Original article

Basal insulin analogs: From pathophysiology to therapy. What we see, know, and try to comprehend?

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Abstract

During the past 10 years, several new basal insulin analogs have been developed. There has been for 3 years controversy on the potential increased risk for cancer with insulin glargine, which ceased with the publication of the ORIGIN trial in 2012. In insulin-treated persons with type 2 diabetes, it is usual to recommend that plasma insulin concentrations remain within a 50–200 pmol/L range in order to avoid overinsulinization, a potential causative factor for increased mitogenicity. Such concentrations are achieved when daily doses of insulin glargine or NPH insulin approximate 0.4 units/kg. However, the total plasma insulin concentrations are much greater in persons treated with insulin detemir and especially insulin degludec. These insulins derive their protracted action from the insertion of a long chain fatty acid moiety to the insulin molecule thereby increasing albumin binding. As a consequence, in persons with type 2 diabetes, stable total plasma concentrations as high as either 1600 or 6000 pmol/L are observed for insulin detemir or degludec, respectively. At present, the free to bound ratio of plasma insulin concentrations remains unknown for these two compounds. A first requirement is to understand how these insulins are eliminated or degraded and secondly to quantify the respective contributions of the free and bound fractions. Therefore, prior to early phase 2 or 3 randomized clinical trials, a better comprehension of the metabolism of all the new insulins would be invaluable.

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Keywords: Basal insulin analogs; Pathophysiology

Résumé

Analogues prolongés de l’insuline : de la physiopathologie à la thérapie. Ce que nous voyons, savons et cherchons à comprendre.

Au cours des 10 dernières années, plusieurs analogues prolongés ont été développés. Pendant 3 ans, l’insuline glargine a été accusée d’augmenter le risque potentiel de cancer. Cette controverse a cessé en 2012 avec la publication de l’étude ORIGIN. Chez les patients diabétiques de type 2 insuliniés, il est habituellement recommandé de maintenir les concentrations plasmatiques d’insuline entre 50 et 200 pmol/L afin d’éviter l’hyperinsulinisation, un facteur potentiel d’accroissement de la mitogénicité. De telles concentrations sont obtenues quand les doses quotidiennes de glargine ou de NPH sont voisines de 0,4 unités/kg. Toutefois, les concentrations totales d’insuline plasmatique sont beaucoup plus élevées chez les personnes traitées par l’insuline détémir ou dégludéc. La longue durée d’action du profil de ces insulines provient de l’insertion sur la molécule d’une longue chaîne d’acides gras, laquelle permet sa fixation sur l’albumine. Pour cette raison, les diabétiques de type 2 traités par ces insulines ont des concentrations stables d’insuline plasmatique totale, mais avec des taux respectifs de 1600 à 6000 pmol/L pour la détémir et la dégludéc. À ce jour, le rapport des concentrations insuline libre sur insuline liée reste inconnu pour ces deux types d’insuline. Il serait donc utile de savoir comment ces deux insulines sont métabolisées et dégradées. De plus, il conviendrait de quantifier les contributions respectives des formes libres et liées. De manière générale, avant d’entamer des essais cliniques randomisés de phase 2 ou 3, il serait souhaitable d’avoir une meilleure compréhension du métabolisme de toutes les nouvelles préparations insuliniques.

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The clinical assessment of new insulin analogs involves several types of clinical studies. The most classical are early phase 2 or 3 randomized trials [1–4]. The newly developed preparations are usually compared for both efficacy and safety in...
the setting of head-to-head comparisons. The reference “comparator” insulin preparation is generally chosen from among similar medications, which have been available on the market for several years and used worldwide in routine clinical practice. For instance, insulin detemir and insulin degludec have generally been compared with NPH insulin and insulin glargine [1–10]. The latter has been regarded for many years as the reference basal long-acting insulin preparation in term of duration of action [11–16]. Prior to phase 2 or 3 clinical trials, the pharmacokinetics and pharmacodynamics of these new therapeutic agents are usually tested in relatively low numbers of healthy volunteers or persons with diabetes [17,18] in an attempt to collect information to guide treatment scheduling prior to further investigation for efficacy, safety and tolerability in large scale randomized trials. Despite such precautions, adverse events still remain a possibility even several years after marketing of these substances especially when used in a chronic disease such as diabetes and especially in persons with type 2 diabetes, who are commonly exposed to polypharmacotherapy [19–23].

