How to achieve a predictable basal insulin?

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**Summary**

The development of insulin analogues over the last two decades have aimed at optimising the pharmacokinetic profile of subcutaneously injected insulin for therapeutic use in diabetes mellitus. Rapid acting analogues were successfully engineered and marketed in the late 1990’s. In engineering long-acting analogues it has been a particular challenge to obtain action profiles that would be predictable from day to day in the same person. The most recent approach has been to acylate the insulin molecule with a fatty acid which provides the insulin molecule with a specific affinity for albumin. The first clinically available agent of this type is insulin detemir. Pharmacological studies have shown that reversible albumin binding will protract absorption following subcutaneous injection but still allow the insulin molecule to be recognised by the insulin receptor following dissociation from the carrier protein. Moreover, the molecular features of insulin detemir are attractive in that the molecule can be formulated as a neutral aqueous solution and does not precipitate after injection. Together with an important buffering mechanism effected by plasma albumin binding, this explains a highly significant reduction of within-subject variability of pharmacodynamic response observed in repeat isoglycamic clamp studies where insulin detemir was compared to other basal insulin products. No safety considerations have been identified in using albumin as an insulin carrier to protract and buffer insulin action. In assessing the clinical attractiveness of insulin analogues, it is furthermore critically important to consider how the molecular modifications impact efficacy and safety. A number of pharmacological studies have shown that insulin detemir overall retains the molecular pharmacological properties of native human insulin, including a physiological balance between metabolic and mitogenic potencies. Taken together, insulin detemir provides an attractive novel approach for predictive basal insulin delivery to people with diabetes.

**Key-words:** Insulin analogues · Variability · Albumin binding.

**Résumé**

Le développement des analogues de l’insuline au cours de ces 20 dernières années a permis d’optimiser le profil pharmacocinétique de l’insuline injectée par voie sous-cutanée pour le traitement du diabète. Les analogues rapides ont été développés et mis sur le marché avec succès à la fin des années 90. Pour développer des analogues de durée d’action prolongée, la difficulté consistait à obtenir un profil d’action qui puisse être reproductible d’un jour à l’autre pour un individu donné. L’approche la plus récente a consisté en l’acétylation de la molécule d’insuline par un acide gras, ce qui permet à la molécule d’insuline d’avoir une affinité de liaison spécifique pour l’albumine. Le premier agent de ce type est l’insuline détémir. Les études pharmacologiques ont montré que la liaison réversible entre l’insuline détémir et l’albumine permet de prolonger le temps de résidence dans le tissu sous-cutané lors d’une injection sous-cutanée, mais permet toujours à la molécule d’insuline d’être reconnue par les récepteurs de l’insuline après s’être dissociée de sa protéine de transport, l’albumine. De plus, les caractéristiques moléculaires de l’insuline détémir sont intéressantes par le fait que cette molécule peut être présentée en solution aqueuse neutre et qu’elle ne précipite pas après l’injection. Associé à un mécanisme important de stabilisation du à la liaison à l’albumine plasmatique, ceci explique la réduction hautement significative de la variabilité inter-individuelle de la réponse pharmacodynamique observée avec l’insuline détémir, par comparaison avec les autres insulines basales, lors des études de clamps isoglycémiques répétés. Aucun problème particulier de sécurité lié à l’utilisation de l’albumine comme transporteur de l’insuline pour prolonger et stabiliser l’action de l’insuline n’a été mis en évidence. Lorsque l’on évalue l’intérêt clinique des analogues de l’insuline, il est extrêmement important de considérer comment les modifications de la structure moléculaire influent sur l’efficacité et la sécurité d’emploi. De nombreuses études cliniques ont montré que, globalement, l’insuline détémir conserve les propriétés pharmacologiques moléculaires de l’insuline humaine, incluant le maintien de l’équilibre entre les pouvoirs métaboliques et mitogènes. Par l’ensemble de ses propriétés, l’insuline détémir représente une nouvelle et intéressante approche pour permettre aux patients diabétiques de disposer d’une insuline de base prédictible.

