Starting insulin treatment in type 2 diabetes

Jencia Wong, Associate Physician, and Dennis Yue, Professor of Medicine, The Diabetes Centre, Royal Prince Alfred Hospital and Faculty of Medicine, University of Sydney, Sydney

Summary

Almost all patients with type 2 diabetes will eventually fail to respond adequately to oral hypoglycaemic drugs and will require insulin therapy. A regimen of bedtime intermediate-acting insulin in combination with daytime oral drugs is acceptable to patients, simple to start and results in rapid improvement in glycaemic control. It can be started safely in general practice and is the most practical way of implementing insulin in the face of a worldwide epidemic of type 2 diabetes.

Key words: metformin, sulfonylureas, thiazolidinediones.

(Aust Prescr 2004;27:93–6)

Introduction

The emerging epidemic of type 2 diabetes, coupled with finite health resources, requires the treatment of hyperglycaemia to be simple and efficiently managed. Type 2 diabetes is a progressive disease and eventually almost all patients will require insulin to maintain good glycaemic control. Knowing when and how to start insulin in general practice is central to the optimal management of type 2 diabetes.

The need to start insulin therapy in a newly diagnosed patient with type 2 diabetes is relatively uncommon. It should be considered when there is considerable weight loss, severe symptoms of hyperglycaemia or the presence of significant ketonuria. Many of these patients can be converted back to oral drugs once glycaemic control has been established and there is some recovery of pancreatic β cell function.

A more common problem is when and how to commence insulin in patients with type 2 diabetes who are in 'secondary failure'. The term secondary failure refers to the 'failure' of oral hypoglycaemic drugs to maintain glycaemic control. The United Kingdom Prospective Diabetes Study (UKPDS)[1] clearly showed that most people with type 2 diabetes will experience progressive pancreatic β cell dysfunction, despite excellent control. The secondary failure rate in this study was 44% after six years of diabetes. Since the time of the UKPDS, targets for glycaemic control have become increasingly stringent so secondary failure of oral hypoglycaemic drugs now occurs much sooner and is almost invariable.

The younger, the sooner, the better

The key to when to start insulin is to identify the appropriate glycated haemoglobin (HbA1c) target for an individual patient. Despite the promulgation of various 'guidelines', there is no single HbA1c concentration which suits everyone. For example, the younger patients already on maximal oral therapy and as much lifestyle modification as they can manage, would benefit greatly in the long term from early introduction of insulin, even if their HbA1c is only minimally elevated (e.g. 7%). The important point here is the **early** introduction of insulin, as the lifetime risk of complications for young patients is great. On the other hand, older patients who are not symptomatic and have no microvascular complications such as retinopathy, can be allowed to remain in 'secondary failure' at an HbA1c of 8–9%. In these patients, prognosis is governed mainly by macrovascular disease, which is not greatly influenced by glycaemic control.

New oral drugs or insulin?

Traditionally metformin plus a sulfonylurea has been the mainstay of oral treatment. Patients understandably often want to know whether they should try adding a third drug or begin insulin. The addition of acarbose can usually only decrease the HbA1c by 0.5% at best, so one would only consider its use if a slight improvement in control is needed. Repaglinide and sulfonylureas should not be used in combination, as they are both insulin secretagogues. The response to therapy with a thiazolidinedione (pioglitazone or rosiglitazone) can be more profound with improvements in HbA1c of 1–2%. The decision whether to start insulin or to add a thiazolidinedione would depend on factors such as patient acceptance, coexisting conditions (thiazolidinediones are contraindicated in oedematous states and heart failure) and access to medicines. At this stage it matters less which drug or 'pathway' is used, but more that the patient's glycaemic target is reached.

Sometimes it is necessary to let patients try triple oral drug therapy. If nothing else, it serves to convince them that insulin is indeed necessary. In this situation, it is important not to delay insulin therapy for more than a few months. A trial of triple therapy for two months should be sufficient to assess whether it is likely to be effective or not.

