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Glucagon-Like Peptide-1 Receptor Agonists

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Continuing Education Activity

Glucagon-like peptide-1 agonists are a class of medications utilized in the treatment of type 2 diabetes and obesity. This activity will highlight the indications, mechanism of action, administration, adverse effect profile, and contraindications for these drugs. The use of an interprofessional team of nurses, primary care providers, pharmacists, and endocrinologists remains pertinent to care for patients prescribed this class of medications.

Objectives:

- Review the mechanism of action of GLP-1 receptor agonists.
- Identify the potential adverse effects of GLP-1 receptor agonists.
- Outline the methods of administration for GLP-1 analogs and the clinical monitoring necessary for patients prescribed GLP-1 receptor agonists.
- Explain the importance of collaboration and communication among an interprofessional healthcare team to improve outcomes for patients receiving GLP-1 agonists.

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Indications

Glucagon-like peptide-1 (GLP-1) agonists (also known as GLP-1 receptor agonists, incretin mimetics, or GLP-1 analogs) represent a class of medications used to treat type 2 diabetes mellitus and, in some cases, obesity. Examples of drugs in this class include exenatide, lixisenatide, liraglutide, albiglutide, dulaglutide, and semaglutide. According to the American Diabetes Association, metformin remains the preferred first-line therapy for treating type 2 diabetes. However, the addition of a GLP-1 analog should be considered in patients with a contraindication or intolerance to metformin, in patients with a hemoglobin A1c greater than 1.5% over target, or in patients who do not reach their target A1c in three months, particularly in patients with atherosclerosis, heart failure, or chronic kidney disease.[1][2][3][4] Furthermore, semaglutide and high-dose liraglutide are FDA approved as pharmacologic treatments for obesity or can be prescribed to overweight patients with comorbidities. The utilization of GLP-1 analogs is an object of research with favorable hemoglobin A1c results and weight loss results in patients with type-1 diabetes mellitus. Of note, higher costs, as well as tolerability, remain significant barriers to prescribing these medications.[5][6][7][8]

Structurally, there are two broad categories of these agents; human GLP-1 backbone agents and exendin-4 backbone agents.

Human GLP-1 backbone:

- Dulaglutide
- Albiglutide
- Liraglutide
- Semaglutide

Exendin-4 backbone:

- Exenatide (two formulations)
- Lixisenatide

Tirzepatide is a GIP analog that activates both the GLP-1 and GIP receptors.

Because of safety concerns, research on another agent, taspoglutide, has been halted in phase III trials.[9]

Mechanism of Action

Glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide (GIP), both incretin hormones inactivated by dipeptidyl peptidase-4 (DPP-4), stimulate insulin secretion after an oral glucose load via the incretin effect.[10][11] In type 2 diabetes, this process can become blunted or even be absent; however, the utilization of pharmacological levels of GLP-1 can revive insulin excretion. The benefits of this form of therapy to treat type 2 diabetes include delayed gastric emptying and inhibiting the production of glucagon from pancreatic alpha cells if blood sugar levels are high. Furthermore, GLP-1 receptor agonists can decrease pancreatic beta-cell apoptosis while promoting their proliferation.[12][13][14]

This class of medications has also been shown to promote an average weight loss of 2.9 kilograms compared to placebo, in addition to lowering both systolic and diastolic blood pressure and total cholesterol. In terms of cardiovascular effects, GLP-1 agonists can improve left ventricular ejection fraction, myocardial contractility, coronary blood flow, cardiac output, and endothelial function while reducing infarction size and overall risks for a cardiovascular event. [15][16] Other functions of GLP-1 include increased glucose uptake in the muscles, decreased glucose production in the liver, neuroprotection, and increased satiety due to direct actions on the hypothalamus. GLP-1 analogs have also exhibited lower all-cause mortality as well as a hemoglobin A1c reduction of about one percent compared to control groups in patients with type-2 diabetes mellitus.[17][8]

Administration

Many formulations of GLP-1 agonists, all of which historically were injectable and administered subcutaneously due to poor oral bioavailability, can be prescribed in the United States. Lixisenatide and liraglutide dosing are once-daily, albiglutide, dulaglutide, semaglutide dosing is once weekly, and exenatide can be dosed either as a twice-daily or a once-weekly injection. Recently, the FDA approved an oral formulation of semaglutide. Researchers have suspended trials investigating taspoglutide as a novel GLP-1 analog due to gastrointestinal side effects and hypersensitivity reactions.[18][19][9]

Summary of dosing frequency for some commonly prescribed GLP-1 receptor agonists:

- Dulaglutide - once weekly
- Albiglutide - once weekly
- Liraglutide - once daily
- Semaglutide - one weekly subcutaneously, daily orally
- Exenatide BID - twice daily
- Exenatide QW - once weekly
- Lixisenatide - once daily
- Tirzepatide - once weekly

Depending on the drug prescribed, the medication may come as a single- or multi-dose pen, and patients may need a separate prescription for needles with various needle gauge requirements. Patients have shown improved satisfaction with once-weekly exenatide compared to a twice-daily regimen, and studies have demonstrated their preferences for narrow needles. However, concerns regarding compliance with a once-weekly, as opposed to a daily regimen, have also been raised. GLP-1 analogs, combined with long-acting insulin in a single injection, have also been introduced to the pharmaceutical market.[20][8] This regimen potentially provides synergism with insulin-lowering fasting and post-absorptive blood sugars and GLP-1 agonists targeting postprandial blood sugars. This strategy may lower the risk of hypoglycemia due to less reliance on bolus and even basal insulin and may offset potential weight gain experienced with insulin.[21][22]

