

Review

The Physiological Rationale for Oral Insulin Administration

EHUD ARBIT, M.D., F.A.C.S.

ABSTRACT

Insulin remains the most effective and durable drug in the armamentarium for the treatment of advanced-stage diabetes. Nevertheless, clinical studies have shown that even on insulin treatment, a significant percentage of patients fail to attain lasting glycemic control. Well-recognized reasons for this failure include issues related to patients' noncompliance with an injectable drug and the late stage at which insulin is prescribed, but less explicit reasons related to the nonphysiological way insulin is currently administered are equally important. Parenteral insulin targets peripheral tissue rather than the liver with pharmacokinetics that do not replicate the normal dynamics of endogenous insulin release. Oral insulin is one of several alternative methods of insulin administration that are in clinical stages of development. The oral route of insulin delivery takes advantage of the portal-hepatic route of absorption. A review of relevant physiology is herewith provided.

INTRODUCTION

INSULIN WAS INTRODUCED into clinical practice more than 80 years ago, with its intended goal being the attainment of near-normal glucose concentrations for a sustained period of time. But that objective has remained elusive, as several articles in the literature have recently revealed.

In the UKPDS 49 study, only 28% of patients achieved a hemoglobin A_{1c} (HbA_{1c}) below 7% after 9 years of insulin therapy.¹ In the NHANES III survey study, which included national samples of non-Hispanic whites, non-Hispanic blacks, and Mexican Americans over the age of 20 years, 52% of patients on injected insulin had an HbA_{1c} of >8%.² Hayward et al.³

examined the insulin therapy protocols prescribed by general practice physicians at a large staff-model health maintenance organization. In 1,738 patients with type 2 diabetes, the mean decrease in HbA_{1c} value was 0.9 percentage points, and 60% of them had an HbA_{1c} value that exceeded 8.0% after 2 years of therapy. In a parallel cohort, 43% of patients taking sulfonylureas had an HbA_{1c} value exceeding 8.0%.

It should be pointed out that this poor glycemic control is not due to the inadequacy of insulin *per se*, but rather, and in part, due to the late stage of the disease at which it is traditionally started. With the disease so far advanced, it is a challenging task to attain and maintain normoglycemia with injectable insulin.

Nonetheless, insulin remains the ultimate agent for supplementing insulin deficiency, and is the sole agent for replacement therapy once endogenous insulin secretion ceases. Among the drugs available for the treatment of diabetes, it has several distinct advantages. Besides being an endogenous natural hormone, insulin given in sufficient quantities can overcome any degree of insulin resistance, and as such has no known upper dose limit. This implies that, barring hypoglycemia (which is simultaneously the intention of the drug and its most serious adverse effect), insulin can be given in amounts predicated entirely on the requirement of reaching euglycemia. Although it is possible to achieve excellent glycemic control with intensive insulin therapy,^{4,5} the results in general have been highly variable, depending mainly on the regimen employed and the aggressiveness with which it was pursued.

Why then is insulin therapy only partially effective, and how can it be improved? There are a number of deficiencies in the way insulin is currently utilized. In general, it is administered in a nonphysiological way, to the wrong target, with pharmacodynamics that do not replicate the normal dynamics of its endogenous release. Furthermore, insulin is traditionally prescribed as a last resort, usually after the failure of oral antidiabetic agents.⁶

THE ULTIMATE TARGET, THE LIVER

The release of insulin from a subcutaneous injection site is analogous to systemic administration, targeting principally the extrahepatic insulin-dependent tissues: muscle and, to a lesser extent, kidney. For muscle in a healthy individual to metabolize glucose maximally, i.e., to dispose of ~ 400 mg/m²/min, it has been found that ~ 200 – 300 μ U/mL of insulin is required.^{7,8} In a patient with diabetes given the same amount of insulin, muscle disposes of less than two-thirds as much glucose (270 mg/m²/min). Even at higher concentrations of insulin, the disposal of glucose is unlikely to increase much further than 290 mg/m²/min, for the insulin effect has reached a plateau, presumably because of the prevailing insulin resistance in muscle.

