Too Much or Too Little? The Double Jeopardy of Subcutaneous Insulin Therapy in Diabetes

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A quote variously attributed to either Woodrow Wilson or Winston Churchill describes golf as “an ineffectual attempt to put an elusive ball into an obscure hole with implements ill-adapted to the purpose.” There are many analogies with the challenges faced with insulin therapy in diabetes. In health, nondiabetic β-cells detect changes in ambient glucose, facilitated by signals from circulating hormones such as glucagon-like peptide 1 and perhaps neural signals (1), allowing insulin secretion to be altered appropriately. Critically, insulin is then released in an oscillatory fashion into the portal circulation so that the levels in the portal vein are approximately fourfold higher than those seen in systemic circulation (2).

With exogenous insulin therapy in diabetes, this situation is fundamentally different. In addition to the significant clinical challenges of determining regimen and appropriate insulin doses and timing while allowing for factors such as pharmacokinetics and variability in absorption, exogenous insulin is delivered subcutaneously so that the usual ratio of portal-to-systemic insulin is lost. This means that the direct actions of insulin to suppress net hepatic glycemic output might be lessened and/or the peripheral actions of insulin to promote glucose disposal, particularly in skeletal muscle, might be increased. What are the implications of this for insulin therapy in diabetes, i.e., does this matter for patients and clinicians?

In this issue of Diabetes, Gregory et al. (3) compared the differential effects of systemic and portal insulin delivery during hypoglycemia. To do this, they used an elegant model, studying healthy dogs with a number of surgically implanted intravascular catheters that allowed for the delivery of an identical insulin infusion selectively either into the portal vein (Po) or systemically (Pe). Insulin was infused at a rate four times higher than basal requirements, an amount sufficient to raise circulating insulin and create a gradual fall in blood glucose in both Pe and Po studies. Their intricate experimental setup, including hepatic and portal vein sampling combined with tracers and ultrasonic flow probes, also allowed them to measure hepatic and whole-body glucose turnover.

As expected, Pe insulin resulted in a greater proportional rise in peripheral insulin levels, which rose sixfold as opposed to a twofold increase in portal insulin levels. In contrast, Po infusion of an identical rate of insulin maintained the portal-to-peripheral ratio with both rising around fourfold. The effects of the differing routes of insulin infusion on glucose levels were striking. Plasma glucose fell faster with Pe than with Po delivery, reaching a level of 56 mg/dL compared with 70 mg/dL after 60 min, respectively. The mechanism for this faster fall in blood glucose with Pe became apparent when glucose turnover was examined. Blood glucose is in a state of perpetual dynamic flux, and when levels are stable, glucose production (mostly hepatic) is balanced by glucose removal from blood. In the study, both routes of insulin delivery reduced glucose production and increased disappearance, thus leading to a fall in blood glucose, but the relative potencies were different. Under these experimental conditions, the effect of Pe insulin to increase glucose disappearance exceeded the effects of Po insulin to reduce glucose production.

Counterregulatory hormonal responses to falling blood glucose were mounted as predicted by the prevailing blood glucose. Therefore, the differential effects of the route of insulin delivery in this study were not mediated by a change in counterregulatory neurohumoral defenses. A second series of studies used a similar experimental design but with the addition of somatostatin and glucagon infusions to prevent the hypoglycemia-induced glucagon rise, simulating the situation in type 1 diabetes and perhaps late insulinopenic type 2 diabetes where the glucagon response to hypoglycemia is lost (4). The message however was broadly similar to the first protocol but with glucose levels falling more profoundly with the loss of glucagon defenses.
increasing risk of hypoglycemia.

ripheral glucose uptake, primarily in the skeletal muscle, predominate output. With higher insulin dosing into periphery, the effects on peripheral insulinization of the liver at basal rates with increased hepatic glucose cutaneously) as opposed to normal portal release results in undershoots (5). These are some important considerations though when extrapolating the findings to humans, apart from possible species differences. The animals examined in the current study were nondiabetic and healthy with normal insulin resistance. In diabetes, it is possible that muscle insulin resistance might be more resistant to the effects of peripheral delivery (6).

At face value, a clinician’s reaction might be to assume that if systemic insulin is more potent at lowering blood glucose, then patients would simply adjust insulin dosing accordingly. The sting in the tail however is shown by a previous study from the same group using their catheterized dog model (7) to compare portal and peripheral insulin infusions at basal levels. Strikingly, the differential effects of portal and peripheral insulin delivery were the opposite of those reported in the study by Gregory et al. (3), with the main effect of switching insulin from portal to peripheral being on the liver with a twofold increase in hepatic glucose production.

Taken together, these studies suggest that insulin-treated patients face a double jeopardy. At euglycemia, basal insulin therapy delivered systemically may be insufficient to suppress hepatic glucose production so that patients may have to systematically “over-replace” insulin therapeutically to keep glucose production in check. Getting it wrong though, with higher insulin levels and the effects of the skeletal muscle “glucose sink,” means that blood glucose falls more rapidly with peripheral insulin delivery than it might with portal insulin delivery (Fig. 1).

Armed with this knowledge, is there anything that clinicians should do differently? A number of “hepatic-selective” insulin analogs are being developed and may offer a more physiological therapy (8,9). Intraperitoneal insulin delivery partly reaches the portal circulation before the peripheral circulation. Small numbers of patients have had intraperitoneal insulin pumps implanted. Currently in Europe and Australia, a surgically implanted peritoneal port might offer an alternative method for intraperitoneal insulin delivery by an external pump in selected small numbers of patients (10). In the meantime, the only clinical solution is to continue to try and use the currently available implements—insulin analogs where appropriate, glucose monitoring, technology, and patient education—to match insulin to requirements as best as possible.

The canine models used by Gregory et al. (3) have some obvious advantages over rodent models that are usually used more in this type of preclinical research. A major advantage is the ability to implant multiple intravascular catheters to allow detailed measures of glucose turnover. Another important distinction is that hepatic glucose output corrected for body weight in rodents is markedly higher than in larger animals so that dogs more closely resemble human metabolism (5). These are some important considerations though when extrapolating the findings to humans, apart from possible species differences. The animals examined in the current study were nondiabetic and healthy with normal insulin resistance. In diabetes, it is possible that muscle insulin resistance might be more resistant to the effects of peripheral delivery (6).

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