

The Incretins:

Medications for Treatment of Diabetes



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A new class of antihyperglycemic agents has recently been introduced: sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitors or incretin enhancer.¹ This drug decreases the rapid breakdown of the GI hormone glucagon like peptide-1 (GLP-1), which is normally secreted from the small intestine in response to food intake. GLP-1 stimulates insulin secretion in a glucose-dependent manner, inhibits glucagon (a hormone that increases blood glucose) and has other effects including slowing gastric emptying and modulating appetite.

Sitagliptin is an oral medication given as 100 mg q.d. It has been studied in monotherapy, in combination with metformin, sulfonylureas, thiazolidinediones and combination of metformin and a sulfonylurea. The degree of A1C reduction is 0.7% to 0.8% but is more if A1C is > 8% at baseline.

Because the action of GLP-1 on insulin secretion is glucose dependent, hypoglycemia is not observed with sitagliptin treatment unless it is combined with an insulin secretagogue or insulin. The drug has proven safety and tolerability in clinical studies—no dose titration is needed. It is contraindicated in impaired renal function (creatinine clearance < 60 ml/min).

Other DPP-4 inhibitors (vildagliptin and saxagliptin) are not available in Canada.

What are the options?

Combination therapy is usually more effective than increasing metformin. Antihyperglycemic

Meet Rachel

Rachel is a 50-year-old administrative assistant who lives a sedentary lifestyle and has Type 2 diabetes. She was diagnosed 3 years ago.

Physical

- BMI: 33 kg/m²
- Waist circumference: 92 cm
- No diabetes complications
- BP: 130/80 mmHg
- Receives metformin 750 mg b.i.d.
- Fasting glucose: 8.1 mmol/L
- A1C 8%

She is trying to follow her lifestyle plan but cannot lose weight. Referral to diabetes centre was arranged. Rachel will also need to increase metformin to 1 g b.i.d. or add a second agent to attain glucose targets:⁵ Pre-meal glucose 4-7 mmol/L, 2 hour p.c. glucose 5-10 mmol/L (or 5-8 mmol/L), A1C < 7%.

agents available are depicted in Table 1—each has a different mechanism of action, benefits and side-effects.²

Other incretin preparations

Because of the very short circulating half-life of GLP-1, its use as a native hormone in the treatment of Type 2 diabetes would necessitate administering it as a continuous IV infusion to attain therapeutic action. This is clearly impractical. The search for long-acting mimetics or analogues with GLP-1 action with less vulnerability to DPP-4 enzyme breakdown, have so far resulted in two injectable preparations:^{1,5}



Table 1

Antihyperglycemic agents

Class	Drug	Expected decrease in A1C	Hypoglycemia	Other therapeutic considerations
α -glucosidase inhibitors	Acarbose	0.5-0.8%	None*	<ul style="list-style-type: none"> • Weight neutral • Recommended in combination with other drugs • GI side-effects
Insulin	Rapid-acting: Lispro, aspart Short-acting: Regular Intermediate-acting: NPH Long-acting: Detemir Glargine	Dose-dependent	Significant risk	<ul style="list-style-type: none"> • Greatest A1C reduction • No maximal dose • Weight gain
Insulin secretagogues	Sulfonylureas: Gliclazide Glimepiride Glyburide Meglitinides: Repaglinide	1-2%	Moderate risk Moderate risk Significant risk Moderate risk	
Metformin	Metformin Long-acting metformin	1-2%	None*	<ul style="list-style-type: none"> • Improved CV outcomes in overweight patients • Weight neutral • Contraindicated in advanced renal disease • GI side-effects
TZDs	Pioglitazone Rosiglitazone	1-2%	None*	<ul style="list-style-type: none"> • More durable glucose control • 6-12 weeks to achieve full effect • Weight gain • Edema • CHF • Higher rate of CHF when combined with insulin • Rare occurrence of fractures in women

*Can be associated with hypoglycemia if combined with drugs that cause hypoglycemia.

NPH: Neutral protamine hagedorn

TZDs: Thiazolidinediones

CHF: Congestive heart failure

- 1. Exenatide** (exendin: exocrine peptide with endocrine action). This preparation was isolated from salivary gland venom of the Gila monster and was found to be a potent agonist of GLP-1 receptor. It is resistant to inactivation by the enzyme DPP-4⁴
- 2. Liraglutide** is a GLP-1 analogue where a fatty acid side chain is added to the molecule to prolong its action by albumin binding. It is more resistant to breakdown by DPP-4.

Both these drugs are injectable subcutaneously—exenatide twice daily and liraglutide once daily. Neither of these drugs are available in Canada. Besides glucose control, patients lose a moderate amount of weight (2kg to 6 kg). The most common side-effects are nausea and vomiting

To go back to Rachel

As you see, when thinking of adding a second agent to metformin there are many options. Sitagliptin is certainly an option with the advantages of glycemic control, no hypoglycemia and no weight gain. Other treatment options to control the elevated blood glucose in this patient include all the drugs mentioned in Table 1. Sitagliptin, however, is new so a long-term safety record is not available. Like many other antihyperglycemic agents, with the exception of sulfonylureas and insulin, there are no studies to show benefit in decreasing microvascular compli-

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Take-home message

- Many options to control blood glucose in Type 2 diabetes are available
- Lifestyle intervention should be emphasized at any stage in the course of the disease
- Many medication groups are available with different benefits and side-effects
- Concomitant with glucose control, reduction of CV risk factors should be undertaken

cation (retinopathy, nephropathy and neuropathy). With the exception of metformin in overweight patients, sulfonylureas and insulin showed decreased myocardial infarction and other diabetes related complications in the long-term follow-up of patients 18.5 years enrolled in UK prospective diabetes study (UKPDS).³ Control of dyslipidemia, hypertension and the use of ACE inhibitors or ARBs and antiplatelet agents when indicated, are proven to decrease morbidity and mortality associated with Type 2 diabetes.²

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References

1. Drucker D, Easley C, Kirkpatrick P: Sitagliptin. *Nat Rev Drug Discov* 2007; 6(2):109-10.
2. Gaede P, Lund-Anderson H, Parving HH, et al: Effect Of A Multifactorial Intervention On Mortality In Type 2 Diabetes. *N Engl Med* 2008; 358(6):580-91.
3. Holman RR, Paul SK, Bethel MA, et al: 10-Year Follow-Up Of Intensive Glucose Control In Type 2 Diabetes. *N Engl Med* 2008; 359(15):1577-89.
4. Eng, J J et al *Biol Chem* 1992, Chen, YE et al *J Biol Chem* 1997, Edwards, CM et al *Am J Physiol* 2001
5. Clinical Practice Guidelines for the Prevention and Treatment of Diabetes in Canada. *Canadian Journal of Diabetes* 2003; 27 (supplement 2).

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