Clinical Pharmacology of Incretin Therapies for Type 2 Diabetes Mellitus: Implications for Treatment

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ABSTRACT

Background: Increased understanding of the role of incretin hormones in maintaining glucose homeostasis has enabled the development of pharmacotherapies that target deficient incretin activity in type 2 diabetes mellitus (T2DM). Incretin therapies are premised on 1 of 2 approaches: (1) augmenting the activity of the hormone glucagon-like peptide (GLP)-1 (GLP-1 receptor agonists) and (2) inhibiting the degradation of GLP-1 by dipeptidyl peptidase (DPP)-4 (DPP-4 inhibitors).

Objective: This review discusses the pharmacokinetic properties and clinical profiles of the GLP-1 receptor agonists (exenatide twice daily, liraglutide once daily, exenatide once weekly, taspoglutide, and albiglutide) and the DPP-4 inhibitors (sitagliptin, saxagliptin, vildagliptin, and alogliptin) available for use or in late-stage development.

Methods: A search of PubMed for literature published between 2000 and mid-2010 was conducted using the names of each agent as key words. Phase III and IV studies were included in the review of efficacy and tolerability. Supplemental searches of abstracts from major diabetes conferences provided additional information on pharmacokinetic properties. Searches of all reference lists were performed to identify additional references of interest.

Results: The PubMed search identified multiple randomized, controlled clinical studies of the GLP-1 receptor agonists and the DPP-4 inhibitors administered as monotherapy or in combination regimens. Reductions from baseline in glycosylated hemoglobin ranged from 0.4% to 1.5% with exenatide 5 to 10 μg/d (7 studies), 0.6% to 1.5% with liraglutide 0.6 to 1.8 mg/d (6 studies), 0.3% to 1.0% with sitagliptin 25 to 200 mg/d (9 studies), 0.5% to 0.9% with saxagliptin 2.5 to 10 mg/d (3 studies), 0.4% to 1.0% with vildagliptin 50 to 100 mg/d (6 studies), and 0.4% to 0.8% with alogliptin 12.5 to 25 mg/d (4 studies). Dosage adjustments and caution in prescribing incretin therapies are recommended in patients with renal disease, with those recommendations varying based on the agent and the degree of dysfunction. Incretin therapies have been associated with few interactions with commonly used antihyperglycemic and cardiovascular therapies.

Conclusion: Based on the pharmacokinetic and therapeutic characteristics described in previously published Phase III and IV studies of incretin therapies, these agents may provide an option for the management of T2DM. (*Clin Ther*. 2011;33:528–576)

Key words: alogliptin, DPP-4 inhibitors, exenatide, GLP-1 receptor agonists, incretin therapies, liraglutide, saxagliptin, sitagliptin, type 2 diabetes, vildagliptin.

INTRODUCTION

Our knowledge of the hormonal regulation of glucose metabolism has advanced beyond awareness of the activities of insulin and glucagon. Incretin hormones are understood to have a key role in the maintenance of glucose homeostasis. The known incretins—glucagon-like peptide (GLP)-1 and glucose-dependent insulinotropic polypeptide (GIP)—are secreted from endocrine cells of the intestinal mucosa in response to food ingestion[1] and have glucoregulatory effects by multiple pathways. In clinical research, for example, the incretins have been reported to stimulate the secretion of insulin by pancreatic β cells. This effect was considered glucose dependent, with the stimulatory effect increasing with blood glucose concentration.[2] Another such mechanism is the suppression of glucagon secretion by pancreatic α cells. Under normal physiologic conditions, glucagon has been reported to stimulate hepatic glucose production as a counterregulatory response to hypoglycemia.[3] GLP-1 has been found to inhibit glucagon release in the presence of elevated blood glucose concentrations, when hepatic glucose production is

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not needed.[4] GLP-1 also has been reported to slow the rate of gastric emptying after meals, thereby decelerating the absorption of food and the appearance glucose in the blood.[5] The administration of GLP-1 has been associated with reduced appetite and increased satiety in humans.[6] Studies in animals have reported that GLP-1 signals brain regions that regulate satiety, possibly by activity on GLP-1 receptors within the central[7] and peripheral nervous systems.[8,9]

