Sitagliptin and metformin combination therapy for type 2 diabetes

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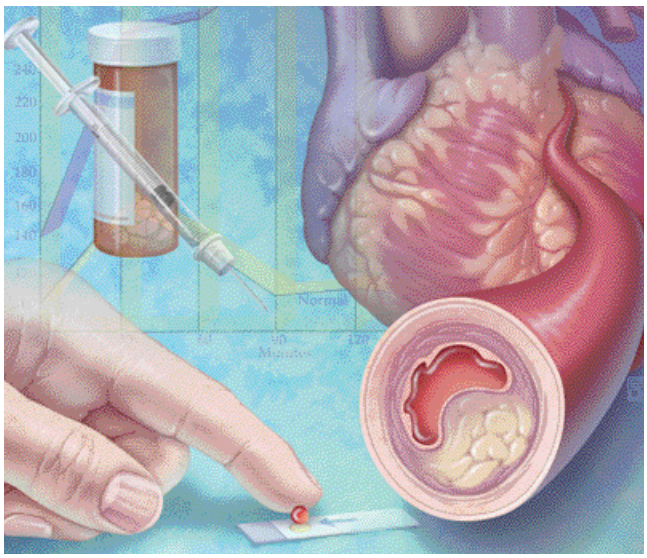

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What is sitagliptin and metformin combination therapy?

The combination treatment Janumet comprises two oral agents for type 2 diabetes: the novel compound sitagliptin and the established drug metformin.

Sitagliptin is a selective inhibitor of the enzyme dipeptidyl peptidase-4 (DPP-4). This enzyme rapidly metabolises the endogenous incretins, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP).[1] In response to the presence of food, GLP-1 is released from the endocrine L cells of the lower small intestine/colon and GIP from K cells in the upper small intestine. Both hormones increase insulin secretion when plasma glucose concentrations are above the normal fasting range. They have an additive effect, but GLP-1 inhibits gastrointestinal motility and gastric emptying, and reduces appetite and food intake to a greater extent than GIP, and also attenuates glucagon secretion. DPP-4 inhibition increases plasma concentrations of GLP-1 and GIP, which are reduced in patients with type 2 diabetes, and therefore has a variety of beneficial effects on glycaemia.

Preclinical data suggest that GLP-1 inhibits pancreatic β-cell apoptosis and therefore increases β-cell mass.[2] As a result, DPP-4 inhibition could represent a durable therapeutic option for what is essentially a progressive disease, but confirmatory data in patients with type 2 diabetes are lacking. In addition, GLP-1 has potentially beneficial effects on cardiovascular and neurological function, liver steatosis and bone health (see the box on page 74).[3] Whether any of these pleiotropic effects are clinically significant consequences of DPP-4 inhibition also awaits confirmation.

Metformin acts by reducing hepatic glucose production, mainly due to inhibition of gluconeogenesis. It also increases nonoxidative skeletal muscle glucose disposal and, because of consequently less 'glucotoxicity', it can improve residual pancreatic β-cell function.[4] At a molecular level, metformin increases insulin-mediated insulin receptor tyrosine kinase activity, which in turn augments a range of insulin signals. It also increases the activity of glucose transporters and indirectly activates AMP-activated protein kinase.[5]

There is evidence from preclinical studies[6] and studies in obese subjects who do not have diabetes[7] that metformin significantly increases circulating GLP-1 levels after the intake of food. Because this effect is independent of DPP-4 activity, it is of potential relevance to its combination with sitagliptin. A further reason for combining these two drugs relates to the fact that, unlike insulin itself and secretagogues such as sulfonylureas, neither sitagliptin nor metformin is associated with hypoglycaemia or weight gain.

Metformin may have its own pleiotropic effects. There is some evidence that it has beneficial effects on cardiovascular disease independent of glycaemia,[8] and that it may also protect against cancer.[9]

When is it used?

Sitagliptin and metformin combination therapy was approved by the TGA in March 2009 as an adjunct to diet and exercise to improve glycaemic control in patients with type 2 diabetes mellitus who are inadequately controlled on metformin alone. It is also approved in patients already taking both the component drugs sitagliptin and metformin separately.

As of August 2009, sitagliptin and metformin combination therapy is listed on the PBS for use in adults with type 2 diabetes. The listing applies to patients whose HbA_{1c} levels are above 7.0% prior

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Main effects of GLP-1 and metformin on organ systems in type 2 diabetes

Effects of GLP-1*

- Increased insulin secretion
- Reduced glucagon secretion
- Delayed gastric emptying
- Increased satiety
- Reduced blood pressure
- Possible cardioprotection
- Possible β-cell protection/growth
- Possible neuroprotection
- Possible enhanced learning and memory
- Possible reduced hepatic steatosis
- Possible increased bone density

Effects of metformin

- Reduced hepatic glucose production/increased insulin sensitivity
- Reduced cardiovascular disease
- Reduced appetite
- Improved β-cell function
- Reduced cardiovascular disease
- Possible protection against cancer

* Inhibition of DPP-4 by sitagliptin will produce GLP-1 effects but not all to a clinically significant extent.

