

## Cross-Reactivity Between Carbonic Anhydrase Inhibitor Confirmed by Lymphocyte Transformation Test: A Case of Methazolamide-Induced Toxic Epidermal Necrolysis

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Carbonic anhydrase inhibitors (CAIs)—acetazolamide, methazolamide, dorzolamide, and brinzolamide—are sulfonamide derivatives that are widely used to reduce ocular pressure in patients with glaucoma. Sulfonamides comprise a class of drugs with a high risk of inducing delayed hypersensitivity reactions [1]. Therefore, sulfonamide-containing agents that are potent CAIs have been reported to cause fatal Stevens–Johnson syndrome (SJS) and toxic

epidermal necrolysis (TEN) [2,3]. Previous studies have suggested that human leukocyte antigen (HLA)-B\*59:01 is strongly associated with methazolamide-induced SJS/TEN in East Asian patients [2-4]. Furthermore, an association was reported between HLA-B\*59:01 and acetazolamide-induced SJS/TEN in 2 Korean patients, suggesting the possibility of cross-reactivity between acetazolamide and methazolamide, which are structurally similar to sulfonamide CAIs [5]. Although T cell–mediated immunologic cross-reactivity between CAIs could be expected, this has not been demonstrated in vitro. We report the first case of methazolamide-induced TEN in a patient harboring HLA-B\*59:01 that was characterized by cross-reaction with 3 CAIs based on the lymphocyte transformation test (LTT).

A 43-year-old man presented with a maculopapular rash that covered his body surface and ulceration of the conjunctiva and urethra. His previous medical history was unremarkable, and he had not recently taken medications, except for methazolamide to treat suspected central serous chorioretinopathy on days 14, 13, and 1 before the first day of admission. Upon admission, he had conjunctival injection, erosive lesions on the oral mucosa and urethra, and widespread blistering eruption rash involving approximately 40% of his body surface area (whole trunk, face, and genital lesion). The patient was hospitalized with an initial diagnosis of syphilis and initially received penicillin; however, his condition did not improve. To confirm whether methazolamide was the cause of the skin manifestations, we performed HLA typing and an LTT with methazolamide and other CAIs. HLA typing revealed A\*02:01/A\*11:01, B\*40:01/B\*59:01, and C\*01:02/C\*15:02 types. Methazolamide was discontinued owing to the suspicion of methazolamide-induced TEN; therefore, we administered 1 mg/kg of methylprednisolone and intravenous immunoglobulin at 0.6 g/kg/d for 3 consecutive days. The methylprednisolone was tapered gradually over 4 weeks, and the patient was discharged after 1 month with improved symptoms and re-epithelization. An LTT was conducted to confirm a causal association between methazolamide and TEN and to detect cross-reactivity with other CAIs. Peripheral blood mononuclear cells were treated with the 3 CAIs

