

New Advances in Diabetes Mellitus Treatment

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Goals and Objectives

Goals:

1. To review the current treatments and innovations in the management of diabetes mellitus.
2. To understand the basic information for new drugs used in diabetes mellitus.
3. To comprehend where in therapy the new drugs are appropriate.

Objectives:

Following completion of this topic, the community pharmacist should be able to:

1. Describe the actions and side effects of new drugs used in diabetes mellitus;
2. Explain the appropriateness of specific treatments and how they are used in diabetes mellitus, and;
3. Educate the patient on how to properly take and use these new drugs.

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INTRODUCTION

Diabetes mellitus is a major health problem in the United States. It affects approximately 7% of the population and is a major contributor to other disease states including hyperlipidaemias, atherosclerosis and coronary artery disease, chronic renal failure, and various neuropathies and retinopathies. Moreover, while many disease states are in decline due to improved preventative and interventive medicine, the incidence of diabetes mellitus is increasing worldwide and is estimated to increase from a worldwide incidence of 125 million diabetic patients in 1997 to 220 million patients by 2010. This increase is attributed primarily to a combination of factors that include a rising trend in obesity, poor dietary choices, and sedentary lifestyles.

REVIEW

The primary goal in the treatment of diabetes mellitus is to reduce circulating levels of glucose. Having accomplished this, the secondary problems that arise from diabetes mellitus will diminish as well. For type 1 diabetics, this must be accomplished through the use of exogenously administered insulin. Most patients require the use of at least two (2) different types of insulin, a faster and shorter acting formulation providing immediate hypoglycaemic effect post-prandially and a slower and longer acting formulation providing sustained hypoglycaemic effects throughout the day. Table 1 summarises the currently available insulin formulations and their classification. Generally, the rapidly acting and short acting insulins are administered immediately prior or during meals while the intermediate and long acting insulins are administered once or twice daily.

Type 2 diabetic patients are typically treated in a step-wise fashion until glycaemic control is obtained. In many cases, as the disease progresses over time, therapy may have to proceed to the next "step" in order to regain control. Initially, type 2 diabetics are advised to adopt lifestyle changes (diet, exercise, smoking cessation). Pharmacologic therapy usually begins with a single oral agent, most often a sulphonylurea or meglitinide or -glucosidase inhibitor. The third step is addition of a second drug of another pharmacological class (e.g. a thiazolidinedione). The fourth step might require the addition of insulin to the therapeutic regimen, followed by higher doses of insulin (often alone) and finally insulin plus additional oral medications. The older, oral drugs currently available for use in type 2 diabetes are summarised in Table 2. The recent additions of pramlintide and exenatide as adjunctive therapies for type 2 diabetes provides new, parenteral options (other than insulin) for those patients who have difficulty controlling their diabetes.

Over the past two (2) years, five (5) new products have become available to treat diabetes mellitus. These drugs, discussed below are the focus of this article. Insulin glulisine (a rapidly acting insulin) and insulin detemir (a long acting or basal insulin) offer additional choices to the insulins that are already available. The marketing of an inhalational form of insulin (a long anticipated event) offers patients a non-invasive alternative for immediate glycaemic control associated with meals. This is important since it may eliminate the need for once, twice, or thrice daily injections of standard rapid or short acting insulins. Pramlintide and exenatide offer new, pharmacologically unique therapies to help control diabetes. While they are parenteral, they provide physicians treating type 2 diabetic patients an alternative to insulin in attaining glycaemic control.

NEW DRUG ENTITIES

INSULIN GLULISINE

Insulin glulisine (Adipra®) was approved by the FDA in April, 2004.

Indications – Insulin glulisine is indicated for hyperglycaemic control in diabetes mellitus patients in adults. It may be used in type 1 or type 2 diabetics who require insulin therapy.

Chemistry – Insulin glulisine differs from human insulin by the replacement of asparagine in the 3 position of the B chain with lysine and the replacement of lysine in the 29 position of the B chain with glutamic acid. These replacements do not change the mechanistic nor pharmacodynamic effects of the insulin. They only alter the absorption rate and half-life of the drug, thus producing a different pharmacokinetic profile, as compared to regular human insulin.