Choice of insulin regimen: the combined oral drug and insulin approach

Many patients and practitioners procrastinate as insulin treatment is erroneously considered to be risky and difficult.

However, the regimen used routinely in our clinic is safe and easy to start.[2] In our opinion this regimen can be started in general practice. The regimen consists of a combination of intermediate-acting insulin before bed, while continuing maximum oral drug therapy during the day.

What to do with the oral drugs?

The patient is asked to remain on all the oral hypoglycaemic drugs that they are currently taking. The only exceptions are:

- if the patient is taking supra-maximal doses of any of the oral drugs, they are reduced to what is recommended in the product information
- if the patient is suffering from the gastrointestinal adverse effects of metformin, it is reduced to a dose which is tolerated
- if the patient is taking three oral hypoglycaemic drugs including acarbose, the acarbose is stopped as its adverse effects usually outweigh its advantage.

Although the oral drugs have 'failed' in the situation of 'secondary failure', they are still exerting considerable hypoglycaemic effects. Clinical studies have shown that if either the sulfonylurea or metformin are stopped altogether, then each needs to be replaced by an extra 20–30 units of daily insulin. In other words, the insulin dosage would need to exceed about 60 units a day before improvement in glycaemic control could occur. This would require a more aggressive insulin regimen and titration, making the process of starting insulin much more difficult. If a thiazolidinedione has been used, this could be continued initially at least, as it may also contribute an insulin sparing effect.

How much insulin and at what time?

For practical purposes, the patient can always be commenced on 10 units of intermediate-acting insulin, given just before bedtime and as late as possible. This timing allows the insulin to exert its maximum action just before dawn (a time of higher insulin resistance) rather than at 2–3 a.m. when it is most likely to cause hypoglycaemia. If the patient is very nervous or reluctant and it is imperative to minimise the risk of hypoglycaemia, however small, then a slightly lower dosage can be used to get the process underway and to gain the patient's confidence. Patients who have symptoms of hyperglycaemia can start at a higher dose of insulin, but this would rarely need to exceed 20–25 units.

The bedtime dose of insulin is best given as isophane insulin. Currently in Australia, there is only one brand of human isophane insulin available. When it becomes generally available, insulin glargine will probably become the basal insulin of choice as its 'flatter' and longer action make it more suitable for this purpose.[3]

What to tell patients on the day they start insulin?

Although everyone has different information needs, comprehensive information given when starting insulin may confuse many patients. They may not remember the more important messages and some may even be scared away from insulin treatment altogether. Our practice is to concentrate on teaching patients how to inject the insulin subcutaneously into the abdomen, using devices such as the FlexPen or InnoLet which are extremely user-friendly and can be taught in a matter of minutes.

The day patients start insulin is also not an ideal time for detailed dietary advice. We only emphasise the need to have regular meals and snacks (including one before bed) containing carbohydrates.

At this stage of diabetes, most patients would be familiar with glucose monitoring and should be asked to perform this. As adjustment of insulin dosage in this regimen is primarily dependent on the morning fasting blood glucose concentrations, testing at this time point is the first priority and should be included every day. For some patients who cannot test their blood glucose for various reasons, it may be necessary to commence insulin without such monitoring and rely on blood glucose monitoring at the doctor's office and HbA1c concentration to make dose adjustments.

Hypoglycaemia is the only risk in starting insulin therapy and however much this risk is minimised, it cannot be completely eliminated. How much to inform patients about it is a difficult question. Too much detail would incur the risk of scaring a reluctant patient away from the correct treatment, but not enough would open the door to medical litigation. This dilemma is of course not unique to commencing insulin and each doctor must make a decision with individual patients. It is reassuring that in patients with type 2 diabetes, hypoglycaemia due to insulin is usually not severe.

How to titrate insulin dosage and monitor progress?

