

Role of Sulfonylureas in Type II Diabetes

Sulfonylureas have been used for many years in the treatment of type II diabetes mellitus. However, newer agents and a better understanding of type II diabetes has recently called their role into question. The question arose from recent guidelines proposed by the American College of Physicians (ACP), which focused on the evidence behind all classes of oral agents used to treat type II diabetes. These guidelines state that clinicians should use metformin as a first-line agent when diet and exercise are not sufficient, but they do not differentiate between the efficacies of other diabetes treatments. With regard to safety, no differences were noted between medications in associated risk for severe hypoglycemia. However, they also state that high-quality evidence shows that the risk for hypoglycemia with sulfonylureas exceeds the risk with metformin or thiazolidinediones and that the combination of metformin plus sulfonylureas is associated with a six times greater risk of hypoglycemia. Although it was not explicitly stated, these statements from the ACP implies that sulfonylureas should be considered third or fourth line agents for the treatment of type II diabetes. This conclusion is consistent with the American Association of Clinical Endocrinologists/American College of Endocrinology guidelines, but differs substantially from the conclusion offered by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes consensus statement, which recommends sulfonylureas as second line agents.

Pros: Sulfonylureas are known to reduce HbA_{1C} which is important considering medical costs of diabetes increase in a significant manner for every 1% increase in HbA_{1C} value of more than 7%. Improvement in glycemic control is often associated with some degree of weight gain, which is a common side effect of many anti-diabetic treatments including insulin, thiazolidinediones, and sulfonylureas. However, of these three options, sulfonylureas seem to be associated with a much lower increase in weight. In addition, sulfonylureas are very inexpensive and readily available.

Cons: Sulfonylureas are believed to favor the development of hypoglycemia, accelerate beta-cell apoptosis and beta-cell exhaustion, and impair endothelial function with increased risk for ischemic complications. Prolonged administration of glyburide, glimepiride, and glipizide produces extrapancreatic effects that contribute to hypoglycemic activity; these effects include reduction of basal hepatic glucose production and enhanced peripheral sensitivity to insulin secondary to an increase in insulin receptors. Hypoglycemia is a major clinical concern with the use of sulfonylureas. Also, improving insulin sensitivity is a primary objective for the prevention and treatment of diabetes due to the rise in prevalence of obesity which is associated with insulin resistance. Sulfonylureas do not improve insulin sensitivity.

Conclusion: Sulfonylureas are a rational treatment approach because they tackle the mechanism of defective insulin secretion which contributes to the development and progression of hyperglycemia. However, clinicians should consider the side effects of sulfonylureas as well as the safety and efficacy of newer agents when deciding when to initiate a sulfonylurea. In Europe, a sulfonylurea known as gliclazide is used which has lower rates of hypoglycemia as compared to the sulfonylureas used in the United States. This should be taken into consideration when referencing the recommendation by the ADA/European Association for the Study of Diabetes consensus statement, which suggests sulfonylureas be used as second-line agents. In contrast to newer agents, the safety of sulfonylureas has been well established. Safety issues of newer GLP-1 agonists and DPP-4 inhibitors have surfaced including the risk of pancreatitis. There are no clear guidelines for when to select a sulfonylurea, so clinical judgment should be used. Safety and efficacy of newer agents should also be taken into consideration.

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