It is therefore not surprising to observe that most categories of antidiabetic medications marketed during the past years have been the subject of recurrent controversies with respect to their safety. Members of the thiazolidinediones were either withdrawn or submitted to limitations in their indication because of the perceived increased risk of serious adverse cardiovascular events, especially with rosiglitazone [24–27] and the greater risk of bladder cancer with chronic pioglitazone treatment at the higher dose level [28]. The possible adverse effects of GLP-1 receptor agonist based therapies inducing an increased risk of pancreatitis and cancers [29–31] is currently a hot topic of debate [32–35] and thus under review by the international and national drug agencies. As a consequence of the self-precaution principle, there appears a new philosophy that consists of publishing prematurely signals of possible deleterious effects of treatments that are used in such chronic diseases as diabetes. For instance, numerous studies and analyses have either raised or refuted concerns regarding the potential association of insulin treatments in type 2 diabetes with incident cancer risk [19–22,36–39]. In 2009, Hemkens et al. [19] published the results of an epidemiological study that suggested that insulin glargine at daily doses above 30 units can result in an increased frequency of cancer. Three years later, this hypothesis has been strongly refuted by the data of the large-scale long-term ORIGIN trial [38]. Retrospectively, such results could have been predictable if more detailed studies on the metabolic and mitogenic effects of insulin glargine and its metabolites had been conducted and published [40–42] before the controversial epidemiologic survey and flawed analysis by Hemkens et al. [19]. Unfortunately, this was not the case and consequently only after a large number of studies/trials were published was insulin glargine finally vindicated [40–43]. However, the debate on the risk for cancer with insulin preparations and other antidiabetic agents (mainly sulfonylureas [22,44,45]) continues. Therefore, given these considerations, there arises the question as to whether it is not better to extend the usual pre-clinical pharmacological studies including detailed pharmacokinetics and pharmacodynamics investigations [14–18] in order to have a better understanding of the body distribution and metabolic degradation/elimination rates of the newly developed basal insulin analogs prior to exposing large populations of patients to these new agents. Such earlier measures would provide better answers when uncertainties on safety of these drugs arise at a later stage in a clinical development program or wide scale clinical practice.

1. What we see and know?

1.1. Characteristics and properties of basal insulin analogs

Following the injection of human insulin into the subcutaneous tissue, the insulin has to be released from its depot in order to reach the systemic blood stream [46]. Thereafter the capillary endothelium provides a further barrier for insulin [47,48] to reach its receptor at multiple sites of action, including muscle, liver and adipose tissue [49]. According to this principle, long-acting insulin preparations have been prepared using one of two predominant methods [11–14]. The first one consists of producing insulin analogs that precipitate at the site of injection due to a low solubility at physiological pH [50]. Achieving a slow dissociation of the subcutaneous insulin depot is the principle used for producing insulin glargine that exhibits a prolonged action profile over a period of 24 hours, approximately [15–17]. The second mechanism, based on the binding of the insulin to albumin, has resulted in the development of another long-acting insulin analog, insulin detemir, available during the past 5 years [51]. The binding to albumin is due to the insertion of a long chain fatty acid moiety on the insulin molecule [14]. In this case, the bound fraction of detemir is slowly released and the free insulin is further transported across the capillary barrier into the interstitial fluid to finally exert its action on the peripheral tissues [51–53]. Insulin degludec, the newest clinically available long-acting insulin, draws its long duration of action from the combination of the two aforementioned properties [14,54,55]. Like insulin glargine, although via a different mechanism there is also the rapid formation of a subcutaneous depot, which with insulin degludec consists of soluble multihexamers at the injection site [55], from which insulin analog is then slowly released and enters into the systemic circulation as a monomeric insulin analog. The acylated monomers, which appear in the systemic circulation, are then further bound to albumin in the plasma. The binding is due to the presence of a long chain fatty acid, which is inserted through a “spacer” (a γ glutamic acid residue) on the C terminus of the B chain at position B29 [14]. The final result of this double retardation i.e. the formation of multihexamers at the site of administration and binding to plasma albumin, results in a flat and stable long-acting glucose lowering profile of action. According to the data from clinical pharmacological studies degludec has a duration of action longer than observed for the other long-acting insulin preparations [56,57]. At this stage, the question arises of whether it is important or not to assess the significance of the different retarding processes employed to achieve a basal supply of insulin.
1.2. Free concentrations of plasma insulin: a key player