A major feature of this regimen is that insulin is added to existing treatment. Glycaemic control should therefore improve immediately and for practical purposes, should not deteriorate. This means that the dose of insulin can be increased relatively slowly, minimising the risk of hypoglycaemia. As described originally, the regimen[2] increased the insulin dosage by 4 units a day if the fasting blood glucose exceeded 8 mmol/L on three consecutive days and by 2 units a day if it exceeded 6 mmol/L. We tend to do it slightly slower and adjust insulin dosage according to these glucose thresholds every 1–2 weeks. The slower pace helps to gain the patient's confidence and reduces the risk of hypoglycaemia. This titration regimen is of course not 'cast in stone' and there are ongoing trials that are exploring the best options.

After 2–3 months, the patient is likely to be on about 30 units of insulin each day and maximum oral drug therapy. Measuring the HbA1c concentration after this interval helps to quantify the

new level of glycaemic control and further increases in insulin dosage can be made accordingly. There is generally a reduction in HbA1c of about 2% and an increase in body weight of several kilograms. If these changes are not evident, one should consider the possibility that the patient has not been taking the insulin regularly or someone unfamiliar with the regimen has reduced or stopped one or more of the oral hypoglycaemic drugs.

In our experience, after about 6–12 months, a further increase in insulin dosage, according to HbA1c concentration, is required. The final daily insulin requirement is about 50–60 units and is higher in those with obesity, higher initial concentrations of HbA1c, and elevated hepatic enzymes which are surrogate measures of fatty liver and insulin resistance.

The advantages of the combined oral drug and insulin regimen

The literature often addresses the question of whether combined oral drug and insulin treatment provides better glycaemic control than insulin alone. This is in a sense a meaningless question because the answer would depend on how much insulin was used. We favour the combined regimen because glycaemic control begins to improve from the day insulin is started. The titration of insulin dosage can be gradual and therefore relatively safe, in an outpatient setting.

The alternative is to stop the oral drugs abruptly. In this scenario, insulin needs to be given at least twice daily and the dose needs to be quickly titrated upward to 70–80 units per day, or glycaemic control may actually deteriorate. This 'insulin alone' regimen is obviously possible, but requires more patient contact, making it less user-friendly for both doctors and patients. All too commonly, we have witnessed deterioration in glycaemic control when both oral drugs were stopped and not replaced with sufficient insulin.

In our experience, it is easier to persuade patients to undertake combined oral drugs and insulin treatment. They are often comforted by the knowledge that they only need to take insulin once, in the privacy of their own home and without a great deal of disturbance to their daytime routine. When they are familiar with insulin injections they become accepting of a more intensive insulin regimen, should this be required.

When to stop oral hypoglycaemic agents?

Sometimes patients develop frequent daytime hypoglycaemia on combined treatment. When this happens, the sulfonylurea dosage should be reduced or ceased if necessary. Apart from this and in the absence of contraindications (such as renal failure or allergy), there is no good evidence that oral hypoglycaemic drugs must be stopped at any stage and our policy is to continue them while glycaemic control remains satisfactory. Most diabetes specialists would support the continuation of metformin indefinitely, because it increases insulin sensitivity. Others advocate stopping the sulfonylurea after insulin treatment is established, an attitude based more on philosophy than real need. Some patients may wish to reduce the number of tablets they take especially when they are already on multiple medications for blood pressure and lipid control. There is nothing wrong with reducing one or more of the oral hypoglycaemic drugs once they are established on insulin therapy, as long as it is recognised that the dose of insulin needs to go up, by an average of 20–30 units per day for each withdrawn drug, to maintain the same degree of glycaemic control.

When to introduce more complex insulin regimens?

In some patients, fasting blood glucose concentrations may be quite acceptable and yet HbA1c remains significantly elevated. In this situation, a second dose of insulin is needed, usually given in the morning before breakfast. A small starting dose of medium-acting insulin in the order of 6–12 units would be reasonable.

Other patients who are at the more insulin-deficient end of the type 2 diabetes spectrum (these patients can be recognised by their relatively lean body weight and younger age) may be better starting on a twice-daily insulin regimen. The insulin sparing effects of oral hypoglycaemic drugs (and therefore the simplification of insulin titration) would still be present in this situation.

