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Letter to the Editors

Aggrenox (Asasantin retard)-induced Stevens–Johnson syndrome

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Stevens–Johnson syndrome (SJS) is a rare, life-threatening and severe blistering mucocutaneous disease, most commonly caused by drugs [1]. The annual incidence of SJS is estimated to 1.1–7.7 cases per 1 million, and the risk of SJS is highest in the first weeks after drug use [2]. Individuals with the alleles HLA-B*1502 and HLA-B*5801 are more susceptible to develop SJS by carbamazepine and allopurinol, respectively [3, 4]. Aggrenox is a fixed-dose combination of aspirin 25 mg and dipyridamole 200 mg in a modified-release form and is recommended for secondary prevention of ischaemic stroke [5, 6]. Common adverse effects of Aggrenox include headache, bleeding and gastrointestinal events. Post-marketing data have reported rare cases of SJS in patients receiving treatment with either aspirin or dipyridamole (Prod. Info. AGGRENOX(R) extended-release oral capsules, 2006) [7]. However, no formal report of SJS associated with Aggrenox has ever been published. Here, we report a patient who developed SJS acutely several hours after exposure to a single dose of Aggrenox.

A 74-year-old ethnic Chinese woman experienced episodes of acute-onset self-limited right-sided weakness and numbness 1–2 weeks prior to this admission. Each episode lasted for minutes to hours. She had a history of hypertension, diabetes mellitus, and an old stroke 10 years previously with the sequela of minimal right hemiparesis. She had been treated with aspirin (acetylsalicylic acid, 100 mg q.d.), pentoxifylline, amlodipine, repaglinide, sennoside, and magnesium oxide for several years. In addition, she had been treated with oral cephalexin and paracetamol for urinary tract infection one and a half year ago in our hospital. No allergy had been noted after taking these medications. She had had no exposure to any herbal or Chinese medicines, nor dipyridamole orally or intravenously for cardiac investigation previously.

Upon admission, she was afebrile with normal blood pressure and pulse rate. Neurologically, there was no significant focal deficit. Blood tests for complete blood counts, glucose, lipids, renal and liver function were unremarkable. Magnetic resonance imaging of the brain showed no acute insult, but chronic subcortical ischaemic encephalopathy at bilateral periventricular areas. Magnetic resonance angiography disclosed mild intracranial atherosclerosis. Transient ischaemic attack (TIA) was diagnosed. Therefore, aspirin was changed to Aggrenox after the third day of admission. Paracetamol was also prescribed at the same time for relief of her headache. Unfortunately, acute-onset progressive skin rash with generalized wheals and plaques, and hyperpigmentation over the face, trunk and four limbs developed the next morning. Fever up to 38°C was also noted. Aggrenox was discontinued soon after the first dose. Her skin lesion progressed in the following 2 days and SJS was diagnosed by a dermatologist. Her Naranjo adverse drug reaction probability scale [8] was 5, indicating a 'probable link'. Steroid with prednisolone (30 mg day^{-1}) was prescribed and her skin lesions improved gradually. Prednisolone was tapered off 1 month later. This patient had HLA-B40 homozygous alleles, i.e. negative for HLA B*1502 and HLA B*1580.

Aggrenox (Asasantin retard), a fixed-dose combination of aspirin 25 mg and dipyridamole 200 mg in an extended-release form, twice daily has better protective effect in secondary prevention of ischaemic stroke or TIA compared with either aspirin alone or extended-released dipyridamole alone [5, 6]. It has been indicated to reduce the risk of stroke in patients who have TIA or ischaemic stroke by the US Food and Drug Administration since 1999. The side effects of Aggrenox were well documented in the European Stroke Prevention Study 2, in which a total of 6602 patients were recruited [5]. Rare reported skin adverse reactions included rash, alopecia, angio-oedema, bruising, ecchymosis, haematoma, and SJS. However, the case with SJS was not formally documented. Previous studies have shown that neither aspirin nor other salicylates, when taken either in single ingredient products or in combination with other compounds, are associated with a significant increase in the risk of SJS or toxic epidermal

necrolysis [9, 10], but these studies did not depict the risk of SJS by combination therapy with dipyridamole plus aspirin. We did not consider this patient's SJS to be related to aspirin because of her previous long-term use of aspirin.

This patient was exposed to Aggrenox and paracetamol several hours before the onset of skin lesion. It was unlikely that the SJS was related to paracetamol, because previous usage in this patient had not resulted in any discomfort. The delayed hypersensitivity mechanism directed by drug-specific T cells is probably the most important mechanism in SJS, but the physiological mechanisms of SJS are not well established yet [10, 11]. The risk of SJS is highest in the first week after drug use, and faster reaction may probably occur in sensitized patients who have had previous milder cutaneous eruptions [2, 10, 11]. The timing of the allergy in this patient was not a typical delayed hypersensitivity. However, we cannot tell exactly whether there was an atypical one or she was in fact pre-sensitized.

Although dipyridamole related to severe adverse skin reaction has been reported [12], there has been no formal report of dipyridamole related to SJS. For increased use of Aggrenox in patients with ischaemic cerebrovascular disease, clinicians should be aware of the possibility of SJS occurring during use.

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