The time action profile should be evaluated by determining the free plasma insulin concentrations and blood glucose levels at regular time intervals after a single or multiple doses of the insulin preparation has been injected into the subcutaneous tissue [14–18]. Normally, the insulin interaction with its receptor is governed by a simple reaction involving the insulin ligand, i.e. the plasma free concentration of insulin [I] and the concentration/number of its cellular receptors [R]. Should [IR] be the insulin bound to the receptor, the relationship between these three parameters can be formulated as follows: [I] × [R] = [IR] × Keq, where Keq is the equilibrium constant [58]. Rearranging this equation and introducing the relative insulin activity expressed as percentage, the latter parameter can be depicted as a function of [I] after log transformation (Fig. 1). As a consequence, the free insulin concentration is the key component for both the metabolic and mitogenic potencies of insulin. In patients treated with routine doses (≈0.2–0.4 unit/kg body weight/day) of basal insulin (insulin glargine) or intermediate-acting (NPH insulin), maximum free plasma insulin concentrations are usually between 50 and 200 pmol/L (Cmax) [53]. Peak values are usually reached during a time interval covering a period from 4 to 8 hours after the insulin subcutaneous bolus of NPH insulin [53] and a plateau for insulin glargine between 4 and 16 hours dependent on the insulin doses employed. These concentrations correspond to free insulin since neither NPH nor glargine are bound to albumin [17,53]. In contrast, the total plasma insulin concentrations (free and bound) are much greater with insulin detemir and degludec since a large fraction of these two insulins is bound to albumin in the circulation [53,55] thereby reaching a total plasma insulin Cmax of approximately 1600 and 6000 pmol/L for detemir [53] and degludec [59,60], respectively, when these two preparations are administered at usual doses. At the present time, there is no clear information on the plasma concentrations of the free moiety for these two insulin preparations. The current specific enzyme immuno-assay (ELISA) methods normally used for measuring the plasma concentrations cannot differentiate between the free and bound fractions. Therefore the bound to unbound ratios are not available.

1.3. Insulin glargine: closure of a controversy

Reverting to insulin glargine it has been demonstrated that, after subcutaneous injection, the parent insulin preparation undergoes an enzymatic removal of the two C-terminal arginine residues at positions B31 and B32 [14,40,41]. This enzymatic cleavage yields A21glycine-human insulin metabolite M1 that accounts for more than 90% of the plasma insulin concentration and metabolic action of the injected glargine [42]. Recent studies have demonstrated that the free plasma M1 concentration, i.e. the total concentration since this metabolite remains totally unbound, is within the usual 50–200 pmol/L range [41], which is similar to that seen with human insulin and NPH insulin [53]. In addition, recent in vitro studies have demonstrated that the insulin glargine metabolites, and more specifically the metabolite M1, have an equivalent mitogenic potency to that of human insulin [40] whereas previous in vitro studies have shown that the intact parent insulin glargine molecule was 7–8 times more mitogenic than the human insulin [61]. The retention time of the intact insulin glargine in the subcutaneous tissue after injection is rather short and the conversion rate into its active metabolite is a rapid and almost complete process. Therefore, the in vitro studies that have been conducted for establishing the risk of inducing cancer by the unmodified parent insulin glargine are irrelevant. Consequently a lot of money has been wasted in attempting to enunciate the self-evident truth that the mitogenicity of insulin glargine is similar to that of the other insulin products, including the human insulin thereby bringing this discussion to a closure [43].

