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Concentrated insulins in current clinical practice

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ABSTRACT

New concentrated insulins (exceeding 100 units/mL) and dedicated devices have recently become available, offering new treatment options for people with diabetes, for basal and prandial insulin supplementation. The concentrated insulin formulations range from 2-fold concentration (insulin lispro 200 units/mL) with rapid-acting prandial action to 5-fold concentration (human regular insulin, 500 units/mL) with basal and short-acting prandial actions. Long-acting basal insulins include degludec 200 units/mL and glargine 300 units/mL. Concentrated insulins have been developed with the goal of easing insulin therapy by reducing the volume and number of injections and in some cases making use of altered pharmacokinetic and pharmacodynamic properties. This review summarizes the unique characteristics of each concentrated insulin to help healthcare providers and people with diabetes understand how to best use them.

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1. Introduction

Glycaemic control in people with diabetes remains suboptimal, and compliance with complex self-care routines, including insulin administration, is problematic [1]. There is a need for insulins that reduce the frequency of hyperglycaemia and hypoglycaemia and can reduce the burden of daily therapy (fewer injections, better delivery systems), especially in insulin-resistant patients using high insulin doses [2,3]. One option that has been explored is insulin with increased concentration [4]. The history of insulin development has been characterised by the evolution of increasing concentrations, having started with an initial U-5 preparation, followed by U-10, U-20, U-40 and U-80, resulting in the most commonly used insulin formulation of human regular insulin and insulin analogues, 100 units/mL (Reg-U100) [4].

U-500 beef regular insulin was the first highly concentrated insulin developed in 1952 to specifically treat people with severe insulin resistance [4]. In 1994, U-500 human regular insulin (Reg-U500) was approved by the United States (US) Food and Drug Administration. This insulin is specifically indicated for people with diabetes who require > 200 units/day insulin (severe insulin resistance) [5]. More recently, newer concentrated insulins have become available and have been shown to be safe and efficacious in people with diabetes [5–8]. Factors such as insulin experience, dosing requirements, and treatment characteristics (bioequivalence, potency, and delivery device features) are important considerations which healthcare providers have an increasing interest in understanding. This review aims to provide information on these aspects of concentrated insulins that are essential to understanding their clinical use.

2. Potential benefits of using concentrated insulins

2.1. *Decreased volume*

Insulin injection volume is particularly important in patients using higher insulin doses. In a meta-analysis of 5 phase 3a clinical trials, approximately 35% of subjects with Type 2 diabetes mellitus treated with basal insulin required > 60 units daily [9]. In addition, people with severe insulin resistance may need to inject > 100 units or 1 mL of Reg-U100 insulin at a time [10]. When switching these people from U-100 insulin regimens to U-500 insulin, the reduced volume of dosing with the U-500 concentration allowed treatment of people with severely insulin-resistant diabetes with 2 to 3 injections daily compared to up to 10 injections a day with U-100 insulins [11,12]. Reg-U500 and the newer concentrated insulin preparations now available (Table 1), may provide potential advantages including decreased number of injections, decreased pain, less frequent pen changes, ability to deliver larger doses, improved pen mechanics, and enhancements of continuous subcutaneous insulin infusion. Such issues may improve adherence and lessen the burden of diabetes care on people with diabetes [13,14].

2.2. *Decreased number of injections*

Injecting large doses of Reg-U100 insulin can introduce challenges for people with diabetes, including difficulties with delivering a dose in a single injection. This is due to the limited capacity of syringes and pens, resulting in the need for additional injections for people to receive a full dose. A practice observed in clinical care has been to divide a single subcutaneous insulin injection into multiple separate injections, when the total amount of a single injection exceeds a prespecified volume [15–17]. With concentrated insulins, decreased injection volume and fewer injections have demonstrated reduced measures of disease burden and ultimately improved experience with injections [18].

2.3. *Decreased pain*

Injecting large volumes can cause injection-site discomfort and pain. One perceived benefit of splitting a large volume of insulin into 2 smaller-volume injections is less injection pain [19]. Results of a randomised controlled trial assessing perceived pain during subcutaneous injections into the abdomen and thigh in people with Type 1 diabetes mellitus or Type 2 diabetes mellitus indicated that high-injection volumes

Table 1 – Concentrated insulins currently available.