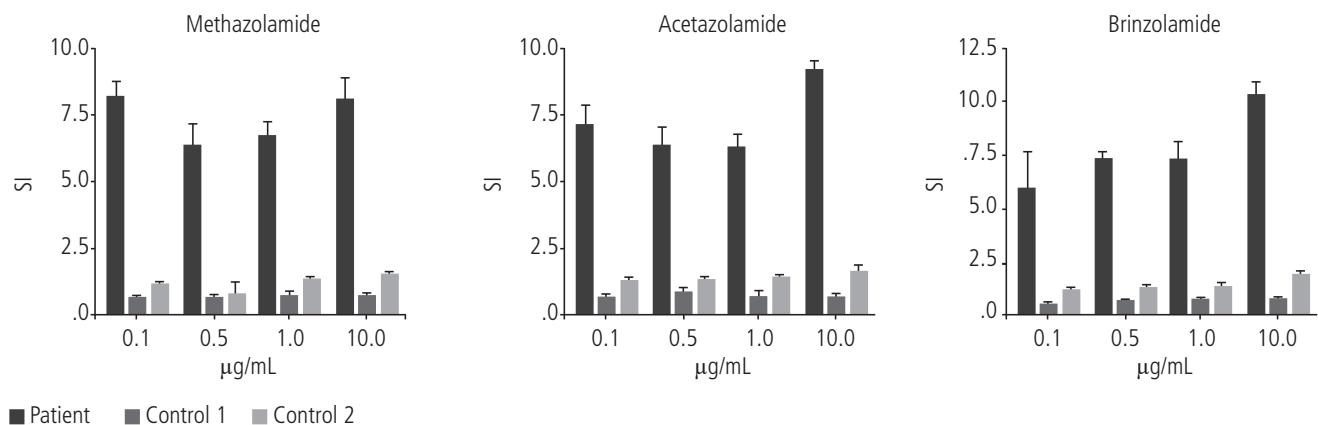


Figure. Results of a lymphocyte transformation test with increasing doses of methazolamide, acetazolamide, and brinzolamide. SI indicates stimulation index.

(methazolamide, acetazolamide, and brinzolamide) at various concentrations followed by 5-day culture. 3H-thymidine was added, and lymphocyte proliferation was measured as 3H-thymidine uptake on day 6 [6]. We compared the patient's results with those from 2 healthy controls who had not been exposed to CAIs previously. The LTT result was interpreted as positive if the patient's stimulation index (SI) was more than 2.0. The patient's SI was >5.0 for all concentrations of methazolamide, acetazolamide, and brinzolamide, whereas the SI values of the 2 normal controls were <2.0 (Figure).

Despite reports of SJS/TEN induced by methazolamide [2-5], even in a topical formulation [7], we report the first case of an HLA-B\*59:01 carrier with methazolamide-induced TEN and positive LTT results for all 3 CAIs. LTT is a safe and reproducible in vitro test for determining the identity of causative agents by assessing the activation of drug-specific T cells [6,8]. It can be applied in the case of reactions to multiple drugs because drug-specific T cells play a role in drug hypersensitivity and have high sensitivity and specificity (70% and 85%, respectively) [9].

In the current case, LTT was performed 1 week after the skin manifestations with fever and revealed cross-reactivity with 3 CAIs, all of which contain chemical compounds with a sulfonamide chemical structure ( $-\text{SO}_2\text{NH}_2$ ), which enables T-cell sensitization to develop along identical pathways. A recent study revealed that CAI-induced SJS/TEN is characterized by more extensive cutaneous involvement and ocular sequelae than SJS/TEN caused by other drugs, albeit with no differences in mortality [10]. It is not certain whether there is significant T cell-mediated immunologic cross-reactivity between individual CAIs; however, the abovementioned findings may point to specific immunopathogenic mechanisms underlying CAI-induced SJS/TEN.

The role of HLAs as key regulators in CD8<sup>+</sup> T cell-mediated drug hypersensitivity is well known. CAI-induced SJS/TEN occurs predominantly in East Asia, and HLA typing has revealed HLA-B\*59:01 frequencies of 2.1% and 1.8% in healthy Korean and Japanese individuals, respectively [2]; in Chinese persons, the frequency is slightly lower (0.35%) [3]. A recent meta-analysis supported the positive association between the HLA-B\*59:01 and HLA-B\*59:01-C\*01:02 haplotypes and risk of methazolamide-induced SJS/TEN [4]. Consequently, physicians should be aware of the possibility of CAI-induced SJS/TEN when administering methazolamide. Moreover, patients should be adequately informed regarding the possibility of adverse events, including the fact that other CAIs, including topical agents, can lead to SJS/TEN. Physicians should be alert to the administration of CAIs in HLA-B\*59:01 carriers and consider additional LTT to investigate cross-reactivity between CAIs. Further studies are warranted to confirm cross-reactivity between these CAIs.

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#### Conflicts of Interest

The authors declare that they have no conflicts of interest regarding present study.

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