Glucose-Lowering Effects of Sulfasalazine in Type 2 Diabetes

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Sulfonamides and salicylates are therapeutic agents clinically useful in treating inflammatory bowel diseases and arthropathies. These drugs have also demonstrated glucose-lowering effects in type 2 diabetes (1–2). Sulfasalazine (SSZ) is a compound that is cleaved in vivo to 5-aminosalicylic acid (a salicylate) and sulfapyridine (a sulfonamide antibiotic). We report a case of a patient with systemic lupus erythematosus (SLE) and type 2 diabetes on high-dose insulin therapy, who after initiating SSZ experienced recurrent severe hypoglycemia and eventually achieved normoglycemia without the need for diabetes medications. After caring for the index patient, and then two others manifesting similar metabolic responses to SSZ, we conducted a systematic chart review to evaluate glycemic effects of SSZ in a cohort of diabetic patients.

HISTORY AND EXAMINATION — A 37-year-old woman with SLE, iron-deficiency anemia, metamaphtemaine usage, and a 1-year history of type 2 diabetes was referred to the Santa Clara Valley Medical Center (SCVMC) diabetes clinic for treatment of severe hyperglycemia. She took 100 units of insulin daily (NPH 35 units b.i.d., regular 10 units t.i.d.), yet her self-monitored blood glucose (SMBG) values consistently exceeded 16.7 mmol/l, and she experienced polyuria/diabetes and blurry vision. Other medications were prednisone 7.5 mg/day and hydroxychloroquine. On examination, the patient was cachexic, weighing 44 kg. Laboratory evaluation revealed normal thyroid, hepatic, and renal function, with no microalbuminuria. The HbA1c (A1C) value was 12.3%. During the next 2 months, insulin doses were gradually increased to 170 units/day, but SMBG values persisted at 13.9–22.2 mmol/l.

The patient subsequently started SSZ (500 mg b.i.d.) for SLE treatment. One month later she was found unresponsive with a blood glucose level of 1.8 mmol/l. Despite decreasing insulin doses to 50 units/day over the next 2 weeks, the patient reported persistent hypoglycemia, with SMBG values <3.9 mmol/l. Insulin was discontinued and glyburide 10 mg b.i.d. was started. Two months later, the patient suffered another severe hypoglycemic episode requiring medical assistance. She then stopped all diabetes medications. Despite a weight gain of >22 kg, the patient’s follow-up A1C was 5.0%, and her SMBG ranged from 4.4 to 6.1 mmol/l. Her physical activity levels changed during this course.

INVESTIGATION — We investigated whether SSZ therapy had glucose-lowering effects in other diabetic patients. Through the SCVMC pharmacy database of 171,690 outpatients, we identified 37 patients from 2001 to 2004 who concomitantly activated prescriptions for SSZ and either insulin, acarbose, sulfonylurea, metformin, or thiazolidinedione. Excluded from analysis were eight patients who took SSZ for <3 months and 11 others with insufficient data for analysis. In the remaining patients with >3 months of SSZ exposure, we performed a chart review to determine A1C values when not taking SSZ (designated either 3–6 months before SSZ initiation or 3–6 months after SSZ discontinuation) in comparison with A1C values when taking SSZ (most recent A1C if continuously taking SSZ or the A1C 0–3 months before SSZ discontinuation).

The 18 analyzable patients all had type 2 diabetes and were prescribed SSZ with a mean dose of 2,278 mg/day (range 500–4,000) for a mean duration of 1.7 years (0.3–3.4) to treat various underlying inflammatory conditions, including psoriatic arthropathy (7), rheumatoid arthritis (7), inflammatory bowel diseases (2), and SLE (2). The difference in average A1C in situations when taking (6.4%) and not taking (8.2%) SSZ was −1.8% (−8.9 to 2.1, \(P = 0.02\) by paired \(t\) test). Of the studied patients, 41% attained an American Diabetes Association (ADA)-defined A1C goal ≤7.0% when not taking SSZ, while 78% reached this goal while taking SSZ (∼0.03 by \(x^2\) test). Regarding diabetes medication dose changes while taking SSZ, four patients stopped all diabetes medications, four lowered doses, four increased doses, and six did not change doses.

Of 18, 13 were considered “responders,” manifesting improved A1C (∆A1C >0.5%) while taking SSZ. The five remaining patients were “nonresponders,” with three having no change (∆A1C <0.5%) and two experiencing increased A1C on SSZ therapy. In comparing the two response groups, there was no difference in age, sex, or SSZ duration (\(P > 0.20\)), but daily SSZ dose (2,540 vs. 1,600 mg, \(P = 0.11\)) trended higher, and baseline A1C (9.1 vs. 6.4%, \(P < 0.02\)) was significantly higher among the responders. When considering only the subgroup of 13 responders, the difference in average A1C in situations when taking (6.3%) and not taking (9.1%) SSZ was −2.7%...
(range −0.9 to −8.9, P < 0.01 by paired t test), with 11 reaching the ADA A1C goal ≤7.0%, 7 achieving normoglycemia (A1C ≤6.0%), 5 discontinuing or lowering diabetes medication doses, and 3 experiencing repeated severe hypoglycemia (SMBG <3.3 mmol/l).

CONCLUSIONS — Although the hypoglycemic potential of salicylate therapy was demonstrated >100 years ago (1) and again recently (2), clinical utility in diabetes treatment has been limited by nausea, vomiting, tinnitus, and deafness associated with high-dose therapy (3–5). Although the mechanisms by which salicylates affect glucose metabolism are not completely elucidated, studies have described both inhibitory effects on hepatic glucose production (6,7) and improved insulin action from inhibition of the kinases IKK-B (inhibitor of βB) and IKK-A (inhibitor of βA) involved in tissue inflammation (8–10). Furthermore, with sulfasalazine, which is cleaved to both a salicylate and a sulfonamide antibiotic, it is possible that the sulfonamide component contributes further to glucose-lowering effects (11,12).

Our case report and retrospective case series illustrate several important points concerning the hypoglycemic effects of SSZ. First, the compelling glucose-lowering effects of SSZ occur at standard prescribed doses as low as 1 g/day. Second, because its glucose-lowering effect has not been previously detailed, SSZ induced unexpected dangerous hypoglycemia in ~17% of our cohort. Third, because the average A1C value decrease for the entire cohort of patients was 1.8%, with a greater percentage achieving an ADA goal A1C while taking SSZ, one can speculate about the general efficacy of SSZ therapy in treating type 2 diabetes. In summary, our results suggest that glycemic control in diabetic patients should be very closely monitored when newly starting SSZ. Furthermore, in view of the dramatic findings in our small retrospective series, further studies examining the metabolic effects of SSZ are warranted.

References