

**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 are a class of drugs with a high risk of inducing delayed hypersensitivity [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 HLA-B\*59:01 is strongly associated with methazolamide-induced SJS/TEN in East Asian patients[2-4]. Furthermore, HLA-B\*59:01 has also been reported in association with acetazolamide SJS/TEN in two 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, *in vitro* studies have not demonstrated its cross-reactivity till date. Herein, we report the first case of a methazolamide-induced TEN with carriage of HLA-B\*5901 that was characterized by a cross-reaction with three CAIs based on LTT.

A 43-year-old man presented with maculopapular eruption on the whole body and ulceration of the conjunctiva and urethra. His previous medical history was unremarkable, and he did not take any recent medications except methazolamide. He had been treated with methazolamide for suspected central serous chorioretinopathy on days 14, 13, and 1 before the first day of admission. Upon admission, he showed conjunctival injection, erosive lesions on the oral mucosa and urethra, and bullous eruption involved approximately 40% of the patient's body surface area (whole trunk, face, and genital lesion). The

patient was hospitalized with an initial diagnosis of syphilis, and he was initially administered penicillin; however, there was no improvement in his condition. To confirm whether methazolamide was the causative drug of his skin manifestation, we performed HLA typing and an LTT with methazolamide and other CAIs. HLA typing revealed A\*0201 and A\*1101, B\*4001 and B\*5901, and Cw\*0102 and Cw\*1502 types. Methazolamide was discontinued owing to the suspicion of methazolamide-induced TEN; therefore, we administered 1 mg/kg of methylprednisolone and IV immunoglobulin intravenously at 0.6 g/kg per day for three 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 the causality between methazolamide administration and TEN and to detect cross-reactivity with other CAIs. Peripheral blood mononuclear cells were treated with the three CAIs (methazolamide, acetazolamide, and brinzolamide) at various concentrations followed by 5-day culture, <sup>3</sup>H-thymidine was added, and lymphocyte proliferation was measured as <sup>3</sup>H-thymidine uptake on day 6 [6]. We compared the patient's results with those from two normal 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 value was higher than 5.0 for every concentration of methazolamide, acetazolamide, and brinzolamide, whereas the SI values of the two normal controls were less than 2.0 (Figure).

Despite some published data showing patients with SJS/TEN to methazolamide [2-5], even in a topical agent [7], our report is the first that the HLA-B\*5901 carrier with methazolamide-induced TEN was positive in LTT with all three CAIs. LTT is a safe and reproducible *in vitro* test to determine the identity of causative agents by assessing the activation of drug specific T cells [6, 8]. In particular, it can be applied in the case of multiple drugs based on the fact that drug-specific T cells play a role in drug hypersensitivity and have a high sensitivity and selectivity of 70% and 85%, respectively [9].

In the current case, LTT was performed 1 week after skin manifestation with fever and showed cross-reactivity with three CAIs. The three CAIs contain chemical compounds with a sulfonamide chemical structure (-SO<sub>2</sub>NH<sub>2</sub>), where the T-cell sensitization develops in identical pathways. A

recent study revealed that CAI-induced SJS/TEN has more extensive cutaneous involvement and ocular sequelae without differences in mortality than SJS/TEN caused by other drugs[10]. It is not certain whether there is significant T-cell mediated immunologic cross-reactivity between individual CAIs; however, these findings may indicate the distinct immune pathomechanism underlying CAI-induced SJS/TEN.

The role of HLAs as key regulators in CD 8+ T-cell mediated drug hypersensitivity is well known. CAI-induced SJS/TEN occurs predominantly in East Asia, and HLA typing of normal subjects has revealed HLA-B\*5901 frequencies of 2.1% and 1.8% in Korean and Japanese individuals, respectively [2], whereas in Chinese subjects, the frequency is slightly lower at 0.35%[3]. A recent meta-analysis supported the positive association between HLA-B\*5901 and HLA-B\*5901-Cw\*0102 haplotype and methazolamide-induced SJS/TEN risk [4]. Consequently, physicians should carefully monitor when administering methazolamide with the possibility of CAI-induced SJS/TEN. 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 for patients with HLA-B\*59:01 carriage and consider additional LTT for cross-reactivity among CAIs. Further studies are warranted to confirm the cross-reactivity between these CAIs.

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### **Conflicts of interest**

All of the authors declare that there is no conflict of interest regarding the publication of this article.

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**Figure 1. Result of lymphocyte transformation test with increasing dose of methazolamide, acetazolamide and brinzolamide**