1.4. Body distribution of insulin and degradation rates

Even though the mechanisms of the metabolic and mitogenic effects of insulin have been extensively investigated [49], many uncertainties still remain concerning its body distribution, mass degradation and flux rates between the various body compartments after an injection of exogenous insulin. For the native endogenous insulin, which is secreted by the β-cells of the human pancreas, the liver is the primary site of insulin uptake, utilization, and degradation, i.e. of the three metabolic processes, which further occur in all insulin-sensitive tissues [62] (Fig. 2). Approximately 50% of portal insulin is removed during its first-pass transit through the liver [63]. One portion of the insulin that is bound to liver receptors in the hepatic cells is used for decreasing the glucose hepatic output [64–66]. There is also a portion of the insulin that is transiently captured by the receptors and then released back into the circulation [62] to exert its metabolic effects in any other insulin-sensitive tissues such as muscle, fat or even the liver. The insulin fraction, which is not extracted by the liver, appears in the systemic circulation and is cleared by either the peripheral tissues and/or the kidney [62,67,68]. The latter organ removes approximately 50% of the circulating insulin by several mechanisms: glomerular filtration, proximal tubular reabsorption and degradation [67]. In cells of peripheral insulin-sensitive tissues (muscles, adipose tissue) the initial step is the binding of insulin to its receptor. The bound insulin can then be further processed intracellularly via multiple
pathways [62,67] (Fig. 2) with one fraction returning intact to the circulation after its release by the insulin receptor whilst the remainder is delivered to the intracellular sites. The intracellular processing of insulin includes:

- utilization for exerting its metabolic effects;
- non-reversible degradation to end products that cannot be reused;
- recycling into the systemic circulation to act on the peripheral tissues, liver, kidney, adipose tissue and the brain.

These metabolic steps are submitted to down regulation, which depends on the insulin levels either in the portal stream or systemic circulation according to whether the site of action is at the liver or peripheral tissues to including the kidney [62,67]. In addition, the role of the different above-mentioned organs in the uptake and utilization of insulin is different in insulin-treated subjects with diabetes from that seen in normal healthy subjects. In the insulin-requiring persons with diabetes, the insulin when administered by subcutaneous injection is directly absorbed into the systemic circulation after its diffusion from the subcutaneous insulin depot [62,67]. In this situation, one part of the injected insulin is bound to liver cells after transit through the systemic circulation with an indirect recycling into the liver via the hepatic artery. In contrast to the fate of endogenous insulin, the exogenous insulin escapes the first-pass removal by the liver and as a consequence it is highly likely that the kidney plays a more important role in its elimination.

2. What we try to comprehend?

2.1. Modelling the insulin distribution and flux rates

According to the aforementioned observations, understanding the whole body distribution of subcutaneously administered exogenous insulin, both its utilization and degradation necessitates the use of complex compartment analysis [63,69,70]. Using such methods implies that several conditions must be met [71]. Firstly, it is necessary that the human body be viewed as an assortment of individual pools or compartments. For insulin, the number of compartments might equate to all the tissues where the insulin is distributed/metabolized. Multiple-compartment analysis however becomes rather difficult as soon as the number of pools is greater than two. Therefore, investigators attempt to simplify the physiology processes in order to develop a minimal model and as parsimonious as possible. The distribution and metabolism of insulin in the body is usually described as a two-pool open system as insulin resides for the most part in extracellular fluids (Fig. 3) [70]. Accordingly, it is hypothesized that insulin’s distribution into two compartments can therefore be represented by the volume of the plasma and the interstitial fluid. After its appearance in plasma the insulin is eliminated through hepatic degradation and to a lesser degree, through
renal extraction or degradation [62,67]. A non-negligible fraction of the plasma insulin is transferred across the endothelial capillary barrier in order to be transferred into the interstitial compartment. One portion of the insulin that enters the interstitial pool is bound to the insulin receptors and further degraded in a non-reversible manner whilst the remainder returns to the plasma compartment. Dea et al. [70] have used this model in healthy male dogs for assessing the mean mass compartmental distribution and flux rates of human insulin (Fig. 3a). The second condition for applying compartment analysis is achieving a steady state, i.e., a stable concentration in both the plasma and interstitial compartments, with an infusion of insulin at a constant rate. The results that are illustrated on Fig. 3a show that the hepatic clearance rate of human insulin is 207 pmol/min that is more than 10 times greater than its estimated binding and degradation at peripheral sites at 14 pmol/min [70]. Such results are somewhat surprising suggesting that hepatic uptake and degradation are overestimated whilst the metabolism and disappearance rates at peripheral sites are underestimated. A two-compartment model has been applied to acylated insulins that are bound to plasma albumin (Fig. 3b) [70]. However in this case the plasma compartment is not homogeneous since this pool is now made up of two subunits corresponding either to the free and bound fractions. The compartmental theory [71] implies that the insulin must be homogeneously distributed in the volume of each pool, therefore the plasma compartment of insulin cannot be described as a single pool. The data provided by Dea et al. [70] for the distribution and flux rates of the acylated insulin detemir cannot be considered a reflection of what occurs in real physiological situations. In other words, it appears that the use of a two-compartment model in this situation with the presumed objective to be as clinically meaningful as possible is far from reality. It is therefore necessary to integrate the two additional conditions. The steady state, which is obtained with the unlabelled insulin i.e. with the exogenous insulin in the present model, should preserve the physiology and should not disturb the equilibrium. This is not the case when a large amount of insulin is administered as a single bolus or an infusion at constant rate. In addition, the use of an unlabelled tracee to obtain a steady state should be combined with the use of a labelled tracer, e.g., a radioactive labelled insulin product that is assumed to behave physiologically exactly like its unlabelled counterpart after being delivered at such small quantities so as not to disturb the system. Such an observation provides a possible explanation for the fact that most studies of the pharmacokinetics of insulin in humans remain usually restricted to the assessment of time profiles of plasma labelled (tracer) or unlabelled (tracee) insulin concentrations [14].