	Regular U-500[a,b]	Regular U-500[a,b]	Glargine U-300[a,c]	Glargine U-300[c]	Degludec U-200[a,d,e]	Lispro U-200[a,e,f]
Device	Vial	Pen	Pen	Pen	Pen	Pen
PK/PD characteristics	Prandial and basal	Prandial and basal	Basal	Basal	Basal	Prandial
Bioequivalent	No	No	No	No	Yes	Yes
Unit increments	5	5	1	2	2	1
Maximum dose (Units)	250 [g]	300	80	160	160	60
Units/device	10,000	1500	450	900	600	600
Storage and handling in use (days)	40	28	42	42	56	28
Minimum daily units[h]	250[i]	54[i]	11	20	11	21

Regular U-500, regular U-500 insulin (Humulin®); Glargine U-300, insulin glargine U-300 (Toujeo®); Degludec U-200, insulin degludec U-200 (Tresiba®); Lispro U-200, insulin lispro U-200 (Humalog 200®); PD, pharmacodynamics; PK, pharmacokinetics.

[a] Hood. *Diabetes Technol Ther* 2017; 19(4): 203–5.

[b] HUMULIN® Prescribing Information, 2016.

[c] TOUJEO® Prescribing Information, 2018.

[d] TRESIBA® Prescribing Information, 2018.

[e] Ovalle et al. *Curr Med Res Op 2018*; 34(6): 1029–1043.

[f] HUMALOG®, Prescribing Information, 2017.

[g] Using dedicated U-500 syringe.

[h] Minimum needed to empty the device before contents expire.

[i] Indicated for people with diabetes requiring > 200 units of daily insulin.

(1.2 mL and 1.6 mL, compared with 0.4 mL and 0.8 mL) led to more injection pain at both injection sites, and injections into the thigh were generally more painful than those into the abdomen [20]. A study by Kabul et al. [18] using a visual analogue scale to assess injection pain demonstrated an improvement in insulin-resistant people with Type 2 diabetes mellitus when transition to concentrated insulin (from high-dose Reg-U100 to Reg-U500 insulin) for both 2- and 3-times daily injections. To avoid injection pain, people on high insulin doses may be inclined to choose insulin concentrations allowing injection of lower volumes.

2.4. *Less frequent pen changes*

People who have higher insulin requirements will use more pens/cartridges. Additionally, people needing higher doses may be candidates for new higher concentrated insulin formulations, most of which are available only in a prefilled, dedicated pen/cartridge; Reg-U500 is also available in a vial [5]. Existing pens are either prefilled or loaded with cartridges containing 100 units/mL insulin, which provide a maximum total of 300 units of insulin per pen and maximum doses between 60 and 80 units [16,19]. In contrast, pens with concentrated insulins contain 450 and 900 units (glargine U-300 [Glar-U300]) [6], 600 units (degludec U-200 [Deg-U200]) [7], 600 units (lispro U-200 [Lispro-U200]) [8] and 1500 units (Reg-U500) [5]. The more insulin units contained in a single pen, the less frequently the person will need to change pens [21]. Unless the final dose delivered by the pen matches the prescribed dose, insulin wastage, double injection, or underdosing will occur [22]. Less frequent pen changes benefit both people on high doses of insulin and on relatively lower doses of insulin. The minimum daily doses required for recommending concentrated insulin are 21 units for Lispro-U200, 11 units for Deg-U200, and 11 units for Glar-U300 (20 units for Max SoloStar) (Table 1). These recommendations relate to the shelf life of the insulin contained within the pen. For example, for Lispro-U200, the pen holds 600 units, so the patient can inject 21 units daily over the 28-day shelf life of the pen [8].

2.5. *Easier delivery of larger doses*

Mechanical aspects of using delivery devices affecting the maximum amount of insulin that can be delivered in a single dose vary across insulin pens and limit the total insulin amount that can be injected at once. For U-100 insulins, a maximum of between 60 units and 80 units using an insulin pen [16,19] can be injected in a single dose, compared to 160 units with Deg-U200 and 300 units with Reg-U500 [5,7].

