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Exenatide

A Viewpoint by Curtis Triplitt and Ralph A. DeFronzo

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The mechanism of action of exenatide for the treatment of type 2 diabetes mellitus is unique in several ways.

- It stimulates glucose-dependent insulin secretion via the glucagon-like peptide-1 (GLP-1) pancreatic receptor and has an additive glycaemic-lowering effect when added to a sulfonylurea. By contrast, nateglinide, which works through the pancreatic sulfonylurea receptor, is ineffective when added to a sulfonylurea.
- It suppresses elevated plasma glucagon levels, leading to a reduction in fasting and post-prandial rates of hepatic glucose production.
- It slows the appearance of glucose into the systemic circulation by reducing the accelerated rate of gastric emptying that is present in type 2 diabetic patients.
- It promotes weight loss by binding to the GLP-1 receptor in the hypothalamus and suppressing appetite.
- It is associated with a very low incidence of hypoglycaemia since, as blood glucose return to normal levels, the effect of exenatide on β- and α-cells wanes.

The quantitative contribution of each of these individual mechanisms to the overall improvement in glycaemic control in humans has yet to be determined. In rodents, exenatide stimulates islet cell neogenesis and inhibits apoptosis, but such effects have not yet been established in man.

In type 2 diabetic patients with a starting glycosylated haemoglobin (HbA_{1c}) of 8.5%, exenatide reduces the HbA_{1c} by ≈1.2–1.4%, while causing progressive, significant weight loss. This is especially beneficial since ≈80% of people with type 2 diabetes are overweight or obese. Exenatide, when combined with metformin, improves glycaemic control, results in weight loss and does not increase the risk of hypoglycaemia. When exenatide is combined with a sulfonylurea, the risk of hypoglycaemia increases slightly because of the continued stimulatory effect of the sulfonylurea on insulin secretion. Thus, as normoglycaemia is approached, a reduction or discontinuation of the sulfonylurea may be required. However, if the HbA_{1c} remains >7.5–8.0%, the sulfonylurea should be continued until the full impact of exenatide on blood glucose levels can be ascertained. When added to combination therapy with metformin plus a sulfonylurea, exenatide and glargine insulin resulted in similar glycaemic control, but exenatide had the advantage of producing significant weight loss. Exenatide also would be expected to have additive glycaemic effects when added to a thiazolidinedione, while limiting weight gain, since exenatide reduces food intake. Trials investigating such effects are currently in progress. One also would expect exenatide to be effective when added to triple oral agent therapy (metformin, thiazolidinedione, sulfonylurea) in poorly controlled type 2 diabetic patients. Exenatide will likely be used in patients with other significant co-morbidities such as renal insufficiency, hepatic dysfunction and heart failure. When metformin (renal insufficiency) and/or a thiazolidinedione (heart failure) are contraindicated, exenatide may be especially advantageous. Preliminary studies suggest that GLP-1 therapy may improve heart failure.

The starting dosage of exenatide is 5μg twice daily before breakfast and the evening meal. Mild-to-moderate nausea occurs in approximately one-third of individuals during the first 1–2 weeks of therapy and dissipates thereafter. After 4 weeks, the dosage of exenatide is increased to 10μg twice daily. Exenatide comes in a cartridge-filled pen which administers either the 5 or 10μg dose. Therefore, it is very easy to administer and, unlike insulin, does not require dose adjustment with each meal.

Future investigative directions for exenatide include further elucidation of long-term efficacy and safety. An extended-release product is currently in development and has the potential to reduce the number of injections needed. Promising data in animals have shown that exenatide increases β-cell mass by increasing islet neogenesis and decreasing β-cell apoptosis. If long-term trials show that β-cell deterioration can be delayed or prevented with ex-

enatide, earlier use in individuals with impaired glucose tolerance and newly diagnosed type 2 diabetics, especially with an extended-release formulation, can be expected. ▲