Pharmacology – Insulin glulisine acts in a manner similar to other exogenously administered insulin products, *viz.* agonistic activity at the endogenous insulin receptor to increase glucose utilisation.

Pharmacokinetics – Insulin glulisine is classified as a rapidly acting insulin. Its onset of action and duration of action are shorter than regular human insulin. In most patients, it should be used in conjunction with a longer acting insulin or a basal insulin analogue.

Dosage – Doses should be individualised for each patient. However, in determining the proper dose when initiating therapy with insulin glulisine, it should be noted that one (1) unit of insulin glulisine is equipotent with one (1) unit of regular human insulin. Therefore, equal doses would achieve the same glucose-lowering ability. Insulin glulisine should be administered not more than 15 minutes *a.c.* or within 20 minutes of beginning a meal.

Administration – Insulin glulisine should be administered by subcutaneous injection as regular human insulin is used. It may be administered as an infusion via an insulin pump. Insulin glulisine may be pre-mixed with NPH human insulin for immediate subcutaneous administration. If the patient requires this method of insulin administration, they should be instructed to withdraw the insulin glulisine first, followed by the NPH insulin. Insulin glulisine should not be mixed with any other forms of insulin for immediate injection. Additionally, when an insulin infusion pump is used, insulin glulisine should not be mixed with ANY insulins (including NPH).

Side Effects – The side effects of insulin glulisine are similar to other insulins.

Storage – Unopened, refrigerated insulin glulisine is stable until the expiration date indicated on the packaging. Both unopened, room temperature-stored and opened (in-use, either refrigerated or room temperature) vials of insulin glulisine should be discarded after 28 days.

Place in Therapy – Insulin glulisine provides an alternative to the existing rapidly or short acting insulins.

PRAMLINTIDE ACETATE

Pramlintide acetate (Symlin®) was approved by the FDA in March, 2005.

Indications – Pramlintide is indicated for adjunctive treatment in type 1 and type 2 diabetes mellitus patients failing to achieve adequate control with insulin and/or oral anti-diabetic treatments.

Chemistry – Pramlintide is an analogue of the pancreatic beta cell hormone amylin. It differs from human amylin by the substitution of proline molecules for alanine (position 25), serine (position 28) and serine (position 29) molecules. Amylin can not be used

therapeutically, due to a propensity to aggregate, forming amyloid fibres. These substitutions minimise that risk, allowing safe use of this amylin agonist.

Pharmacology – Pramlintide acts as an agonist at the endogenous amylin receptor. Human amylin is secreted, with insulin, from the beta cells of the islets of Langerhans in the pancreas and contribute to normal glycaemic control. Activation of the amylin receptors produces numerous physiological/ pharmacological effects including a slowing of gastric emptying (thus delaying absorption of glucose sources), suppression of glucagon secretion (thus lowering hepatic glucose secretion), and a centrally mediated suppression of appetite.

Pharmacokinetics – Pramlintide exhibits an approximate bioavailability of 35% (30-40%) subcutaneously, with a peak plasma concentration within 20 minutes. The half-life is approximately 48 minutes. It is metabolised renally to an active metabolite with similar pharmacokinetics. Despite its renal metabolism, clinical trials did not indicate any difference between patients with moderate or severe renal disease and healthy patients.

Dosage – Dosage is based upon the patient and differs in type 1 vs. type 2 diabetics. The starting dose for type 1 diabetics is 15 mcg immediately prior to meals with a reduction in preprandial rapid- or short-acting insulin dose by 50%. The dose may be increased by 15 mcg increments if needed. The dose should not be adjusted upwards until the patient has been free of clinically significant nausea for a minimum of three days. If nausea persists, the dose should be lowered. All dosage adjustments should be made under the supervision of the health care provider. The starting dose for type 2 diabetics is 60 mcg. The dose may be increased to 120 mcg if necessary and if there is no significant nausea for 3 to 7 days.

