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Review

Insulin aspart pharmacokinetics: An assessment of its variability and underlying mechanisms

Christian Hove Rasmussen [a,b,*], Rikke Meldgaard Røge [a,c], Zhulin Ma [d], Maria Thomsen [a,e], Rannveig Linda Thorisdottir [f], Jian-Wen Chen [g], Erik Mosekilde [b], Morten Colding-Jørgensen [a]

[a] Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark
[b] Department of Physics, Technical University of Denmark, Fysikvej 309, DK-2800 Kgs. Lyngby, Denmark
[c] Department of Pharmaceutical Biosciences, Uppsala University, P.O. Box 591, SE-75124 Uppsala, Sweden
[d] Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Nørrebrogade 44, DK-8000 Aarhus C, Denmark
[e] Niels Bohr Institute, University of Copenhagen, Universitetsparken 5, DK-2100 Copenhagen, Denmark
[f] Ögonkliniken, Skåne University Hospital, Inga-Marie Nilssons gata 38, SE-21428 Malmö, Sweden
[g] Novo Nordisk International Operations A/S, Thurgauerstrasse 36/38, CH-8050 Zürich, Switzerland

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ABSTRACT

Background: Insulin aspart (IAsp) is used by many diabetics as a meal-time insulin to control postprandial glucose levels. As is the case with many other insulin types, the pharmacokinetics (PK), and consequently the pharmacodynamics (PD), is associated with clinical variability, both between and within individuals. The present article identifies the main physiological mechanisms that govern the PK of IAsp following subcutaneous administration and quantifies them in terms of their contribution to the overall variability.

Material and methods: CT scanning data from Thomsen et al. (2012) are used to investigate and quantify the properties of the subcutaneous depot. Data from Brange et al. (1990) are used to determine the effects of insulin chemistry in subcutis on the absorption rate. Intravenous (i.v.) bolus and infusion PK data for human insulin are used to understand and quantify the systemic distribution and elimination (Pørksen et al., 1997; Sjöstrand et al., 2002). PK and PD profiles for type 1 diabetics from Chen et al. (2005) are analyzed to demonstrate the effects of IAsp antibodies in terms of bound and unbound insulin. PK profiles from Thorisdottir et al. (2009) and Ma et al. (2012b) are analyzed in the nonlinear mixed effects software Monolix® to determine the presence and effects of the mechanisms described in this article.

Results: The distribution of IAsp in the subcutaneous depot show an initial dilution of approximately a factor of two in a single experiment. Injected insulin hexamers exist in a chemical equilibrium with monomers and dimers, which depends strongly on the degree of dilution in subcutis, the presence of auxiliary substances, and a variety of other factors. Sensitivity to the initial dilution in subcutis can thus be a cause of some of the variability. Temporal variations in the PK are explained by variations in the subcutaneous blood flow. IAsp antibodies are found to be a large contributor to the variability of total insulin PK in a study by Chen et al. (2005), since only the free fraction is eliminated via the receptors. The contribution of these and other sources of variability to the total variability is quantified via a population PK analysis and two recent clinical studies (Thorisdottir et al., 2009; Ma et al., 2012b), which support the presence and significance of the identified mechanisms.

Conclusions: IAsp antibody binding, oligomeric transitions in subcutis, and blood flow dependent variations in absorption rate seem to dominate the PK variability of IAsp. It may be possible via e.g. formulation design to reduce some of these variability factors.

* Corresponding author at: Novo Nordisk A/S, Novo Allé, DK-2880 Bagsværd, Denmark. Tel.: +45 4444 8888, mobile: +45 3079 1857.
E-mail address: chvr@novonordisk.com (C.H. Rasmussen).

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Contents

1. Introduction

Rapid-acting insulin is widely used in the treatment of type 1 diabetes mellitus (T1DM) and later stages of type 2 diabetes mellitus (T2DM). A meal-time injection of rapid-acting insulin, for instance IAsp, provides the control of post-prandial glucose excursions after food intake. Even in a strictly controlled clinical environment, and for fasting healthy volunteers, the use of rapid-acting insulin is associated with variability in the rate at which the insulin is absorbed systemically and in the subsequent blood glucose-lowering effect (Heinemann et al., 1998). A proper understanding of the processes that drive the PK and the associated variability is therefore an important step both in helping patients to obtain a more accurate control of their blood glucose levels and in assisting in the development of better insulin products for the treatment of diabetes.

