

NEW DRUG PROFILE: Exenatide

S. Seethalakshmi

INTRODUCTION:

There are various drugs available for the treatment of type-2 diabetes and the main disadvantage with these drugs include hypoglycemia and weight gain (with sulfonylureas, thiazolidinediones), lactic acidosis (with biguanides) and edema (with thiazolidinediones), in addition to restrictions for use in organ dysfunction. It has been shown in diabetes that cell failure is progressive, despite therapy with sulfonylureas and biguanides. So, an ideal anti diabetic agent should delay/arrest, if not reverse the cell decline which can be used synergistically with current therapies with no added adverse drug reaction profile or serious adverse drug reactions, thus reducing long term complications and hence morbidity and mortality. To help these patients further, a new class of agents incretin mimetics has been developed. Exenatide¹ is the first drug in the incretin mimetic class and is indicated for treatment of Type 2 diabetes mellitus.

PROPERTIES OF THE DRUG:

Exenatide is a synthetic 39- amino acid peptide with incretin properties similar to the native glucagon-like peptide. Unlike GLP-1, it is resistant to in vivo proteolytic degradation by dipeptidase -4 resulting in a significantly longer elimination half-life. Randomized trials have shown exenatide to be efficacious in improving glycemic control when combined with either metformin or Sulfonylureas.

After subcutaneous administration of 10 microgram dose the mean C_{max} is about 193- 220mcg/mL. AUC: 993-1066mcg /mL Median t_{max} : 2.1 hr .Mean apparent volume of distribution: 28.3 L

Exenatide exhibited significant resistance to enzymatic degradation by Dipeptidyl Peptidase IV (DPP- IV) where as GLP(Glucagon like peptide)-was rapidly degraded by this enzyme. Elimination occurs in kidneys via Glomerular filtration followed by proteolytic inactivation, in renal tubules.² Mean $t_{1/2}$: 2.4 hrs

Exenatide is given subcutaneously 60 minutes prior to morning and evening meals. It is initiated as 5 microgram bd and can be increased to 10 microgram bd after 1 month of treatment, seeing the response. It is recommended for patients on metformin or sulfonylurea who have suboptimal glycemic control.

Adverse effects mainly include nausea³ (44%), vomiting, hypoglycemia, diarrhea, dizziness and headache.

CORRESPONDING AUTHOR :

Dr. S. SEETHALAKSHMI

Professor of Pharmacology

Sri Ramachandra Medical College

Sri Ramachandra University, Chennai

email: seethakrishna97@hotmail.com

Of these nausea is self limiting in 15-30% of patients. Since Exenatide delays gastric emptying, drugs like lovastatin, digoxin and oral contraceptive pills are to be taken 1 hour prior. Careful clinical monitoring is necessary for drugs with narrow therapeutic index.

MECHANISM OF ACTION

Exenatide is an incretin mimetic drug indicated for treatment of Type 2 diabetes mellitus. Incretin hormones are the hormones produced by the gastrointestinal tract in response to nutrient entry, resulting in stimulation of insulin secretion (insulinotropism). Glucagon like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP) are two such examples. Gut insulinotropic agents like GLP-1 are secreted by enteroendocrine L-cells of gastrointestinal tract (duodenum, jejunum, ileum and colon) in response to food.

Therefore decreased incretins levels would result in significant post-prandial hyperglycemia as manifested in impaired glucose tolerance.

In type-2 diabetes there is a decreased GLP-1 responses and decreased insulin secretion as compared to non-diabetics.

Exenatide improves glycemic control by both acute and chronic glucoregulatory mechanisms in patients with Type 2 Diabetes mellitus⁴. It has structural similarity and binds to the receptor for GLP-1 Glucagon like peptide-1 and displays a similar broad range of activities relevant to improving glycemic control. In the beta-cell, exenatide stimulates insulin secretion in a glucose dependent fashion and has been shown to essentially normalize the loss of first-phase insulin secretion in patients with type 2 diabetes. In the alpha-cell, it normalizes the pathologic hyper secretion of glucagon in a glucose-dependent fashion, thereby reducing hepatic glucose production in the postprandial state. The glucose dependency of both of these mechanisms has been well-documented, protecting the patient from hypoglycemia while these delicately counterbalanced hormones are normalized simultaneously.

