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Sodium-glucose co-transporter inhibitors

Clinical applications

SUMMARY

Inhibition of the sodium-glucose co-transporter 2 in the kidney lowers blood glucose by increasing glucose excretion in the urine. The associated osmotic diuresis and urinary loss of sodium reduces blood pressure.

Canagliflozin and dapagliflozin are sodium-glucose co-transporter 2 inhibitors that have been studied as monotherapy and in combination with other drugs for type 2 diabetes. They reduce concentrations of glycated haemoglobin by 6–9 mmol/mol (0.5–0.8%) more than placebo.

Patients may lose 2–3 kg during treatment. Hypoglycaemia is more likely to occur if a sodium-glucose co-transporter 2 inhibitor is used in combination with other drugs that lower blood glucose. Low density lipoprotein cholesterol increases during treatment.

Glycosuria increases the risk of genitourinary infections. Increased calcium excretion could potentially reduce bone density.

Long-term studies are investigating the cardiovascular safety of these drugs. These studies could also yield data about a possible increased risk of malignancy.

Introduction

The currently available oral therapies for type 2 diabetes all have limitations which mean that patients' therapeutic goals[1] may not be easily and safely achieved, even when combinations of drugs are prescribed. New blood glucose-lowering therapies that are effective and well tolerated are needed.

The role of the kidney in the maintenance of blood glucose has been relatively overlooked. It is now the target of the sodium-glucose co-transporter (SGLT) inhibitors.

Renal glucose homeostasis

The kidney has an important role in glucose homeostasis through gluconeogenesis and reabsorption of filtered glucose. In healthy adults, approximately 180 g/day of glucose is filtered at the glomerulus and virtually all is reabsorbed by SGLTs.[2]

Drugs which inhibit the co-transporters increase glucose excretion and treat diabetes in a different way from other therapies. The associated natriuresis may also reduce blood pressure.

Many co-transporter inhibitors are in various stages of clinical development. Of greatest contemporary relevance to Australian prescribers are dapagliflozin and canagliflozin. Others in at least phase II development are empagliflozin, ertugliflozin and ipragliflozin.

Clinical effects

An aim of treatment for type 2 diabetes is to optimise glycaemic control (and thus reduce the risk of chronic complications) without inducing hypoglycaemia, weight gain or other adverse effects. SGLT2 inhibitors reduce the plasma glucose concentration without stimulating insulin release. Hypoglycaemia should thus be a risk only when these drugs are given with an insulin secretagogue (a sulfonylurea) or insulin. The loss of calories through glycosuria means that SGLT2 inhibitors promote weight loss.

Glycaemic control

The glycaemic efficacy of dapagliflozin has been studied in several thousand patients in a range of trials as monotherapy and in combination with other oral drugs or insulin. At its recommended dose of 10 mg daily, dapagliflozin produces placebo-adjusted mean reductions of 6–9 mmol/mol (0.5–0.8%) in glycated haemoglobin (HbA1c) from initial concentrations of 7.5% or over, when given for at least three months.[3] These effects are similar whether the drug is given as monotherapy, in initial combination with metformin, or as add-on therapy to metformin, a sulfonylurea, a thiazolidinedione or insulin. As with other oral therapies for type 2 diabetes, the greatest mean reductions (>1%) are in patients with the highest pre-treatment HbA1c (>75 mmol/mol (>9%)). There is also a fall in mean fasting plasma glucose of at least 1 mmol/L. These results are broadly similar to those in comparable studies of other oral drugs for lowering blood glucose.[4] There is evidence from add-on studies with two-year follow-up that the glycaemic effect of dapagliflozin is sustained.[5]

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Dapagliflozin appears ineffective in patients with an estimated glomerular filtration rate (eGFR) less than 60 mL/min/1.73 m^2. It has not been adequately assessed in patients aged 75 years or over and so is not currently recommended for use in this age group.

Canagliflozin 300 mg daily appeared to have similar efficacy to dapagliflozin in a similar range of phase III studies ranging from monotherapy to add-on therapy with other oral drugs and insulin.[6] It is possible, however, that the lower specificity for SGLT2 relative to SGLT1 might mean that canagliflozin has greater (SGLT1-associated) renal and gastrointestinal glucose losses than dapagliflozin. Such a hypothesis needs to be addressed in head-to-head studies which also consider relative tolerability and safety.

In contrast to studies of dapagliflozin in renal impairment which have not shown a statistically significant glycaemic effect, canagliflozin led to a significant mean reduction of 0.4% in HbA1c over placebo in patients with an eGFR of 30–50 mL/min/1.73 m^2.[7]

Weight

Dapagliflozin causes weight loss (typically 2–3 kg and mostly visceral fat) in the first 2–3 months which then plateaus. Canagliflozin has a similar effect.