The liver, on the other hand, is exquisitely sensitive to insulin.⁹ Within a few minutes, hepatic glucose output is effectively shut off by a portal insulin concentration of 50 μ U/mL in a healthy individual, and by ~ 100 μ U/mL in a patient with diabetes.^{7–9}

Moreover, muscle response to insulin has a delayed onset of action (a lag time of >30 min), and once functioning, it has a sustained duration of action.⁹ In contrast, the liver, because of its acute sensitivity to insulin, responds quickly and for only a short time.¹⁰ This rapid “on–off” switch provides the liver with a degree of flexibility that is highly advantageous in controlling such metabolic processes as postprandial glucose variations. The delayed onset and the sustained effect of glucose disposal by muscle are presumably the culprit in the insulin-related hypoglycemic episodes particularly prevalent in type 1 diabetes mellitus, where glycogen storage reserves are impaired.¹¹

The implication here is that no matter how high the concentration of peripheral insulin is in a patient with diabetes, muscle cannot dispose of more glucose. At physiologic systemic insulin concentrations (those that do not place such a patient in jeopardy of severe hypoglycemia), muscle is fairly inefficient at metabolizing glucose. In patients with diabetes, however, hepatic resistance to insulin can be readily overcome by using a portal insulin concentration of ~ 100 μ U/mL, which can be safely attained. Furthermore, from a practical, clinical standpoint it would appear obvious that targeting an organ (liver) that has a rapid “on–off” switching mechanism is more advantageous than targeting one (muscle) having a delayed onset of action and sustained function.

Traditionally, skeletal muscle was thought to be the major site of insulin resistance, and impaired glucose uptake in muscle was considered the culprit in diabetic hyperglycemia. This concept has been challenged, however, and there are compelling arguments to implicate insulin resistance in the liver as more important for glycemic control.^{12–14} In the postabsorptive state, the majority of glucose uptake occurs in insulin-independent tissue, e.g., the central nervous system.¹⁵ Muscle, on the other hand, accounts for only 20–25% of glucose disposal, and probably half of that is simply the result of

mass action by glucose (systemic insulin levels are low in this state).

It thus appears that glucose release from the liver, which in the postabsorptive state is responsible for 75–85% of the postabsorptive glycemia, rather than glucose uptake in the muscles, is more apt to be affected by changes in insulin sensitivity or availability. Unrestrained and abnormally increased rates of hepatic glucose release are observed in patients with type 2 diabetes.^{16,17} Thus, in an absolute sense, the liver is a more important site of insulin resistance in the postabsorptive state than is skeletal muscle. The same applies to glucose uptake in the postprandial state, in which roughly 40% of ingested glucose is immediately extracted by splanchnic tissue (the liver). Of the remaining 70%, a further 15% is sequestered by splanchnic tissue; 30% is taken up by skeletal muscle; the central nervous system, adipose tissue, blood cells, and the kidneys account for the remainder.¹⁸ Thus in terms of glucose disposal the liver is responsible for a larger proportion than muscle.

In the postprandial state, furthermore, glucose output suppression from the liver also plays a major role in glucose homeostasis. In normal individuals, postprandial suppression of endogenous glucose output from the liver is as high as 60–80%.¹⁹ In patients with impaired glucose tolerance and diabetes, this suppression is inadequate, a failure that is considered the primary cause of excessive increases in plasma glucose concentrations.²⁰ Studies have found that in normal subjects, the inhibition of early-phase insulin release during glucose infusion reduces the suppression of hepatic glucose output by nearly 50%, without affecting glucose disposal in muscle.²¹ It has also been demonstrated that in patients with diabetes, restoration of the early insulin response by intravenous administration of supplemental insulin following a meal results in reduced postprandial hyperglycemia and prevents delayed hyperinsulinemia.²²

Thus, balancing all the elements of hepatic glucose uptake versus muscle disposal and the suppression of glucose release from the liver, it becomes apparent that the liver is the principal player in glucose homeostasis, and should logically be the prime target for intervention.

