Premixed insulin analogues: A new look at an established option

Ted Wu

There are many regimens available when initiating and intensifying insulin for people with type 2 diabetes. Once-daily basal insulin is commonly prescribed, but the latest evidence from multiple sources shows that premixed insulin analogues are virtually indistinguishable from basal analogues in terms of HbA_{1c} reduction, hypoglycaemia and weight gain. As such, they are recommended as equal first-line therapies in terms of insulin initiation and intensification by bodies such as the Royal Australian College of General Practitioners, National Health and Medical Research Council and International Diabetes Federation. This article reviews some of the evidence behind these recommendations, as well as providing some practical guidance regarding how premixed insulin should be started, titrated and intensified. As in other areas of diabetes, one size does not necessarily fit all, and the choice of insulin regimen should ideally be matched to the individual requirements of the patient.

The last decade has seen a huge proliferation in the number of classes and combinations of medications used to treat high blood glucose that results from type 2 diabetes. Despite this, insulin will still be required eventually in the majority of people with type 2 diabetes due to the progressive nature of the beta-cell loss inherent in the disease process. Several insulin options are available in type 2 diabetes, including basal only, premixed only and basal–plus/basal–bolus regimens. This review will provide some practical guidance on the use of premixed insulin in the Australian primary care setting.

When should insulin be initiated?

All diabetes treatments apart from insulin have a maximum dose associated with their use, and as a direct consequence have an average HbA_{1c} lowering potential associated with them, which range from about 0.5% to 1.5% (0.05–16.4 mmol/mol). Insulin has no equivalent maximum dose and, at least in theory, has unlimited HbA_{1c} lowering potential given the ability to up-titrate the dose to achieve the desired glycaemia response. Thus, the simplest clinical indication of when insulin should be started is when the alternative therapies are no longer able to achieve the desired level of glucose lowering.

In this most common scenario of insulin initiation, people with type 2 diabetes are already on multiple agents and have a high HbA_{1c}. Self-monitoring of blood glucose (SMBG) is not often used in type 2 diabetes that is well controlled with agents not associated with hypoglycaemia, but in people who need to start insulin, SMBG is necessary to identify the pattern of hyperglycaemia and ensure hypoglycaemia is avoided. This will help to determine the insulin regimen most suited to that individual (see Initiation of insulin, below).

Human or analogue premixed?

Human premixed insulin has been in clinical use for many decades, while currently available analogue premixed insulins have been available in Australia for just over a decade. It should be noted that the analogue component only refers to the short-acting component of the premixed insulin: that is, the currently available

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1. Daily premixed insulin analogues have been shown to achieve roughly the same results as basal insulin at the time of insulin initiation.
2. When starting insulin once a day, keep all other anti-hyperglycaemic therapies going.
3. Start with a safe dose (e.g. 10 units) and then titrate regularly to achieve optimal outcomes.
4. For intensification, evidence has demonstrated that premixed twice a day is about as good as basal–plus/basal–bolus, but with much less complexity.
5. Given the very similar clinical outcomes, the choice of premixed or basal/basal-bolus comes down to individual patient factors and preferences.

Key words

- Insulin initiation
- Insulin intensification
- Insulin titration
- Premixed insulin

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1. While basal insulin may be the most familiar insulin initiation strategy, this should not necessarily be interpreted as meaning that basal insulin is superior to premixed insulin when starting people on insulin therapy.
2. The choice of single-dose premixed versus basal insulin in clinical practice comes down to individual patient factors rather than the notion that one regimen may always be superior to another.

analogue premixes contain either insulin aspart or insulin lispro (in contrast to human premixed where the short-acting component was human neutral insulin). The basal component is still protaminated insulin and being the equivalent to human protanimated insulin (NPH) has a shorter half-life than the basal insulin analogues such as insulin glargine.

