Insulin Glargine (HOE901)

First responsibilities: understanding the data and ensuring safety

In this issue, Heinemann et al. (1) and Ratner et al. (2) provide the results of studies of insulin glargine (formerly known as HOE901), the most recent addition to the growing family of insulin analogs and formulations. The authors report insulin glargine's pharmacodynamic characteristics (1) and data concerning its safety and efficacy when administered to subjects with type 1 diabetes who were treated with regular insulin (2). Insulin glargine is produced by recombinant DNA technology with 2 modifications of the native human insulin structure: substitution of the amino acid glycine for the native asparagine at position A21 of the A-chain of human insulin and the addition of 2 arginine molecules to the NH2-terminal end of the B-chain of human insulin. The resulting insulin glargine demonstrates an isoelectric point at pH 6.7, which is in contrast to the native molecule's isoelectric pH of 5.4. As a result, glargine is soluble at acidic pH and less soluble at physiological pH. Insulin glargine is supplied as a clear colorless solution at acidic pH balances. Upon subcutaneous injection, the acid in the vehicle is neutralized and pH balances. Upon subcutaneous injection, the acid in the vehicle is neutralized and glargine precipitates, thereby delaying its absorption and prolonging its duration of action. At the time this editorial was written, the Food and Drug Administration (FDA) was conducting its review of insulin glargine.

Heinemann et al. (1) document the results of single-dose double-blind crossover euglycemic clamp studies in healthy male volunteers and compare the time-action profiles of subcutaneously injected glargine, NPH insulin, and placebo. Prior pharmacodynamic studies using insulin glargine have evaluated formulations with higher and lower zinc concentrations than the current formulation (zinc 30 μg/ml), and they have only been reported in abstract form or in review articles. The work of Heinemann et al. demonstrates that glargine provides an essentially peakless profile of action with its onset of action at 2–4 h and with a duration >24 h. By comparison, NPH human insulin was again documented to provide a substantial peak in action at 4 h with a subsequent decline in activity through the duration of the 30-h study. The authors conclude that insulin glargine provides a flatter metabolic profile than NPH insulin. Theoretically, this could prove to be advantageous in accommodating the basal insulin requirements of patients with diabetes.

Ratner et al. (2) report initial results for the U.S. Study Group of Insulin Glargine in Type 1 Diabetes. In their article, they describe the results of a large randomized prospective 28-week trial of insulin glargine versus NPH insulin. Patients with type 1 diabetes who were previously treated with regular and NPH insulin participated in the study. Prior reports of clinical efficacy with insulin glargine have involved short-term studies and few are available except as abstracts or in review articles (3). This protocol could not be masked, because glargine is a clear solution and NPH insulin is a milky suspension. In the study, subjects who were randomized to insulin glargine administered it as a single bedtime injection. Subjects randomized to NPH insulin remained on the NPH schedule that they were using before randomization (once daily at bedtime or twice daily before breakfast and at bedtime). Dose titration of both insulin glargine and NPH insulin was performed on the basis of capillary blood glucose monitoring results. The goal was to achieve a fasting blood glucose level between 4.4 and 6.7 mmol/l (80–120 mg/dl), as limited by symptomatic hypoglycemia. The protocol examined glycemic control and hypoglycemia as end points. Insulin glargine was well tolerated without evidence of antibody formation and with only minimal injection site reactions. Insignificant reductions from baseline in glycohemoglobin (GHb) were demonstrated in both groups. Insulin glargine demonstrated a significantly greater reduction in fasting plasma glucose levels. After the initial titration phase (2 months), there was also a significant reduction in hypoglycemia, including nocturnal and severe hypoglycemic episodes.

These two articles are among many studies conducted with insulin glargine that will be published in Diabetes Care and other journals. They leave the reader with a sense of promise, but without the firm conviction that insulin glargine is clearly superior to other long-acting forms of insulin. The pharmacodynamic study suggests that the peakless profile of action should provide an advantage that can be used to produce clinically meaningful improvements in glycemic control. The clinical trial's demonstration of a reduction in hypoglycemia and in fasting plasma glucose levels appears to provide an opportunity to advance further glucose lowering to achieve a reduction in GHb. However, in this study, no change in GHb was evident. This characteristic does not lessen glargine's potential significance. Reducing hypoglycemia is a worthy end in itself. Several recent reports have attested to the importance of reducing the frequency and severity of hypoglycemic reactions.