THE IMPORTANCE OF INSULIN-RELEASE PHARMACOKINETICS

The pharmacokinetics of insulin release has dual importance in glucose homeostasis, and also has clinical implications. On one hand, perturbation of the normal dynamic pattern of insulin release in patients with prediabetes and diabetes has important metabolic consequences, even though it does not alter the amount of insulin released over time. It is the pharmacokinetic mismatch between plasma insulin and glucose concentrations that is responsible for clinical hypoglycemic episodes, as well as for the superfluous and lingering peripheral hyperinsulinemia.

An early and invariable sign of β -cell dysfunction is loss of the normal dynamic pattern of insulin secretion, specifically loss or attenuation of the early or first-phase response. It is widely believed that attenuation of first-phase insulin release is the earliest detectable defect of β -cell function in those destined to develop type 2 diabetes.^{23,24} It has also been suggested that this dynamic defect in insulin secretion actually plays a pathogenic role at each stage of impaired glucose regulation,²⁵ that it is independent of insulin resistance, and that it is a predictor of the progression from normal to impaired glucose tolerance and thence to diabetes.²⁶ Several studies have demonstrated the importance of β -cell dysfunction and the loss of early-phase response, restoration of which is absolutely necessary to the control of normal glucose homeostasis.

In patients with diabetes, iatrogenic restoration of the early insulin response by intravenous administration of supplemental insulin in response to a meal results in reduced postprandial hyperglycemia and prevents delayed hyperinsulinemia.²⁷ The timing and magnitude of the first-phase insulin response are critical for receptor-mediated insulin action and glucose tolerance, so that small decreases in this early response can have dramatic effects on later glucose excursion. For an individual to remain glucose tolerant, the early-phase insulin secretion must be sufficient to match any increase in insulin resistance.²³ Consequently, a normally functioning β -cell that secretes in-

sulin in a normal dynamic pattern can protect against diabetes even in the face of increasing insulin resistance. Although insulin resistance can unmask a coexisting β -cell defect, it is compromised β -cell function that is obligatory for the development of type 2 diabetes.

THE POTENTIAL FOR REDUCTION IN THE RISK OF HYPOGLYCEMIA

Oral insulin, by virtue of its rapid absorption and elimination, has the theoretical potential to replicate the dynamic pattern of early-phase insulin secretion with its significant metabolic consequences, but without exerting further demands on the already compromised β cell. Furthermore, insulin delivery directly into the portal circulation (which is the physiologic way) is likely to reduce the risk of hypoglycemia despite the benefit of a significant postprandial glucose reduction. This is because insulin regulates hepatic glucose output in a direct fashion and does so within minutes, because of the exquisite insulin sensitivity of the liver.

In contrast, nonhepatic tissues are much less sensitive to insulin and respond slowly, because of the necessity that insulin first be delivered peripherally, then cross the endothelial barrier and muscle membrane, and finally phosphorylate the glucose.²⁸ As a result, early-phase insulin, or oral insulin that mimics its release, is apt to affect primarily the liver. Thus it is unlikely to make any significant alteration in peripheral glucose disposal, which is more likely to result in hypoglycemia.

The suggestion that portal insulin delivery may be associated with a reduced risk of hypoglycemia has been advanced by several randomized and nonrandomized studies conducted in the early 1990s. They compared the results of insulin infusion into the subcutaneous space and into the intraperitoneal cavity^{29–31} (~50% of intraperitoneal substrates are absorbed via the portal circulation³²). In addition to these reports, a long-term (4-month) study was done of direct intraportal insulin infusion through an umbilical vein.²⁶ The goal in each case was to determine the optimal site for insulin deposition by pump. In terms of glycemic control, results were either equally good or

superior in patients treated with intraperitoneal or direct intraportal insulin infusion. Similar results in terms of glycemic control and reduced incidence of hypoglycemia were observed in studies of patients with diabetes on peritoneal dialysis when the insulin was administered along with the peritoneal dialysate.^{33,34}

Most notable in all these studies was the fact that intraperitoneal or intraportal insulin infusion was associated with fewer blood glucose excursions and significantly fewer episodes of severe hypoglycemia, as compared with subcutaneous insulin treatment of patients with insulin-dependent diabetes mellitus, in spite of similar or even superior glycemic control. The decrease in hypoglycemic episodes has been ascribed to a less negative glucose balance (glucose production vs. glucose utilization), and to a treatment-induced improvement in glucagon response.^{35,36}

If portal (physiologic) insulin delivery is potentially protective against hypoglycemia, then we must determine why the insulin secretagogues, which enhance endogenous insulin release into the portal circulation, are still associated with a risk of hypoglycemia.