Handy hints

The inevitable need for insulin therapy in most patients is best discussed early in treatment when the need for insulin therapy is not imminent. This message should be continuously reinforced as it helps to set expectations and eases the transition to insulin later on.

Giving practice injections of saline at the time when insulin therapy is being considered may help to allay the anxiety surrounding the injection process. This helps the patients' acceptance of therapy. Diabetes educators can be an additional ongoing source of support and information for your patient, at this time of change.

Conclusion

We are confronting the prospect of having to treat more than one million patients with diabetes in Australia. It will soon be untenable for general practitioners to send all their patients requiring insulin to specialists or diabetes clinics to have this implemented and monitored. The regimen of giving an insulin injection before bed to complement the use of maximum oral hypoglycaemic drugs for patients with diabetes in secondary failure, is easy and safe to implement in general practice as the first step of introducing insulin treatment.

References

1. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837-53. (randomised trial)
2. Yki-Jarvinen H, Ryysy L, Nikkila K, Tulokas T, Vanamo R, Heikkila M. Comparison of bedtime insulin regimens in patients with type 2 diabetes mellitus. A randomized, controlled trial. Ann Intern Med 1999;130:389-96. (randomised trial)
3. Phillips P. Insulins in 2002. Aust Prescr 2002;25:29-31.

Further reading

American Diabetes Association. Insulin administration. Diabetes Care 2003;26(S1):S121-4.

Dunning T. Insulin delivery devices. Aust Prescr 2002;25:136-8.

Conflict of interest: none declared

Self-test questions

The following statements are either true or false
(answers on page 105)

5. In lean young patients with type 2 diabetes, insulin therapy should be delayed as long as possible.
6. Oral hypoglycaemic drugs should be stopped when a patient with type 2 diabetes starts insulin.

Patient support organisation

Diabetes Australia

Diabetes Australia is a federation of twelve organisations – the eight State and Territory Associations of Diabetes Australia, the Australian Diabetes Society, the Australian Diabetes Educators Association, the Kellion Diabetes Foundation and The Diabetes Research Foundation – Western Australia.

The State and Territory associations (see below) and their shopfronts provide ongoing support as well as products, services, information and education for people with diabetes and their families.

Contacts

National office

Diabetes Australia
GPO Box 3156 CANBERRA ACT 2601
Phone: 1300 136 588 (local call cost)
Fax: (02) 6330 1535
E-mail: admin@diabetesaustralia.com.au
Web site: www.diabetesaustralia.com.au

Australian Capital Territory

Grant Cameron Community Centre
27 Mulley Street HOLDER ACT 2611
PO Box 3727 WESTON ACT 2611
Phone: (02) 6288 9830
Fax: (02) 6288 9874
E-mail: diab.act@diabetes-act.com.au
Web site: www.diabetes-act.com.au

New South Wales

26 Arundel Street GLEBE NSW 2037
GPO Box 9824 SYDNEY NSW 2001
Phone: (02) 9552 9900; 1300 136 588 (local call cost)
Fax: (02) 9660 3633
E-mail: info@diabetesnsw.com.au
Web site: www.diabetesnsw.com.au

Queensland

Cnr Merivale & Ernest Streets
SOUTH BRISBANE QLD 4101
GPO Box 9824 BRISBANE QLD 4001
Phone: 1300 136 588 (local call cost)
E-mail: info@daq.org.au
Web site: www.daq.org.au

Northern Territory

Shop 2 Tiwi Place TIWI NT 0810
PO Box 40113 CASUARINA NT 0811
Phone: (08) 8927 8488
Fax: (08) 8927 8515
E-mail: info@diabetesnt.org.au

Western Australia

48 Wickham Street EAST PERTH WA 6004
PO Box 6097 EAST PERTH WA 6892
Phone: (08) 9325 7699
Fax: (08) 9221 1183
E-mail: info@dawa.asn.au