A tale of two insulins: Understanding basal insulin therapy in type 2 diabetes

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Chapter 10

Summary and recommendations
This thesis ‘tells the tale’ of the two currently available basal insulin analogues, insulin detemir (Levemir®, Novo Nordisk A/S, Bagsværd, Denmark) and insulin glargine (Lantus®, sanofi-aventis, Paris, France), in the treatment of patients with type 2 diabetes. After the first two chapters, which provide an introduction to (basal) insulin therapy in type 2 diabetes, chapters 3 and 4 discuss data on the two basal insulin analogues obtained by pharmacodynamic studies and case reports. The next two chapters address the importance of certain aspects of trial design, such as the definition of hypoglycaemia and the frequency of study visits. The final three chapters report the results of the Lantus® vs. Levemir® Treat-To-Target (L2T3) study, a large, multinational, randomised, clinical trial, comparing insulin initiation with insulin detemir vs. insulin initiation with insulin glargine, in patients with type 2 diabetes not achieving adequate glycaemic control on oral glucose-lowering agents.

Chapter 2 reviews the evidence on the various insulin preparations currently available and the insulin treatment regimens commonly used to treat patients with type 2 diabetes. As also briefly discussed in chapter 1, the prandial and basal insulin analogues were developed to overcome the shortcomings of therapy with the conventional human insulin preparations. However, while pharmacodynamic studies did show benefits in terms of more physiological action profiles for the analogues, subsequent clinical trials found that the clinical advantages were limited to a reduction in hypoglycaemia. When considering the different insulin regimens used in clinical practice, chapter 2 (in accordance with the joint guideline of the American Diabetes Association and the European Association for the Study of Diabetes) recommends that insulin therapy is initiated in type 2 diabetes by means of a basal insulin preparation once-daily. Given the above-mentioned limited clinical advantages of the basal insulin analogues over the conventional basal NPH insulin, the lower cost of NPH insulin and the relatively low risk of hypoglycaemia in type 2 diabetic patients starting insulin, NPH insulin is the most cost-effective drug for this purpose. However, when insulin dose titration is limited by hypoglycaemia, patients should be switched to one of the two basal insulin analogues. A final important recommendation of this chapter is that when the current glycaemic target of HbA1c <7% is not
achieved despite successful basal insulin dose titration (i.e. fasting plasma glucose level <5.6 mmol/l), or when titration is limited by hypoglycaemia, treatment should be swiftly intensified by the addition of prandial insulin or by switching to biphasic insulin.

Before any newly developed drug can be used in clinical practice it needs to be registered by regulatory bodies such as the Food and Drug Administration (FDA) in the U.S. and the European Medicines Agency (EMEA) in Europe. With regard to the registration of new insulin preparations, the EMEA considers data on time-action profiles provided by glucose clamp studies to be ‘of primary importance to demonstrate therapeutic equivalence or differences’ between products. However, the clamp studies examining the new basal insulin analogues reported conflicting results. In an attempt to reconcile the data, and hypothesising that differences in study design contributed to the discrepant outcomes, we organised an expert meeting of the four leading European clamp groups involved in studies of basal insulin analogues.

There was a high level of consensus among the expert groups, for instance about the relevant physiological principles, the preferred experimental conditions and the desired mode of reporting of glucose clamp studies. Nevertheless, a few differences of opinion remained and this was perhaps the reason that some of the participating groups could not agree to the publication of a consensus statement following the meeting. Aiming to still provide some guidance for clinicians and investigators on this difficult research field, chapter 3 summarises the consensus reached by the expert groups and explains the different methods used and the inherent limitations of the technique. In short, the major limitation of glucose clamp studies when investigating basal insulin preparations is that the experimental situation differs from the situation in clinical practice. For example, some studies have examined healthy volunteers, while the tested insulin preparations are used by diabetic subjects. Also, study participants are fasted for 24 to 32 h and only a single insulin injection is administered, situations which hardly occur in daily life. Given the inherent limitations of the glucose clamp technique and the lack of reproducibility of the study outcomes, chapter 3 concludes that the results of clamp studies of basal insulins should be regarded as no more than
an indication of the metabolic action of these preparations. Clinical trials are essential to determine insulin action.

