Achieving Optimal Glycemic Control in Patients with Poorly Controlled Diabetes: Bedtime Insulin versus Pioglitazone

Aljabri K, Kozak SE, Thompson DM. Addition of pioglitazone or bedtime insulin to maximal doses of sulfonylurea and metformin in type 2 diabetes patients with poor glucose control: a prospective, randomized trial. Am J Med 2004;116:230–5.

Study Overview

Objective. To compare the effectiveness of pioglitazone or bedtime isophane (NPH) insulin in patients with poorly controlled diabetes already on maximal therapy with both a sulfonylurea and metformin.

Design. Prospective, randomized, nonblinded, open-label controlled trial.

Setting and participants. All patients were recruited from a single diabetes care center in Vancouver, Canada. Eligibility criteria included age 30 to 85 years, duration of type 2 diabetes > 1 year, current administration of maximally tolerated doses of metformin and an insulin secretagogue, and a most recent hemoglobin A_{1c} (HbA_{1c}) of > 8.0% while undergoing stable diabetes treatment for > 12 weeks. Exclusion criteria included previous use of insulin or a thiazolidinedione, class III or IV New York Heart Association heart failure, myocardial infarction or stroke within the last 6 months, liver disease, serum creatinine > 2 mg/dL, proliferative retinopathy, excess alcohol use, current glucocorticoid use, or pregnancy or breast feeding. All patients had received diabetes education and had been performing ambulatory blood glucose monitoring. Study participants could take angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or lipid-lowering drugs if on a stable dose for > 6 weeks and if they did not change the dose of these medications during the study.

Intervention. Study participants were randomized to either pioglitazone or NPH insulin. Patients allocated to the pioglitazone arm were initially started on a dose of 30 mg/dL in addition to their other diabetic medications. After 4 weeks, if blood glucose remained consistently above 108 mg/dL, the dose was increased to 45 mg/dL. Patients allocated to the bedtime NPH insulin group were initially started on a single 0.3 U/kg dose in addition to their oral hypoglycemic agents. Patients were instructed on how to increase their dose to achieve a fasting glucose level below 108 mg/dL. The trial lasted 16 weeks.

Main outcome measures. The primary outcomes were overall glycemic control (fasting blood glucose < 108 mg/dL), frequen-

cy of hypoglycemic episodes (serum glucose < 68 mg/dL), and HbA_{1c}, triglyceride, and cholesterol levels. Quality of life was measured using the Diabetes Treatment Satisfaction Questionnaire. Study outcomes were measured at baseline and at 16 weeks.

Main results. 62 patients consented to participate ($n = 31$ for each arm). One patient from the pioglitazone arm and 3 from the insulin arm withdrew. Baseline characteristics were similar between the 2 groups. At 16 weeks, 23% of pioglitazone-treated patients and 21% of insulin-treated patients had achieved HbA_{1c} levels < 7.0% ($P = 0.86$). There were no statistically significant differences in weight gain (both groups gained approximately 2.5 kg over the course of the trial), or reductions in blood pressure, HbA_{1c} level, triglycerides, or low-density lipoprotein cholesterol. Fewer patients experienced hypoglycemia in the pioglitazone group as compared with the insulin group (37% versus 68%; $P = 0.02$). High-density lipoprotein cholesterol levels increased on average by 4 mg/dL in the pioglitazone group and were unchanged in the bedtime NPH insulin group ($P = 0.02$). No differences were found in quality of life measures between the 2 groups.

Conclusion. The addition of either pioglitazone or bedtime insulin improved glycemic control in patients with type 2 diabetes who were already being treated with maximally tolerated doses of a sulfonylurea and metformin. Pioglitazone treatment resulted in fewer episodes of hypoglycemia and improved high-density lipoprotein cholesterol levels.

Commentary

Epidemiologic evidence has revealed increasing prevalence

rates of type 2 diabetes mellitus [1,2], with an estimated 14.4% of the U.S. adult population having either diagnosed diabetes, impaired fasting glucose, or undiagnosed diabetes [3]. Over half of diabetic patients ultimately require insulin therapy [4]. However, insulin therapy has several disadvantages that can limit its effectiveness in the clinical setting. Dosing regimens can be complex or unpleasant, and weight gain is virtually inevitable. Furthermore, intensive insulin therapy is associated with increased episodes of hypoglycemia. Data on the effectiveness of alternative pharmacologic interventions for individuals who have failed standard double therapy with a sulfonylurea and metformin are needed to help identify acceptable non–insulin-based therapies.

Pioglitazone is a thiazolidinedione that can improve glycemic control in patients already on metformin or a sulfonylurea [5]. This open-label trial compared bedtime insulin with pioglitazone. While the results of this study are promising, several limitations exist. First, the study was very small. This substantially limited the overall power of the study to detect a difference in several of its key outcomes. Reductions in HbA_{1c} levels and fasting glucose levels tended to be lower in the insulin-treated groups, although this difference was not statistically significant. Second, the study was conducted for a short duration. Relapse rates for diabetics are high, and it is unclear if patients on one particular therapeutic option may be less likely to relapse. Finally, despite the clinical trial setting, only a minority of patients achieved optimal control in either group. These outcomes underscored the challenges in treating diabetics and also makes the authors' results less appealing for clinical practice.

Applications for Clinical Practice

For patients with type 2 diabetes who have not achieved optimal control with metformin and an oral insulin secretagogue, the addition of either bedtime NPH insulin or pioglitazone appears efficacious at improving glycemic control; however, only a minority of patients actually achieve optimal glycemic control. Pioglitazone offers the additional advantage of being an oral agent and being associated with fewer hypoglycemic episodes. Studies of longer duration and involving larger numbers of diabetics are needed.

–*Review by Harvey J. Murff, MD, MPH*

References

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A Prediction Rule for Serious Outcomes of Syncope in Emergency Room Patients May Reduce Admissions

Quinn JV, Stiell IG, McDermott DA, et al. Derivation of the San Francisco Syncope Rule to predict patients with short-term serious outcomes. Ann Emerg Med 2004;43:224–32.

Study Overview

<u>Objective</u>. To derive a clinical prediction rule that identifies patients at risk for short-term serious outcomes following an episode of syncope or near syncope.

<u>Design</u>. Prospective cohort study.

<u>Setting and participants</u>. All patients presenting to an urban emergency department (ED) with syncope or near syncope were enrolled. Patients with altered mental status, substance abuse, seizure, or trauma were excluded. Treating physicians recorded all potential clinical predictors at the time of enrollment. All patients were followed for 7 days following their enrollment date.

<u>Main outcome measures</u>. Sensitivity and specificity of a clinical rule (San Francisco Syncope Rule) to predict a serious outcome within 7 days of initial ED evaluation. Serious outcomes were defined broadly as conditions requiring hospitalization or return visit to the ED including death, myocardial infarction, stroke, hemorrhage, and pulmonary emboli.