ABBREVIATIONS: DPP-4 = dipeptidyl peptidase-4; GIP = glucose-dependent insulinotropic polypeptide; GLP-1 = glucagon-like peptide-1.

to initiation of sitagliptin despite treatment with metformin and in whom a combination of metformin and a sulfonylurea is contraindicated or not tolerated. It is also listed as continuation therapy in patients with type 2 diabetes who have previously received and been stabilised on a PBS-subsidised regimen of oral diabetic medicines that includes metformin and sitagliptin. A streamlined authority prescription is required. It is not approved by the TGA or listed on the PBS for use as part of triple oral therapy.

Sitagliptin and metformin combination therapy is contraindicated in patients:[10]

- with renal disease or renal dysfunction, usually a serum creatinine level of 133 µmol/L or above in males or 124 µmol/L or above in females, or an estimated creatinine clearance of less than 60 mL/min/1.73 m^2. This is because sitagliptin is primarily excreted unchanged in the urine through active tubular secretion and metformin can also accumulate in patients with renal failure. Sitagliptin and metformin combination therapy should also be temporarily discontinued in patients undergoing radiological studies involving intravascular administration of iodinated contrast materials that may impair renal function
- with known hypersensitivity to sitagliptin or metformin
- with acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. This relates to the reported association between metformin and lactic acidosis, the occurrence of which remains rare[11]
- who are pregnant or lactating. There are no adequate, well-controlled studies in pregnant women (Category C). Animal studies do not suggest that either component is teratogenic, but congenital rib abnormalities and increased birthweight have been reported in studies in rats that are given high doses of sitagliptin.[10]

How is it administered?

Sitagliptin and metformin combination therapy is given twice daily with meals and is available in three formulations: 50 mg sitagliptin (as phosphate monohydrate) plus 500 mg, 850 mg or 1000 mg metformin hydrochloride. The tablets are bioequivalent to coadministration of the same doses of sitagliptin and metformin as individual tablets. Since the pharmacokinetics of sitagliptin appear unaffected by age, gender, race and body mass index, the dose regimen for this component is 50 mg twice daily but the different tablet formulations allow metformin dose titration.

How effective is it?

In a large six-month study of patients with type 2 diabetes and inadequate glycaemic control on diet and exercise alone, there was an additive response when sitagliptin and metformin were given together, with a 1.9% reduction in HbA_{1c} levels from a baseline of 8.8%.[12]

When sitagliptin and metformin combination therapy is given to patients with type 2 diabetes and poor glycaemic control on metformin,[13-18] the placebo-subtracted reduction in HbA_{1c} levels is of the order of 0.7%. This change is similar to that when sulfonylurea or glitazone drugs are used with metformin instead of sitagliptin.

What needs monitoring?

The response to sitagliptin and metformin combination therapy is assessed through monitoring of blood/plasma glucose concentrations and periodic (typically three to six monthly) measurement of HbA_{1c} levels.

Before sitagliptin and metformin combination therapy is initiated, renal function should be verified as being within the recommended levels. Subsequent annual assessment of renal function should be performed with more frequent monitoring in patients at risk of renal dysfunction and in the elderly, particularly those aged 80 years and above. Sitagliptin and metformin combination therapy should be discontinued if evidence of significant renal impairment is detected.

Metformin treatment is associated with a reduction in serum vitamin B_{12} concentrations, but anaemia very rarely supervenes and supplementation rapidly restores normal plasma concentrations.

What are the common side effects?

In clinical trials, the overall incidence of adverse events reported in patients receiving sitagliptin plus metformin was similar to that reported with metformin alone. Established adverse events associated with metformin include diarrhoea,

nausea, vomiting, flatulence, abdominal discomfort, indigestion, asthenia and headache. Nevertheless, up to 5% of patients in trials of sitagliptin monotherapy experienced nasopharyngitis. Rare hypersensitivity reactions, including anaphylaxis, angioedema, urticaria, cutaneous vasculitis and Stevens-Johnson syndrome, have also been reported from postmarketing surveillance in patients treated with sitagliptin.[10]

No clinically significant abnormalities in routine laboratory tests have been reported in clinical trials investigating sitagliptin plus metformin combination therapy.

What about precautions and interactions?

Apart from renal monitoring and awareness of the possibility of acidosis, hypoglycaemia may occur in patients treated with sitagliptin plus metformin when recognised precipitants are present. These precipitants include undernutrition, strenuous exercise, and concomitant use with other blood glucose-lowering agents (such as sulfonylureas and insulin) or ethanol.

No clinically significant drug interactions have been recorded for sitagliptin. Drugs that interact with metformin include frusemide and nifedipine, as well as cationic compounds such as amiloride, digoxin, ranitidine and trimethoprim, which are eliminated by renal tubular secretion and may compete for common renal tubular transport systems.[10]

Conclusion

Although there are no long-term efficacy and tolerability studies, available data suggest that the combination of sitagliptin and metformin has similar efficacy in controlling glycaemia to other metformin-based dual therapies. The lack of hypoglycaemia, weight gain and potentially serious side effects such as fluid retention and osteoporosis are potential advantages of this combination therapy over combinations of sulfonylureas or glitazones with metformin. The coformulation of sitagliptin and metformin should increase compliance, especially in patients who are taking many medications. MT

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