GLUCOREGULATORY MECHANISM OF EXENATIDE:^{4,5}

Acute	Chronic
Enhancement of glucose – dependent insulin secretion	Reduction in food intake.
Restoration biphasic insulin responses.	Reduction in body weight.
Suppression of in appropriate high glucagons secretion	Enhancement of insulin sensitivity
Slowing of gastric emptying	Potentiation of glucose induced pro insulin bio synthesis

Exenatide is comparable to Insulin in reducing baseline fasting blood glucose levels.

In addition, it is, well- tolerated, decreases body weight, has better postprandial glycemic control⁶, is rarely associated with hypoglycemia.

Pharmacotherapeutics and Contraindications

Exenatide, a functional analogue of the GLP-1 is a valuable adjunctive therapy option in patients with Type-2 diabetes mellitus who have inadequate glycemic control despite receiving treatment with Metformin and/or sulfonylurea. In the two randomized, nonblind, insulin –controlled, phase III trial of 26 and 52 weeks duration, patients receiving exenatide 10 microgram twice daily experienced continuous and progressive weight loss and had durable reduction in HbA1c.^{7,8}

It is important to remember that it is not indicated in diabetes mellitus type1 or diabetic ketoacidosis and that it is not an insulin substitute. It is not recommended for diabetics with end stage renal disease (creatinine clearance < 30 ml/ min) and severe gastrointestinal disease (like gastroparesis). The FDA has received 30 reports of acute pancreatitis in patients taking exenatide for treatment of type 2 diabetes.

Twenty-seven of the 30 patients had at least one other risk factor for acute pancreatitis such as gallstones, severe hypertriglyceridemia, and alcohol use. It is yet to be studied in pregnant or lactating mothers.

The other DPP-IV inhibitors are vildagliptin, sitagliptin and saxagliptin (currently in development), similar to exenatide rely on GLP-1 actions for the treatment of type 2 diabetes mellitus.

REFERENCES:

1. D. Hinnen, L. L. Nielsen, A. Waninger, and P. Kushner et al. Incretin Mimetics and DPP-IV Inhibitors: New Paradigms for the Treatment of Type2 Diabetes: J Am Board Fam Med, November 1, 2006; 19(6): 612 - 620.
2. Kolterman OG, Kim DD, ShenL et al. Pharmacokinetics, phramacodynamics ,and safety of exenatide in patient as with Type II diabetes mellitus. AmJ Health Syst Pharm 2005 Jan 15;62(2): 173-81
3. Buse JB, Henry RR, Han J, et al. Effects of exenatide (exendin-4) on glycemic control over 30 weeks in sulfonylurea-treated patients with type -2 diabetes. Diabetes Care 2004 Nov; 27(11): 2628-35.
4. Nielsen LL, Young AA, Parke DG .Pharmacology of Exenatide (synthetic exendin-4): a potential therapeutic for improved glycemic control of type 2 diabetes. Regul Pept 2004;117:77-88
5. Risto S., Cvetkovic, Greg.I.Plosker et al, Exenatide, A review of its use in Patients with Type 2 diabetes Mellitus. Drugs; 2007; 67(6)935-954.
6. KoltermanOG , Buse JB, Fuse man MS. et al. Synthetic exendin-4 significantly reduces postprandial and fasting plasma glucose in subjects with type2 diabetes. J ClinEndocrinol Metab 2003 Jul;88(7):3082-9
7. Heine RJ, Van Gaal LF, Johns D, et al .exenatide versus insulin glargine in patients with sub optimally controlled type 2 diabetes. a randomized trial. Ann Intern med 2005 Oct 18;143(8):559-69
8. Nauck MA, Duran S, Kim D et al .A comparison of twice daily exenatide and biphasic insulin aspart in patients with type 2 diabetes who were suboptimally controlled with sulfonylureas and metformin: a non 0-inferiority study. Diabetologia 2007 Feb;50(2): 259-67