Currently, the available data concerning insulin glargine create a situation similar to the circumstances in 1996, when lispro insulin was first marketed in the U.S. In the case of lispro insulin, good pharmacodynamic data and promising studies suggested that hypoglycemia reduction was possible. Studies demonstrating improvements in GHb have only recently been published (4,5). In particular, the research of Lalli et al. (5) demonstrates the difficulty of translating the theoretical benefits of new therapy into clinically significant benefits. The reported regimen used combinations of lispro and NPH in various ratios at each meal. Certainly, the initial patients of the study group were not treated with the regimen that they eventually studied. Adaptations were required due to the context of the society in which the patients lived (Italy) and because of the content of the patient education program that was available to them. The researchers' understanding of the pharmacodynamics of lispro and their extensive clinical experience resulted in the development of a technique that worked well for their patients. Their results are nothing short of spectacular, and they are clearly the product of painstaking clinical observation complemented by excellent clinical research. Clinicians have
worked very hard to develop techniques to use the insulin formulations that have been available for decades. It will inevitably take time to learn how to actually exploit the theoretical advantages of insulin glargine.

At the University of North Carolina, an insulin glargine study site, we tried to identify subjects who had done poorly on multiple daily injection regimens, despite maximal interventions. This was driven by our unwillingness to change the insulin regimens of our patients who were doing well. The subjects we sought would have been excellent candidates for insulin pump therapy. However, they had either refused pump therapy or faced financial barriers that prevented them from using an insulin pump. Other patients enrolled in the study, motivated by personal interest or a desire to mitigate health care expenses. Because the study was not masked, both subjects and investigators were fully aware of what formulation of insulin each individual was taking. As Ratner et al. (2) suggest, this may have subconsciously limited our enthusiasm to aggressively manipulate the dose of an unfamiliar product in subjects who were often quite well controlled. (The average GHb concentration of the participants was 7.7%, but many were significantly higher, because only subjects with GHb concentrations >12% were excluded.) In our small sample, the most dramatic responses to insulin glargine were in patients who could not achieve glycemic control targets without unacceptable levels of hypoglycemia, despite multiple attempts with various regimens involving essentially all possible combinations of available insulin formulations. Not only did their glycemic control improve during glargine therapy, but it also worsened with the withdrawal of insulin glargine at the conclusion of the study. In the other subjects who were randomized to glargine, it was less clear whether their enthusiasm was based on real improvements or on the belief that the newer product represented an advancement in medicine.

Based on the theoretical benefits, the available data concerning insulin glargine, and my limited experience, I predict that patients with type 1 diabetes who have difficulty with glycemic control will be helped by insulin glargine. I suspect that the passage of time and the accumulation of clinical experience will enable us to take full advantage of the pharmacodynamics of this product, alone and in combination with lispro insulin. Just as the use of lispro insulin (instead of regular insulin) for the therapy of type 1 diabetes is rapidly increasing in specialty clinics and offices, the use of glargine (in all probability) will be rapidly adopted in those practices. It is even within the realm of possibilities that the "poor man's pump" (multiple daily injection regimens using insulin pens) may prove to be as effective, less expensive, and more convenient than continuous subcutaneous insulin infusion with the use of insulin glargine. Data that suggest the benefit of glargine therapy in type 2 diabetes also exist in abstract form. Full publication of those results in combination with clinical experience may reveal the potential of insulin glargine as an insulin supplement in patients with moderate insulin deficiency and as a basal insulin replacement in patients with more complete insulin insufficiency. Many other potential uses of insulin glargine will also require specific study before they can be widely considered, such as its use in pregnancy and as a form of immunomodulatory therapy in the prevention of autoimmune diabetes.