Blood pressure

In phase III studies both dapagliflozin and canagliflozin are associated with a significant mean reduction in systolic blood pressure of 1–6 mmHg more than placebo.[3,6] This change in systolic pressure is more than expected from weight loss and mild dehydration (haematocrit typically increases 1–3%). It reflects the osmotic diuresis and natriuresis associated with the mechanism of action of these drugs. The concomitant drug-related reductions in diastolic blood pressure are smaller than the systolic changes, but are still statistically significant. There is no attenuation of blood pressure effects in the case of canagliflozin given to patients with an eGFR of30–50 mL/min/1.73 m^2.[7]

Adverse effects

In clinical trials of dapagliflozin, 3.2% of patients discontinued because of adverse events. These included genitourinary infections and raised serum creatinine.

Cardiovascular safety

The incidence of clinical events related to intravascular volume depletion (such as symptomatic postural hypotension and dehydration) was approximately double for dapagliflozin compared with placebo or comparator drugs in phase III studies.[3] There was a similar result for canagliflozin.[6] With both drugs, there was no significant excess of severe events associated with their use, and discontinuations due to polyuria, nocturia or dehydration were rare. In the case of canagliflozin, a reduction in intravascular volume was most evident when the drug was taken by patients with an eGFR less than 60 mL/min/1.73 m^2, who were aged 75 years or over, or taking loop diuretics. In these patient groups it is recommended that therapy begins with 100 mg rather than 300 mg daily.

Dapagliflozin[3] and especially canagliflozin[6] increase serum low density lipoprotein cholesterol (placebo-adjusted changes 4.6% and 8.2% respectively). A meta-analysis of 14 clinical studies of dapagliflozin did not show an increase in macrovascular disease,[3] but longer-term studies are needed to detect whether the risk of atherosclerosis is increased. However, in a similar meta-analysis[6] there was a transient excess of cardiovascular events (mainly stroke) in the first month of treatment with canagliflozin. This did not appear to be related to clinically evident reductions in intravascular volume that might facilitate thrombosis. This analysis included events from the long-term cardiovascular safety trial Canagliflozin Cardiovascular Assessment Study (CANVAS) which is ongoing. A postmarketing cardiovascular safety trial of dapagliflozin (DECLARE-TIMI58) that is designed to last up to six years is also in progress.

Renal function and genitourinary infections

In studies of dapagliflozin[3] and canagliflozin[6], there have been small reversible falls in the eGFR. These were greatest (around 10%) in patients with moderate renal impairment.

Monitoring of renal function is recommended before starting an SGLT2 inhibitor and at least yearly thereafter. Renal function should be checked before and periodically after starting other drugs that may influence renal function. More frequent monitoring (3–6 monthly) should be considered in patients with an eGFR approaching the level at which SGLT2 inhibition should be discontinued (60 mL/min/1.73 m^2 for dapagliflozin and 30 mL/min/1.73 m^2 for canagliflozin).

In patients with micro- or macroalbuminuria, canagliflozin is associated with an approximate 50% reduction in urinary albumin excretion. This is sustained for up to a year. Dapagliflozin does not appear to influence albuminuria.

There is a mildly increased risk of non-recurrent uncomplicated urinary tract infection with SGLT2 inhibitors,[3,6] especially in females and patients with a previous history of urinary tract infection. However, both dapagliflozin and canagliflozin increase the risk of genital fungal infections five-fold in both males and females. The most frequent are vulvovaginal infections (most commonly candidal) that respond

to conventional antifungal drugs. However, because no data on prevalence of circumcision have been reported in phase III studies, the relative risk of balanoposthitis in uncircumcised men may be much greater than vulvovaginal infections in women.

Cancer

In clinical studies of dapagliflozin there was an imbalance in the numbers of cases of cancer. The excess of bladder, breast and prostate malignancies[3] contributed to the drug's rejection by the US Food and Drug Administration (FDA).[8] The manufacturers are, however, continuing surveillance to determine whether the imbalance is due to the play of chance or a true drug-related adverse effect. There was no apparent increase in the risk of malignancy in pre-clinical and clinical studies of canagliflozin.[6]

Bone health

Canagliflozin and dapagliflozin cause mildly increased calcium excretion with consequent secondary hyperparathyroidism – effects which may be transient.[3,8] This is mechanistically similar to the action of loop diuretics which increase urinary calcium in parallel with sodium excretion and are recognised risk factors for osteoporosis. There have been no reports of renal calculi during SGLT2 inhibitor treatment.

Bone density data for dapagliflozin over one year did not show a significant change at any site, but canagliflozin studies showed a small decrease which was attributed to the effects of weight loss. There was, however, a greater number of fractures with canagliflozin compared with comparator drugs. This led the FDA to mandate a bone safety study as part of a postmarketing pharmacovigilance program.[7]

Other concerns

Hepatic impairment reduces glucuronidation and so increases dapagliflozin exposure. There are no clinically meaningful interactions with drugs likely to be prescribed with canagliflozin and dapagliflozin, although changes in renal function associated with their use may need to be considered in relation to renally excreted co-prescribed drugs such as metformin.

There is no evidence that canagliflozin and dapagliflozin are associated with hepatotoxicity, but neither is recommended for patients with severe hepatic impairment.[3,6] The long-term cardiovascular safety studies should provide data on liver function abnormalities and other potential end points of interest flagged by the FDA. These include malignancies, pancreatitis, hypersensitivity and photosensitivity reactions, fractures and adverse pregnancy outcomes.[9] Studies in children with diabetes are also needed.