2.2. The high plasma concentrations of detemir and degludec: are these of concern?

Reverting to the compartment analysis of insulin detemir, the results indicate (Fig. 3b) that the liver clearance and the degradation rate by peripheral cells are equal to 223 pmol/min and 21 pmol/min, respectively [70]. These results seem to be within the same range as those found for human insulin (Fig. 3a). For that reason there arises the question of whether
the data provided by such methodology is reliable or not. At the present time, the main question that remains and which has not received any answer is to gain further insight into the metabolic handling of the “enormously” high circulating concentrations of insulin detemir or degludec (1600 pmol/L and 6000 pmol/L, respectively) resident in the peripheral circulation, predominantly bound to albumin, [52,53,59,60] following either a single injection [52,53] or following sustained treatment [59,60] with these acylated insulin preparations. According to the aforementioned results, the disappearance rate of insulin detemir in the liver appears similar to that of human insulin. This implies that peripheral target tissues are likely to be chronically exposed to a high concentration of the insulins. Consider that 5000–10,000 pmol/L is the steady state total plasma concentration of degludec, which is achieved after several days of treatment, when daily doses are set at 0.4 unit/kg/day. Such a concentration corresponds to a reservoir in the whole plasma of 3–6 units, since 1 unit of degludec is equal to 6 nmol [5,6]. This approximates to forty to one hundred times greater than that seen with the other insulin preparations such as insulin glargine, with plasma concentrations ranging between 50–200 pmol/L (100 μU to 400 μU for the whole plasma pool). The difference between basal insulins is also reflected in the biological half-life of these insulins being approximately 25.4 hours with insulin degludec versus 12.5 with insulin glargine. Insulin degludec is still detected in plasma up to 96 hours after administration. At the present time, the depiction of the distribution and metabolism of insulin degludec is not available in the public domain. Fig. 4 illustrates the numerous questions that can be raised by these unsolved problems. For that reason, the availability of reliable data would be of considerable importance for assessing the possible adverse impact of sustained high levels of insulin on various tissues such as the vascular bed and occult neoplasm with the possible increased risk of enhanced atherosclerosis [72] or cancer [73,74].

