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Advances in Diabetes Therapy in the Elderly

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ABSTRACT

Diabetes is increasing in prevalence and the choice of medication is expanding with the recent introduction of a new class of oral hypoglycaemics. Emerging data on the older oral hypoglycaemics is adding to the complexity of diabetes management, particularly in the elderly for whom special consideration of adverse effects and dosing are required. As diabetes progresses the inevitable decline in pancreatic β -cell function diminishes the efficacy of the oral hypoglycaemics and insulin is required. The new synthetic long-acting insulin analogues are useful in the elderly both for ease of administration and to minimise hypoglycaemia. Exogenous insulin often does not provide optimal control of diabetes and it is envisioned that in the future, therapy may target preservation of pancreatic β -cell function to produce long-term glycaemic control with endogenous insulin.

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INTRODUCTION

Type 2 diabetes mellitus is becoming more prevalent and its incidence increases with age – prevalence peaking between 65 to 74 years of age.¹ Despite this, there are very little data specifically examining the use of oral hypoglycaemics in the elderly. Diabetes management is becoming complex with the introduction of a new class of oral hypoglycaemics, the incretin mimetics. Emerging evidence on the safety and efficacy of the older oral hypoglycaemics is adding to the complexity of diabetes management. The published guidelines recommend an aggressive approach to diabetes management, with the introduction of metformin at diagnosis, in an attempt to reduce progression of pancreatic β -cell dysfunction.² However, as diabetes progresses, β -cell decline is often inevitable and the addition of insulin becomes necessary. The new synthetic long-acting insulin analogues have pharmacokinetic properties that better mimic insulin profiles in a non-diabetic person.

INCRETIN MIMETICS

The concept of an incretin effect was derived from the discovery that an oral glucose load was more effective at releasing insulin than intravenous glucose.³ This effect results from the release of intestinal peptides from L and K cells in the gastrointestinal tract in the presence of glucose in the gut.⁴ These intestinal peptides or incretins, the glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide have additional non-insulinotropic effects including suppression of glucagon

secretion in the presence of glucose and slowing gastric emptying. In animal studies, glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide have been shown to preserve β -cell mass by increasing regeneration and reducing apoptosis.^{5,6} Glucagon-like peptide-1 is rapidly degraded by the dipeptidyl peptidase-4 enzyme to an inactive metabolite and this was a major hurdle in developing an incretin mimetic.⁴ This hurdle has been overcome by the development of a glucagon-like peptide-1 analogue resistant to degradation (e.g. exenatide) and the selective inhibitors of the degrading enzyme (e.g. sitagliptin, vildagliptin).

Glucagon-Like Peptide-1 Analogue

Exendin-4, a naturally occurring intestinal peptide with 53% amino acid homology to glucagon-like peptide-1, is resistant to degradation by the dipeptidyl peptidase-4 enzyme. Exenatide, a synthetic exendin, was the first glucagon-like peptide-1 analogue approved for use.³ Exenatide is administered subcutaneously before the two main meals of the day and has a mean half life of 3.3 to 4 hours.⁴ In selected clinical trials (mean age 53 to 59 years), the addition of exenatide to oral hypoglycaemics resulted in a significant decline in haemoglobin A1c (HbA1c) when compared with placebo. However, when exenatide was compared to insulin glargine (long-acting) or insulin aspart (ultra short-acting) there was no significant difference in HbA1c.³ There was no difference in fasting glucose but postprandial glucose was lower with exenatide when compared with insulin.^{7,8}

Weight loss due to exenatide was dose dependent and progressive with mean weight loss in selected clinical trials ranging from 1.6 to 2.8 kg at 30 weeks to 5.3 kg at 3 years.⁴ The most common adverse effects, nausea and vomiting, were dose dependent and appeared to decline after eight weeks. Pancreatitis occurs at the rate of 0.27 events per 1000 patient years based on spontaneous reporting. However, in 90% of cases there was another risk factor present that could confound the association between exenatide and pancreatitis.⁹

Exenatide (not listed on the Australian Pharmaceutical Benefits Scheme) is indicated as adjuvant therapy in type 2 diabetes with metformin and/or a sulfonylurea. No dose adjustment is necessary in the elderly but it is contraindicated in the presence of severe renal impairment (creatinine clearance < 30 mL/min).