Additionally, delivering larger doses can be more difficult particularly for people with impaired dexterity, may require an extended thumb reach [23] or additional/continued force to inject the full dose [19,23]. Furthermore, when administering insulin, people must ensure they are holding the needle under the skin to allow sufficient time to deliver the full dose, which can be increasingly difficult when attempting to inject large doses. Using concentrated insulins in new pen devices reduced the injection force needed as compared to a similar U-100 prefilled pen device [13]. Because the volume is reduced by half in case of switching from U-100 to U-200, the throw of the plunger is likewise reduced by the same magnitude for any given dose of insulin. People with diabetes expressed preference for the use of a U-200 concentrated insulin pen compared to a U-100 insulin pen because of an improved injection experience related to reduced injection volume and reduced injection force of the pen [24].

2.6. *Insulin pump enhancements*

Commercially available insulin pumps are not currently calibrated for use with concentrated insulins and none are approved for use in continuous subcutaneous insulin infu-

sion (CSII). Several retrospective studies have reported the use of pumps in people requiring large doses of insulin [25–27].

In a pilot study, Lispro-U200 administered by CSII improved duration of euglycaemia with a trend towards improved postprandial glucose control; patient satisfaction improved with Lispro-U200 versus Reg-U500 by CSII [28].

Potential advantages with using concentrated insulins in pumps include (i) higher maximum bolus; (ii) higher maximum basal rate; (iii) less frequent infusion set change/reservoir refills; and (iv) improved acceptability of insulin pumps in obese or severely insulin-resistant individuals with Type 2 diabetes mellitus requiring high insulin doses [28]. The availability of concentrated insulins could lead to development of more compact pumps with smaller reservoirs [29]. However, current insulin pumps use U-100 insulin; therefore, use of more concentrated insulin is off-label. Patients would have to convert insulin doses themselves, which presents a potentially dangerous source of error.

3. Insulin pharmacokinetics and pharmacodynamics

3.1. *Pharmacokinetic/pharmacodynamic relationship*

Assessment of the pharmacokinetic (PK) and pharmacodynamics (PD) properties of a drug formulation is critical to understanding its time-action profile and the drug's benefits [30]. PK parameters determine the concentration of drug and metabolites that are achieved in blood, plasma, or other tissues, whereas PD parameters examine how a drug affects the body. In general, the extent of a drug's PD interactions within an individual is affected by drug PK parameters, such as absorption, distribution, metabolism, excretion and, frequently, drug concentration. However, the relationship between PK and PD is less direct with insulins that exert pharmacologic effects through binding to cell surface receptors [31]. In patients with diabetes, altered insulin sensitivity can result in altered PD activity for the same PK concentration in different individuals.

3.2. *Clamp technique allowing study of pharmacokinetic/pharmacodynamic properties*

Both PK and PD properties of insulin preparations can be examined simultaneously using the euglycaemic clamp technique, which allows characterisation of the concentration-time and action-time profiles of any insulin product. During a glucose clamp, a specific dose of insulin is administered and the decrease in the blood-glucose concentration in response to the injected insulin is prevented by an intravenous glucose infusion [32]. The glucose infusion rate (GIR) needed to maintain steady euglycaemic values reflect the blood-glucose–lowering effect of the applied insulin. The representation of the measured GIRs over time describes the time-action profiles of the insulin products. During the study, insulin plasma levels can be measured and used to determine the PK profile. Repetitive clamp studies can be used to evaluate variability in PK/PD parameters [32,33].

3.3. *Factors including dose and concentration can affect pharmacokinetic/pharmacodynamic characteristics*

In a vial or pen, insulin exists primarily in hexameric forms which are stable [22]. The percent of insulin hexamers is affected by concentration (higher concentration favours hexamerisation), excipients such as zinc, and the structure of the insulin. Insulin has to dissociate into dimers or monomers before it can be absorbed into the capillaries [22,33,34]. At the interface between the surface of the insulin depot and the interstitium, there is a drop in insulin concentration which, coupled with the diffusion of excipients, favours dissociation into monomers and dimers.

The volume of the insulin depot (proportionate to insulin amount) increases as a cube while the surface area (representing the diffusion area) increases as a square [22]. As demonstrated in Fig. 1, a larger dose or higher concentration of insulin results in a reduction of the diffusion area to the amount of insulin to be absorbed, which usually leads to a right shift in the time-action of the insulin (delayed and lower peak, longer duration). That is, because of the smaller surface area concentrated insulins take longer to diffuse into tissues and reach capillaries to get absorbed.

