Review

How long should a long acting insulin analogue be?

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Abstract

After the discovery of insulin in the last century, rapidly efforts were undertaken to prolong the duration of action of injected insulin, in a naïve attempt to achieve physiological insulin profiles by just one injection of insulin a day [1]. However, the insulin profile achieved by beta-cells is quite different from a continuous supply of insulin. Indeed, when reflecting on the gold standard in insulin therapy, the beta-cell itself, one can distinguish between on the one hand the small amounts of insulin being produced almost continuously aimed at keeping anabolism going and on the other hand the peaks of insulin released at moments where meals are entering the system. The main target organ for both the basal and the bolus insulin secretion of the beta-cell is the liver, with a substantial first pass effect. The major asset of the insulin secretion of the beta-cell is that it is glucose-sensitive and thus, in periods without meals, no peaks of insulin release will occur, but more importantly, when metabolism needs to switch to catabolism, also the basal secretion will diminish and shut down, allowing gluconeogenesis and glycogenolysis in liver to occur.

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1. Physiological insulin profiles

After the discovery of insulin in the last century, rapidly efforts were undertaken to prolong the duration of action of injected insulin, in a naïve attempt to achieve physiological insulin profiles by just one injection of insulin a day [1]. However, the insulin profile achieved by beta-cells is quite different from a continuous supply of insulin. Indeed, when reflecting on the gold standard in insulin therapy, the beta-cell itself, one can distinguish between on the one hand the small amounts of insulin being produced almost continuously aimed at keeping anabolism going and on the other hand the peaks of insulin released at moments where meals are entering the system. The main target organ for both the basal and the bolus insulin secretion of the beta-cell is the liver, with a substantial first
pass effect. The major asset of the insulin secretion of the beta-cell is that it is glucose-sensitive and thus, in periods without meals, no peaks of insulin release will occur, but more importantly, when metabolism needs to switch to catabolism, also the basal secretion will diminish and shut down, allowing gluconeogenesis and glycogenolysis in liver to occur.

Therefore, when considering an ideal long acting insulin analogue, features such as continuous coverage allowing continuous presence of basal insulin in order to avoid hepatic glucose output when not warranted, but also preferential hepatic effects and glucose-sensitive levels would be ideal. In the present arsenal of analogues we are not there yet. Still, the first feature of continuous coverage is being approached rapidly with the manufacture of novel insulin analogues [2].

2. From NPH to the first generation long-acting insulin analogues

First attempts at protraction for subcutaneously administered insulin, were based on chemically induced precipitation or complex formation. By adding excess amounts of zinc or large proteins like protamine, regular insulin hexamers would aggregate into big complexes, that took time to dissociate after injection under the skin. These protraction methods used e.g. to manufacture NPH insulin, led to prolongation of the insulin action to between 6 and 14 h, with some preparations giving releases longer than 24 h (e.g. Ultralente®) [3]. The major issue with these protraction methods is the unpredictability of the release process, leading to major variation in profile, prohibiting fine titration with these insulins in many patients, exposing them to hypoglycemia when titration to tight target HbA1c is attempted. In particular nocturnal hypoglycemia is an issue with these insulins.

A major improvement came from the introduction of glargine, again based on a physical protraction method, but induced through manipulation of the insulin molecule, leading to more predictable protraction and reduced variability [4]. Detemir is the first insulin analogue where in addition to manipulation of the parent insulin molecule by amino acid substitution, the molecule was enlarged by adding a free fatty acid chain [5]. By this addition, di-hexamers can be formed and binding to proteins such as tissue or plasma albumin can occur. This interesting phenomenon opens new ways of protraction as no physical precipitation at the injection site occurs, but di-hexamerisation and protein binding will determine the release profile. Duration of action of both long-acting insulin analogues approaches 24 h and most importantly their release patterns are much more predictable than for the old long-acting insulins, with less variability reflected in clinic by less hypoglycemia, in particular nocturnal [6]. Indeed, in clinical trials, typically designed as treat-to-target trials, aiming for similar glucose control between test drug and comparator, equal glycemic control between the analogues and the comparators is demonstrated, but with a clearly reduced hypoglycemia risk [7].