However, even though it is only the short-acting component that is an analogue insulin, there are still advantages to its use over the older human premixed insulins. A more rapid onset-of-action means that the newer analogue premixed insulins are more effective at lowering post-prandial rises in glucose. Just as importantly, because the rapid-acting analogues have a shorter duration of action than human insulin, there is a much lower risk of hypoglycaemia, especially in the hours prior to the next meal. In a meta-analysis, Davidson et al (2009) found that premixed insulin containing the analogue aspart was associated with 50% reduced rates of nocturnal hypoglycaemia and 65% less major hypoglycaemia than human premixed insulin. This reduced risk of hypoglycaemia allows the analogue premixed insulins to not only be used more safely, but also in new ways, such as once-daily usage. In the local context where both human and premixed insulins cost the same to the end-user, analogue premixed is to be preferred to human premixes in almost all cases of type 2 diabetes.

Initiation of insulin

When choosing a starting regimen of insulin, the choice is either basal insulin analogue or premixed insulin analogue as both options can be given once daily. While basal insulin may be the most familiar insulin initiation strategy, this should not necessarily be interpreted as meaning that basal insulin is superior to premixed insulin when starting people on insulin therapy. Two separate randomised controlled trials (RCTs) in insulin-naïve people directly compared once-daily analogue premixed insulin aspart to basal insulin glargine (Strojek et al, 2009; Yang et al, 2013). In both cases, there was a slightly greater reduction in HbA_{1c} in the groups using analogue premix compared to insulin glargine. The result was statistically significant in the case of Strojek et al (2009), but, in both instances, a ~0.1% advantage to premixed insulin is of little clinical relevance. The marginally better result was driven by better post-prandial blood glucose levels at the evening meal, which was when the premixed analogue was administered. It is worth noting that average fasting glucose results were equivalent for premixed and basal insulin. Hypoglycaemia rates were slightly greater in the premixed group, but again the difference between the two insulin regimens was not clinically meaningful.

Given that both analogue premixed and basal insulin can be initiated once daily and have roughly equivalent HbA_{1c} lowering and hypoglycaemia rates, it is possible to view the two regimens as equally valid options for a person with type 2 diabetes requiring insulin. This is reflected in guidelines such as the Royal Australian College of General Practitioners' (RACGP and Diabetes Australia, 2014) *General Practice Management of Type 2 Diabetes*, the National Health and Medical Research Council's (Colagiuri et al, 2009) *National Evidence Based Guideline for Blood Glucose Control in Type 2 Diabetes* and the International Diabetes Federation's (IDF, 2012) *Global Guideline for Type 2 Diabetes* which all have premixed and basal insulin as equal first-line options of insulin. As the RACGP guidelines state, "all insulins work effectively and there is no wrong choice when commencing insulin".

Patient factors

The choice of single-dose premixed versus basal insulin in clinical practice thus comes down to individual patient factors rather than the notion that one regimen may always be superior to another (Wu et al, 2015). One obvious consideration is that of post-prandial glucose rise. SMBG becomes important in the first stages of insulin use because it can identify the glycaemic defect that contributes to raised HbA_{1c}. Those with high post-prandial and fasting blood glucose readings would preferably be started with premixed insulin while those with isolated fasting glucose levels only would be better served with basal insulin only. There are several other patient characteristics that might influence the

Table 1. Patient factors to consider at insulin initiation (adapted from Wu et al, 2015).

Favours premix	Consideration	Favours basal
>3 mmol/L (>54 mg/dL)	What is the post-prandial glucose increment?	<1 mmol/L (18 mg/dL)
No	Is the patient likely to manage basal–bolus therapy when intensification is needed?	Yes
Yes	Is there a large carbohydrate intake at one or two meals?	No
Yes	Is the patient's lifestyle predictable (e.g. eating pattern, working hours)?	No

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1. The simplest method to titrate insulin is to consider the pre-meal glucose for the meal following the injection.
2. Outdated methods of starting premixed insulin can be not only cumbersome, but often result in worse glycaemic outcomes, leading to clinician frustration and, worse still, patient distrust of insulin.

decision of premixed or basal insulin including distribution of carbohydrate intake, regularity of meals and whether the patient is likely to manage basal–bolus therapy for intensification. These factors are summarised in *Table 1*.