Subcutaneous administration of increasing human insulin concentrations results in slower absorption and appearance of insulin in the plasma. The higher the insulin concentration is, the slower its diffusion into tissues will be, resulting in a more prolonged insulin absorption time and effect [35]. Similarly, because of the larger surface area per insulin molecule, a smaller dose of the same insulin concentration will be absorbed faster than a larger one [36]; thus, larger insulin doses lead to a right shift in the PK/PD profile which has been demonstrated in various populations (Type 1 diabetes mellitus [37]; Type 2 diabetes mellitus, obese [38] and healthy participants [39]).

3.4. *Bioequivalence*

Bioequivalence is a PK term describing formulations with the same active ingredient and similar patterns of absorption into the bloodstream; equivalent release of bioequivalent formulations should result in equivalent rate and magnitude of drug absorption [40].

To demonstrate bioequivalence, clinical studies usually examine each drug's plasma concentration-time curve, assessing the rate and extent of absorption. Bioequivalent drugs must meet predetermined limits on PK parameters, mostly the total area under the time-concentration curve (AUC, which reflects the extent of exposure) and the maximum plasma concentration (C_{max}, or peak exposure) [40]. For insulins, glucose clamp data for the demonstration of PD bioequivalence (i.e., similar total GIR-AUC and maximum glucose infusion rate [GIR_{max}]) have also to be provided.

3.4.1. *Concentrated insulins that are not bioequivalent*

Generally, higher insulin concentrations decrease the volume/surface-ratio and therefore are absorbed more slowly [22]. This causes a "right-shift" (lower C_{max}, longer time to reach maximum plasma concentration [t_{max}], and duration

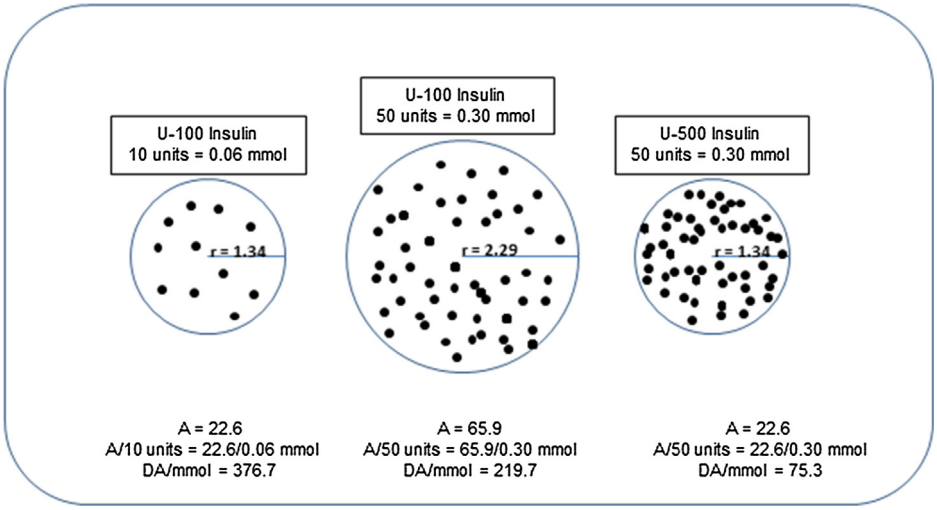

Fig. 1 – Change in concentration alters the surface area/absorption interface when concentrating insulin[a]. [a]Each dot within a sphere represents 1 unit of insulin. [b]Hood. *Diabetes Technol Ther* 2017; 19(4): 203–5. Units, mmol; r, radius; A, surface area ($4\pi r^2$); DA/mmol, ratio of diffusion (surface) area to mmol insulin to be absorbed[b]; DA, diffusion area; 1 unit insulin = 6.0 nmol; Radius Calculations: [volume = $4/3\pi r^3$, 10 units=(1.33)(3.14)xR^3, R^3 = 2.389; R = 1.34; 50 units = R^3 = 11.945; R = 2.29].