As both glargine and detemir fail to cover the full 24 h in all patients, the search for longer acting insulin analogues is on. How long should a basal analogue be? At least 24 h in all patients, allowing in case of once daily administration the achievement of a plateau of basal insulin that can be topped up every 24 h. Having an even longer insulin analogue would make sense, as it would allow topping up of the plateau at even less frequent intervals. So, why not weekly or monthly? For ease of use, surely, but some issues remain. The beta-cell can shut off the basal secretion of insulin in case of less insulin requirements, but in case an extremely long acting insulin analogue is used, paradoxically less flexibility of the regimen may be induced, as the impact of therapeutic decisions to alter dose may be very slow. Thus, there may be an upper practical limit to the duration of a basal insulin analogue that is not glucose-sensitive in its release. Most clinicians will find a duration of about 3 days acceptable to wait for therapeutic effect to build up, but waiting longer may be problematic.

3. Future

Industry has again picked up interest in the design of long-acting insulin analogues, looking for ultra-long-acting analogues, but till now stay with the principle of once daily administration. Indeed, in a phase 2 study the new ultra-long insulin degludec was tested in a three-times-weekly regimen showing initial positive results [8], but phase 3 studies demonstrated that administering this basal insulin only 3 times a week did not achieve equal efficacy and safety as the once daily administered product, making the company leave this concept for now. The degludec program did demonstrate the very long duration and stability of this new insulin, as studies both in type 2 and type 1 diabetic patients demonstrated that injections could be given at any time of the day, spread between 8 and 40 h apart. When compared to glargine, this analogue showed an additional decrease in hypoglycemia, in particular nocturnal hypoglycemia risk. This analogue was designed following-up on the strategy used for detemir, coupling (via a linker) a free fatty acid chain to the insulin molecule, allowing not only di-hexamer, but multi-hexamer formation at the site of injection, leading to durations of action well above 24 h [9]. Another novel long-acting insulin analogue is manufactured by yet another path: PEGylation. By linking insulin lispro to a carrier, polyethylene glycol (PEG), molecular mass is increased, gain prolonging duration of action, leading to better 24 h coverage. Initial results confirm the long-acting profile of this molecule, but some issues with effects of the PEG on liver will need to be investigated [10]. The challenge for clinicians will lie in learning how to use these ultra-long acting insulin analogues and how to deal with situations like exercise and prolonged fast.

4. What can be expected from a long-acting insulin (and what not)?

In type 1 diabetes, the role of a long-acting insulin analogue is clear: it should provide full basal coverage partnering with the short acting bolus insulin at meals. In type 2 diabetes, the problems start, as false expectations are created. In this disease, insulin is mainly added to treatment when oral glucose lowering agents or GLP-1 analogues do not succeed in keeping glucose control on target. The main purpose of basal
insulin here is to suppress hepatic glucose output, keeping fasting glucose levels under control and supplementing the beta-cell mealtime insulin peak (eventually aided by sulfonylurea or GLP-based therapies). A mistake is made, when in the face of progressive beta-cell failure, attempts are made to fully control postprandial glucose excursions by further increasing the dose of a basal insulin, leading to extremely high insulin doses, without good glycemic control, but leading to weight gain. At that time, mealtime insulin should be added. Therefore, the introduction of the ultra-long acting insulin analogues should not create the false hope that with ‘one shot a day’ glucose levels will be controlled in all type 2 patients at all times forever! Having access to ultra-long insulin analogues will bring flexibility and better, more stable glucose control for more patients, but will not dispense from adding bolus insulin as beta-cell failure progresses.

5. Conclusion

The answer to the question on requirements of duration of action of a basal insulin analogue is ‘it depends’. It depends on the patients’ own capacity to produce insulin and it depends on what one wants to do with the basal insulin: if a patient leads a very stable life, injecting his or her basal insulin at the same time every day, then 24 h is enough. However, most people lead not so stable lives and injection times will differ. Having a stable, ultra-long acting basal insulin will then allow build up of a stable basal plateau, thus allowing an active lifestyle, without compromising good and stable glucose control or risking hyper- and hypoglycemic episodes.

Conflict of interest

The authors have a competing interest to declare.

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