Toxic Epidermal Necrolysis Induced by the Topical Carbonic Anhydrase Inhibitors Brinzolamide and Dorzolamide

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Brinzolamide and dorzolamide are highly specific topical carbonic anhydrase inhibitors (CAIs). They lower intraocular pressure (IOP) by reducing the rate of aqueous humour formation without serious side effects. Although systemic CAIs are the most potent medications for lowering intraocular pressure for conditions with ocular hypertension, many cases with adverse systemic reactions have been reported, including Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN). Here, we report 2 cases of TEN that were associated with topical CAIs rather than systemic CAIs.

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INTRODUCTION

Carbonic anhydrase inhibitors (CAI) are commonly used for lowering the intraocular pressure (IOP) in glaucoma and other ophthalmologic conditions. Carbonic anhydrase inhibitors are sulfonamide derivatives that are known to cause a range of adverse reactions, including benign transient cutaneous rashes to life-threatening conditions, such as Toxic epidermal necrolysis (TEN). Systemic CAIs are among the most potent medications for lowering IOP, but their use is accompanied by troublesome side effects. In the dermatologic literature, there are reports of Stevens-Johnson syndrome (SJS) and TEN associated with systemic CAIs in people of Japanese or Korean descent.

Topical application of intraophthalmic CAIs is now recommended to control intraocular pressure, as

since the introduction of topical CAI in 1995 there have been significantly lower incidences of various side effects. However, SJS-TEN associated with topical CAI has been recently reported. Here, we report 2 cases of TEN that were induced by topical CAIs, brinzolamide and dorzolamide, in 2 Korean men.

CASE REPORT

Case 1

A 45-year-old Korean man, who had alcoholic liver cirrhosis, suddenly developed blurred vision accompanied by a headache. After emergency ophthalmic surgery, topical brinzolamide was applied to his eyes to control post-operative intraocular pressure resulting from pre-existing glaucoma. Two weeks later, after applying brinzolamide 3 times a day, the patient reported pruritic erythematous to violaceous targetoid papules with erosions on the oral and genital mucosa. The patient complained of intermittent high fever (> 38°C). Erythematous patches developed on the face, palms and soles in the early stage, and then extended to other skin surface areas. Three days later, skin

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Fig. 1. (A) Variable sized scattered vesicles on erythematous patches seen over the entire body of patient 1. (B) Vesicles and erythematous patches became dusky, red-colored confluent patches with Nikolsky sign. Widespread necrolytic skin detachment finally developed after 7 days of disease progression. (C) Dusky, red-colored confluent patches on the face and neck. Note the flaccid bullae caused by necrolytic epidermis on the auricle of patient 2.

detachment developed over approximately 50% of his body surface area (Fig. 1A, B). Laboratory studies revealed an elevated LDH level (743 U/L; normal value 218~472 U/L) without any other significant changes. The blood cell count, rapid phase reactants, liver function tests, renal function tests and electrolytes were within normal limits in the early stage of the illness. He was initially treated with oral prednisolone at 45 mg per day, but epidermal detachment progressed to over 80% of his body. Intravenous immunoglobulin (IVIG) of 10 g was introduced, but a persistent high fever $>38.5^{\circ}\text{C}$ and neutropenia prohibited continuation of IVIG therapy. The skin lesions improved with re-epithelialization, although his general condition deteriorated. The patient developed acute renal failure due to excessive water and albumin loss from the body surface. The patient died from sepsis on the 20th day after the initial skin lesion developed.

Case 2

A 45-year old Korean man, who had chronic hepatitis B, developed oral ulcers and generalized purpuric targetoid papules. For the previous 2 weeks, he had been applying dorzolamide for the treatment of early open-angle glaucoma. Physical examination revealed intermittent fever, tense palmar

and plantar bullae with erythematous targetoid papules (Fig. 1C). Mucosal erosions were observed in his oral cavity, conjunctiva, urethral orifice and perianal area. During the early course of the disease, laboratory studies revealed elevated levels of LDH (818 U/L, normal level; 218~472 U/L) and CRP (17.3 mg/dl, normal level; 0.1~1 mg/dl) and abnormal liver function tests (AST 42 U/L, ALT 56 U/L). Three days later, the scattered targetoid papules became very large, confluent patches and epidermal detachment developed over nearly 90% of the body surface area. The patient was treated with IVIG 80 mg/day for 4 days from the early stage of the disease, but he became hypovolemic and hyponatremic due to the denuded skin. The patient was admitted to the intensive care unit (ICU) and received ventilator therapy due to renal failure and pulmonary edema. His condition gradually improved after starting ICU care and the skin was in the process of re-epithelialization. He was discharged after 46 days of the hospital course.

DISCUSSION

Brinzolamide and dorzolamide are highly specific topical CAIs, which lower intraocular pressure

(IOP) by reducing the rate of aqueous humour formation¹. Although systemic CAIs are the most potent medications for lowering intraocular pressure for primary open-angle glaucoma and other conditions with ocular hypertension, many cases with adverse systemic reactions have been reported, including Stevens-Johnson syndrome (SJS), TEN, fulminant hepatic necrosis, aplastic anemia, drug hypersensitivity, metabolic acidosis, serum sickness and nephritis^{2,3}. Therefore, topical application of intraocular CAIs is recommended to control intraocular pressure, as this route of administration lowers ocular hypertension without serious adverse reactions.

In healthy people, topical CAIs can enter the blood circulation via ocular structures, such as the conjunctiva, cornea and lens¹. However, the blood level is not high enough to cause adverse reactions⁴. Yet, topical CAIs have the potential to induce SJS-TEN in patients, as they are sulfonamide derivatives that behave similarly to systemic sulfonamide³. Metabolic inactivation of topical CAIs occurs primarily in the liver through oxidative O- and N-dealkylation by cytochrome P450 isoenzymes, and metabolites are eliminated primarily in the urine^{1,5}. Therefore, brinzolamide is not recommended in the USA⁶ and in Europe⁷ for the treatment of patients with severe renal impairment (creatinine clearance <30 ml/min)¹. In patients with hepatic impairment, topical CAIs are not recommended, or they should be used with caution, because of abnormal pharmacokinetics in such patients¹.

For our patients, both had liver disease; one had cirrhosis and the other had an inactive hepatitis B. The use of topical CAIs was dangerous in these patients with underlying liver diseases, as they were at risk for developing SJS-TEN. In the dermatological literature, 1 case of TEN was reported, for which dorzolamide was the suggested cause. However, the patient was also medicated with timolol and latanoprost⁸. The experience with our 2 cases confirmed that both brinzolamide and dorzolamide could induce TEN when used as topical CAIs, as our patients only received these topical CAIs. In the ophthalmology literature, TEN has been reported to be induced by other topical ophthalmologic agents with a fumigant mixture⁹ and perfume¹⁰.

As to the mechanism to induce TEN, the reactive metabolites of sulfonamides are known to cause idiosyncratic reactions. If the metabolites are not detoxified properly, they can act as a hapten

that binds with endogenous proteins, which then triggers an immune reaction. Haptenated compounds may also be directly toxic to cells. These 2 cases illustrate that topical CAIs can induce TEN similar to that by systemic sulfonamides. There are several reports of SJS or TEN after taking systemic CAI, especially among Asians. CAIs are sulfonamide derivatives. Whether taken systemically or as a topical agent, the risks for developing SJS or TEN can be the same.

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