Incretin hormones have been reported to contribute indirectly to glucose regulation by promoting the health and function of β cells. Data from in vitro studies support an antiapoptotic effect of GIP and GLP-1 on β cells,[10,11] and in studies in Wistar rats, GLP-1 was associated with increases in β-cell neogenesis.[12] In humans, GLP-1 also has been reported to increase responsiveness of β cells to glucose.[13]

The duration of physiologic activity of the incretins is short. After their release, GLP-1 and GIP are rapidly metabolized in the circulation by the enzyme dipeptidyl peptidase (DPP)-4. Radiolabeled GLP-1 and GIP were reported to have circulating $t_{1/2}$ values of <2 minutes in rats.[14] Studies in humans have reported plasma $t_{1/2}$ values of 1 to 2 minutes for GLP-1 and 7 minutes for GIP.[15,16] After the cleavage of active GLP-1 or GIP by DPP-4, the inactive metabolites of both hormones have been found to be eliminated primarily by renal excretion.[17]

The contribution of the incretin system to maintaining glucose homeostasis has been found to be impaired in patients with type 2 diabetes mellitus (T2DM). The insulinotropic activity of GIP is lost, and that of GLP-1 is partially, but not entirely, attenuated.[18,19] The administration of exogenous GLP-1 in patients with T2DM has been associated with near-normal glycemia, whereas GIP has been reported to have little clinical effect.[20,21] Given that the insulinotropic effect of GIP is abolished in patients with T2DM, the preservation or augmentation of the effects of GLP-1 has provided a logical basis for the development of incretin therapies. However, the short $t_{1/2}$ of GLP-1 necessitates continuous intravenous infusion for such a treatment to be beneficial, and infusion is an impractical therapeutic modality. Therefore, research has been focused on the development of peptides that stimulate the GLP-1 receptor, but with less susceptibility to inactivation by DPP-4. The resultant therapies, the GLP-1 receptor agonists, mimic the activity of endogenous GLP-1. A second strategy is to inhibit the activity of DPP-4, thereby preserving the activity of endogenous GLP-1 and GIP. The DPP-4 inhibitors are based on this approach. This article reviews the pharmacokinetic properties and clinical effects of the GLP-1 receptor agonists and the DPP-4 inhibitors in the treatment of T2DM, with the goal of elucidating the place of these therapies in clinical practice.

MATERIALS AND METHODS

A literature search of PubMed was conducted for literature published between 2000 and mid-2010 using as key words the names of each reviewed agent (*exenatide, liraglutide, exenatide once weekly, taspoglutide, albiglutide, sitagliptin, saxagliptin, vildagliptin,* and *alogliptin*). For studies of clinical efficacy and tolerability, only large-scale (defined as ≥150 patients), randomized, controlled, Phase III and IV studies in T2DM were included. For the discussion of pharmacokinetic properties, a supplemental search of abstracts from major diabetes conferences (eg, annual meetings of the American Diabetes Association or the European Association for the Study of Diabetes) was undertaken. Searches of all reference lists were performed to identify additional references of interest.

RESULTS

Pharmacokinetic Properties

Drug $t_{1/2}$; dosing frequency; and patterns of absorption, metabolism, and excretion are relevant to treatment selection. This section reviews the pharmacokinetic properties of each GLP-1 receptor agonist and DPP-4 inhibitor and discusses the implications for their use (**Table I**[22-52]).

GLP-1 Receptor Agonists

Exenatide Twice Daily

Exendin-4 is a 39–amino acid peptide derived from the oral secretions of *Heloderma suspectum* (Gila monster). The 1-to-30 amino acid sequence of exendin-4 was reported to have a 53% homology with mammalian GLP-1, a 30–amino acid peptide.[53] Exenatide, which was approved by the US Food and Drug Administration (FDA) in 2005 as a T2DM therapy,[54] is an injectable synthetic formulation of exendin-4.[23] Studies using the rat insulinoma-derived RINm5F cell line, a β-cell model, reported exendin-4 binding at GLP-1 receptors. Binding was associated with the production of intracellular cyclic adenosine monophosphate and the potentiation of glucose-induced insulin release.[55]