COMMENTARY

Smarter Modeling to Enable a Smarter Insulin

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> I dream things that never were, and I say "Why not?"
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> —George Bernard Shaw

Pancreatic β-cells secrete insulin to maintain physiological health. While the glucose level is the principle driver of insulin secretion, β-cells also respond to other regulatory inputs including circulating metabolites (most notably amino acids), regulatory hormones, gut peptides, and neurotransmitters. Insulin secretion increases when glucose levels are high, thereby increasing total body glucose utilization and suppressing endogenous glucose production. Of critical importance, insulin secretion is suppressed when glucose levels are low, which protects against life-threatening hypoglycemia.

There have been remarkable advances to enhance efficacy and safety of insulin therapy since the discovery of insulin 100 years ago. Insulin pharmacokinetics has been optimized through both formulation and modification of the peptide itself. Sophisticated mechanical devices can provide continuous insulin delivery and continuous glucose monitoring. Pancreatic islets can be transplanted, and bihormonal pumps more closely mimic normal physiology. Despite technological advances, most insulin-dependent patients do not achieve physiological glucose control. The risk of severe hypoglycemia is particularly troublesome because it limits the ability to safely achieve optimal glycemic control, which in turn makes it harder to protect against the long-term risk of microvascular complications (1,2). To underscore this point, half of the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) cohort experienced severe hypoglycemia (~40 episodes per 100 patient-years) (3). Furthermore, self-reported severe hypoglycemia is associated with 3.4-fold increased risk of death during a 5-year follow-up period (4).

The pursuit of a glucose-responsive insulin (GRI) therapy is an ambitious technical objective. In type 2 diabetes, incretin therapy enhances insulin secretion when glucose levels are high but does not cause hypoglycemia because it does not promote insulin secretion when glucose levels are low. Similarly, GRI technology aims to mimic the ability of β-cells to respond differentially to high versus low glucose. At least three approaches have been attempted, broadly including the following:

- Insulin formulations with glucose-responsive release properties, either in the form of subcutaneous microemulsion or a defined nanoparticle (5,6)
- Glucose-regulated insulin clearance (7,8)
- An insulin with intrinsic activity that is glucose responsive (9)

At least one GRI (MK-2640) advanced into clinical studies but failed to achieve clinical proof of concept despite having achieved improved therapeutic index in small and large animal models (10,11). Thus, from a drug discovery perspective, there is an important unmet research need to improve the predictive value of experimental results obtained in preclinical animal models. In this issue of *Diabetes*, Yang et al. (12) address this unmet need by providing a mathematical model (Pharmacokinetic Algorithm Mapping GRI Efficacies in Rodents and Humans [PAMERAH]) to predict whether a GRI can provide a favorable outcome in clinical studies based upon preclinical observations in mice and rats. Their compartmental model describes the complex set of integrated interactions that control plasma glucose. The mathematical details may prove daunting to most readers of *Diabetes* (including the authors of this Commentary), but the insights are nonetheless potentially important. Most importantly, the model is testable. Furthermore, data obtained in pursuit of an optimized GRI will permit further refinement of mathematical models. Similar mathematical models integrating pharmacokinetics (PK) and pharmacodynamics (PD) are often applied in drug discovery projects, but the extensive literature about insulin PK/PD contributed to the ability to construct the high-quality PAMERAH model. Of particular note, Yang et al. (12) suggest that a universal signature of glucose responsiveness is the ability of GRI

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therapy to enhance hepatic glucose uptake in hyperglycemia more than an equivalent concentration of a non-GRI treatment. This is consistent with the hypothesis that an insulin preferentially active at the liver might diminish hypoglycemia risk (13). Nevertheless, an optimized GRI would need to achieve the optimal balance among all the pharmacodynamic actions of insulin.

GRI technology can transform insulin therapy, but the model underscores the challenge in its design and the inability to directly translate rodent pharmacology to humans. Here are some of the principal challenges that must be successfully addressed.