2.3. Insulin: a “bifaceted hormone”?

It has been proposed over many years that hyperinsulinaemia is a risk factor for adverse vascular outcomes in persons with type 2 diabetes. However, some studies seem to indicate that insulin could be a “bifaceted” hormone [72] with beneficial anti-atherogenic effects at doses resulting in near physiological circulating levels but with deleterious pro-atherogenic action when insulin doses are high enough to result in supraphysiological (pharmacological) levels [75]. This debate continues, recognising the complex relationship between insulin cardiovascular disease and the role of hyperglycaemia. It is well understood that the overall exposure to insulin can increase in different ways including elevated daily insulin doses used in insulin-requiring patients with type 2 diabetes in an attempt to overcome insulin resistance usually associated with being overweight. In addition the increasing longevity of persons with diabetes means that life time exposure to insulin treatment will be greater due to an earlier and earlier implementation of the insulin treatment during the natural time course of the disease. Since the review by Stout in 1990 [76] a large number of retrospective observational studies have suggested that exogenous insulin in persons with type 2 diabetes may be associated with increased risk of diabetes related complications [39] although this is not an universal finding [77]. The debate continues relating to the role of insulin and atherosclerosis when supraphysiological doses of insulin are used in type 2 diabetes in an attempt to achieve normoglycaemia. Many of the studies suggested prematurely that insulin treatments in type 2 diabetes, irrespective of the category of insulin used, were found to be associated with an increased risk of cancer [19,36,37,39,73,74]. However, the landmark long-term ORIGIN trial showed no differences in the rate of cardiovascular disease or cancers (considered as a whole or site specific) between basal insulin glargine and standard care treatment arms throughout the median 6.2 years follow-up [38]. In this trial the median daily doses of insulin administered was maintained within a physiological range, between 0.31 unit per kg of body weight by year 1 and 0.40 unit per kg by year 6. However, it should be noted that in the ORIGIN trial women only represented 35% of the total population of 12,537 participants. Consequently, the null effect of insulin glargine on the incidence of breast cancer could have been biased in the ORIGIN trial. Nevertheless, the latter result is in agreement with the findings of Morden et al. [78] who did not report...
any association between insulin glargine-only use and increased risk of breast cancer. Therefore, it can be concluded that long-term treatment with exogenous insulin even in a population with high cardiovascular risk does not result in an increased risk for cardiovascular disease or any cancer at the daily doses used in this trial. Other retrospective studies have been recently published restricted to databases collected in the setting of primary care practice in either the United Kingdom [39] or France [79,80]. No clear conclusion can be drawn from all these observational studies concerning the potential detrimental role of the dose and duration of the insulin treatment. The findings from the original ORIGIN trial [38] are very reassuring with further data expected from its continuation for an extra period of 2 years.

2.4. The debate continues

Reverting to the questions that have been raised in the title of this review: “What we see, know, and try to comprehend?” An attempt to summarize the above observations is as follows. Firstly, we see that the total insulin concentrations in plasma are quite different between the two main categories of clinically available basal insulin analogs. The concentrations are much higher for those compounds that are produced using an insertion of a long chain fatty acid on the B chain of the insulin molecule. Secondly, we have a good level of knowledge on the mechanisms by which native insulin is secreted by the human pancreas and subsequently distributed, metabolized and eliminated. However, we do not comprehend how high doses of insulin become pro-atherogenic and promote the development of cancers, especially when persons with type 2 diabetes are exposed to long-term treatments with insulin. In February 2013, an advisory panel of the Food and Drug Administration (FDA) requested additional clinical tests with insulin degludec in order to address the question as to whether the trend towards a potential risk of cardiovascular events observed from a meta-analysis of phase 3 trials is a reality or not when this new compound is compared with older insulins [81].

Therefore, we strongly suggest that our knowledge and understanding of the metabolism of all the newer basal insulin preparations should be expanded and subsequently shared with the medical community as a priority. The availability of such information is limited for the acylated-based generation of long-acting insulin preparations and therefore it remains difficult to fully comprehend their clinical pharmacology.

During the 17th century, Nicolaus Steno, a Danish catholic bishop and scientist, enunciated his famous aphorism: “Beautiful is what we see, more beautiful is what we know, most beautiful is what we do not comprehend”.

Concerning the new generation of insulins, this aphorism seems to be somewhat lost in translation at least for the part as when it comes to the patient’s safety. The recommendation “primum non nocere” should overwhelm any presumption of innocence.

Disclosure of interest

Louis Monnier has received honoraria from Novartis, Astra Zeneca and Sanofi for involvement in advisory boards and/or lecturing.

David Owens has received honoraria from Boehringer Ingelheim, Elli Lilly, NovoNordisk, Roche Diagnostic and Sanofi for involvement in advisory boards and/or lecturing.

Claude Colette declares no conflict of interest with the content of this review.

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