Likely place in therapy

The current Australian indications for dapagliflozin in patients with type 2 diabetes managed with an appropriate diet and exercise regimen are:

- monotherapy when metformin is contraindicated or not tolerated
- initial combination therapy with metformin when metformin monotherapy is unlikely to achieve adequate glycaemic control (such as when the initial HbA1c is very high)
- add-on combination with metformin or a sulfonylurea when these drugs alone do not provide adequate glycaemic control
- add-on combination with insulin (alone or with one or both of metformin or a sulfonylurea) when these regimens do not provide adequate glycaemic control.

Canagliflozin has a similar range of indications, but with less restrictions than dapagliflozin based on renal function and age.

Blood glucose-lowering therapies that are associated with weight loss are understandably attractive to the majority of patients with type 2 diabetes who are either overweight or obese. The only other therapies with this property are metformin and especially the glucagon-like peptide 1 (GLP1) analogue class that includes exenatide and liraglutide. These analogues are injectable therapies and they can cause significant gastrointestinal symptoms, primarily nausea. However, they appear to have a more durable effect on body weight and are more potent blood glucose-lowering therapies than the SGLT2 inhibitors.

Given the cost of new diabetes therapies, and the long-term experience with metformin and sulfonylurea drugs, SGLT2 inhibitors could be an alternative to incretin-based therapies (dipeptidyl peptidase inhibitors or GLP1 analogues) in combination with either metformin or a sulfonylurea when one or other of these drugs is contraindicated or not tolerated. However, their mode of action suggests they may be a useful adjunct to more established therapies, including potential use in type 1 diabetes.

Conclusion

The inhibitors of the sodium-glucose co-transporter improve glycaemic control with a low incidence of hypoglycaemia and have beneficial effects on body weight and blood pressure. They have the convenience of once-daily dosing and their mechanism of action means that they can be combined safely with other oral glucose-lowering drugs and insulin.

Q:

SELF-TEST QUESTIONS

True or false?

7. Canagliflozin and dapagliflozin increase low density lipoprotein cholesterol.

8. An inhibitor of the sodium-glucose co-transporter should not be combined with insulin because of the risk of hypoglycaemia.

Answers on page 35

Their main adverse effects are increases in genitourinary infections, dehydration-related symptoms including postural hypotension, and raised serum low density lipoprotein cholesterol. Ongoing surveillance including large-scale cardiovascular safety trials should provide objective data on the possible increased risk of stroke, fracture and malignancy.

Timothy Davis has served on Australian diabetes advisory boards which have considered dapagliflozin (Bristol-Myers Squibb, AstraZeneca), canagliflozin (Johnson & Johnson), empagliflozin (Boehringer Ingelheim) and ertugliflozin (Merck Sharp and Dohme, Pfizer). He has received speaker's fees and sponsorship to attend meetings from Bristol-Myers Squibb, AstraZeneca, Boehringer Ingelheim and Merck Sharp and Dohme, and research funding from Merck Sharp and Dohme.

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REFERENCES

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012;55:577-96.
2. Wright EM, Loo DD, Hirayama BA. Biology of human sodium glucose transporters. Physiol Rev 2011;91:733-94.
3. Australian Government Department of Health and Ageing. Therapeutic Goods Administration. Australian Public Assessment Report for Dapagliflozin propanediol monohydrate. 2013. www.tga.gov.au/pdf/auspar/auspar-dapagliflozin-propanediol-monohydrate-130114.pdf [cited 2013 Nov 14]
4. McIntosh B, Cameron C, Singh SR, Yu C, Ahuja T, Welton NJ, et al. Second-line therapy in patients with type 2 diabetes inadequately controlled with metformin monotherapy: a systematic review and mixed-treatment comparison meta-analysis. Open Med 2011;5:e35-48.
5. Bolinder J, Ljunggren O, Johansson L, Wilding J, Langkilde AM, Sjöström CD, et al. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type2 diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. Epub ahead of print 2013 Aug 1.
6. FDA Briefing Document. NDA 204042. Invokana (canagliflozin) Tablets. Applicant: Janssen Pharmaceuticals, Inc. 2013 Jan. www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/UCM334550.pdf [cited 2013 Nov 14]
7. Yale JF, Bakris G, Cariou B, Yue D, David-Neto E, Xi L, et al. Efficacy and safety of canagliflozin in subjects with type 2 diabetes and chronic kidney disease. Diabetes Obes Metab 2013;15:463-73.
8. Burki TK. FDA rejects novel diabetes drug over safety fears. Lancet 2012;379:507.
9. Food and Drug Adminstration. FDA approves Invokana to treat type 2 diabetes [news release]. 2013 Mar 29. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm345848.htm [cited 2013 Nov 19]

FURTHER READING

Thynne T, Doogue M. Experimental and clinical pharmacology. Sodium-glucose co-transporter inhibitors – mechanisms of action. Aust Prescr 2014;37:14-6.

Canagliflozin. New drugs. Aust Prescr 2014;37:28-35.

Dapagliflozin. New drugs. Aust Prescr 2013;36:174-9.