**Mots-clés :** Analogues de l’insuline · Variabilité · Liaison à l’albumine.
The rationale for insulin analogue development

Exogenous insulin as a therapy for diabetes mellitus represents one of the great medical breakthroughs of the twentieth century. Nevertheless, some eighty years since its first clinical deployment, most patients with insulin-treated diabetes have to contend with erratic blood glucose control with prevailing hyperglycaemia, which results in a high burden of morbidity and premature mortality [1]. Thus, throughout the history of insulin development, pharmaceutical companies have sought to refine the formulations of their insulin products to better control glycaemia. Over the last two decades, the most significant developments in this endeavour have involved the modification of the insulin molecule itself to produce analogues of human insulin.

Driving this enterprise has been the goal of more accurately matching exogenous insulin supply with the dynamic physiological needs of the body. In healthy people, insulin is secreted into the portal vein with its output is continuously modulated in response to nutrient and other stimuli. The resulting dynamic profile of insulin secretion is typically characterised by a slow rise to a peak followed by a slow decline [8]. This replicates neither the basal nor prandial insulin secretion profile [11-13]. An early discovery in the development of insulin analogues, however, was that some changes in the amino acid sequence of non-binding regions of insulin could nevertheless change the molecule’s ternary structure so as to affect metabolic and mitogenic activity. When compared to human insulin, the prototype analogue B10 aspart had an increased IGF-I receptor:insulin receptor affinity ratio and an increased receptor residence time. At high doses, this analogue was carcinogenic in rodents [14-16], highlighting the importance of testing the full pharmacodynamic profile of insulin analogues.

Why do we need a predictable basal insulin analogue?

The development of basal insulin analogues has come more slowly, and seeks to address different needs. Firstly, an ideal basal insulin should have a protracted action, to minimise injection frequency, and a steady rate of absorption to avoid peak plasma concentrations. This means that absorption rate needs to be slowed rather than accelerated, with an obvious strategy being to increase or prolong self-association. But another goal that is of particular importance when considering a basal insulin is that its absorption profile should be reproducible. This is because the rate of entry into the systemic circulation of injected insulin is highly dependent on local environmental factors such as blood flow rate, so the pharmacokinetic profiles that follow standardised injections can vary both between and within individuals [17-20]. The opportunity for variable absorption to occur is much greater for basal than prandial insulin formulations precisely because the former have a longer subcutaneous residence time and also because most are designed to form a precipitate rather than soluble depot. In fact, the formulation of insulin products designed to give a precipitate depot represents the earliest of all attempts to modify insulin’s absorption kinetics, the goal being to decrease injection frequency. The earliest such basal insulins were made by addition of protamine (neutral protamine Hagedorn [NPH]) or excess zinc (Lente, Ultralente insulin) in order to form suspensions that would slowly dissolve once injected. However, a preformed precipitate requires thorough resuspension before injection to
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ensure that the correct insulin concentration is administered, and varying degrees of incomplete resuspension by patients is a major source of pharmacodynamic variability [21-23].

Furthermore, the mean absorption profiles of conventional basal insulins are also not ideal [22]. As an example, NPH insulin is characterised by a peak in absorption rate that occurs 4-6 hours after injection [24]. When the problem of a peak in absorption rate is combined with the problem of unpredictability in absorption, it follows that the exact time and extent of this peak effect after any one injection can never be precisely predicted. This in turn incurs a risk of hypoglycaemia and as basal insulins are often dosed in the evening there is a real risk of nocturnal hypoglycaemia. This is the most feared side effect of insulin therapy and tolerance of this risk becomes the limiting factor for dosing [25, 26].

Thus, research into basal insulin analogues has sought to improve both the mean pharmacokinetic profile and variability about this mean.

 Improving basal insulins: first steps

Novo Nordisk drug discovery laboratories have pursued a number of strategies in search of these goals. One of the first principles investigated was to modify the amino acid sequence of human insulin in an attempt to shift the iso-electric point of the molecule towards neutrality, and hence reduce solubility at physiological pH values. This approach enables the analogue to be injected as a solute (when formulated in an acidic medium) and so avoids dosing errors arising from incomplete resuspension before injection. The insulin subsequently precipitates in the pH-neutral subcutaneous environment to create a solid phase that dissolves slowly to protract absorption. However, it has been suggested that the formation and redissolution of a precipitate might introduce another source of variability [27]. Indeed, the prototype analogues based on this principal were not developed clinically because of low bioavailability and variability of action [28, 29].

Figure 1

More recently, the same principle was developed successfully to produce insulin glargine (Gly\(^{A21}\) Arg\(^{B11}\) Arg\(^{B12}\) human insulin) (Fig. 1). In this molecule, two arginine residues are added to the C-terminus of the B-chain to shift the isoelectric point from pH 5.4 to 6.7 [24, 30].

