Oral Combination Therapy for Type 2 Diabetes

Aviles-Santa L, Sinding J, Raskin P. Effects of metformin in patients with poorly controlled, insulin-treated type 2 diabetes mellitus. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1999;131:182–8.

Study Overview

Objective. To evaluate the efficacy of metformin in combination with insulin in patients with type 2 diabetes who have poor glycemic control with insulin therapy alone.

Design. Randomized, double-blind, placebo-controlled trial.

Setting and participants. 43 patients with poorly controlled type 2 diabetes who were receiving insulin therapy and being treated in an outpatient diabetes clinic at a university medical center.

Intervention. Participants were randomly assigned to receive placebo or metformin in conjunction with insulin for 24 weeks. Metformin was administered as 500-mg tablets in doses increasing from 1000 mg daily to the maximum 2500 mg daily (at week 8) and adjusted to prevent adverse events.

Main outcome measures. Glycemic control (hemoglobin A_{1c} [HbA_{1c}] levels and hypoglycemic events), insulin dose, body weight, blood pressure, and lipid and lipoprotein profiles were assessed through 24 weeks. Drug tolerance was assessed through incidence of nausea, vomiting, abdominal pain, bloating, flatulence, diarrhea, and anorexia.

Main results. HbA_{1c} levels decreased by 2.5% (95% CI, 1.8 to 3.1 percentage points) in the metformin group, a significantly greater change ($P = 0.04$) than the decrease of 1.6% in the placebo group. Average final HbA_{1c} levels were 6.5% in the metformin group and 7.6% in the placebo group. The insulin dose in the placebo group increased 22.8 units (96% CI, 11 to 44 units), or 29% more than the dose for the metformin group ($P = 0.002$), which decreased slightly. Patients in the placebo group gained an average of 3.2 kg of body weight (95% CI, 1.2 to 5.1 kg); patients in the metformin group gained an average of 0.5 kg of body weight ($P = 0.07$). Total cholesterol and low-density lipoprotein cholesterol levels decreased in both groups. High-density lipoprotein cholesterol and triglyceride levels did not change.

Conclusion

This combination of better glycemic control, lower levels of insulin use, and lack of significant weight gain or hypoglycemia demonstrates that metformin is an effective adjunct to insulin therapy in patients with type 2 diabetes.

Commentary

Metformin was originally approved by the U.S. Food and Drug Administration for use alone or in combination with sulfonylurea compounds and was recently approved in combination with insulin. Although the value of the metformin–insulin combination has not been studied as thoroughly as other therapeutic strategies, the combination has been used for some time in Europe [1]. Limitations of the current study include a relatively small cohort of patients and short tracking period (about 6 months). Nonetheless, it is a first step in documenting the potential value of metformin–insulin therapy in patients with poor glycemic control.

Although HbA_{1c} levels did not reach the target 5.6% level in either group, the improvement in metformin–insulin patients was statistically and clinically greater than in placebo–insulin patients. Also, the metformin–insulin combination was more effective in controlling patients' weight. Both results are encouraging, given that improved control of HbA_{1c} levels and weight can help promote patient compliance and long-term glycemic control, thereby reducing the many adverse complications of diabetes.

Applications for Clinical Practice

Until recently, sulfonylureas were the only oral hypoglycemic agents approved in the United States. Their high failure rate frequently led physicians to add other oral agents and insulin to the therapeutic regimens of diabetic patients [2,3]. With the recent approval of new therapies, oral combination therapy is becoming increasingly more common. Physicians should be alert to the new advancements in therapy and be attentive to differences in value and effectiveness for subcohorts of patients.

References

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3. Melander A. Oral antidiabetic drugs: an overview. Diabet Med 1996;13(9 Suppl 6):S143–7.