The necessity of clinical practice for the elucidation of the clinical effects of insulin preparations is also illustrated in \textit{chapter 4}. After we had found substantially reduced daily insulin dose requirements in a female type 2 diabetic patient in whom basal insulin therapy was changed from insulin detemir to insulin glargine (from 206 units/day of detemir to 104 units/day of glargine), we switched two more patients with type 2 diabetes from detemir to glargine. After two 6-week periods of systematic dose titration (targeting fasting plasma glucose $<5.6 \, \text{mmol/l}$) of first insulin detemir and subsequently insulin glargine, daily basal insulin doses had decreased from 102 to 81 units in the second patient and from 126 to 104 units in the third.

Pre-clinical studies had already demonstrated that the modifications of the human insulin molecule resulting in insulin detemir (i.e. removal of threonine from position B30 and attachment of myristic acid to position B29) interfered with receptor binding, leading to a lower affinity for the human insulin receptor of insulin detemir vs. other insulins. In order to compensate for the reduced potency, insulin detemir is formulated at a higher molar concentration: 2400 nmol/l vs. 600 nmol/l for all other insulin preparations. This ratio was based on clinical trials examining patients with type 1 diabetes, showing comparable glycaemic control with insulin detemir and NPH insulin, provided that four times the molar dose was used. However, the above three cases suggest that for the treatment of type 2 diabetes a higher molar dose ratio may be needed. This was confirmed by our meta-analysis of the three published randomised trials investigating basal insulin initiation with insulin detemir in type 2 diabetes, which suggested a six-fold greater molar dose requirement. The reason for the difference in molar dose ratio between type 1 and type 2 diabetes is not clear.

The main recommendation of \textit{chapter 4} is that clinicians should be aware of potentially increased or reduced insulin dose requirements when they change a patient’s basal insulin preparation.
Chapter 5 addresses the importance of a uniform definition for hypoglycaemia. Standardised reporting of hypoglycaemia is highly desirable as this allows comparison of data across studies. In 2005 the American Diabetes Association proposed to define hypoglycaemia as an event accompanied by a measured plasma glucose concentration ≤3.9 mmol/l. This threshold was chosen based on the results of hyperinsulinaemic clamp studies performed in non-diabetic subjects, i.e. a situation that is very different from clinical practice. The main criticism on this plasma glucose definition has been that it may lead to overestimation of the frequency of relevant hypoglycaemia, which in turn could have considerable clinical and commercial implications. The aim of the analyses presented in chapter 5 was to quantify the relationship between various plasma glucose threshold values for the definition of hypoglycaemia and the frequency of hypoglycaemia, using randomised clinical trial data. Our main finding was that the chosen threshold or cut-off plasma glucose value greatly affects the estimated frequency of hypoglycaemia: the higher the cut-off point for the definition of hypoglycaemia, the higher the reported frequency, particularly that of asymptomatic events. Moreover, the specificity to identify patients with severe hypoglycaemia was considerably reduced when using higher plasma glucose definitions for hypoglycaemia.

It is important to note that the data that we used for these analyses were from two large randomised controlled trials performed in patients with type 2 diabetes who were inadequately controlled on oral therapy and started insulin glargine. The frequency of hypoglycaemia is much lower in this population than in patients with type 1 diabetes and those with a longer duration of (insulin-requiring) type 2 diabetes. Still, when using the American Diabetes Association definition also in this population more than 40% experienced hypoglycaemia. As discussed above, these events were usually asymptomatic and of limited use to identify patients at risk of severe hypoglycaemia. Additionally, most clinicians consider exposure to biochemical hypoglycaemia of between 3.5 and 4.0 mmol/l as not clinically relevant and strict avoidance of such glucose levels is likely to have an adverse effect on average glycaemia. To increase the clinical relevance, chapter 5 recommends that when hypoglycaemia is to be defined by a predetermined plasma glucose level this should be lower than the ≤3.9 mmol/l threshold proposed by the American Diabetes Association, particularly for patients with type 2 diabetes who start insulin therapy.
Chapter 6 explores whether factors related to the design of clinical trials, specifically of the published Phase 3 and 4 clinical studies examining insulin initiation in type 2 diabetes using insulin detemir, insulin glargine or NPH insulin, significantly affect study outcomes such as HbA1c and hypoglycaemia. Using ten randomised controlled trials, obtained by a systematic Medline search, associations between the frequency of contact with the study team as per study protocol and the study outcomes HbA1c reduction and endpoint daily insulin dose were evaluated. Similarly, associations between endpoint insulin dose, which is related to the study design factors titration frequency and titration target, and the outcomes HbA1c reduction, hypoglycaemia rate and weight gain were explored. To investigate the influence of so-called non-specific benefits of trial participation, the association between contact frequency and HbA1c was also determined in trials examining the initiation of a DPP-4 inhibitor (an oral glucose-lowering agent).

