*Fisher's exact test.

†The proportion of high COCS was compared between the patients receiving each medication and those not receiving the medication in all patients.

‡The proportion of high COCS was compared between the groups depending on causative medication.

§Patients who were taking NSAID with the other medication simultaneously before the onset of disease were included in the NSAID group.

¶Odds ratio could not be calculated because there was no patient who showed high COCS in allopurinol or anticonvulsant groups.

which are known to induce SJS in western countries, showed low COCS regardless of whether they took NSAIDs simultaneously or not. This suggests that anticonvulsants or allopurinol may not be the culprit for severe ocular complications in Korean. In addition, we re-analyzed the comparison between NSAIDs (n = 38) and anticonvulsants (n = 36) after excluding subjects (n = 4) who took NSAIDs and anticonvulsants simultaneously. The P value was still significant ($P = .0002$), indicating that NSAID showed significantly higher correlation with high COCS than anticonvulsant.

Recent studies reported that certain human leukocyte antigen (HLA) types are associated with severe COCs in SJS/TEN induced by cold medicine.^{8,9} Therefore, NSAIDs may be related to severe COCs as suggested.⁴ Our study results showed clinical evidence that NSAIDs were associated with severe COCs in Korean SJS/TEN. In Korean, interactive effects between PTGER3 SNPs and HLA-A*02:06 was similar to those in Japanese.¹⁰ Therefore, the association of NSAIDs with severe COCs may be common in Asians. This report is important because it provides information supporting the association between NSAIDs and severe COCs in Asian with SJS/TEN.

This study had some limitations. Given that the cases caused by classic NSAIDs with a high risk of SJS/TEN (eg, phenazone derivatives, oxicams, coxibs) may be absent in our study, the hypothesis of a higher risk of severe COCs in SJS/TEN related to

NSAID would be re-enforced by the presence of severe COCs in such a group. Also, it was difficult to exclude "protopathic bias" to assess the causality between NSAIDs and severe COCs. It is possible that some of the cases in the NSAID group would be more likely idiopathic cases. However, the disagreement on real causality does not seem to alter the observation of a more severe COCs induced by NSAIDs. Although we could not investigate the history of prior exposure to the drug more than 2 months before the onset of the disease or the length of exposure, it does not seem to affect the identification of the causative medication. We did not analyze HIV status. Considering the low incidence of HIV in Korea and negative results in all patients who underwent serologic test for HIV (n = 40), the lack of analysis of HIV may not affect the outcome.

In conclusion, NSAIDs including cold medicine might be associated with severe COCs in Korean patients with SJS/TEN.

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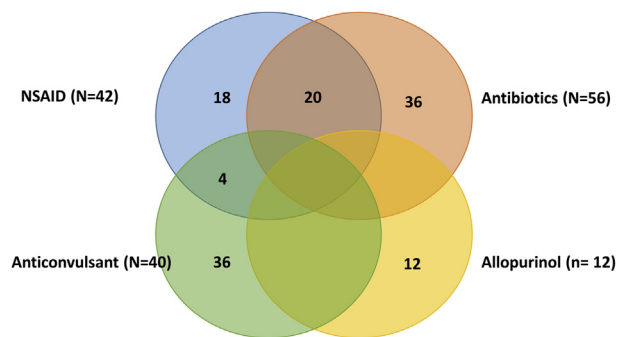


FIGURE E1. Distribution of patients with SJS/TEN in each group. *NSAID*, Nonsteroidal anti-inflammatory drug; *SJS*, Stevens-Johnson syndrome; *TEN*, toxic epidermal necrolysis.

TABLE E1. Ingredients in cold medicines that are commonly available in South Korea

Name of products	Company	Ingredients				
		NSAIDs	Content per tab. (mg)	Dose per day (mg)	Others	Content per tab. (mg)
Pan cold-S	Dong-Wha Pharm.	AAP	150	900	Caffeine anhydrous	20
					Chlorpheniramine maleate	1.25
					D,L-Methylephedrine HCl	8.75
					Guaifenesin	41.65
Panpyrin	Dong-A Pharm.	AAP	200	600	Caffeine anhydrous	30
					Chlorpheniramine maleate	2
					Ethenzamide	100
Tylenol cold-S	Janssen Korea	AAP	325	975	Dextromethorphan hydrobromide	15
					Pseudoephedrine HCL	30
					Chlorpheniramine maleate	2
Whituben-Q	Ildong Pharm.	AAP	180	1080	Dextromethorphan hydrobromide	8
					D,L-Methylephedrine HCl	12.5
					Guaifenesin	20.8
					Pseudoephedrine HCL	15
					Triprolidine hydrochloride hydrate	0.66
Haben-Plus	Korean Drug	AAP	180	1080	Dextromethorphan hydrobromide	7.5
					Thiamine nitrate	4
					Pseudoephedrine HCL	15
					Riboflavin	2
					Lysozyme chloride	10
					Chlorpheniramine maleate	1.25
					Ascorbic acid coated 96% powder	15.63
					Galgeun-Tang extract	83.4

AAP, Acetaminophen; NSAID, nonsteroidal anti-inflammatory drug; tab., tablet.

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