

Stevens-Johnson Syndrome Associated with Glipizide Therapy

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We describe a patient with Stevens-Johnson syndrome (erythema multiforme major) associated with an increase in glipizide dosage administration. Glipizide is a second-generation sulfonylurea commonly used to treat patients with noninsulin-dependent diabetes mellitus. Although several reports have documented Stevens-Johnson syndrome caused by first-generation sulfonylureas, our case appears to be the first report of a second-generation sulfonylurea associated with Stevens-Johnson syndrome.

Case Report

A 31-year-old Hispanic man presented with a 5-day history of a painful skin eruption that first appeared on his hands and then spread to his feet and ears. The skin eruption was widely distributed by 3 days. The patient denied experiencing fevers, chills, headaches, photophobia, pruritus, arthritis, hematuria, dysuria, shortness of breath, cough, rhinorrhea, or fatigue. He also denied having a recent history of foreign travel, camping, or exposure to ticks. There were no sick contacts and no history of cold sores or genital lesions.

The medical history was significant for noninsulin-dependent diabetes mellitus of 3 years' duration, treated with 5 mg of glipizide daily for 1 year without adverse reactions. Two days prior to the onset of the eruption, the glipizide dosage was increased to 10 mg daily. Two days after the eruption started, the patient was seen by his primary care physician, who prescribed fexofenadine. The patient denied taking over-the-counter medications or having a history of drug allergies.

On examination, there were hundreds of tender dusky red-to-purple targetoid macules coalescing into large plaques and involving his head, ears, face, neck, chest, back, arms, legs, and the volar surfaces of his hands and feet. The vermilion border of the lips displayed areas of dusky ery-

thema and hemorrhagic crust, and his buccal and lingual mucosa had erosions and exudate (Fig 1). He also had bilateral conjunctivitis with mucoid discharge. His genitourinary examination results were normal.

Laboratory work-up revealed a serum glucose level of 203 mg/dL at admission and a hemoglobin A_{1c} of 9.8% (normal: 3.2–5.6%). His erythrocyte sedimentation rate was slightly elevated, at 12 mm/h (normal: 0–10 mm/h). The complete blood count was unremarkable, with a white blood cell count of 6.51×10^3 cells/ μ L (differential of 4.29×10^3 neutrophils/ μ L, 1.66×10^3 lymphocytes/ μ L, 0.49×10^3 monocytes/ μ L, 0.04×10^3 eosinophils/ μ L, and 0.03×10^3 basophils/ μ L). Liver function tests revealed no abnormalities and the following levels: aspartate transaminase, 22 U/L; alanine transaminase, 38 U/L; alkaline phosphatase, 93 U/L; total bilirubin, 0.8 mg/dL; and direct bilirubin, 0.1 mg/dL. Coagulation studies results, electrolytes, lipid profile, and urinalysis results were within normal limits. Antinuclear antibodies were negative. Blood cultures, urine culture, and results of the rapid plasma reagin test were negative. Serum testing for cryptococcal antigen, human immunodeficiency virus, *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, hepatitis B virus, and hepatitis C virus were negative. Chest radiograph was unremarkable.

A 4 mm punch biopsy specimen of a representative skin lesion was taken from the patient's left arm. Histologic examination revealed necrotic keratinocytes at the dermoepidermal junction and an area of full-thickness epidermal necrosis. There was a sparse perivascular infiltrate of lymphocytes and histiocytes in the superficial dermis. Features of vasculitis were not seen (Fig 2).

The patient's clinical presentation and histologic findings were consistent with Stevens-Johnson syndrome (SJS), or erythema multiforme major. During the patient's

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Figure 1. Dusky erythema, hemorrhagic crust, and erosions on the patient's oral mucosa, along with diffuse purpuric macules on the chest.

hospital stay, glipizide was discontinued and was replaced with 7 units of insulin (70/30) administered subcutaneously in the morning and 5 units at night; petrolatum was applied to his skin and lips three times a day. His oral lesions rapidly healed, no new skin lesions or areas of denuded skin appeared, and the intensity of skin and oral lesion pain decreased. The patient was discharged 3 days after admission. On outpatient follow-up 2 days after discharge, we observed continuing resolution of his lesions.

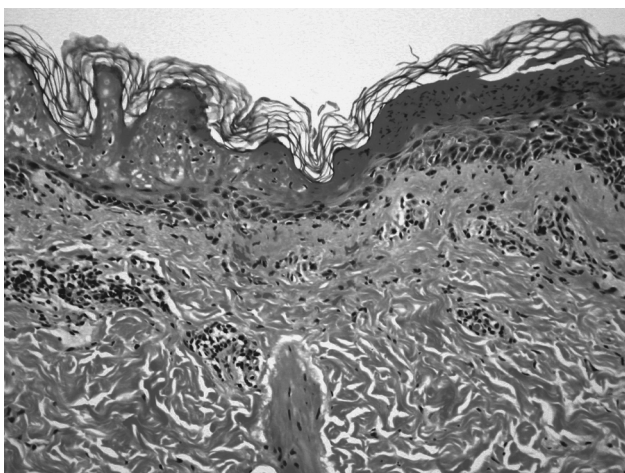
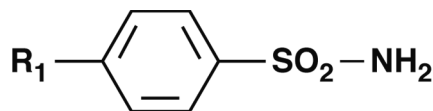