The limitations of the insulin glargine data that have been developed through regulatory approval processes and that remain incompletely available in the peer review literature have wider implications for new drug development, marketing, and prescribing. Diabetes professionals are often called on to help in the design and execution of drug trials and in the dissemination of the data in promotional and continuing medical education presentations. It is increasingly critical for us to exert our colleagues in the pharmaceutical industry to both conduct appropriate trials and to publish the findings of those trials. The usefulness of every new product in each and every clinical situation for which it is marketed must be thoroughly scrutinized through trials and data analysis. My commentary is not specifically directed to the insulin glargine developers or to the members of the FDA who are involved in the drug approval process. The studies that are published in this issue and other studies that have been presented as abstracts are logical and practical. However, they represent only an initial step in documenting the safety and efficacy in treating the full panoply of patients with diabetes. In fact, the developers of glargine should be applauded for the availability of several full research reports in peer-review literature. These and other articles under editorial review will likely be published to coincide with the launch of insulin glargine. By contrast, it is an outrage that the data for a number of other products marketed for various indications in the therapy of diabetes are available only under Freedom of Information Act queries to the FDA. It is even more infuriating when claims are implied by data presented in promotional material, although there are neither available raw data nor plans to conduct the appropriate trials to fully investigate those claims.

Second, as a community of diabetes professionals, we need to help the pharmaceutical industry understand the limitations of their data, whether published or promotional. We need to suggest trials and/or gather clinical data in a systematic fashion to highlight the need for further study or to generate hypotheses. As an example, the reviewers of this manuscript have raised the issue of how the use of insulin glargine would compare with the use of human ultralente insulin. Given that there are both strong proponents and opponents of ultralente use, this topic appears to be deserving of exploration in, at least, limited trials. Also, we should remember that tremendous interindividual differences among drug responses exist. We should be careful to recognize that no approaches work optimally in all patients, regardless of the clinical trial data available. The usefulness of an approach that considers each patient interaction as an "n = 1" clinical trial cannot be underestimated.

Finally, as a community generally eager to adopt the use of newly released products for the therapy of diabetes, we need to be judicious in exploring the usefulness of all new technology. Careful individualized education should be part and parcel of each prescription for new products. We cannot underestimate how patients with diabetes, over the course of months and years, become finely attuned to their treatment regimens with purposeful and subconscious behaviors that vary from individual to individual. In addition, patients should be encouraged to contact their health care teams quickly if problems arise with new therapy. Not only can we provide assistance, but we may also learn from the experiences and observations of our patients. As a medical community equipped to understand and investigate adverse events, we need to report them promptly to both the pharmaceutical industry and to the FDA through the MedWatch program (on-line reporting avail-
available at http://www.fda.gov/medwatch/, by phone at 800-FDA-1088, and by fax at 800-FDA-0178). It is only through this process that we can ensure the safety of every new product and device. These principles are certainly relevant to insulin glargine. Particularly among patients with type 1 diabetes treated in specialty practice, there will appropriately be significant interest in using this product. Care must be taken to educate the patient to not mix glargine with other formulations of insulin (because the glargine will precipitate instantly) and to review both sick-day rules and the management of hypo- and hyperglycemia. It would be prudent to encourage more frequent monitoring, particularly at bedtime and midsleep, for at least a week after switching formulations. Obviously, the provision of specific guidelines for contacting the health care team if problems should ensue will be important in minimizing adverse events.

These are exciting times in diabetes treatment and research. Many of the pharmacological obstacles to ideal patient care are gradually being surmounted. The availability of a true basal insulin is certainly a long-awaited advance. Careful attention to experience in clinical use on our part, combined with the initiation of additional studies and the promise of their published results, will define how well we can use this new technology to benefit our patients.

JOHN BUSE, MD, PHD

From the Diabetes Care Center, University of North Carolina, Durham, North Carolina.

Address correspondence to John Buse, MD, PhD, University of North Carolina, Diabetes Care Center, 5316 Highgate Dr., Suite 125, Durham, NC 27713. E-mail: jbuse@med.unc.edu.

J.B. is a consultant for and has received honoraria and research support from Aventis Pharm and Eli Lilly and Co.

Acknowledgments — Thanks to Jennifer Camia Grant and Lyn Reynolds for extremely helpful editorial suggestions.

References