Exenatide Once Weekly: A Review of Pharmacology and Treatment Considerations in Type 2 Diabetes

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ABSTRACT

Purpose: The pathophysiology of type 2 diabetes mellitus is complex and involves multiple organs and hormones, suggesting that successful treatment may require therapies that target multiple mechanisms. Exenatide, a glucagon-like peptide 1 receptor agonist, has a multifaceted mechanism of action involving pancreatic α and β cells, hepatic glucose production, gastric motility, and satiety. Exenatide once weekly (a twice-daily formulation is also available) utilizes continuous release from biodegradable microspheres. This review discusses relevant efficacy and tolerability outcomes with exenatide once weekly in the context of its pharmacology.

Methods: The medical literature was searched to identify relevant data on the pharmacology and clinical effects of exenatide once weekly.

Findings: Exenatide once weekly, like the twice-daily formulation, has been shown to improve glycemic parameters, promote weight loss, result in beneficial changes in cardiovascular risk factors, and is well-tolerated.

Implications: The characteristics of exenatide once weekly make it a treatment option for patients with type 2 diabetes. (*Clin Ther*. 2016;38:582–594)

Key words: delayed-action preparations, exenatide, pharmacology, type 2 diabetes.

INTRODUCTION

Diabetes is a chronic, complex illness requiring long-term medical care to minimize disease progression and complications. In 2012, 9.3% of the US population (29.1 million people) had diabetes, with most of these cases (90%–95%) being type 2 diabetes (T2D).[1,2] Diabetes complications include cardiovascular disorders, blindness, end-stage renal failure, and a need for amputations, as well as an increased risk for other disabling conditions.[2,3] Data from the UK Prospective Diabetes Study[4] suggest that the risk for these complications is strongly associated with a lack of glycemic control.

The pathophysiology of T2D involves not only the triumvirate of insulin resistance in the muscle and liver and abnormal β-cell function but also additional organ systems and processes, including accelerated lipolysis of fat cells, incretin deficiency/resistance, hyperglucagonemia, increased glucose absorption in the kidney, and appetite dysregulation in the brain.[5] Multiple pathophysiologic defects suggest that the treatment of T2D should target multiple pathophysiologic mechanisms.

Determining appropriate treatment options for patients with T2D has become challenging. Guidelines from the American Diabetes Association/European Association for the Study of Diabetes and the American Association of Clinical Endocrinologists recommend metformin as first-line therapy; however, in patients unable to achieve glycemic control on metformin alone, glucagon-like peptide (GLP)-1 receptor agonists (RAs) are a recommended add-on therapy.[6,7]

The mechanism of action of GLP-1RAs in lowering plasma glucose mimics that of the intestinal hormone GLP-1 (released as a result of nutrient ingestion) and is multifaceted, involving the stimulation of glucose-dependent insulin secretion from pancreatic β cells; suppression of glucose-dependent glucagon secretion from pancreatic α cells, which reduces hepatic glucose production in the liver; a decrease in gastric motility to slow nutrient absorption; and the induction of a feeling of satiety.[8] Therefore, the mechanism of action affects many of the pathophysiologic defects in T2D.[5] A number of GLP-1RAs are available in the United States, including

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exenatide (BID or once-weekly [QW] formulations), liraglutide (once-daily formulation), albiglutide (QW formulation), and dulaglutide (QW formulation), all of which are indicated for the improvement of glycemic control in adults with T2D, in combination with diet and exercise, and are administered via SC injection.

Exenatide was the first-in-class GLP-1RA available as a BID formulation (injected within 1 hour before mealtime), with a ~2-hour T_{max} and a 2.4-hour $t_{1/2}$.[9] Subsequently, a long-acting QW formulation was developed by incorporating the active molecule, exenatide, into microspheres, enabling the continuous release of the drug at a consistent rate.[10] This review discusses the relevant efficacy and tolerability outcomes with exenatide QW in the context of its pharmacology.

METHODS

The medical literature was searched to identify relevant data on the pharmacology and clinical effects of exenatide QW.

RESULTS

Pharmacology

Exenatide is a synthetic version of exendin-4, a peptide derived from the lizard species *Heloderma suspectum*. Exendin-4 has an amino acid sequence that is ~50% homologous to human GLP-1, yet binds to the GLP-1 receptor with an affinity similar to that of native GLP-1.[11,12] Differences in the amino acid sequence at the cleavage site render exenatide resistant to degradation by dipeptidyl peptidase 4, thus prolonging its circulating half-life.[11]

The BID and QW formulations have different pharmacokinetic and pharmacodynamic profiles. The extended-release formulation of exenatide is made possible by the incorporation of a fixed dose of exenatide 2 mg into biodegradable poly-(D,L-lactide-co-glycolide) polymer microspheres ~0.06 mm in diameter (Figure 1).[13] The microspheres are reconstituted in a premeasured aqueous solution for suspension before injection. The poly-(D,L-lactide-co-glycolide) polymer is degraded by natural (ie, noncatalyzed) hydrolysis of the ester linkages into lactic and glycolic acids that are eliminated as carbon dioxide and water. Drug release occurs in 3 stages, known as *initial release, diffusion release,* and *erosion release*. During initial release, loosely bound drug molecules on or close to the surface are liberated as the microspheres hydrate immediately after administration, which may lead to a transient rise in drug concentration. Polymers are then hydrolyzed into smaller fragments, at which point diffusion release initiates. During diffusion release, exenatide molecules enter the circulation at a relatively constant rate from interstices of the microsphere fragments. Finally, the poly-(D,L-lactide-co-glycolide) matrix fully hydrolyzes, releasing the remaining exenatide. The gradual release of exenatide from the QW formulation eliminates the need for dose titration. Exenatide QW is available for administration in a single-dose tray or a new, prefilled, single-dose pen device. The pen device minimizes assembly and simplifies reconstitution of the dose compared with the single-dose tray.

Pharmacokinetic Profile

Several studies have characterized the pharmacokinetic profile of exenatide QW in patients with T2D. On administration of exenatide QW, 1% to 2% is available immediately, whereas the remaining drug is gradually released from microspheres over time.[14] Single dosing of SC placebo or exenatide 2.5, 5, 7, or 10 mg was associated with a biphasic concentration–time profile: Initial drug release occurred within 2.1 to 5.1 hours, followed by peaks at 2 and 7 weeks.[14] With regular QW dosing (15-week course of SC placebo, exenatide 0.8 mg QW, or exenatide 2 mg QW), mean exenatide levels exceeded the minimal effective concentration (50 pg/mL) within 2 weeks and achieved steady state by weeks 6 to 7, resulting in consistent concentrations of exenatide (Figure 2).[14] Similarly, the concentration minimally effective for reducing fasting plasma glucose (FPG) levels was exceeded within 2 weeks with the 2-mg dose. Similar results were observed in 2 early studies of a 10-week course of exenatide QW, where steady-state plasma concentrations were reached by week 8.[15,16]

Efficacy Outcomes

The efficacy of exenatide QW has been examined in six 24- to 30-week randomized trials—the DURATION (Diabetes Therapy Utilization: Researching Changes in A_{1c}, Weight and Other Factors Through Intervention With Exenatide Once Weekly) trials.[17–22] The DURATION-1 and -5 studies compared the relative efficacy and tolerability of long-acting,