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin, an oral dipeptidyl peptidase-4 inhibitor, is rapidly absorbed with peak plasma levels attained after 1 to 4 hours. Approximately, 80% of the dose is excreted unchanged in the urine and dose reduction is required in renal impairment.⁴ In a meta-analysis, sitagliptin and vildagliptin either as monotherapy or add-on therapy,

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reduced HbA1c by 0.74% compared with placebo (95%CI -0.85 to -0.62).³ In individual trials of dipeptidyl peptidase-4 inhibitors (mean age 51 to 57 years), non-inferiority was established with thiazolidinediones and glipizide but not metformin.¹⁰⁻¹³ A 52 week trial comparing sitagliptin and glipizide (mean age 57 years) showed a decline in efficacy of sitagliptin after 30 weeks.¹⁰ Dipeptidyl peptidase-4 is expressed in many tissues including lymphocytes.¹⁴ Although this was not thought to be of physiological significance, clinical trials of dipeptidyl peptidase-4 inhibitors have shown an increased risk for urinary tract infection and nasopharyngitis. Headaches have also been reported but in contrast to exenatide, gastrointestinal adverse effects were not increased and weight remained unchanged.³

Sitagliptin is approved by the Australian Pharmaceutical Benefits Scheme for combination therapy with metformin or a sulfonylurea in patients with HbA1c above 7%. Sitagliptin is administered orally once daily with no dose adjustment necessary in the elderly except in the presence of renal impairment.

THIAZOLIDINEDIONES

Pioglitazone and rosiglitazone are agonists of the nuclear receptor peroxisome proliferator-activated receptor- γ . Activation of proliferator-activated receptor- γ results in transcription of genes involved in carbohydrate and lipid metabolism. The thiazolidinediones increase hepatic and peripheral insulin sensitivity and result in a reduction of HbA1c (approximately 1%).¹⁵ Adverse effects include an increase in cardiac failure, fluid retention and anaemia. There is evidence that the thiazolidinediones may increase peripheral fractures in women.^{15,16} Weight gain and an increase in adiposity is common with redistribution from visceral deposits to subcutaneous fat with the added advantage of reducing fatty liver.^{2,17}

Rosiglitazone

The recent controversy regarding the cardiovascular safety of rosiglitazone has caused concern for patients and physicians. A meta-analysis by Nissen et al., showed an increase of around 40% in the risk of myocardial infarction with rosiglitazone.¹⁸ There were a number of limitations to this study, which make interpretation of the results unclear. The trials were primarily designed to assess glycaemic control, there was no standard method for assessing outcomes, and comparisons with both placebo and active treatment were included. However, a recent interim analysis of the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes trial showed results compatible with the meta-analysis by Nissen et al., with a trend towards increased risk of myocardial infarction. These results need to be interpreted with caution as the trial is incomplete with a low event rate and a high rate of loss to follow-up.¹⁹

Of concern is a study in patients (over 65 years of age) on pioglitazone or rosiglitazone that demonstrated an increase in the risk of congestive heart failure (RR 1.6; $p < 0.001$), acute myocardial infarction (RR 1.4; $p = 0.02$) and mortality (RR 1.29; $p = 0.03$).²⁰ As a result of these findings, the product information for rosiglitazone has been revised to state that it is no longer indicated for triple oral therapy with metformin and sulfonylureas or in combination with insulin. Rosiglitazone is contraindicated in patients with New York Heart Association Class I to IV heart failure and acute coronary syndromes.

Pioglitazone

In contrast to the findings in Nissen et al.'s meta-analysis, there is no evidence that pioglitazone increases the risk of ischaemic events. In fact, there is some suggestion that pioglitazone may have cardioprotective effects. There is evidence that pioglitazone has a beneficial effect on lipid profile (increases high-density lipoprotein, reduces triglycerides), reduces systolic blood pressure and has beneficial effects on carotid wall thickness.¹⁷ The PROspective pioglitAzone Clinical Trial In macroVascular Events study demonstrated a marginally significant 16% reduction in the secondary endpoints of death, myocardial infarction and stroke.²¹ Pioglitazone is approved for use as triple oral therapy with metformin and sulfonylureas or in combination with insulin. In contrast to rosiglitazone, pioglitazone is only contraindicated in patients with New York Heart Association Class III to IV heart failure.