Administration – Pramlintide is administered by subcutaneous injection immediately prior to each major meal (defined as 250 or more Kcal or 30 or more Gm of carbohydrate). It may be administered using a standard U-100 insulin syringe, according to the directions provided. The lowest dose of 15 mcg corresponds to the 2.5 unit increment on the syringe (0.025 ml) with an increase of 2.5 for each additional 15 mcg dose of pramlintide (e.g. 30 mcg = 5 unit increment, 45 mcg = 7.5 unit increment, 60 mcg = 10 unit increment, and 120 mcg = 20 unit increment). Optimally, the patient should use a 0.3 ml syringe for most accurate dosing. NOTE: Pramlintide must be administered alone. It should not be mixed with any insulins.

Side Effects – Pramlintide may augment insulin-mediated hypoglycaemia. Patients should ensure proper insulin dosing, especially when beginning therapy or adjusting the dose, to minimise this. Other side effects most commonly associated with pramlintide include headache, nausea, vomiting, and allergic reaction.

Storage – Unopened pramlintide should always be refrigerated. Unopened, refrigerated pramlintide is stable until the expiration date indicated on the packaging. Open, in-use pramlintide may be stored either at room temperature or refrigerated, but should be discarded after 28 days.

Place in Therapy – Pramlintide provides a new adjunctive therapy that in some type 2 patients allow better glycaemic control without having to add insulin to their regimen and in some type 1 patients to achieve better control with lower doses of insulin or without having to increase their dose of insulin.

EXENATIDE

Exenatide (Byetta®) was approved by the FDA in April, 2005.

Indications – Exenatide is indicated as adjunctive therapy in type 2 diabetic patients who are not achieving adequate glycaemic control

under standard medications (metformin, the sulphonylureas, or combinations thereof).

Chemistry – Exenatide was first discovered as a protein produced by the gila monster and secreted in its saliva. It was later identified as a glucagon-like peptide 1 (GLP-1) sharing an approximate amino acid homology of 50% with that hormone. GLP-1 is an incretin, a series of hormones produced by the endocrine cells of the intestine. Its structural difference from GLP-1 provides a much longer half-life, thus accounting for its viability as a pharmacologic agent.

Pharmacology – Exenatide acts as an agonist at endogenous GLP-1 receptors. The primary pharmacodynamic response resulting from GLP-1 activation is a cAMP mediated increase in insulin synthesis and secretion in the beta cells of the pancreas. Secondary actions in other tissues that also contribute to its efficacy include a reduction in glucagon secretion, a slowing of gastric emptying, and a reduction in food intake.

Pharmacokinetics – Exenatide administration will result in peak blood levels in approximately 2 hours and demonstrates a half-life of approximately 2.5 hours, although measurable exenatide is present as long as 10 hours after dosing. It is eliminated primarily by glomerular filtration with subsequent metabolism. No dosage adjustment is required in patients with mild to moderate renal disease, although clearance was reduced in patients with end-stage renal disease.

Dosage – The starting dose of exenatide is 5 mcg within 60 minutes before morning and evening meals. The dose may be increased to 10 mcg following 1 month of therapy if necessary.

Administration – Exenatide is administered subcutaneously in the thigh, abdomen, or upper arm.

Side Effects – Hypoglycaemia occurs in a dose dependent manner and is greatly influenced by oral hypoglycaemic medications and diet. Other side effects include dizziness, jitteriness, headache, diarrhoea, nausea, and vomiting.

Storage – Exenatide is supplied in prefilled pens and should be stored refrigerated. The pens should be discarded after 28 days of initial use, even if drug remains in the pen.

Place in Therapy – Exenatide offers a new adjunctive therapy that in some type 2 patients allow better glycaemic control without having to add insulin to their regimen.

INSULIN DETEMIR

Insulin detemir (Levemir®) was approved by the FDA in June, 2005.

Indications – Insulin detemir is indicated for the treatment of type 1 diabetes mellitus in adult and pediatric patients and in adult type 2 diabetics requiring basal (long-acting) insulin for glycaemic control.