of action and, sometimes lower AUC). Indeed, the 5-fold concentration of Reg-U500 results in a right shift of its PK/PD profile compared to Reg-U100 [14]. Although the AUCs (overall exposure) for Reg-U100 and Reg-U500 were similar, the 2 formulations were not bioequivalent because C_{max} was substantially lower with Reg-U500. A delay in PK (serum insulin t_{max}) and PD (t-GIR_{max}) between Reg-U500 and Reg-U100 was observed at the 100-unit dose and perhaps the 50-unit dose. At the 100-unit dose, both Reg-U100 and Reg-U500 had a mean onset of action within 15 min, and the mean end of action (tR_{last}) occurred later for U-500 at the 50-unit (19.7 versus 18.3 h) and 100-unit doses (21.5 versus 18.3 h). Single-dose euglycaemic clamp studies conducted in healthy obese and normal-weight subjects, and normal-weight patients with Type 1 diabetes mellitus were used to simulate the PK/PD activity profile of Reg-U500 insulin administered 1-, 2-, or 3-times daily at the same daily dose of approximately 500 units [41]. For all dosing regimens, steady-state PK seemed to be reached rapidly 24 h after the initial dose.

In clinical studies, Glar-U300 is a longer acting insulin formulation than Glar-U100 and achieves similar glycated haemoglobin (HbA_{1c}) reduction with less hypoglycaemic risk (mostly for nocturnal hypoglycaemia) in people with Type 2 diabetes mellitus who have been prescribed larger insulin doses [42]. The comparison of Glar-U300 and Glar-U100 in a randomised, double-blind, crossover euglycaemic clamp study conducted over a 36-hour period in people with Type 1 diabetes mellitus did not demonstrate bioequivalence, for either PK or PD parameters [43]. Particularly, with the right shift of the Glar-U300 concentration curve (later time to 50% AUC for serum insulin and GIR time curves over 0 to 36 h), the AUC was smaller in the first 24 h at least partially due to the right shift with a greater AUC from 24 to 36 h and there was a lower C_{max}/GIR_{max} with Glar-U300. Glar-U300 maintained blood glucose control of $\leq$105 mg/dL approximately 5 h longer (30-hour median) than Glar-U100. Thus, Glar-U300 provides a more even PK and PD profile and a longer duration of action than Glar-U100.

3.4.2. *Concentrated insulins that are bioequivalent*

The concentrated versions of insulins degludec and lispro were formulated to counteract the right shift described above. In a double-blind, crossover, randomised, 26-hour euglycaemic clamp study, the PK/PD properties of Deg-U100 and Deg-U200 were compared under steady-state conditions in people with Type 1 diabetes mellitus. Post hoc analysis demonstrated that Deg-U100 and Deg-U200 were bioequivalent with comparable glucose-lowering effects at steady-state; other PK/PD parameters tested were also similar [44].

Degludec is a second-generation acylated basal insulin analogue forming long chains of hexamers [45]. Hexamer dissolution only occurs at the end of each chain, yielding a smaller dissolution area than the surface area of the depot itself. Thus, the ratio of the diffusion area to the number of insulin molecules has less effect on PK/PD [22]. Additionally, the duration of action is further extended by the acylated moiety via reversible binding to albumin in the vascular and interstitial compartments, unrelated to the depot itself [22]. The properties and clinical activity of degludec have been previously reviewed [33,45].

A phase 1, single-centre, open-label, 2-sequence, 4-period, randomised, crossover, 8-hour euglycaemic clamp, bioequivalence study compared the PK and PD of Lispro-U100 and Lispro- U200 after subcutaneous administration of 20 units to healthy participants [46]. Comparison of the PK parameters (AUC and C_{max}) and PD parameters (GIR-AUC and GIR_{max}) for Lispro-U200 versus Lispro-U100 confirmed both formulations are bioequivalent. Median differences for PD time variables were less than 6 min and all 95% CIs encompassed zero [46].

One reason why Lispro-U200 does not have an altered PK/PD profile relative to Lispro- U100 may be, partially, due to the B-chain alteration in the amino acid sequence of both

Lispro-U200 and Lispro-U100. The switch of lysine and proline leads to a strong destabilisation of hexamer formation [22]. Because a greater proportion of insulin in the depot is already in monomeric and dimeric forms, this results in a more rapid absorption. The dose-related right shift in the PK/PD of Lispro-U200 is less pronounced than that of Reg-U100, which suggests that the ratio of the diffusion area to the number of insulin molecules has less effect [22]. Other reasons for the shift towards hexamers include a change in zinc content and a change in buffering agent from phosphate to trometamol [46].