Practical issues: Dosing, titration and concomitant therapies

Once the decision is made to start premixed insulin, new initiation guidelines make it as easy as starting basal insulin analogues. The current approach is to simply add 10 units of premixed insulin analogue before the meal with the largest post-prandial excursion (usually the evening meal), while at the same time continuing all current anti-diabetes medications. The addition of this amount of premixed insulin on top of existing treatment should be effective in achieving some degree of glucose lowering, but at the same time, it is very unlikely to cause hypoglycaemia in a patient who is by definition above target HbA_{1c} and has high post-prandial glucose. However, it should be realised that, in the majority of cases, it is very unlikely that this alone will achieve euglycaemia; it is merely a safe way to start insulin use in an individual. What will get the patient to target is dose titration. The simplest method to titrate is to consider the pre-meal glucose for the meal following the injection. If the patient starts on one pre-dinner injection, titrate according to the pre-breakfast glucose readings. If the pre-meal glucose is >7 mmol/L, then the insulin dose should be increased by 2 units. If the glucose is <4 mmol/L, then the dose should be decreased by 2 units. If the dosing is with breakfast, the titration is against the pre-dinner blood glucose level. This process is repeated every 3–7 days until the glucose levels fall consistently within the target range. This simple, incremental, repeated dose titration will ensure that the majority of individuals should reach target glucose levels safely. This type of approach has been called the "start low and go slow" method and is the approach advocated by the RACGP (2014) guidelines.

These streamlined procedures (made possible by the low risk of post-meal hypoglycaemia associated with rapid-acting insulin analogues) remove the need for complex and often fraught manoeuvres such as stopping all oral hypoglycaemic agents when starting insulin, initiating with twice-daily injections of premixed insulin, estimating starting dose on weight and splitting the dose via a strict formula of two-thirds of the total daily dose before breakfast and one-third before dinner. These outdated ways of starting premixed insulin were not only cumbersome, but often resulted in worse glycaemic outcomes immediately after starting insulin initiation, leading to clinician frustration and, worse still, patient distrust of insulin. When examined closely by Roth et al (2015), some of these old ways of prescribing premixed insulin have been found to have no scientific basis and so are no longer adhered to. Thus, it is now preferable to start premixed insulin using the simplified methods described at the start of this section.

Insulin intensification

Just as people progress from oral glucose-lowering medicines to insulin, those that begin on simple once-daily insulin often need to move onto different insulin regimens after some time,

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1. Two main options for insulin intensification exist: either multiple premixed insulin injections or prandial insulin in addition to basal insulin.
2. While it is often assumed that basal–bolus type regimens are by their nature superior to premixed insulin, this has not been borne out in evidence from clinical trials.
3. In general, premixed insulin should be considered where patients are unwilling or unable to cope with the increased injections, complexity and testing that is required with basal–plus/basal–bolus regimens.

Table 2. Patient factors to consider for future insulin intensification (adapted from Wu et al, 2015).

Favours premix	Consideration	Favours basal–bolus
Prefers fewer injections	Patient preference regarding number of injections	Comfortable with more frequent injections
Prefers less frequent monitoring	Patient preference regarding self-monitoring of blood glucose	Comfortable with more frequent monitoring
Poor	Patient ability to inject (e.g. cognitive ability, manual dexterity, need for carer)	Good

a process called insulin intensification. Two main options exist: either multiple premixed insulin injections or prandial insulin in addition to basal insulin (termed basal–plus or basal–bolus insulin). Someone on once-daily premixed at dinner could be experiencing high post-prandial glucoses at breakfast, and could benefit from a second injection of premixed at breakfast. Another common scenario is that someone on basal insulin at night time could be getting higher post-prandial glucose levels at dinner while experiencing excellent fasting glucose levels in the morning. Under those circumstances, up-titration of basal insulin could result in nocturnal hypos and thus changing from basal to premixed once-daily before dinner could be preferable. Alternatively, an injection of prandial rapid-acting insulin at dinner to compliment the basal at night could be considered (basal–plus one). However, this approach increases the number of injections required (and with two insulins rather than one), thus inherently increasing complexity.