Chemistry – Insulin detemir differs from human insulin by the omission of threonine in the 30 position of the B chain and the addition of a C-14 fatty acid chain to the lysine in the 29 position of the B chain. These alterations increase the half-life and duration of action of the insulin by greatly increasing its binding to plasma albumin.

Pharmacology – Insulin detemir acts in a manner similar to other exogenously administered insulin products, *viz.* agonistic activity at the endogenous insulin receptor to increase glucose utilisation.

Pharmacokinetics – Following subcutaneous absorption, insulin detemir exhibits 60% bioavailability. It is slowly absorbed over 24 hours with a peak plasma concentration at approximately 7 (6-8) hours. It is 98% bound to plasma proteins and demonstrates a dose-

dependent 5-7 hour half-life. Clearance and blood levels may be altered in patients with renal or hepatic disease. In the case of the former, clearance could be decreased while in the later, blood levels have been shown to be lower.

Dosage – The dose of insulin demetir should be determined based upon the needs of the patient for adequate glycaemic control. For patients converting to insulin demetir from other long acting insulins, the initial dose will be the same, unit for unit, and then adjusted accordingly for optimal control. For insulin-naive patients, the starting dose is typically 0.1-0.2 units/Kg once daily or 10 units once or twice daily. For once daily dosing, it should be administered either with the evening meal or at bedtime. For twice daily dosing, the evening dose may be administered with the evening meal, at bedtime, or 12 hours after the morning dose.

Administration – Insulin demetir is administered by subcutaneous injection, similar to other insulins. It should not be mixed with any other insulins. It may not be administered by an insulin infusion pump.

Side Effects – The side effects of insulin demetir are similar to other insulins.

Storage – Unopened, refrigerated insulin demetir is stable until the expiration date indicated on the packaging. Opened, in-use insulin demetir may be stored at room temperature (less than 86°F) or refrigerated and used for up to 42 days.

Place in Therapy – Insulin detemir provides an alternative to the existing long acting or basal insulins. Its dose-dependent duration of effect allows individual controls based upon the particular needs of a patient.

INHALATIONAL HUMAN INSULIN

Insulin human, inhalation (Exubera®) was approved for use by the FDA in January, 2006.

Indications – Exubra® is indicated for the treatment of adult patients with type 1 or type 2 diabetes mellitus.

Chemistry – Exubra® is human insulin, identical to that produced by the pancreas.

Pharmacology – Exubra® acts at the insulin receptors as normally secreted insulin would, to regulate glucose utilisation.

Pharmacokinetics – Exubra® is absorbed as quickly as the subcutaneously administered rapidly-acting insulins (faster than regular insulin). The peak plasma concentration occurs at 50 (30-90) minutes. Dosage may have to be adjusted in patients with renal impairment.

Dosage – Initial doses for Exubra® are based upon body weight – 0.5 mg/Kg – and rounded down to the nearest whole mg dose. Doses may be adjusted to achieve optimal glycaemic control. It is available in 1 mg and 3 mg blister pack doses. The 1 mg dose is equivalent to 3 units of regular human insulin and the 3 mg dose is equivalent to 8 units of regular human insulin.

Administration – Exubra® is intended for inhalational use, employing the specific inhaler provided. If the patient also uses inhalational bronchodilators, those should be administered prior to inhalation of the Exubra®. The patient should be educated thoroughly on the proper use of the inhaler.

Side Effects – Hypoglycaemia may occur with Exubra® as with other insulins. Additional side effects reported in clinical trials include cough, epistaxis, laryngitis, respiratory complaints, rhinitis, and sinusitis.

Storage – The blister packs should be stored at room temperature (NOT refrigerated). Blister packs stored after opening the protective foil overwrap should be discarded after 3 months. The inhaler should be replaced following 1 year of use.

Place in Therapy – Exubra® provides a non-invasive (non-injectable) alternative to the rapidly or short-acting insulins. Its advantages in this respect may include improved patient compliance and fewer adverse reactions associated with repeated injections.