The absorption process preceding the appearance of insulin in plasma is a complex process which is influenced by many factors. Volume and concentration of the injected solution, oligomeric transitions in subcutis, dose and diffusion rate in the s.c. tissue (Brange et al., 1990) are important determinants of the PK, as are variations in local subcutaneous blood flow and skin temperature (Hildebrandt et al., 1985). Furthermore the level of antibody-binding may also influence the observed insulin profile (Chen et al., 2005).

The present article investigates the main sources of variability observed in the PK profiles for subcutaneously administered IAsp. Available sources of information from the literature form the basis of an in-depth investigation into to the most important processes, that determine the PK. Each process is described mathematically and quantified in terms of parameters, so that a combined model for the PK can be constructed. The model is semi-mechanistic, since only the main mechanisms are included. This, along with the combination of many data sets in the construction of the model, ensures that it is identifiable in its parameters. The model is used in connection with clinical data from two recent studies (Thorisdottir et al., 2009; Ma et al., 2012b) and a population PK analysis to determine the parameters that account for most of the observed clinical variability.

2. Material and methods

Micro CT scanning of s.c. tissue: A micro CT scanning technique for subcutaneous depots developed by Thomsen et al. (2012) is used to quantify the spatial distribution of IAsp in subcutaneous pig tissue in high resolution (voxel size 27 μm). A 0.1 mL injection was performed *ex vivo* in an excised piece of pigskin and IAsp (70%) was mixed with the contrast agent Xenetix300 (30%) in order to distinguish the injected fluid from s.c. tissue. Histological cross sections colored for insulin confirmed that the contrast agent and insulin do not separate in subcutis.

Disappearance and oligomer data: The effect of self-association of IAsp on the PK is assessed from a disappearance study by Kang et al. (1991). Seven healthy normal-weight males aged between 22 and 43 years were studied on five occasions receiving different ^{125}I-labeled insulin analogs (zinc-free) and human insulin (2 zinc/hexamer). The residual radioactivity measured directly over the injection site was followed for up to 8 h. These disappearance profiles should be proportional to the remaining insulin in the injection depot. The data are analyzed in conjunction with equilibrium constants estimated for the self-association system (Brems et al., 1992; Birnbaum et al., 1996; Chitta et al., 2006) to link the disappearance data with the relative presence of the oligomers.

Distribution and elimination: Six healthy normal-weight males were administered an i.v. bolus injection with human insulin and frequent samples of plasma insulin were collected for 60 min (Pørksen et al., 1997). Three of these PK profiles were obtainable digitally for use in the quantification of the systemic distribution and elimination of insulin. Additionally, mean PK data from i.v. infusion of human insulin at 1400 pmol/min in 10 healthy normal-weight males (Sjöstrand et al., 2002) are used in conjunction with the bolus data for the quantification.

Antibody measurements and PK effects: Twenty-three men and women with T1DM aged 21–63 years were treated with multiple daily injections of biphasic IAsp (BIAsp30, 70% crystalline) over 12 weeks in the clinical study by Chen et al. (2005). Following this period, two 24 h free and total IAsp profiles were collected at two occasions one week apart. The IAsp antibody binding level was also measured for these two occasions. This data set is used to determine the effect of IAsp antibodies on the PK.

Single-dose pharmacokinetics: Single-dose total IAsp PK from the studies in Thorisdottir et al. (2009) and Ma et al. (2012b) are used for a population PK analysis. The two studies both included nineteen patients with T1DM, aged from 22 to 65 and 22 to 63, respectively, treated with different insulin preparations in a cross-over setup. Only the IAsp data are considered in the present analysis.

3. Results

3.1. The subcutaneous depot

During a s.c. injection, the insulin distributes itself between the layers of fat cells and connective tissue in the s.c. tissue. As calculated in Rasmussen et al. (2012) based on data from Hewitt (1954) and as reported by Crandall et al. (1997), the fluid volume between the fat cells only constitutes about 10% of the volume of the subcutaneous tissue. Using the same CT scanning technique applied by Thomsen et al. (2012), the Novo Nordisk group has performed several real-time CT scanning runs with no indication of bursting or expansion of the s.c. tissue (data not shown).

Using spatial concentration data from Thomsen et al. (2012), Fig. 1(a) shows an injection depot stemming from the s.c.