While we found significant dose-response relationships between the predetermined contact frequency as well as the endpoint insulin dose and the study outcome HbA1c reduction, only frequency of contact was an independent predictor of improvement in glycaemic control. Both the frequency of face-to-face visits and that of telephone contacts independently predicted HbA1c improvement. However, a higher frequency of telephone contacts may be particularly beneficial, presumably due to their focus on insulin dose titration. Examining the DPP-4 inhibitor trials, contact frequency was not positively associated with HbA1c. Nor did we find significant associations between daily insulin dose and the study outcomes hypoglycaemia and weight gain in the insulin studies.

In conclusion, the frequency of contact with the study team is highly correlated with the improvement in glycaemic control achieved in basal insulin initiation trials in type 2 diabetes. In addition to the obvious implications for the design and interpretation of clinical trials examining different insulin preparations, this analysis provides an important lesson for patient care: frequent contact and dose titration can facilitate successful insulin initiation.
As mentioned in chapter 1, clinical studies directly comparing insulin detemir and insulin glargine were limited. That is why, in 2005, we started devising a randomised controlled trial, investigating the initiation of basal insulin therapy in type 2 diabetes using either insulin detemir or insulin glargine. The study’s rationale, methods and main baseline results are described in chapter 7. In brief, the Lantus® vs. Levemir® Treat-To-Target (L2T3) study was a multinational, open-label, parallel-group, randomised trial carried out in 122 centres across 20 countries. Insulin-naive patients with type 2 diabetes for ≥1 year and inadequately controlled on oral glucose-lowering drugs, including at least 1 g/day of metformin, were randomised to 24-week treatment with either insulin detemir twice-daily or insulin glargine once-daily. Patients randomised to insulin glargine were instructed to increase their insulin dose by 2 units every 2 days until their fasting plasma glucose was <5.6 mmol/l. The systematic titration of insulin detemir was slightly more complicated: first, both the morning and evening dose were increased by 1 unit every 2 days to achieve fasting and pre-dinner plasma glucose ≤6.9 mmol/l. Subsequently, the evening dose was increased by 2 units every 2 days until fasting plasma glucose <5.6 mmol/l, after which the morning dose was increased to pre-dinner glucose <5.6 mmol/l. The primary study aim was to demonstrate the non-inferiority of insulin glargine to insulin detemir regarding the percentage of patients reaching HbA1c <7% at the end of the treatment period without having symptomatic hypoglycaemia confirmed by a plasma glucose measurement of ≤3.1 mmol/l during these 24 weeks. Important secondary outcomes were HbA1c, diurnal plasma glucose profiles, hypoglycaemia, weight, insulin dose and quality of life.

The rationale for dosing insulin detemir two times daily was that, when we were designing the L2T3 study, only one trial had examined the addition of once-daily insulin detemir to oral therapy in type 2 diabetes. In this study, once-daily insulin detemir performed worse than once-daily NPH insulin, achieving end-of-study HbA1c levels of 8.40 and 7.89%, respectively. Also, twice-daily detemir administration appeared to result in greater improvements in HbA1c. Thus, we chose to dose insulin detemir twice a day. It is important to realise, however, that this aspect of the study’s design may have influenced certain study outcomes such as the quality of life scores.
The reason for choosing a combined primary outcome was that lowering glycaemia inevitably results in an increased risk of hypoglycaemia and that good glycaemic control actually implies achievement of target HbA1c with no or only few hypoglycaemic episodes. Taking the findings of chapter 5 into account, our primary plasma glucose definition for hypoglycaemia was a level ≤3.1 mmol/l. To promote the standardised reporting of hypoglycaemia we also determined the frequency of hypoglycaemia as defined by the American Diabetes Association, i.e. plasma glucose ≤3.9 mmol/l.