METFORMIN

Metformin has been used for over 40 years and is considered the treatment of choice for type 2 diabetes, particularly in obese patients. Metformin improves liver and peripheral sensitivity to insulin and reduces basal production of glucose by the liver. Gastrointestinal adverse effects lead to discontinuation of metformin in around 5% of patients.²² Lactic acidosis is a rare adverse effect that has restricted the use of metformin in patients with conditions that predispose to tissue hypoxia, such as cardiac, liver or renal failure. Metformin is contraindicated in patients with a creatinine clearance below 30 mL/min and in the elderly. These contraindications have been questioned following a meta-analysis showing that the incidence of lactic acidosis in patients (mean age 57 years) with type 2 diabetes not receiving metformin (9.9 events per 100 000 patient-years) was similar to patients taking metformin (8.1 per 100 000 patient-years).²³ In addition, lactic acidosis has occurred in patients with coexisting conditions, such as renal failure, which could itself be responsible for lactic acidosis.²⁴ It is important to clarify the validity of the contraindications for metformin as it is often withheld in patients who may benefit from its use as an effective oral hypoglycaemic with vascular protective effects. The UK Prospective Diabetes study showed that over 10 years in a subgroup of 342 obese subjects (mean age 52.8 years) monotherapy with metformin resulted in an absolute reduction in risk of diabetes-related deaths (5%), all-cause mortality (7%), myocardial infarction (6%) and stroke (3%).²⁵ These findings have been supported in subsequent trials and systematic reviews.²²

SULFONYLUREAS

Sulfonylureas are insulin secretagogues and have been available for over 50 years. The efficacy of the sulfonylureas is similar to metformin with a reduction in HbA1c of 1.5%. The main adverse effect of sulfonylureas is hypoglycaemia, which can be prolonged particularly in the elderly or in patients with renal impairment. Another common adverse effect is weight gain, which may not be of as much concern in the elderly. Sulfonylureas are widely used although some concerns have been raised regarding their long-term durability in terms of glycaemic control and possible negative effect on pancreatic β -cell function.

Table 1. Comparison of the available oral hypoglycaemics for use in the elderly

Oral hypoglycaemics	Contraindications/precautions	Adverse effects	Elderly patients
Sulfonylureas	Renal or hepatic insufficiency	Hypoglycaemia, weight gain	Choose short-acting sulfonylureas
Metformin	Avoid if creatinine clearance < 30 mL/min, cardiac or hepatic insufficiency or other hypoxic states	Gastrointestinal, lactic acidosis	Weight neutral, anorexia, minimal hypoglycaemia, avoid dose > 2 g/day
Acarbose	Small bowel disease, significant renal impairment (creatinine clearance < 30 mL/min)	Gastrointestinal, flatulence, bloating	Lower efficacy
Thiazolidinediones	Congestive heart failure	Weight gain, fluid retention	Increased fracture risk, minimal hypoglycaemia, cardiovascular risk with rosiglitazone
Dipeptidyl peptidase-4 inhibitors	Dose reduction in renal impairment	Headaches, infections	Weight neutral, minimal hypoglycaemia, minimal long-term data

ALPHA GLUCOSIDASE INHIBITORS

The alpha glucosidase inhibitors, such as acarbose, delay carbohydrate absorption in the gastrointestinal tract, do not cause hypoglycaemia and are useful for targeting postprandial hyperglycaemia. HbA1c reduction with the alpha glucosidase inhibitors (0.8%) is less than metformin or the sulfonylureas and gastrointestinal adverse effects such as flatus, abdominal pain and cramps may limit their use.²⁶

ORAL HYPOGLYCAEMICS IN THE ELDERLY

Presented with a vast array of therapies it can be difficult to make decisions about diabetes management. Initially, it is important to weigh the benefits of tight glycaemic control against the risks. The American Geriatrics Society recommends a target HbA1c of below 7% but if the patient is frail or has a short life expectancy a target HbA1c of below 8% is recommended.²⁷ In the elderly, targeting cardiovascular risk factors such as hyperlipidaemia and hypertension may reduce rates of disease and death more than intensive glycaemic control.²⁷ The Veteran Affairs Diabetes Trial in patients (mean age 60.4 years) with suboptimally controlled type 2 diabetes showed no reduction in cardiovascular events in the group allocated to intensive glycaemic control over a median follow-up of 5.6 years.²⁸ In addition, patients whose life expectancy as assessed by comorbid illness and functional status is less than five years, are unlikely to benefit from tight glucose control.²⁹

