Clinical focus

The rationale for combining GLP-1 receptor agonists with basal insulin

The progressive nature of type 2 diabetes mellitus (T2DM) dictates the need for an individualised, stepped interventional approach. The current approach to treatment intensification includes the addition of increasingly complex insulin regimens that involve prandial insulin dosing. However, the more intensely diabetes is treated with many of the current treatment options, the greater the risk of hypoglycaemia, weight gain and, possibly, cardiovascular mortality.1-3 One of the key challenges in patient management is how to achieve glycaemic goals while mitigating these risks.

Pharmacological approaches aimed at enhancing the incretin effect in T2DM have been pursued.4 Two main classes of incretin therapies are now in use: glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. GLP-1 receptor agonists mimic the effects of endogenous GLP-1; they stimulate glucagon-mediated insulin secretion and suppress glucagon secretion (Box 1). But, unlike DPP-4 inhibitors, they have the additional clinical benefits of delaying gastric emptying and decreasing appetite.

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The current clinical data are limited by the lack of any data on the long-term effects of GLP-1 receptor agonists over additional prandial regimens; they may be beneficial or deleterious.

Although cost, gastrointestinal side effects and long-term safety should be taken into account when considering this combination, it appears to be growing in popularity and is likely to be an important therapeutic option for T2DM in the future.

Summary

- Type 2 diabetes mellitus (T2DM) is progressive; the more intensively it is treated, the greater is the risk of hypoglycaemia and weight gain. Achieving treatment intensification while mitigating these risks presents a challenge to patient management.
- Basal insulins provide control of fasting glucose; however, their utility in the control of postprandial glucose excursions is limited.
- Glucagon-like peptide-1 (GLP-1) receptor agonists stimulate glucose-mediated insulin secretion, suppress glucagon secretion, delay gastric emptying and decrease appetite. Use of GLP-1 receptor agonists in combination therapy with basal insulin offers an alternative approach to intensification of insulin therapy.
- Prospective interventional trials demonstrate that GLP-1 receptor agonists added to basal insulin decrease postprandial glucose levels, lower HbA1c levels, decrease weight and lower basal insulin requirements without increasing the risk of major hypoglycaemic events.
- The current clinical data are limited by the lack of any data on the long-term effects of GLP-1 receptor agonists over additional prandial regimens; they may be beneficial or deleterious.

Pharmacological rationale

Basal insulins provide control of fasting glucose; however, their utility in the control of postprandial glucose excursions is limited. Current treatment algorithms advocate the addition of prandial insulin in patients who have not reached their glycaemic targets with basal insulin. T2DM is characterised by impaired insulin secretion, inappropriately high glucagon secretion and increased insulin resistance. Exogenous insulin addresses only one aspect of this pathophysiology. GLP-1 receptor agonists suppress glucagon secretion by α cells, suppress appetite and delay gastric emptying. These effects decrease postprandial glucose excursions, potentially negating the need for prandial insulin. Based on the known mechanisms of action of GLP-1 receptor agonists, their use in combination therapy with basal insulin might offer an alternative approach to aid in maximising HbA1c control, while managing body weight and minimising the risk of hypoglycaemia.
Although all GLP-1 receptor agonists share the same basic mechanism of action, differences in their pharmacokinetics result in variations in their effects on fasting blood glucose and postprandial glucose excursions. Data suggest that continuous GLP-1 exposure might downregulate effects on gastric emptying, with a subsequent impact on postprandial glucose excursions. Short-acting GLP-1 receptor agonists (eg, exenatide, lixisenatide), which provide intermittent GLP-1 exposure, have a greater effect on postprandial glucose excursions, suggesting that their use could, in theory, better complement the activity of basal insulin. Short-acting GLP-1 receptor agonists exert their most pronounced postprandial glucose effects following the first meal after drug administration. Clinical studies are needed to verify whether there will be any advantage to administering lixisenatide in conjunction with the largest meal of the day.