Figure 2. A 4 mm punch biopsy specimen showing necrotic keratinocytes at the dermoepidermal junction. Full-thickness necrosis can be seen at one edge of the biopsy specimen. (Hematoxylin and eosin staining, $\times 10$ original magnification)

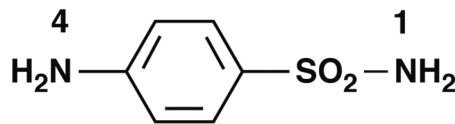
Discussion

To our knowledge, our case report is the first published association between glipizide (or any second-generation sulfonylurea) and SJS (or erythema multiforme major). The majority of SJS cases are attributed to drugs, but infectious causes (such as *Mycoplasma pneumoniae*) have also been implicated.^{1,2}

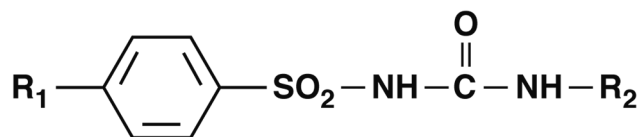
Among drugs, antibacterial sulfonamides (eg, trimethoprim-sulfamethoxazole) are most strongly associated with SJS, followed by nonsulfonamide antibiotics, anticonvulsants, nonsteroidal antiinflammatory drugs, and allopurinol.² Sulfonylureas are oral hypoglycemic drugs that lower serum glucose levels by stimulating the secretion of insulin from pancreatic beta cells, reducing serum glucagon levels, and/or increasing insulin sensitivity in its target tissues.³ Sulfonylureas were derived from the antibacterial sulfonamides and share a common para-substituted arylsulfonamide backbone. However, sulfonylureas have an additional urea group and lack the para-NH₂ group at the N4 position of antibacterial sulfonamides. Specific sulfonylureas have differing substitutions at one of the nitrogen residues in the urea group and at the para position of the benzene ring (Fig 3).³ Glipizide is a second-generation sulfonylurea. Compared to first-generation sulfonylureas, second-generation



para-substituted arylsulfonamide backbone



general antibacterial sulfonamide structure



general sulfonylurea structure

Figure 3. Chemical structures of the sulfonamides and sulfonylureas.

sulfonylureas have larger more-nonpolar side chain substitutions, which lead to increased potency.⁴ Several adverse cutaneous reactions have been attributed to glipizide, including oral lichen planus, psoriasis, and pigmented purpuric dermatosis.⁵ Previous reports have documented Stevens-Johnson syndrome associated with chlorpropamide, a first-generation sulfonylurea.⁶⁻⁹

While an infectious cause for this patient's SJS cannot be excluded, the patient denied experiencing any respiratory infection symptoms, and chest radiography revealed no abnormalities. It is likely that the patient's SJS eruption is drug related, given the patient's recent increase in glipizide dosage after an uneventful year on his initial dosage. SJS drug reactions are believed to occur through an idiosyncratic delayed-type immune-mediated process. Current evidence suggests that certain drugs can be metabolized into reactive drug products by enzymes such as cytochrome P450s (eg, the para-NH₂ group of antibacterial sulfonamides can be converted into reactive hydroxylamine or nitroso groups).^{10,11} These reactive drug products are then neutralized by enzymes such as epoxide hydrolase, glutathione-S-transferase, or N-acetyltransferase.¹² SJS reactions might then occur in individuals with a decreased ability to detoxify these reactive metabolites (eg, patients who had adverse drug reactions to sulfonamides were shown to have decreased N-acetylation activity).^{13,14}

Several nonmutually exclusive hypotheses have been proposed to explain the ability of these reactive drug metabolites to trigger drug reactions. The hapten hypothesis postulates that reactive drug metabolites function as haptens because they are unable to trigger immune responses, owing to their low molecular weight. The reactive metabolites covalently bind endogenous proteins and create immunogenic foreign complexes that trigger T-cell-mediated immune responses and a subsequent drug reaction.¹⁵ The danger hypothesis suggests that these reactive metabolites may also create oxidative stress and cell damage leading to elaboration of a danger signal, contributing to an immune response.¹⁶

We speculate that a combination of these mechanisms may have occurred in this patient. During the patient's first year of glipizide administration, the amount of glipizide-reactive products may not have exceeded the threshold he was able to metabolize. However, upon the increase in glipizide dosage from 5 to 10 mg, the patient's detoxification system may have been exceeded such that glipizide-reactive drug metabolites accumulated to a level sufficient to trigger an immune response through a combination of hapten-carrier protein conjugates and direct cytotoxicity. It

is interesting to note that sulfonylureas lack the para-NH₂ group that can be converted into the hydroxylamine and nitroso reactive groups believed to be responsible for antibacterial sulfonamide SJS reactions.¹⁷ In this patient, glipizide must then have been converted into a different and as yet unidentified type of reactive drug metabolite.

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