Finally, the rationale behind the extensive quality of life investigation was that the initiation of insulin therapy is often delayed in type 2 diabetes, exposing patients to many years of uncontrolled hyperglycaemia. Reasons for the reluctance to start insulin include fear of painful injections and hypoglycaemia and negative beliefs about low self-efficacy, personal failure and illness severity. Thus, it seemed important to gain more knowledge about the effects of different (basal) insulin preparations on fear of hypoglycaemia, treatment satisfaction and other aspects of quality of life.

Chapter 8 reports the results of the L2T3 study. In total, we treated 964 patients with either insulin detemir or insulin glargine. Study subjects were about 58 years old, with diabetes duration of 10 years and baseline HbA1c level of 8.7%. Regarding the primary outcome, insulin glargine was non-inferior to insulin detemir, with approximately 25% of patients achieving target HbA1c without symptomatic hypoglycaemia ≤3.1 mmol/l in either treatment group. While the proportion of patients reaching HbA1c <7% was also similar between treatments, significantly more patients on insulin detemir attained HbA1c <6.5%. As for the glucose levels during the day, insulin glargine resulted in a significantly greater decrease of fasting plasma glucose, while insulin detemir achieved significantly larger reductions in pre- and post-lunch, pre- and post-dinner and bedtime levels. The frequency of hypoglycaemia was comparable between the two insulins, except for a minor difference in the rate of daytime symptomatic hypoglycaemia in favour of insulin glargine. Mean weight gain during the study was 0.8 kg higher for insulin glargine, but daily insulin doses were significantly higher for insulin detemir. Quality of life improved, without differences between treatments for diabetes symptom distress, fear
of hypoglycaemia or general well-being. Treatment satisfaction, however, showed a more pronounced increase in the insulin glargine group.

As briefly mentioned above, the interpretation of these results is affected by the difference in dosing schedule for the two insulins. Advantages of the one over the other, such as the lower glucose levels during the day for insulin detemir and the reduced risk of daytime hypoglycaemia and more increased treatment satisfaction for insulin glargine, may be explained by the twice-daily dosing and more complex titration of detemir compared with glargine. The considerable difference in daily dose requirements has been attributed to the twice-daily dosing of insulin detemir as well. Yet, NPH insulin dosed twice-daily does not lead to dose escalation and recent trial data suggest that, although doses are indeed higher in patients using insulin detemir twice- vs. once-daily, once-daily detemir doses are still higher than once-daily NPH and glargine doses. This is also supported by our findings in the three patients described in chapter 4. However, based on one of these recent trials, which found non-inferior HbA1c reductions for once-daily detemir vs. once-daily NPH, once-daily use of insulin detemir has been increasingly advocated. Therefore, with advancing knowledge, it is now clear that another ‘treat-to-target’ trial comparing both basal insulin analogues using an identical, once-daily dosing regimen is needed. Such a study just commenced patient recruitment (ClinicalTrials.gov number: NCT00909480).

Finally, to investigate the important clinical question whether, in addition to metformin, insulin secretagogues should be continued as well when patients with type 2 diabetes initiate basal insulin therapy, Chapter 9 compares the 498 L2T3 participants who continued their treatment with insulin secretagogues during the study with the 367 who stopped these agents at randomisation. We found that continuing both metformin and insulin secretagogues resulted in a greater frequency of hypoglycaemia and more weight gain compared with maintaining only metformin in combination with basal insulin. Daily insulin doses, however, were significantly lower in patients continuing insulin secretagogues. The difference between groups in HbA1c reduction was not significant, which was probably related to our method of analysis. As recommended for the analysis of baseline and follow-up measurements
in controlled trials, we performed analysis of covariance (ANCOVA). This method controls for any imbalance between groups at baseline. There was indeed a baseline difference in our study: patients who continued insulin secretagogues at randomisation had higher mean HbA1c than those who discontinued. Site-investigators were apparently more inclined to retain secretagogue-treatment when a patient’s baseline HbA1c was high and to discontinue it when baseline HbA1c was relatively low. In order to overcome such prescription bias, a controlled trial, randomising type 2 diabetic patients who start basal insulin therapy in addition to treatment with metformin and insulin secretagogues to either continuation or discontinuation of insulin secretagogues, is highly recommendable.