Adverse Effects

The most frequently exhibited side effects from GLP-1 agonists include nausea, vomiting, and diarrhea that could lead to an acute kidney injury due to volume contraction. Dizziness, mild tachycardia, infections, headaches, and dyspepsia may also occur. Patients should receive counseling that this class of drugs increases satiety, and transient, mild nausea may occur if they attempt to eat while feeling full. Increasing the dosage of these medications should occur slowly if nausea is present. Injection-site pruritus and erythema are also common, most notably with the longer-acting medications in this class.[10][23][12]

There is a low risk of minor episodes of hypoglycemia; however, research has not described any major hypoglycemic episodes at this time. Patients can form antibodies to particular GLP-1 analogs that could affect the efficacy of these medications, particularly with exenatide. This immunogenicity could lead to injection site reactions and even potential anaphylaxis. Studies have shown that these adverse effects typically lead to an overall low discontinuation rate of around ten percent.[9][24][25] Anti-drug antibodies were more common, and titers were higher with the weekly dosed formulation of exenatide than with the twice-daily formulation of exenatide.[26]

Combination therapy with GLP-1 agonists and dipeptidyl peptidase-4 inhibitors is not a current recommendation due to statistically insignificant glycemic improvement and enhanced hypoglycemic effects. The interactions between GLP-1 agonists and other oral anti-diabetic medications remain unclear.[8][27]

Contraindications

Contraindications to utilizing GLP-1 agonists include hypersensitivity and pregnancy as prohibitions to prescribing this class of medications. Some form of contraception is the recommendation with GLP-1 agonists in women of childbearing age. Additionally, patients with severe gastrointestinal diseases such as gastroparesis and inflammatory bowel disease should avoid GLP-1 analogs. Concern for long-term consequences on the thyroid gland using GLP-1 agonists has been a topic of investigation. In rodent models, liraglutide stimulated calcitonin release and led to hyperplasia of thyroid gland C-cells and tumors. The effects on humans remain unclear, with further investigations being necessary. Consequently, GLP-1 agonists are not recommended in patient populations with a personal or family history significant for multiple endocrine neoplasia 2A, multiple endocrine neoplasia 2B, or medullary thyroid cancer.[28][29][9][30]

While the mechanism remains largely unknown, acute pancreatitis, including potentially fatal hemorrhagic and necrotizing types, has been noted in users of GLP-1 analogs. Whether a causal relationship exists between GLP-1 analogs and pancreatitis or pancreatic cancer is unknown at this time. Nonetheless, GLP-1 agonists should not be prescribed in patients with a history of pancreatitis and should be discontinued in those who develop pancreatitis while taking this medication.[24][31][32]

Monitoring

GLP-1 analogs are principally renally eliminated. Dosing adjustments of GLP-1 agonists are not necessary due to hepatic or mild renal impairment. Moderate renally impaired patients, on the other hand, should avoid weekly exenatide, and dosing escalations should be considered carefully in patients on twice-daily exenatide. Likewise, lixisenatide use requires caution in this patient population. Dosing increases of twice-daily exenatide for patients 70 years and older merit evaluation of the potential risks and benefits.

Patients with severe renal dysfunction should not take GLP-1 agonists. If a GLP-1 agonist is added to a regimen already consisting of a sulfonylurea or long-acting insulin, patients require monitoring for hypoglycemia. A decrease in the insulin dose may even become necessary, depending on the GLP-1 analog selected. Patients taking GLP-1 analogs should periodically have their hemoglobin A1c measured and have their glycemic patterns examined. The clinician should follow the international normalized ratio (INR) in patients prescribed warfarin, as a GLP-1 agonist may alter the absorption of this medication by delaying gastric emptying. Healthcare providers should also monitor patients taking GLP-1 agonists for signs and symptoms consistent with pancreatitis. The FDA currently has recommended against routinely monitoring calcitonin levels for medullary thyroid cancer.[30][24][8]

Toxicity

Research into GLP-1 analog overdoses remains limited. Reports exist of symptoms such as nausea, vomiting, diarrhea, excessive belching, and abdominal pain due to toxic ingestion of medication within this class; however, no serious complications, such as pancreatitis or hypoglycemia, have been noted in case studies. Treatment consists of supportive care, including antiemetics, to control excessive nausea and vomiting.[25][33]

Enhancing Healthcare Team Outcomes

The treatment of type 2 diabetes and obesity should involve an interprofessional team, including a primary care provider (MD, DO, NP, or PA), diabetes educator (nurse or pharmacist),

pharmacist, and possibly an endocrinologist. Providers and pharmacists n collaborate on the decision to try a GLP-1 agonist and include a complete medication review in their decision. The interprofessional approach will maximize positive outcomes and minimize adverse events. [Level 5]

Clinicians, pharmacists, dieticians, and nursing should all educate patients on potential side effects and drug interactions of GLP-1 agonist therapy, and patients should have regular follow-up appointments with their primary care provider to monitor blood glucose levels, weight, and kidney function, as well as for signs and symptoms consistent with pancreatitis. Nursing can be beneficial in this by monitoring and reporting any concerns to the prescriber and/or pharmacist. A registered dietitian nutritionist should work with the patient to make appropriate food choices. A cohesive interprofessional team approach that can further the goal of GLP-1 therapy should highlight maximizing blood sugar control and weight loss while minimizing potential adverse reactions. [Level 5]

Review Questions

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