Special Considerations for Inhaled Insulin – Exubra® is a rapidly acting insulin. Patients should realise that they will still require injectable forms of long acting or basal insulins. Patients with underlying respiratory disease (COPD, chronic bronchitis, asthma) should not use Exubra®.

SUMMARY AND CONCLUSION

This overview has provided the pharmacist with information on the latest drugs available for use in the treatment of diabetes mellitus. The new drugs offer 1) alternatives (insulin glulisine, insulin detemir, and inhalational insulin) to existing therapies and 2) important new drugs (pramlintide and exenatide) that may be added to current therapies to provide better glycaemic control. As with all new drugs, patients should be counselled and educated on the proper use of these agents.

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Table 1
Classification and Pharmacokinetics of Different Insulins

Classification	Insulins	Onset of Action (hrs)	Peak (hrs)	Typical Duration of Activity (hrs)
Rapidly acting				
	Insulin aspart	0.25-0.5	1-2	3-5
	Insulin lispro	0.25-0.5	1-2	3-5
	Insulin glulisine	0.25-0.5	1-2	3-5
	Inhalational insulin	0.25-0.5	1-2	3-5
Short acting				
	Regular insulin	0.5-1	2-3	3-6
Intermediate acting				
	NPH	2-4	4-6	8-12
	Lente	3-4	6-12	12-18
Long acting (basal)				
	Ultralente	6-10	10-16	18-20
	Insulin glargine	4-5		22-24
	Insulin demetir	2-4	6-8	up to 24 (dose dependent)

Table 2
Summary of Oral Anti-Diabetic Medications Available for Type 2 Diabetes Mellitus

Class & Drugs	Mechanism of Action	Pharmacodynamic Effects	Side Effects and Precautions
Sulphonylureas – Chlorpropamide (Diabinese®) Tolazamide (Tolinase®) Tolbutamide (Orinase®) Glyburide (DiaBeta®, Micronase®) Glipizide (Glucotrol®) Glimepiride (Amaryl®)	These drugs block the potassium channel of the beta cells in the islets of Langerhans	This action will increase the secretion of endogenous insulin, thus aiding in peripheral glucose utilisation. These drugs lower both post-prandial and fasting glucose.	Common side effects include a disulfiram-like reactions, and phototoxicity. These are less a problem in the three newer (bottom) drugs
Meglitinides – Repaglinide (Prandin®) Nateglinide (Starlix®)	Same as the sulphonylureas	Same as the sulphonylureas	These drugs lack the typical side effects of the sulphonylureas. *
Biguanides – Metformin (Glucophage®)	The exact mechanism of action of metformin is not known	Decreases hepatic glucose production, decreases absorption of dietary glucose and increases peripheral insulin efficacy. Metformin lowers post-prandial but not fasting glucose.	Common side effects include diarrhoea, nausea and vomiting, and flatulence. A more rare but serious problem is lactic acidosis. Metformin should not be used in patients with COPD, asthma, liver or kidney disease. It is especially effective in obese patients.
α -Glucosidase inhibitors – Acarbose (Precose®) Miglitol (Glyset®)	These drugs inhibit intestinal α -glucosidase.	This action results in an inability to breakdown and delays absorption of dietary carbohydrates. They lower post-prandial but not fasting glucose.	The primary side effect reported with these drugs is flatulence.
Thiazolidinediones – Rosiglitazone (Avandia®) Pioglitazone (Actos®)	Act as an agonist at the peroxisome proliferator activated (PPAR) (receptor	These agents increase the sensitivity of peripheral tissues to the actions of insulin. They lower both post-prandial and fasting glucose.	Frequently reported side effects include headache, muscle pain, and edema. These may cause fluid retention. Hepatic enzymes should be monitored during therapy, since there is a low risk for hepatotoxicity.

** Since the meglitinides and sulphonylureas act by the same mechanism of action, either one or the other should be used. The two classes should not be co-administered in combination oral anti-diabetic therapies.*