A second strategy attempted by Novo Nordisk to improve on the kinetic profile of basal insulins was to engineer a stable hexamer. In theory this would be injected as a solute, remain as a solute after injection, but absorb slowly due to the prolonged self-association of the insulin and the slow transport of hexamers across capillary walls. Such an insulin, Co(III)insulin, was achieved by substituting the zinc ions situated in the core of the hexameric structure with cobalt ions [31, 32]. As predicted, Co(III) insulin was found in laboratory experiments to absorb slowly as a hexamer, but then gradually dissociates into monomers in the circulation. Despite 'behaving' as the theory predicted, however, the compound was found to offer no real pharmacological advantages over NPH insulin.

The development of insulin detemir

A strategy quite recently investigated at Novo Nordisk has been to acylate fatty acid side chains to analogues of human peptide hormones including insulin [33, 34]. This has culminated in the development and clinical availability of insulin detemir [Lys\(^{B29}\)(N-tetradecanoyl)des(B30)human insulin] in which the amino acid threonine has been removed (Fig. 1). The effect of this fatty acid is to stabilise self-association and permit reversible insulin-albumin binding. Importantly, this principle has allowed insulin detemir to be formulated as a solute in a neutral liquid preparation that does not precipitate at any stage in the administration-absorption process, thereby avoiding key sources of variability.

The precise mechanisms underlying the pharmacokinetic properties of insulin detemir have been elucidated in a series of physicochemical and pharmacological studies reported by Havelund and coll. [35]. In these investigations, insulin detemir was compared to various other insulin analogues differing in terms of self-association profiles and albumin affinity. In a series of size exclusion chromatography experiments, the composition of eluent was modified so as to simulate chemical changes in the depot following injection, and the comparator insulin analogues were eluted to investigate the extent of their self-association. The data suggested that hexameric insulin detemir moves to a hexamer-dihexamer equilibrium once injected into the subcutaneous environment. It is thought that dihexamers form by contact between the myristic acid side chains, which are situated at the poles of each insulin detemir hexamer [36]. This increase in self-association state occurred as pharmaceutical preservatives (phenol and cresol) were removed to simulate equilibration with physiological electrolytes in the depot. Size exclusion chromatography

also showed that insulin detemir can bind to albumin in all its association states i.e. dihexamic, hexameric, dimeric and monomeric. This experiment therefore suggested that there might be two mechanisms by which the absorption of insulin detemir is protracted in the injection depot: retention by reversible albumin binding and delayed absorption due to self-association.

The relative importance of these mechanisms was then studied by measuring disappearance rates for radio-labelled insulin analogues after subcutaneous injection in pigs [35]. The disappearance T\(_{50\%}\) time for insulin detemir was 10.2 hours, which was longer than that of an acylated monomer (2.9 hours), an acylated weakly-associating hexamer (6.9 hours) and an acylated stable hexamer (8.8 hours). This hierarchy implies that self-association is an important factor in the slow absorption of insulin detemir. However, the T\(_{50\%}\) values for all of these albumin-binding analogues (including the acylated monomer) were longer than that of the stable non-binding hexamer, Co(III)insulin (2.8 hours), indicating that albumin binding also delays absorption. It was therefore hypothesised that self-association of insulin detemir causes molecules to be retained in the depot for long enough to establish albumin binding, which further delays absorption. It is also possible that depot interstitial albumin effects a particularly high retention of insulin detemir because the high state of self-association of insulin detemir might allow multiple binding contacts to be made between fatty acid side chains and albumin molecules.

Insulin detemir also binds reversibly to albumin in the circulation [33, 34], but comparisons of plasma residence times with other acylated analogues with differing albumin binding affinities suggest that retention of insulin detemir in the circulation does not contribute to the overall protraction of action as much as depot retention [35].