4. Improved adherence

Investigators have hypothesised that the challenges experienced by individuals who administer high doses of insulin could be reduced with concentrated insulins [29,47]. Concentrated insulins offer the possibility of improved adherence by reducing the number of daily insulin injections and leading to less difficulty in delivering larger doses, less discomfort at the injection site, and less frequent pen changes. No controlled studies have been conducted directly comparing adherence of people with diabetes taking large insulin volumes in a single injection to people taking additional injections needed to split the dose when a predetermined volume is exceeded. However, some data suggest that adherence may be improved using concentrated insulins. In an observational records-based study of 1099 people with Type 2 diabetes mellitus taking insulin, there was an inverse linear relationship between adherence and the number of injections prescribed [48]. People requiring only 1 injection per day compared to those requiring 4 injections per day had significantly greater adherence (78.3% ± 17.8 versus 60.8% ± 21.7 [$P < 0.0001$], respectively). Therefore, frequency of injections was associated with adherence [48].

Significantly improved adherence was demonstrated in a retrospective analysis of a large US healthcare claims database in people with Type 1 diabetes mellitus or Type 2 diabetes mellitus receiving Reg-U500 insulin as compared to those receiving higher doses (≥150 units/day) of Reg-U100 insulin [18,49]. Kabul et al. [18] reported on an analysis of a prospective randomised clinical trial of severely insulin-resistant people with Type 2 diabetes mellitus who switched from high-dose, high-volume U-100 insulin requiring multiple daily injections (median 5, range 2–10) to 2- or 3-times daily U-500. According to responses on the Treatment-related Impact Measure-Diabetes (TRIM-D) questionnaire, participants taking 2-times daily dosing reported better improvements in overall and treatment burden, daily life, and compliance domains than those on 3-times daily Reg-U500 dosing. This further supports the contention that reducing the number of injections improves adherence and disease burden.

Furthermore, in a recent cross-sectional study by Van Brunt et al. [21], people with diabetes on prandial insulin were surveyed about insulin wastage and injection habits when insufficient insulin remained in a disposable prefilled pen/cartridge to administer a full dose in a single injection. Overall, 63.5% of participants split the dose across 2 prefilled pens/cartridges (administered 2 injections to obtain a full dose), 15.0% used what remained in their current pen (underdosed), and 36.3% discarded prefilled pens/cartridges still containing insulin (wasted). Additional injections and increasing complexity of insulin regimens can result in poorer acceptance and adherence. Thus, if people change pens less often (because there are more units in the pen), these circumstances may occur less frequently.

5. Current concentrated insulins: Practicalities

There are 4 currently available concentrated insulins. These are listed in Table 1, and a summary of the potential benefits of concentrated insulins is listed in Table 2. Practicalities of the use of the 4 concentrated insulins are summarised below.

5.1. *Insulin glargine U-300*

Glar-U300 is basal insulin approved in the United States and Europe [6,50]. At 300 units/mL, it is 3-fold concentrated compared to Glar-U100 [51], and is distributed as a pen (SoloStar) that dispenses doses in 1-unit increments [6]. The FDA recently approved a Glar-U300 pen (Max SoloStar) which contains 900 units of insulin and can dose up to 160 units at a time in doses of 2-unit increments (Table 1) [6].

Compared to Glar-U100 (which contains 300 units) [51], each pen of Glar-U300 contains either 450 units or 900 units [6]. The volume of each injection is a third smaller; however, the maximum single-injection dose is unchanged at 80 units for SoloStar but is increased to 160 units for Max SoloStar [6,51]. Both Glar-U300 preparations are stable at room temperature (when in use) for 42 days; therefore, the pen's contents will be used within this time frame if ≥11 units daily (SoloStar) and ≥20 units daily (Max SoloStar) are prescribed [6,51].

5.2. *Human regular U-500 insulin*

Reg-U500 comes in a 20-mL vial containing 10,000 units, which can be administered in doses up to 250 units using a dedicated 0.5-cc Reg-U500 syringe or with a pen that contains 1500 units and can dose up to 300 units at a time [5]. Both delivery systems dose in 5-unit increments. Once in use, the insulin in the pen is stable at room temperature for 28 days

Table 2 – Summary of potential benefits of concentrated insulins.

