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EDITORIAL

Subcutaneous Injection versus Subcutaneous Infusion of Insulin: Are the Rates of Absorption Truly the Same?

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The question is, is insulin absorption after subcutaneous (SC) injection of a prandial insulin/insulin analog prior to a meal comparable to that of infusion of the same insulin dose as a bolus via an insulin pump? You might say, this is easy; let us check what published studies tell us about this topic. A search in PubMed using search terms, "injection infusion insulin subcutaneous pharmacokinetic" resulted in 69 hits on August 26, 2011. However, according to their titles, only two publications from 1983 studied this question.[1,2] In one study, a pharmacokinetic (PK) model was used to describe the plasma concentration time profile after SC administration of insulin in patients with type 1 or type 2 diabetes.[1] Continuous SC insulin infusion for 1 h at a rate of 3 ml/h (2–3 U/ml) resulted in comparable PK parameters to those generated by SC injection of insulin (40 U/ml). The authors concluded from their study that the absorption kinetics of insulin did not differ significantly between two modes of SC insulin administration in the patients studied. In the other study, six human insulin or porcine insulin preparations of either porcine were investigated after intravenous or SC infusion at two different rates (study I) and three preparations were investigated after SC bolus injection (study II) in healthy men, but SC injection or infusion were not studied in a head-to-head manner.[2] For us, these studies, which are performed with outdated techniques and inappropriate study designs, are not conclusive.

Are there reasons to believe that there might be clinically relevant differences in insulin absorption between SC injection and infusion? Let us review the relevant factors.

Timing

After insertion of the needle of an insulin syringe or insulin pen through the skin into the SC tissue, the insulin dose is administered within a few seconds. The insulin injected forms a depot from which the insulin molecules are absorbed via the capillaries into the blood stream. Over time, this depot in the SC tissue will dissipate. With insulin pumps, the catheter is also inserted into SC tissue (probably into other skin layers as well; discussed later) and some insulin is continually infused (basal insulin infusion), forming an insulin depot of a given size around the tip of the insulin catheter. Once the user presses the button on his pump to apply an insulin bolus, the infusion rate of the same insulin is increased several-thousand-fold to apply the programmed dose. In practice, there are considerable differences between insulin pumps with respect to the time required to apply the full dose. According to data presented at the last Advanced Technologies and Treatments for Diabetes meeting in London (published as an abstract), SC infusion of 5, 10, and 25 U insulin required 3, 6, and 16 min with a patch pump (OmniPod). Using a conventional pump (Animas OneTouch Ping),

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Abbreviations: (PK) pharmacokinetic, (SC) subcutaneous

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95% of the insulin was applied within 1 min; however, with other conventional pumps (MiniMed Revel/Veo) infusion times were 3, 5, and 5 min. The results of this study need confirmation; however, such differences in delivery rate may be expected to produce different absorption profiles.

Work done with ultrafast-acting insulins have demonstrated that speed of absorption can make a difference: Linjeta, the ultrafast-acting regular human insulin developed by Biodel, reaches half-maximal serum insulin levels after SC injection within 12 min.[3,4] With such rapid absorption rates, one can assume that differences in bolus infusion rates between different insulin pumps become even more relevant. Appropriately designed clinical studies are needed and should include a study arm with SC injection of insulin.

Modern insulin pumps allow infusion of the insulin bolus with different bolus time course characteristics. The aim is to adjust the rate of absorption of prandial insulin to a given meal composition such that post-prandial glycemic excursions are minimized. Although a number of clinical trials have been performed showing differences in postprandial glycemic excursions with different bolus types, the results are not convincing.[5] Additional studies are needed to evaluate PK profiles with prandial insulin requirements in different patient groups with different meal compositions to allow definition of the "optimal" PK profile for a given patient with diabetes, and which also take the type of SC insulin administration into consideration. Studies showing that injection of rapid-acting insulins 15 min before the meal reduces postprandial excursions illustrate the possible importance of such studies.[6]

Insertion Site/Insertion Depth

The needle length used for SC injection varies from 4 to 12 mm. Typically, the catheter of an insulin pump has a length of 6 to 10 mm with steel needles and 13 to 17 mm with Teflon catheters. If differences in blood perfusion exist between different SC tissue layers, application depth might have an impact on insulin absorption. However, to our knowledge, there are no publications addressing this question. At least, a PubMed search using search terms "insulin absorption skin subcutaneous" on August 27, 2011 did not yield relevant hits. Aside from the question of application depths, the conditions existing in the SC tissue at the insulin depot site might also vary between SC injection and continuous SC infusion. A catheter inserted for insulin infusion stays in place for several days and imposes local trauma and subsequent irritation. The constant delivery of insulin at the same site may or may not prolong the local body reaction to this. Subsequently, the disposition of insulin or local degradation at the infusion site might be different compared with SC injection of insulin at an insulin naïve location. Furthermore, patients tend to administer their insulin over and over again at the same injection and infusion site, altering the skin at that site (lipohypertrophy), which may also alter insulin absorption in an unpredictable manner.[7]

An interesting development is application of insulin into the dermis with very short needles, so-called microneedles. Infusion of regular insulin or insulin lispro intradermally resulted in significantly more rapid insulin absorption than SC application.[8,9] With the use of microneedles, a good portion of the insulin is probably absorbed via the lymphatic system and not the capillaries.[10]

Basal Rate

A prandial insulin dose with an insulin pump is initiated for the first time at a given time after insertion of the catheter into SC tissue and after the start of basal insulin infusion. Priming the insulin pump/insulin catheter and the particular basal rate that is applied influence the size of the insulin depot around the tip of the catheter. However, our knowledge about the size of this pool and which factors influence its dispersion and absorption is limited. Most probably, this depot contains several units of insulin. Blood flow in the SC tissue and temperature will have an effect on the actual depot size. The question remains whether the size of the depot has an impact on the absorption rate of a given insulin bolus. Again, to our knowledge, no formal studies have been performed that address this question.

Type of Insulin

If conditions in an insulin pump have an impact on the insulin (e.g., the temperature in the vial is influenced by body temperature), the PK properties of a specific insulin formulation and SC infusion and injection might induce different metabolic effects. This might be of particular relevance with ultrafast-acting insulin in which the absorption rate is increased.

Duration of Catheter Insertion

As indicated earlier, presence of an insulin catheter in the same site for several days may have an impact on

the absorptive properties at that site. Therefore, it is not surprising that studies have shown that the metabolic time action profile of a certain insulin dose applied by means of an insulin pump within the first 12 h after insertion of the insulin catheter is lower and later in comparison with that after 72 h.[11] Thus another factor that has to be taken into account is the duration of catheter insertion.

Summary

The aspects discussed here highlight possible factors that affect SC tissue insulin absorption rates of insulin depending on the type of administration. Only the performance of adequately designed studies examining these factors and how they interact to influence absorption rates will clarify this issue. Until then, it is prudent to advise patients that there might be differences in the effects of identical doses of insulin that are delivered by different methods.

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