Limiting variability through solubility and reversible albumin binding

The solubility of insulin detemir before and following injection is likely to limit the variability arising from patient dosing errors or erratic dissolution of a precipitate. But there is a second mechanism by which insulin detemir is believed to attenuate variability in time-action profile from injection to injection. This arises from buffering effects brought about by albumin binding in the circulation [37]. Insulin detemir is 98% albumin-bound in the circulation [33, 34], and this property means that variations in absorption rate arising from changes in depot blood perfusion are minimised. This is because the absorption rate of insulin from depot to circulation depends largely on concentration differences of free insulin between the two compartments. In the case of subcutaneously deposited human insulin, diffusion can occur into and back out of the capillary lumen. An equilibrium for absorption rate is therefore established, but this changes with changing blood flow rate. Thus, an increase in the blood flow
rate will decrease the capillary concentration and increase the absorption rate while a reduced flow rate will decrease the concentration difference between blood plasma and depot and thereby slow the absorption rate. In the case of insulin detemir, however, absorption into capillary plasma is followed by immediate and almost complete binding to circulating albumin meaning that reverse diffusion of insulin detemir is negligible, as albumin-bound detemir complexes are too large to readily traverse the capillary wall. Therefore, the absorption rate of insulin detemir effectively becomes independent of the blood flow rate and more or less constant, depending only on the outward rate of diffusion.

Even if there were to be changes in absorption rate, there is evidence from pharmacokinetic experiments in dogs describing half-lives in different tissues and trans-capillary transport rates [38-40] to suggest that plasma albumin binding would further buffer the effect of this in target tissues. Only 2% of circulating insulin detemir is unbound and available for trans-capillary transport, and hence the equilibration of distal interstitial concentrations with plasma concentrations. Therefore, changes in plasma concentration are slow to affect target tissue interstitial concentrations. In contrast, any change in the absorption rate of a non albumin-bound insulin will result in an almost immediate corresponding increase in distal interstitial compartments (Fig. 2).

Is albumin binding a safe strategy for protraction?

It is, of course, important with any new principle of hormone engineering to establish the safety of the departure. In the case of reversible albumin binding, concerns about drug-drug interactions and circulating fatty acid homeostasis need to be allayed. In fact, any such concerns are likely to be unfounded simply because the molar serum concentration of therapeutic doses of insulin detemir will barely reach 1:50,000 that of albumin. Furthermore, there are at least eight fatty acid binding sites per albumin molecule so insulin detemir will occupy only a small fraction of available albumin fatty acid binding sites. Nevertheless, the potential for competitive interactions with other albumin-bound drugs has been studied in vitro, and at drug-albumin concentration ratios as high as 1:1 no interactions occurred between insulin detemir and phenylbutazone, warfarin, ibuprofen, diazepam, tolbutamide, glibenclamide, aspirin or valproate, nor with a series of free fatty acids [42].

Given the concerns raised by the increased IGF-I affinity of the prototype analogue B10 aspart described above, the receptor interaction profile of insulin detemir has also been studied in vitro cell models [16, 43]. In these studies, insulin detemir acted as a full agonist of the insulin receptor, albeit with a relatively reduced molar potency [43]. Importantly, however, insulin detemir has been shown to preserve the relative affinity ratio for insulin receptors:IGF-I receptors and the insulin receptor dissociation rate seen for natural human insulin [16]. Thus, no concerns about increased mitogenicity arose with insulin detemir, and this was confirmed in human osteosarcoma cells.

From pharmacological theory to pharmacodynamic assessment

The first hint that insulin detemir would actually deliver its promise of predictable pharmacokinetic and glucose-lowering time-action profiles in clinical use was seen in 24-hour isoglycaemic clamp studies [44, 45]. A randomized, double-blind, six-period cross-over study of 12 people with type 1 diabetes compared single injections of insulin detemir dosed at 0.1, 0.2, 0.4, 0.8, and 1.6 U/kg with an injection of 0.3 IU/kg NPH insulin [44]. This study demonstrated a linear dose-response relationship for insulin detemir for pharmacokinetic (AUCinsulin detemir) and pharmacodynamic (AUCGIR) parameters. In addition, insulin detemir had an equivalent total glucose lowering action to NPH insulin on a unit for unit basis, but insulin detemir had a longer duration of action and a reduced maximal effect. At the higher doses, the meas-
urable duration of action of insulin detemir exceeded 24 hours, while at 0.4 U/kg the mean duration of action was approximately 20 hours, suggesting that many patients would be able to dose the drug once daily. Finally, the study also showed much narrower confidence intervals for the parameters of maximum glucose infusion rate (GIR_{max}) and duration of action for insulin detemir than NPH insulin, suggesting that the overall variability (between and within subjects) from injection to injection had been lower. A reduced overall variability for insulin detemir in comparison to NPH insulin was also demonstrated in a preclinical study comparing pharmacokinetic profiles across and within three cohorts, namely adults, adolescents and children [46]. Here, lower coefficients of variation in AUC, C_{max}, and t_{max} indicated that insulin detemir was more consistent in its pharmacokinetic profile across patients in all three age-groups. Furthermore, there was greater consistency across age groups in the pharmacokinetic profile of insulin detemir, whereas there was a significant difference in the profiles produced by NPH insulin between adults and children.

