How Do the New Insulin Secretagogues Compare?

The availability of diabetes drugs with new properties in the last several years has prompted excitement about potential new and unique advantages for diabetes care. That has certainly been the case with the new insulin secretagogues, repaglinide and nateglinide, which have earlier onset and shorter duration of action than the sulfonylureas. The niche that insulin secretagogues occupy brings unique challenges to determining their therapeutic role. At present, they are expected to be effective only for a distinct window in the natural history of the disease process, stimulating insulin secretion as it is in the process of waning. One of our challenges is to enlarge that window and to define its limits more clearly as we are working toward near-normal glycemic control. So how, in practice, do the new secretagogues compare with older, more familiar agents that act at the very same sulfonylurea receptor? What criteria determine which patient will benefit more from one class or another? Do the newer agents in fact lead to better glycemic control? Do they fulfill the promise of stimulating insulin secretion while reducing hypoglycemia risk? Is there any reason to think one may offer benefits over another in preserving β-cell function early in the course of type 2 diabetes, leading to prolongation of tight control without requiring insulin? And the question we can't avoid: Are they worth the extra cost compared with the earlier agents? Several recent reviews provide excellent surveys of the literature on the new insulin secretagogues (1,2). But several of these questions have not been answered and, given the costs and other realities of clinical research, some of them may never be. Still, it's good to revisit the questions periodically to see where we've been and what new information we'd like to see.

This discussion is precipitated by one of those uncommon head-on comparisons of insulin secretagogues, which appears in this issue of *Diabetes Care*. Cozma et al. (3) address one of the most basic questions with a cross-over comparison of the acute effect of single doses of the insulin secretagogues repaglinide, glipizide, and glibenclamide on the response to a standardized meal. They conducted the studies in patients with type 2 diabetes with relatively well-preserved β-cell function and in nondiabetic control subjects matched for age, sex, and BMI. The doses of secretagogue were selected for equipotency of effect on the insulin response to a standard meal integrated over the whole 4-h duration of study. This allowed the study to focus attention on the temporal aspects. The authors then measured glucose, insulin, and C-peptide responses; determined peak concentrations, times to peak, and integrated areas under the curve; and calculated C-peptide secretion using a deconvolution strategy.

Why conduct such a study with nondiabetic subjects and the particular patient population selected rather than with a more heterogeneous group perhaps better representative of patients with all stages of type 2 diabetes? Because the better the function of the target organ for a secretagogue, the greater the hormonal response to that drug and the greater opportunity for drug differences to manifest. The findings included substantial (and largely expected) differences between the drugs in the temporal pattern of insulin secretion—and much more modest differences in integrated glucose responses and in the peak glucose or insulin concentrations or times to peak. The differences were more pronounced in the nondiabetic subjects than in even this highly select diabetic population. We might infer that the differences on integrated glucose response may indeed be much harder to detect in a population with even less β-cell function. The design and findings in this study suggest that the patient selection question calls for stratification by the level of β-cell function at entry and longitudinal measures of the insulin secretion-insulin action relationship in studies comparing chronic treatment with these drugs. That may help to prevent or resolve conflicting reports or inferences about their comparative efficacy (4–8).

In parallel with these studies on repaglinide, Kahn et al. (9) conducted acute studies comparing nateglinide with glyburide. They demonstrated that earlier stimulation of insulin release with nateglinide resulted in slightly faster glucose disappearance but accomplished that with a markedly smaller increase in integrated insulin secretion, i.e., earlier insulin release reduced the insulin requirement to respond to a meal challenge. That offers a physiologic advantage that may not show up in efficacy studies focused solely on the glycemic response.

What about efficacy in decreasing HbA_{1c} and minimizing the risk of hypoglycemia? The large randomized clinical trials (4–8) have shown approximate equivalence for efficacy between repaglinide and sulfonylureas and slightly lower efficacy for nateglinide in terms of magnitude of HbA_{1c} lowering. But it is important to recall that the magnitude of HbA_{1c} lowering observed may be highly dependent on the initial level of glycemic control. Depending on the stage of disease at which a drug is most useful, the apparent difference in efficacy may be more or less. There are several other particularly pertinent head-on comparisons that address the questions we've posed. Damsbo et al. (10) addressed the hypoglycemia question by comparing repaglinide and glyburide using a protocol in which subjects were studied on one day in which three meals were eaten and a second day in which lunch was omitted to mimic a missed meal. While the average blood glucose throughout the days did not differ between the drug regimens used, subjects on glyburide had a mean glucose nadir in the hypoglycemic range on the omitted meal day, while those on repaglinide did not, indicating a clinically important advantage to the shorter duration secretagogue. In principle, reduction in hypoglycemia would be expected to facilitate reduction in dietary intake and re-

duce weight gain. We are awaiting additional data, as it has implications for altering the slope of the downward spiral of type 2 diabetes.

What about potential benefits in preserving β-cell function? Hollander et al. (11) found that chronic treatment with nateglinide compared with glyburide resulted in a similar postprandial glycemic response to a solid meal, again with a lower integrated insulin response with nateglinide. One implication of this effect in the Hollander and Kahn studies is less hyperinsulinemia, which may translate to improved target organ insulin sensitivity—less insulin resistance. But it is also intriguing that these two studies indicate that the earlier stimulation of insulin secretion delivers at least an equal glycemic response with less β-cell "stress." Perhaps that is a lead suggesting an avenue for greater long-term preservation of β-cell function.

More aggressive diagnostic criteria and goals for glycemic control mean that patients with less severe disease are becoming candidates for treatment, so the fraction of patients we treat who resembles the population studied by Cozma et al. can be expected to increase. The decline in repaglinide efficacy seen in the Cozma study from nondiabetic subjects to subjects with diabetes and good β-cell function, however, raises concerns that the stage at which the effects of the new secretagogues become unacceptably small may be quite early. In parallel with that, our changing glycemic goals are also shifting the transition to insulin to an earlier stage in the natural history of type 2 diabetes. It is worth recalling that based on the U.K. Prospective Diabetes Study experience, in which the insulin- and sulfonylurea-treated groups did not have worse outcomes, the relationship of atherosclerosis to hyperinsulinemia is not a reason to delay the transition to insulin.

These studies provide glimpses of some greater advantage the new insulin secretagogues may offer in one patient's setting versus another. Better stratification by insulin secretory function and better attention to changes in insulin secretion/insulin action relationships during treatment and to the interaction of drug choice with aggressive medical nutrition therapy in future head-on clinical trials would allow us to better judge the role for the new insulin secretagogues. At present, there is no one-size-fits-all answer to whether "they're worth it."

ROBERT M. COHEN, MD
BARBARA A. RAMLO-HALSTED, MD

From the Division of Endocrinology/Metabolism, Department of Medicine, University of Cincinnati College of Medicine and Medical Service, Cincinnati VA Medical Center, Cincinnati, Ohio.

Address correspondence and reprint requests to Robert M. Cohen, MD, Division of Endocrinology/Metabolism, P.O. Box 670547, University of Cincinnati Medical Center, 3125 Eden Ave., Cincinnati, OH 45267-0547. E-mail: robert.cohen@uc.edu.

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