In general, the secretagogue sulfonylureas can be ranked in order by their decreasing risk of causing hypoglycemia, a ranking based on their half-lives. The longer its half-life, the more likely it is that an agent will induce hypoglycemia. The first-generation sulfonylureas (tolbutamide and tolazamide) have half-lives of 4–7 h. The second-generation agents are more potent than the first, but their risk of causing hypoglycemia is substantially reduced because of their shorter half-lives.

The newer nonsulfonylurea insulin secretagogues (the meglitinide derivatives repaglinide and nateglinide) are associated with a further reduction in hypoglycemic episodes.³⁷ Repaglinide, a benzoic acid derivative of meglitinide, has a short half-life (roughly 90 min), and is undetectable in the circulation 4 h after infusion. The risk of hypoglycemia is mitigated even if the patient misses a meal, which is a problem with the more commonly used sulfonylureas. Pooled data from early clinical studies have shown the risk of severe hypoglycemia with repaglinide to be less than half that associated with traditional sulfonylureas.³⁸

The *d*-phenylalanine derivative nateglinide, with its rapid association/dissociation kinetics, elicits a twofold reduction in overall insulin exposure and a 45% reduction in incremental glucose area under the curve, compared with glibenclamide.³⁹ Despite this significant reduction in glucose seen with nateglinide, hypoglycemia is rare. Incidentally, similar observations have been made with insulin. Regular insulin has a duration of action lasting between 4 and 6 h, which often results in delayed hyperinsulinemia and hypoglycemia prior to the next meal. The newer insulin analogues have a more rapid onset of action (40–50 min after injection vs. 60–90 min for regular insulin) and a shorter duration of action (3–4 h). They provide at least similar glycemic control compared with regular insulin, and carry less risk of hypoglycemia.^{40,41} It would appear that the short duration of systemic exposure to insulin (mainly muscle exposure) and the decremental insulin area under the curve are central for the avoidance of hypoglycemia.

An important corollary can be gleaned from the condition of persistent hyperinsulinemic hypoglycemia, whereby continuous low levels of insulin (hyperinsulinism) are released chronically, resulting in severe hypoglycemia. This rare condition is the most common cause of persistent hypoglycemia in infants and children, as well as adults.^{42,43} In infants and children persistent hyperinsulinism is caused by a congenital disorder of focal or diffuse hyperplasia (nesidioblastosis), and in adults it is most commonly a result of an acquired islet adenoma. Early nomenclature such as “persistent hyperinsulinemic hypoglycemia of infancy” was superseded by “persistent hyperinsulinism” to denote the fact that the pathophysiology was one of insulin dysregulation related to inadequate suppression of insulin release at low plasma concentrations of glucose rather than hyperinsulinemia *per se*, as insulin levels are rarely dramatically elevated in this condition.^{44,45} Hypoglycemia thus results from a persistent and chronic low-level and dysregulated insulin release, producing a diminished output of glucose by the liver, inadequate conservation of glucose, enhanced entry of glucose into cells, and suppression of lipolysis and ketogenesis (which requires only a slight increase in

insulin), thereby decreasing the availability of alternative fuels.

EARLY VERSUS LATE START FOR INSULIN THERAPY

Insulin therapy has generally been relegated to last on the list, presumably because of the necessary injections. The traditional approach has been a progressive and stepwise introduction of diet and exercise, followed by oral antidiabetic agents, and only when these failed was insulin finally resorted to. Additionally, this stepwise strategy was usually applied at a slow pace, with long intervals between steps. By the time patients with type 2 diabetes were prescribed insulin, they had typically had the disease for more than 10–15 years, with well-established complications.⁶

Fortunately, there is a growing consensus among clinicians that the gradual approach may be the wrong one, and that earlier, more aggressive intervention may not only prevent complications, but could actually modify the inexorable course of the disease.^{46–48} There seems to be a window of opportunity early in the course of diabetes during which at least some β -cell dysfunction is still reversible, and insulin secretion can be restored. (Even in advanced diabetes, several studies have shown that actual remissions, which are characterized by normoglycemia and the absence of the need for hypoglycemic medications, can be achieved with intensive insulin therapy.^{49–52}) Much of the improvement in β -cell function is attributed to better metabolic control and specifically to the reprieve from glucotoxicity. However, there is also growing speculation that the improvement may be due to decreased demand on the β cell (“ β -cell sparing”). Reduction of that demand is achieved either by decreasing insulin resistance, or by supplementing insulin with an exogenous supply.