Avoiding hypoglycaemia may be more relevant in the elderly as it can increase the risk of myocardial infarction and falls, with resultant fracture, disability and functional decline. Therefore, drugs that cause less hypoglycaemia, such as metformin, the thiazolidinediones or incretin mimetics may be preferable to the sulfonylureas (Table 1). Alternatively, using the short-acting sulfonylureas, such as gliclazide, instead of long-acting sulfonylureas, such as glimepiride or glibenclamide, may be appropriate (Table 2).

The incretin mimetics are well suited for managing diabetes in the elderly as the risk of hypoglycaemia is minimal unless combined with a sulfonylurea. Sitagliptin may be preferable to exenatide for ease of use, as sitagliptin is administered orally while exenatide is administered subcutaneously and sitagliptin is weight neutral while exenatide causes weight loss.

Adverse effects of the oral hypoglycaemics have an increased significance in the elderly. As opposed to young obese patients, inhibition of appetite is not a beneficial effect of metformin in the non-obese elderly.

Table 2. Sulfonylureas available in Australia

Sulfonylureas	Dose	Duration of action	Excretion
Glibenclamide	2.5-20 mg	18-24 h	Liver/kidney for active metabolite
Gliclazide (modified-release)	40-320 mg (30-120 mg)	12-16 h	Liver
Glimepiride	1-4 mg	24 h	Liver
Glipizide	2.5-40 mg	16-24 h	Liver

Anorexia, suboptimal oral intake and weight loss from metformin may not be appropriate in this age group. In addition, vitamin B12 deficiency, resulting from reduced oral intake or poor diet, is more common in the elderly and may be worsened by metformin use. A case control study in Chinese patients found that increasing the metformin dose and duration of treatment were significantly associated with the risk of vitamin B12 deficiency.³⁰ When metformin is used in the elderly, the dose should be conservative and not titrated up to the maximum recommended dose of 3 g/day.

In elderly patients with renal impairment, suitable choices may include a sulfonylurea excreted by the liver, such as gliclazide, which also has the shortest duration of action (Table 2). Sitagliptin can also be considered in elderly patients with a creatinine clearance below 30 mL/min, provided the dose is reduced to 25 mg daily. Alternatively, the thiazolidinediones, particularly pioglitazone, may be useful with the advantages of lower risk of hypoglycaemia, weight gain and the potential for preservation of β -cell function.³¹ A diabetes outcome progression trial in patients (mean age 56 to 57 years) with type 2 diabetes demonstrated better durability of glycaemic control with rosiglitazone as compared with glyburide or metformin.³² Rate of loss of pancreatic α -cell function was slowed and insulin sensitivity improved.³²

INSULIN ANALOGUES

Insulin analogues are insulin-like molecules with alterations in their amino acid sequence resulting in different pharmacokinetics. Insulin analogues became available 10 years ago and include the long-acting insulin analogues, detemir (Levemir) and glargine (Lantus), and the ultra short-acting insulin analogues, aspart (NovoRapid), glulisine (Apidra) and lispro (Humalog) (Table 3).

Table 3. Comparison of insulin analogues and insulin

Insulin type	Generic name	Brand name	Onset of action	Duration of action
Ultra short-acting analogue	Aspart, glulisine, lispro	Novorapid, Apidra, Humalog	0-0.25 h	3.5-4.5 h
Long-acting analogue	Detemir, glargine	Levemir, Lantus	0.25-4 h	24 h
Short-acting insulin	Neutral (human)	Actrapid, Humulin R	0.5 h	4-6 h
Long-acting insulin	Isophane (human)	Humulin NPH, Protaphane	1-2 h	12-18 h

Long-Acting Insulin Analogues

Insulin glargine has an amino acid substitution resulting in a molecule that is less soluble at body pH. This results in the formation of an amorphous precipitate in the subcutaneous tissues from which insulin is gradually absorbed. As insulin glargine is soluble in acid pH, the acidic solute used may cause stinging at the injection site.³³ Insulin glargine is listed by the Australian Pharmaceutical Benefits Scheme for use in type 1 and type 2 diabetes.