In light of these results, a second clamp study of large scale was undertaken specifically to assess the within-subject variability of insulin detemir in comparison to NPH insulin and insulin glargine [45]. This parallel-group, double-blind study randomized 54 people with type 1 diabetes. Each subject received an injection of one of the comparators (dosed at 0.4 U/kg) and was then given a 24-hour euglycaemic (5.5 mmol/l) clamp procedure during which GIR was measured. The whole procedure was repeated on four separate occasions so that each subject received the same basal insulin comparator four times. Selected GIR profiles from 24 patients in the study are illustrated in figure 3. These typify the finding that the GIR time-action profiles were significantly more consistent in subjects receiving insulin detemir injections (CV for GIR_{AUC}, 27%) compared to those receiving insulin glargine (CV, 48%, p<0.001) or NPH insulin (CV, 68%, p<0.001). There was also a lower within-subject variability in GIR_{max} for insulin detemir, the respective CVs being 23%, 36% and 46% (p<0.001, insulin detemir vs each comparator). Hence, this study showed that both the duration of action and peak effect of insulin detemir are more consistent, injection to injection, than previously available basal insulins.

The implication of this study was that it might be possible to favourably shift the balance between hypoglycaemic control and hypoglycaemic risk using insulin detemir.

### Predictability in the clinical arena

The potential benefits of a 'more predictable' basal insulin have now been tested in a series of phase 3 clinical trials comparing insulin detemir to NPH insulin, summarised in table I. These have consistently illustrated reduced variability with insulin detemir as evidenced by significantly lower standard deviations in glycaemic parameters such as fasting plasma glucose. One study [47] specifically measured within-subject variability in a subset of patients with type 1 diabetes (n = 133) being treated with either once-daily insulin detemir or NPH insulin as the basal component of basal-bolus therapy. These patients underwent continuous interstitial glucose monitoring for a 3-day period, and the data were used to calculate the individuals’ mean fluctuation in glucose over 24 hours from their 24-hour mean blood glucose concentration. A statistical analysis of these data suggested that the degree of within-patient fluctuation in interstitial glucose was lower with insulin detemir both over 24 hours (by some 14%, p = 0.039) and over the nocturnal hours (by some 22%, p = 0.005).

But is this greater consistency in blood glucose profile of real clinical benefit? The trials have generally employed protocols aiming at pre-specified glycaemic targets (generally based on fasting plasma glucose) so consequently endpoint data
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Describing glycaemic control have tended to be equivalent in the published studies. However, the risk of hypoglycaemia has been consistently reduced with insulin detemir – particularly so for nocturnal hypoglycaemia (table I), which is especially related to the basal component of insulin therapy. This is remarkable because none of the published studies included hypoglycaemia as a primary endpoint so they lacked statistical sensitivity to treatment differences in this outcome. A recent study of basal-bolus therapy in 131 patients with type 1 diabetes (so far published in abstract form) has employed a two 4-month period crossover design to examine hypoglycaemia as the main endpoint [55]. This has confirmed the risk reduction for insulin detemir relative to NPH insulin, showing statistically significant risk reductions of 50% for nocturnal events and 18% for all events.

Another consistent finding has been that in contrast to NPH insulin, insulin detemir has not been associated with increases in mean body weight in studies of type 1 diabetes, and has been associated with a significantly lower weight gain in type 2 diabetes. Whether this effect relates to reduced variability is unknown. It can be speculated that insulin detemir-treated patients might benefit from a reduction in calorie intake as a result of their perceiving a reduced threat of hypoglycaemia, or they might have a reduced appetite arising from reductions in plasma insulin or glucose fluxes. Clearly, however, it does seem likely that the more predictable profile of insulin detemir is directly responsible for the relative risk reduction for hypoglycaemia, as originally predicted.

Table I
Overview of clinical data from published trials of insulin detemir vs NPH.

