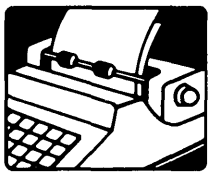
Editorial



Lessons from Studies of Insulin Pharmacokinetics

Insulin was introduced into therapy in 1922. Since then, several modifications in the insulin production procedure have resulted in insulin preparations of various action profiles (rapid onset, intermediate acting, prolonged), of improved purity, and with structure identical to native human insulin.[1] The availability of exogenous insulin, in contrast to physiologic endogenous insulin secretion, is not related to substrate availability or prevailing level of glycemia. Rather, exogenous insulin availability will depend on the pharmacokinetics of the insulin preparation and the route of insulin delivery.[2-5] A critical determinant of insulin availability is its absorption characteristics from subcutaneous tissue. Subcutaneous insulin regimens are based on the assumption that insulin absorption and availability are predictable and reproducible. Yet, many factors may influence insulin absorption and alter insulin availability. Indeed, the intraindividual variation in insulin absorption from day to day is ~25% and between patients is up to 50%.[2,5]

There are regional differences in insulin absorption, especially for rapidly absorbed regular insulin.[2-6] These differences have been attributed to variation in blood flow. Absorption is fastest from the abdomen, followed by the arm, buttocks, and thigh. The variation is sufficiently great that random rotation of injection sites should be avoided. Rather, any given infection (e.g., prebreakfast) should be administered in the same region to decrease day-to-day variability.

Other factors influencing absorption of regular insulin, and generally attributed to variation in blood flow, include ambient temperature, exercise, local massage, and smoking. These also need to be considered in daily management. For example, if planning exercise (e.g., jogging) shortly after an injection, one might avoid giving that injection into a limb that will be undergoing that exercise (in the case of jogging, the thighs).[7]

One of the therapeutic challenges related to insulin absorption is the desirability of achieving rapid increments of plasma free insulin at the time of meal consumption. Timing of the injection has been shown to be important, with desired injection time 30–60 min before eating rather than injection just before eating.[8-10] The proposition has also been raised that insulin absorption rate may be increased by local massage of the injection site[4,11] or by the use of a jet injector.[12,13] These issues are further examined in two articles in this journal.

Linde confirms the influence of massage, demonstrating a dramatic effect on insulin absorption and showing this to be independent of subcutaneous blood flow. The massage technique, however, is probably not practical for clinical purposes—30 min of massage commencing 30 min after the injection. Further studies are needed to determine a practical way for patients to take advantage of the massage effect.

Malone et al. demonstrate that the increased insulin absorption seen with jet injectors for regular insulin[12,13] is also seen with intermediate-acting (NPH) insulin. Although this is interesting, an earlier peak of NPH insulin is unlikely to offer any clinical advantage. Indeed, even the pharmacokinetic advantage of jet-spray injection of regular insulin needs to be confirmed in longer-term clinical trials. The relatively small benefits demonstrated may not outweigh the substantial cost of jet injectors and their relative inconvenience.[12,13] Furthermore, the benefit sought by most patients making an investment in jet injectors, reducing pain, may not be achieved. In my clinical experience, few patients continue to use these devices after their initial period of enthusiasm wanes (usually a few weeks to months).

Is an insulin pump a better investment? From a pharmacokinetic standpoint, I vote yes. By virtue of using only rapidly absorbed regular insulin, continuous subcutaneous insulin infusion (CSII) results in less variation in insulin action, which is greater (in absolute terms) with longer-acting insulins.[5] Furthermore, with CSII there is a smaller subcutaneous depot.[5,14] Because the size of the insulin depot may be important in exercise induction of hypoglycemia (by mobilization of said depot), and larger depots may contribute to greater variation in insulin absorption, it may be desirable to aim for the smallest depot, i.e., CSII. On the other hand, the smaller depot may explain the increased risk of diabetic ketoacidosis in CSII patients if there is pump failure or catheter occlusion.

Pharmacokinetically, CSII may be the preferred way to

deliver insulin. What concerns patients, however, is the inconvenience of CSII. One concern patients have is that their pump may interfere with sexual activity or desirability. Helve et al. (in this issue) have devised a simple approach to interrupting CSII and substituting an injection of intermediate-acting insulin, without sacrifice in glycemic control. This seems to solve the problem for patients not wanting their pump some nights. Note, however, that Schiffrin had earlier devised a program combining night use of CSII with daytime preprandial syringe injections of regular insulin.[15] This approach seems useful for patients who do not want to wear their pump during the day but tolerate it at night.

The overnight period is also important because many patients demonstrate increased early-morning insulin requirements, the dawn phenomenon.[16,17] This has led several pump manufacturers to include the feature of programmability of the basal rate. Decreasing the basal rate might reduce the risk of nocturnal hypoglycemia, whereas increasing the basal rate in the early morning might avert the dawn phenomenon. To my knowledge, however, no controlled clinical trial has confirmed these predictions. In this context the article herein by Hildebrandt et al. is particularly interesting. Their study addresses the important pharmacokinetic questions that lie at the heart of the assumption that programming basal rates will lessen problems. There is a substantial lag of ~3 h between the time infusion rate is changed (up or down) and the time insulin absorption rates change. They question the need for programmable basal-rate pumps and suggest that, if a rapid change in actual insulin availability is desired, discontinuing infusion for 2–3 h should precede a decrease in basal rate, whereas bolus infusions should initiate an increase in basal rate. These seem to be fair conclusions but may not always be practical or necessary. For example, retaining programmability but initiating changes earlier than their anticipated need would also solve the problem. Clearly, careful controlled trials are needed to help define the role, if any, of programmability of basal rates.

For those who continue to use conventional syringe injections, articles in this issue by Colaquiri and Villalobos as well as Forlani et al. further examine the question of miscibility of insulins. These studies have used the glucose-clamp technique in diabetic subjects and thus are different from earlier studies. As also seen in earlier studies, the current results suggest there is some loss of activity of regular insulin if it is mixed with lente or ultralente insulin and allowed to stand for as little as 2 min. The loss of action apparently does not occur when regular insulin is mixed with NPH insulin. There seem to be two practical clinical points. First, if patients are having significant glycemic excursions surrounding meals, and need more rapid insulin effect, there may be some loss of rapid insulin activity. This can be tested by temporarily switching to separate injections. Second, maintain constancy of technique for measuring insulin dosage and administering insulin to avoid these effects surreptitiously altering insulin availability.

Where will all of this lead? It seems that mechanical devices offer the greatest hope of reproducing insulin absorption, easily profiling meal-related doses, and defining programmed overnight infusions. The pharmacokinetic advantages of CSII are sufficient to warrant consideration of CSII for all insulin-treated patients. Life-style considerations may limit acceptability for now. In the long run, however, the mechanical approaches should prevail. This may involve implantable approaches, given the more rapid absorption of intraperitoneal insulin demonstrated by Micossi et al. in this issue, and the recent development of pump insulins with a decreased potential for aggregation. Regardless of the approach, further studies—both pharmacologic and clinical—are needed to better define the details of the use of insulin as a therapeutic agent.

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