### Clinical evidence

Clinical data from prospective and retrospective studies evaluating the efficacy of exenatide in combination with...
Retrospective observational and clinical practice studies examining GLP-1 receptor agonists combined with basal insulin have consistently shown improvements in HbA1c and postprandial glucose levels, with concomitant weight loss and no marked increase in the risk of hypoglycaemia.\(^\text{11}\)

Advantages:
- reduced exogenous insulin requirement
- weight maintenance or loss
- ability to target both fasting and postprandial hyperglycaemia
- relatively low risk of hypoglycaemia

Concerns:
- adverse effects
- impact on absorption of other drugs
- fixed dosing schedules
- costs — not currently PBS-listed for this indication

The potential benefits of combining a GLP-1 receptor agonist with basal insulin need to be weighed against tolerability, safety and costs (Box 3). In addition, fixed dosing schedules and the potential impact on the absorption of other drugs should be taken into account.

The most commonly reported adverse events with GLP-1 receptor agonists are gastrointestinal; predominantly nausea, vomiting and diarrhoea. Although these adverse events are reportedly worst at the beginning of treatment and reduce over the duration of the study, they still account for a high proportion of withdrawals from trials.\(^\text{24}\) A similar gastrointestinal tolerability profile has been noted in studies combining GLP-1 receptor agonists with basal insulin, with nausea being the predominant gastrointestinal adverse event (exenatide, 41% v placebo, 8%;\(^\text{15}\) lixisenatide, 39.6% v placebo, 4.5%).\(^\text{17}\)

Compared with placebo, higher discontinuation rates due to treatment-emergent adverse events were reported in the basal insulin combination studies with exenatide (9% v placebo, 1%)\(^\text{15}\) and lixisenatide (9.1% v placebo, 3.2%).\(^\text{17}\) The current clinical data are limited by the lack of any long-term safety data. In retrospective studies, the frequency of adverse events as a whole was low; however, discontinuation rates due to adverse events were higher (22%–27%) than have been reported in prospective studies.\(^\text{12}\)

GLP-1 receptor agonists do not replace the use of insulin. Identifying responders and non-responders is a clinical challenge; no data are available to aid in predicting who will or will not respond. If patients have not responded within a reasonable time frame, such as 3 months, then the GLP-1 receptor agonist should be stopped. A United States-based retrospective cohort study has shown adherence rates for exenatide and liraglutide to be less than 60%.\(^\text{25}\) Thus, before stopping therapy it would be pertinent to discuss compliance and administration issues with the patient.

Debate continues as to the true clinical relevance of the possible association between acute pancreatitis and the use of incretin-based therapies. Data from postmarketing reports are conflicting. Two recent studies have examined DPP-4 inhibitors and GLP-1 receptor agonists.\(^\text{26,27}\) In both studies, the majority of the body of evidence was built on the association between pathological changes of the pancreas and the use of DPP-4 inhibitors. The data presented on GLP-1 receptor agonists were limited in terms of sample size\(^\text{26}\) or relative risk.\(^\text{27}\) No cases of pancreatitis have been reported in RCTs of GLP-1 receptor agonists combined with basal insulin.\(^\text{12}\) Diabetes itself places patients at increased risk of developing pancreatitis; thus, it remains to be determined whether the reports of acute pancreatitis are related to the patient’s underlying disease. The issue has come under considerable regulatory scrutiny around the world but, as yet, no conclusions have been reached. The issue is complex and definitive answers will
only come from longer-term data. In the meantime, it is recommended that if pancreatitis is suspected, GLP-1 receptor agonists should be discontinued and, if confirmed, not restarted. GLP-1 receptor agonists should be avoided in patients with a history of pancreatitis.

**Conclusion**

The available data present a strong pharmacological rationale for the combined use of GLP-1 receptor agonists with basal insulin, and these are supported by positive results from short-term clinical trials. Box 4 summarises practical considerations that Australian clinicians should be aware of when considering the use of GLP-1 receptor agonists in combination with basal insulin. The combination may be of particular value for patients who are overweight and for those in whom hypoglycaemia is an especially worrisome potential adverse effect. Although cost and gastrointestinal side effect profiles should be taken into account when considering this combination, it is likely to be an important therapeutic option for T2DM in the future.

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