<table>
<thead>
<tr>
<th>Study publication</th>
<th>Overview</th>
<th>Relative reduction in SD for FBG</th>
<th>Endpoint HbA1c detemir: NPH (%)</th>
<th>Risk reduction, nocturnal hypoglycaemia</th>
<th>ΔWeight detemir: NPH (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standl, et al. 2004 [48]</td>
<td>12-month randomised parallel trial of basal (BD) bolus (HSl) therapy in 288 patients type 1 diabetes.</td>
<td>No data</td>
<td>7.88</td>
<td>29% (ns)</td>
<td>−0.3 + 1.4 (p = 0.002)</td>
</tr>
<tr>
<td>Vague, et al. 2003 [49]</td>
<td>6-month randomised parallel trial of basal (BD) bolus (IAsp) therapy in 447 patients type 1 diabetes.</td>
<td>11% (p &lt; 0.001)</td>
<td>7.60</td>
<td>34% (p = 0.005)</td>
<td>−0.2 + 0.7 (p &lt; 0.001)</td>
</tr>
<tr>
<td>De Leeuw, et al. 2005 [50]</td>
<td>12-month randomised parallel trial of basal (BD) bolus (IAsp) therapy in 315 patients type 1 diabetes.</td>
<td>No data</td>
<td>7.53</td>
<td>32% (p = 0.016)</td>
<td>−0.1 + 1.2 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Home, et al. 2004 [51]</td>
<td>4-month randomised parallel trial of basal (BD) bolus (IAsp) therapy in 408 patients type 1 diabetes.</td>
<td>16% (p &lt; 0.001)</td>
<td>7.76</td>
<td>16% (ns)</td>
<td>+ 0.1 + 0.7 (p &lt; 0.04)</td>
</tr>
<tr>
<td>Russell-Jones, et al. 2004 [47]</td>
<td>6-month randomised parallel trial of basal (BD) bolus (IAsp) therapy in 747 patients type 1 diabetes.</td>
<td>22% (p &lt; 0.001)</td>
<td>8.46</td>
<td>26% (p = 0.003)</td>
<td>−0.5 + 0.1 (p = 0.007)</td>
</tr>
<tr>
<td>Hermansen, et al. 2004 [52]</td>
<td>3-month randomised parallel trial of analogue vs human insulin basal (OD/BD) bolus therapy in 595 patients type 1 diabetes.</td>
<td>15% (p &lt; 0.0001)</td>
<td>7.88</td>
<td>55% (p &lt; 0.001)</td>
<td>−1.0 + 0.1 (p &lt; 0.001)</td>
</tr>
<tr>
<td>Raslova, et al. 2004 [53]</td>
<td>5-month randomised parallel trial of analogue vs human insulin basal (OD/BD) bolus therapy in 394 patients type 2 diabetes.</td>
<td>20% (p &lt; 0.001)</td>
<td>7.46</td>
<td>38% (ns)</td>
<td>+ 0.5 + 1.1 (p = 0.038)</td>
</tr>
<tr>
<td>Haak, et al. 2005 [54]</td>
<td>6-month randomised parallel trial of basal (OD/BD) bolus (IAsp) therapy in 505 patients type 2 diabetes.</td>
<td>6.4% (p = 0.02)</td>
<td>7.63</td>
<td>0 (ns)</td>
<td>+ 0.4 + 1.3 (p = 0.017)</td>
</tr>
</tbody>
</table>

The benefits of basal insulins with improved predictability certainly seem likely to be manifest in clinical practice to at least the same extent as they are in the controlled clinical trials. This is because many patients on basal-bolus therapy have now become established on rapid-acting analogues to better control their postprandial glycaemic levels. However, the shorter duration of action of these analogues in comparison to soluble human insulin often obliges an increase in the basal insulin dose [e.g. 56]. This inevitably increases the patient’s exposure to the limitations of traditional basal insulins and to an increased scope for variable absorption and its attendant risks. This has possibly previously undermined the potential benefits of rapid acting analogues. A switch to an improved, more predictable basal insulin might therefore permit a much more favourable balance between control and tolerability to be achieved. This was certainly indicated in a study comparing an all analogue (detemir plus mealtime insulin aspart) basal-bolus regimen to a human insulin-based basal-bolus regimen in type 1 diabetes [52], in which the analogue regimen achieved a significantly lower HbA1c together with a significant 55% risk reduction for nocturnal hypoglycaemia.

References

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