Oral insulin may well be the ultimate route of supplementing insulin requirements without the need for parenteral therapy. However, insulin is not absorbed to any extent through the gastrointestinal tract, presumably because of its molecular size and susceptibility to enzymatic degradation.

Two companies, Nobex Corp and Emisphere Technologies, Inc., are currently in clinical studies with their oral insulin products—insulin absorbed through the gastrointestinal tract and into the portal-hepatic circulation. Nobex Corp. technology relies on a modified insulin-hexyl-insulin monoconjugate 2 (HIM2), in which a single amphiphilic oligomer is covalently linked to the free amino group on the Lys- β 29 residue of recombinant human insulin via an amide bond.⁵³ Compared with non-modified insulin, HIM2 has changes introduced in physiochemical characteristics of the insulin that withstand enzymatic degradation in the stomach and facilitate absorption.

Emisphere Technologies, Inc. uses unmodified insulin linked to carrier molecules, which are small hydrophobic polyorganic compounds (200–400 Da). The carrier molecules bind noncovalently to polypeptides to induce reversible conformational changes to a more transportable/lipophilic complex that enables the drug to cross the intestinal epithelium and be absorbed. The interactions between drug and carrier are reversible; thus, carrier and drug dissociate readily upon absorption in the bloodstream by simple dilution. The transport is transcellular, and no perturbations are caused to the cellular tight junctions. Unlike penetration enhancers and surfactants the carrier molecules do not cause morphological changes to the cellular or nuclear membranes.

A third company, Genex Biotechnology, is in clinical trials with Oraline[®], an insulin formulation that is delivered directly into the mouth via a metered-dose spray (RapidMist[®] device). The insulin from the spray is absorbed systemically through the buccal mucosa and thus circumvents the portal-hepatic route of insulin absorption. There is much optimism in the scientific community about the success of the two orally absorbed insulin products and great expectations abound among patients and clinicians alike. However, these sentiments must be contained until the products have been formulated optimally into elegant and practical dosage forms and have been deemed safe in long-term toxicology studies.

Insulin may confer further advantage over insulin secretagogues as there are indications that by increasing the exigency of the β cells,

these latter drugs are deleterious to β cells and accelerate their demise.^{49,54} Because oral insulin has a relatively short duration of action at this point, it is not anticipated that it can be a substitute for basal insulin. However, it is believed by many that oral insulin could serve as a preprandial formulation, as a bedtime compound, or that it could be combined with an insulin sensitizer or a drug that decreases insulin resistance, e.g., metformin or a thiazolidinedione.

CONCLUSIONS

Insulin, despite being the most potent and durable hypoglycemic agent in the antidiabetic armamentarium, is failing to achieve lasting glycemic control in most patients. This is because it is administered in a nonphysiological way, to the wrong target, with unsuitable pharmacodynamics, and is generally prescribed too late in the course of the disease. Oral insulin, by virtue of its rapid absorption and elimination, replicates the dynamic pattern of early-phase insulin secretion, but without placing further demands on the already compromised β cell. Oral administration has the potential of replacing preprandial insulin requirements and, depending on endogenous insulin reserves, can serve as a supplement to basal insulin. The principal barriers to the wider use of insulin, at least in the early stages of the disease, have been related to perception and the inconvenience of a drug that must be injected, as well as the apprehension of hypoglycemia. These barriers will almost certainly cease to be a problem once an oral insulin product is available.

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Address reprint requests to:

Ehud Arbit, M.D.

Vice President, Medical Research

Emisphere Technologies, Inc.

765 Old Saw Mill River Road

Tarrytown, NY 10591

E-mail: earbit@emisphere.com