Insulin detemir has been modified so that there is a short chain fatty acid attached to an amino acid. This allows reversible binding to albumin in the interstitial fluid and circulation resulting in slower absorption.³³ The profiles of insulin glargine and insulin detemir are relatively flat and reproducible over 24 hours and they can be given as a once daily injection. Insulin detemir is listed by the Australian Pharmaceutical Benefits Scheme for use in type 1 diabetes.

In trials comparing the long-acting insulin analogues to the traditional long-acting isophane insulin, there was no clear benefit in glycaemic control with the long-acting insulin analogues but symptomatic and nocturnal hypoglycaemia was reduced.³³ This finding makes the long-acting insulin analogues an attractive choice for the elderly in whom hypoglycaemia should be minimised. In the elderly who are on maximal doses of oral hypoglycaemics with elevated fasting blood glucose, adding a long-acting insulin analogue to their regimen is a good option.

Some elderly patients may be able to adjust their own insulin based on pattern recognition according to a simple algorithm (Table 4).³⁴ The availability of prefilled disposable devices and once daily dosing should make it relatively easy to introduce insulin. However, patients with failing eyesight or limited dexterity who are unable to use an insulin pen may require an InnoLet injecting device, which is only available for Protaphane or the premixed insulin, Mixtard 30/70.

Table 4. Algorithm for adjusting long-acting insulin analogues in the elderly

Mean fasting blood glucose*	Adjustment
> 12 mmol/L	Increase 4 units
8-12 mmol/L	Increase 2 units
4-8 mmol/L	No change
< 4 mmol/L	Decrease 2 units

*mean for the previous week

Ultra Short-Acting Insulin Analogues

Ultra short-acting insulin analogues have been developed by different amino acid substitutions which reduce the affinity between insulin monomers making dissociation from hexamers and absorption much quicker than the traditional short-acting neutral insulin. The ultra short-acting insulin analogues achieve peak plasma levels in half the time and have twice the peak of traditional insulin.³⁵ Potential advantages of the ultra short-acting insulin analogues are the possibility of injecting just prior to the meal in contrast to neutral insulin, which requires a longer time interval (up to 30 minutes). This is more convenient and flexible and may be advantageous in patients for whom oral intake is unpredictable. Ultra short-acting insulin analogues should theoretically control postprandial glucose peaks better than neutral insulin, but there has only been evidence of improvement in HbA1c in type 1 and not type 2 diabetes.³⁵ Another proposed advantage of the ultra short-acting insulin analogues over neutral insulin is less hypoglycaemia, however, currently there is no convincing evidence that this is the case.

CONCLUSION

The older oral hypoglycaemics, such as the sulfonylureas and metformin, are as effective or more effective than the newer more expensive oral hypoglycaemics, such as the thiazolidinediones, alpha glucosidase inhibitors and incretin mimetics. Additionally, there is a longer history of use with the older oral hypoglycaemics and more intense scrutiny in clinical trials with evidence of possible benefits of metformin on vascular endpoints. The incretin mimetics may be useful in the elderly as they have a reduced risk of hypoglycaemia and potential benefit in preserving pancreatic β -cell mass, however, there are few long-term clinical trials and experience with this new drug class is limited.

Given the available evidence there is no reason to choose any of the new oral hypoglycaemics first over metformin, with the short-acting sulfonylureas remaining a reasonable second choice. The main limitation of the new oral hypoglycaemics is their inability to provide long-term glycaemic control.

It is envisioned that in the future, therapy may target preservation of pancreatic β -cell function to produce long-term glycaemic control with endogenous insulin.

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The material in this article has been accredited by SHPA as suitable for inclusion in an individual pharmacist's CPD plan as outlined in the **shpacpd** program <www.shpa.org.au/docs/cpd.html>. A series of questions that can assist you with evaluating your learning outcomes can be found on the SHPA web site. Answers to these questions can be lodged at <www.shpa.org.au/docs/cpd.html> until March 2010. In **shpacpd** this is considered an Activity Group 2 activity: Improving Knowledge and Skills with assessment. The number of hours will be dependent on the time you have taken to read the article, complete the multiple choice questions and submit the answers.