- *Chemistry: set point and kinetics*. Daily glucose concentrations vary between ~95–150 mg/dL (5.3–8.3 mmol/L) in healthy volunteers; insulin levels range between ~10–50 μU/mL (1.7–8.3 pmol/L) (14). Higher insulin levels (i.e., >50 μU/mL; >8.3 pmol/L) are often required to manage hyperglycemia in patients with diabetes. Insulin levels are suppressed to <5 μU/mL (<0.8 pmol/L) during hypoglycemia (15). In other words, circulating insulin bioactivity varies tenfold to prevent excessive glucose elevation on one end while avoiding hypoglycemia at the other end. A GRI must be near-maximally suppressed when plasma glucose levels are ≤50 mg/dL (≤2.8 mmol/L) while having at least tenfold higher bioactivity when plasma glucose levels are ≥150 mg/dL (8.3 mmol/L). Thus, a threefold decrease in plasma glucose concentration must drive a greater than tenfold decrease in insulin bioactivity. By way of contrast, for enzymes following Michaelis–Menten kinetics, the rates of chemical reactions typically change less than threefold in response to a threefold change in substrate concentration. Consequently, it may be extremely challenging to achieve the necessary greater-than-proportional change in insulin bioactivity in response to glucose levels. Just as the pancreatic β-cell responds rapidly to changes in glucose concentration, the biological activity of a GRI must change on a similarly rapid timescale.
- *Biology: inter- and intrapatient variation*. Certain GRI designs rely on endogenous biological processes. For example, MK-2640 acquired glucose responsivity by virtue of being cleared by the lectin mannose receptor C-type 1 (MRC1) (7,8,10,11). This molecular mechanism has the potential to be altered by interindividual variation in MRC1 expression levels and inherent activity. If an individual patient displayed enhanced MRC1-mediated clearance, this might accelerate the rate of GRI clearance, thereby compromising glucose-lowering efficacy. A very low level of MRC1 expression could diminish, or even abolish, glucose responsiveness. Other GRI technologies use glucose-regulated insulin release from otherwise quiescent drug depots. Differences in administration technique and adiposity at site of injection have the potential to introduce a high degree of both interday and interindividual variation in the dynamic response of this class of GRI. Furthermore, physical exercise may alter blood flow and glucose metabolism, thereby indirectly potentially altering GRI performance. It may be challenging to model all these complexities in a simple experimental protocol (e.g., a euglycemic insulin clamp).
- *Compatibility with current technology*. Advances in biomedical devices—including continuous glucose monitoring and glucagon as a buffering agent against excessively low glucose concentration—are beginning to replicate endogenous pancreatic regulation of insulin secretion in response to ambient glucose levels (16,17). To the extent that these advances succeed at minimizing the risk of hypoglycemia, they have potential to decrease the need for a GRI. Nevertheless, a GRI technology that uses a mechanism compatible with closed-loop technologies might prove doubly valuable relative to those that are incompatible. Indeed, it is possible that a GRI could be optimized to function in the context of a closed-loop system, further refining the ability to provide an optimal combination of efficacy and safety. Of course, to the extent that the pharmacokinetics and pharmacodynamics of a GRI would differ from human insulin, this would necessitate changes in algorithms underlying a closed-loop insulin delivery system.
- *Cost considerations*. List prices of insulin have increased rapidly in the U.S. in recent years (18), which has created a public health crisis for affordable access, especially for uninsured patients. Although space does not permit a thorough discussion of challenges to achieve the right balance between medical economics and technological innovation, these two perspectives are inextricably intertwined. In any case, the current politically charged environment complicates the challenges to attract the investments required to support the high risk/high reward research required to develop a GRI.

MK-2640 provides a case study illustrating uncertainties about whether rodent pharmacology studies will predict clinical efficacy in humans. The mathematical model of Yang et al. (12) holds promise to eventually facilitate design and selection of molecules with improved probability of achieving clinical proof of concept. The same mathematical model can be used for all species, albeit the model's parameters must be estimated by empirical data obtained in each species. Such models also hold promise to define a role for large animal models such as minipigs, despite their increased expense and lower throughput. Ultimately, clinical data will be required to validate any drug candidate and to refine the predictive value of the proposed mathematical model (12). This mathematical model comes at a time of increased interest in mathematical modeling and other in silico approaches to increase the eventual likelihood of success by better targeting investment of time and money in support of research and development.

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