Basal–bolus versus premixed

While it is often assumed that basal–bolus type regimens are by their nature superior to premixed insulin, this has not been borne out in clinical trials. For example, an RCT conducted by Malek et al (2015) compared two strategies in insulin-naïve people with an HbA_{1c} between 53 mmol/mol (7%) and 97 mmol/mol (11%) at baseline: one arm started on premixed once-daily and then intensified to twice- or thrice-daily as necessary, while the other arm started on basal insulin and then intensified to basal–plus or full basal–bolus as required. In the over 400 patients assessed, there was no significant difference in terms of HbA_{1c} achieved (67 mmol/mol [8.3%] for premixed versus 68 mmol/mol [8.4%] for basal–plus); percent reaching an HbA_{1c} of <53 mmol/mol (<7%; 44.9% vs 40.3% respectively) or hypoglycaemic events (59.1% vs 58.0% respectively).

The similarity between the two regimens was further confirmed by a recently published meta-analysis by Giugliano et al (2016), which evaluated all RCTs of basal–bolus versus premixed insulin regimens. The authors found 13 RCTs lasting 16–60 weeks including a total of 5255 patients. When analysed, it was found that there was a non-significant 0.09% difference in HbA_{1c} levels achieved by the two regimens. Further, premixed and basal–bolus showed no significant difference in the rate of hypoglycaemia, weight change or daily insulin dose, despite the greater complexity and number of injections associated with basal–bolus insulin.

Because this recent evidence points to no clinically relevant difference in the efficacy or safety of premixed versus basal–bolus regimens, the clinical implication is that individual patient factors are again central to the decision of whether to choose premixed or basal–bolus for the intensification of insulin treatment when once-daily insulin is no longer sufficient. *Table 2* shows some of the considerations when selecting one strategy over another. In general, premixed insulin should be chosen where patients are unwilling or unable to cope with the increased injections, complexity and testing that is required with basal–plus/basal–bolus regimens.

If initiation and intensification are considered together, it may be worthwhile to keep in mind the concept of "starting as you mean to go

on"; that is, if a patient is unlikely to be able to cope with basal–bolus in the future, then premixed insulin should probably be preferred in the initiation phase (Wu et al, 2015).

Practicalities of insulin intensification with premixed

When intensifying from once-a-day premixed (usually given before the evening meal), it is a simple matter of adding a second injection to the meal at the other end of the day (usually breakfast). The usual procedure is to begin with 4 units, and then titrate as necessary as describe above.

It is again fairly easy to intensify from basal once-daily to premixed once-daily. This is achieved by changing the insulin type and moving the injection from before bed to just before dinner. The type of insulin can usually be changed unit-for-unit. From there, titration will achieve the desired outcome. Patients intensified this way may of course be further intensified to twice- (or even thrice-) daily premixed later, as necessary. Lastly, it should be noted that at the point of insulin intensification, consideration could be given to ceasing sulfonylureas.

Summary

Premixed insulins are considered an equal first-line option for the initiation and also intensification of insulin by the RACGP, NHMRC and International Diabetes Federation. Recent trial and meta-analysis evidence has pointed to little, if any, clinically relevant difference between premixed and basal or basal–plus insulin regimens in terms of outcomes. There is no one insulin strategy that is clearly superior to others in all circumstances. Given the minimal differences, individual patient factors become much more important in selecting the type of insulin treatment. Many patients may be more suited to premixed than basal or basal–bolus insulin. We are in an era where we individualise HbA_{1c} targets for our patients, and there is every reason to suggest that the insulin regimens should also be individualised for people with type 2 diabetes. ■

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