- Decreased injection volume
- Decreased number of injections
- Decreased pain at injection site
- Less frequent pen changes
- Ability to deliver larger doses
- Greater ease in delivering larger doses
- Insulin pump enhancements (higher maximum basal rates, larger maximum boluses, less frequent reservoir fills, and possibly smaller devices in the future)
- Altered pharmacokinetics/pharmacodynamics (protracted duration of action)
- Improved adherence

and in the vial for 40 days. At least 250 units of insulin need to be prescribed daily to use the entire vial during this time frame. About 54 units of insulin are required to be used daily to empty the pen before its contents expire.

Reg-U500 may be able to be used without basal insulin [14] when used in high doses. A randomised prospective trial converting people on high-dose Reg-U100 regimens (range: 201–600 units daily; mean: 287.5 units/day; 70% basal/bolus therapy; median: 5 injections daily) to Reg-U500 administered either 2- or 3-times daily before meals demonstrated the utility of this preparation as insulin monotherapy and gives clinicians a framework for transition and titration of this insulin [12]. Adherence may improve after transition from Reg-U100 to Reg-U500 [41].

5.3. *Insulin degludec U-200*

Deg-U200 is available in 3-mL (total 600 units compared with 300 units for Deg-U100) disposable, prefilled pens and delivers up to 160 units per injection (compared to 80 units for Deg-U100) but has 2-unit increments (compared to 1-unit increments for Deg-U100) [7]. Because both insulins are bioequivalent [44], there is no need for dose conversion between Deg-U200 and Deg-U100 [7]. Deg-U200 is stable for 56 days at room temperature [7]; therefore, the advantage of less frequent pen changes can be realised in people taking as little as 11 units daily [7].

5.4. *Insulin lispro U-200*

Lispro-U200 is a concentrated prandial insulin analogue approved by the US Food and Drug Administration and the European Medicines Agency [8,52]. Lispro-U200 is available in 3-mL (total 600 units versus 300 units for Lispro-U100) disposable, prefilled pens and delivers up to 60 units per injection (same as lispro-U100) in 1-unit increments [8]. Lispro-U200 provides the same-unit dose in half the injection volume compared to Lispro-U100. Lispro-U200 is stable at room temperature for 28 days [8]; therefore, less frequent pen changes with less waste are seen, with doses as small as 21 units daily [8].

The pen provided for Lispro-U200 was found to be preferred over the pen used for Lispro-U100. Reasons for this preference included more units per pen (pen changes are half as frequent), reduced injection force, and a 50% reduction in injection volume [13,24].

6. Conclusions

Clinicians should recognise that the characteristics of concentrated insulins vary (i.e., different units in different devices, nonbioequivalent and bioequivalent), which should be understood when making treatment decisions. Potential benefits of concentrated insulins include reduced injection volume (allowing larger doses to be given); fewer injections; improved experience with injections (i.e., reduced injection pain, less wastage on pens, reduced glide pressure, less frequent pen changes); and alterations in PK and PD characteristics (protracted duration of action) (Table 2). Therefore, concentrated insulin is not just for the obese or insulin-resistant person with diabetes. In the case of Reg-U500, the ability to provide both prandial and basal actions with a single preparation [5] is also a potential benefit. There is evidence to suggest that these differences may improve adherence and/or diabetes-specific, patient-reported outcomes [18,49]. Although not currently approved, use of concentrated insulin in insulin pumps allows for higher basal rates and boluses in people with insulin resistance as well as less frequent reservoir fills. Future benefits may include decreasing the size of insulin delivery devices such as pens and pumps.

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Competing interests

Nanette C. Schloot is an employee and stockholder of Eli Lilly and Company and/or one of its subsidiaries. She is guest scientist at the German Diabetes Centre, Institute for Clinical Diabetology, Düsseldorf, Germany.

Sheila M. Corrigan was an employee and stockholder of Eli Lilly and Company during the initial writing of this review and is now retired.

Robert Panek is a full time employee of Syneos Health.

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Robert C. Hood has served as a consultant for and received research support from Eli Lilly and Company; has served as a consultant for Sanofi, Veritas, and Insulet; and is on the speakers' bureaus of Eli Lilly and Company and Novo Nordisk.

Contributors

NCS and SMC contributed the initial concept of the manuscript. NCS, RCH, SMC, RLP and TH contributed to the scope and drafting of the manuscript and made critical revisions

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