Efficiency of Inhaled Insulin Relative to Subcutaneous Insulin

Stephen Farr PhD, Aradigm Corporation, Hayward, CA

Summary

A review is presented of the factors contributing to the efficiency of inhaled insulin relative to subcutaneous injection of regular insulin. Methods used to assess efficiency are discussed and recent data are compared for two inhalation delivery systems — Novo Nordisk / Aradigm's AERx® insulin Diabetes Management System (iDMS) and the Pfizer / Inhale system. The mean system efficiency of the AERx iDMS in studies involving patients with type 1 diabetes has been shown to range between 13 and 17%, depending on the study design. These data at least are comparable to reported data (10 - 13%) for the inhalation system under development by Inhale Therapeutic Systems. Efficiency of manufacturing the commercial product also will affect the overall system efficiency. When the contribution from this factor is taken into account, it is anticipated that the overall system efficiency for a liquid based system, such as AERx iDMS, will be similar to the current reported values for system efficiency. Because of the complexities of the unit processes associated with the manufacture of respirable dry powders, there is a greater risk of reducing overall efficiency for powder inhalation systems when manufacturing yield is included in the assessment.

Introduction

Currently, parenteral administration is the dosing route for insulin in the treatment of diabetes mellitus. The Diabetes Control and Complication Trial (DCCT) (1) in patients with type 1 diabetes strongly supports intensive treatment consisting of frequent use of "preprandial" insulin. Despite the establishment of the benefits of intensive insulin therapy, controlling blood glucose by means of frequent injections of insulin is still not widely practiced (2,3). Many patients find multiple injections inconvenient and unacceptable and physicians often prefer to prescribe the simplest regimens for their patients in order to ensure compliance. As a result, patients often do not receive the benefit of tight glucose control that can be achieved with multiple insulin injections. A similar reluctance to accept injectable insulin therapy has been documented for patients with type 2 diabetes requiring insulin (4). The recent UKPDS study (5) confirmed the benefits of tight glucose control for patients with type 2 diabetes, as the DCCT had demonstrated in type 1 patients.

Orally inhaled insulin is in clinical development with the objective of providing a convenient and effective therapy for glucose control for patients with diabetes. The pharmacokinetic profile of pulmonary insulin is characterized by faster absorption than subcutaneous (SC) regular insulin, which especially makes it suited to controlling blood glucose excursions following meals (6). However, the amount of insulin required to elicit the same glycemic response following inhaled delivery is greater than for SC dosing (7,8). Understanding the efficiency of inhaled insulin relative to SC therapy is therefore an essential component of the development process.

Definition of System Efficiency

The overall system efficiency determines the amount of insulin manufactured and delivered by pulmonary administration that produces an equivalent effect to one unit of insulin manufactured and given by SC injection. The system efficiency, $E_s$, of inhaled insulin is thus intimately and inter-dependently affected by the formulation and packaging of the drug product, the performance of the delivery device in the hands of patients, and the permeability of the lung membrane for absorption of insulin.

It is estimated, relative to SC delivered insulin, from the product of the efficiencies of various contributing factors shown by the following equation:

$$E_s = E_m \times E_d \times E_r \times (E_A \text{ or } E_B)$$

$E_m$ is the manufacturing efficiency. During clinical development, calculation of system efficiency tends to ignore losses associated with the manufacturing process but, as the product moves towards commercialization, the importance of manufacturing efficiency increases due to issues relating to cost and supply capacity of insulin. A discussion of the comparative efficiencies of manufacturing liquid and dry powder inhalation systems is given in the Manufacturing Efficiency section.

$E_d$ is the efficiency of the inhalation device in generating an aerosol dose for administration to the patient, and $E_p$ is the proportion of the delivered aerosol likely to deposit in the deep lung (the so-called fine particle fraction, FPp). Both these parameters are measured routinely in vitro. Aradigm has conducted studies in vivo using gamma scintigraphy to determine that the product of $E_d$ and $E_p$, termed the fine particle dose (FPD), approximates the actual dose depositing in the lung (9).

$E_A$, by normal convention, is the fraction of the lung dose of insulin that is absorbed into systemic circulation relative to subcutaneous insulin. System efficiency calculated using this factor is thus the overall bioavailability of inhaled insulin.

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relative to SC administration. Instead of $E_A$, it is possible to substitute another term $E_B$, which is determined from the main pharmacodynamic action of insulin (i.e., change in blood glucose). $E_B$ arises from the absorbed fractions of delivered insulin and is the extent of glycemic response after inhaled insulin compared to that obtained following SC administration. Thus, system efficiency calculated from $E_B$ instead of $E_A$ is expressed in terms of overall bioeffectiveness (sometimes called biopotency) relative to SC administration.

**Pulmonary Absorption of Insulin**

Evidence to date (7,8) in humans and animals shows that not all of the insulin depositing in the lung is absorbed and enters the blood stream. It is known that regional deposition is a significant variable determining the rate and extent of insulin absorption and a "parallel pathway for elimination" scheme has been proposed following insulin delivery to the lung (10). Mucociliary clearance is one such mechanism that will compete with absorption for insulin, but the actual rate of all the unabsorbed insulin is currently unknown. The limited available data in the literature suggest an insulin bioavailability of around 20% by comparing the dose originally deposited in the lung to regular insulin given by subcutaneous injection (11). It is anticipated that the greater the penetration into the peripheral parts of the lung, the higher the pulmonary bioavailability (10,12). Equally important, of course, is the reproducibility of delivery. In particular, it is known that sub-optimal breathing technique (such as breathing too shallowly or at a high flow rate) results in reduced dose to the lung (13,14), and hence lower bioavailability.

**Methods to Determine System Efficiency**

Various methods have been used to determine the system efficiency of insulin administered by inhalation. Typically, these are single dose, cross-over studies in which inhaled insulin is compared with SC administration of regular insulin.

**Studies in healthy fasting subjects**

Fasted healthy volunteers may be used but the range of insulin doses is restricted by the risk of inducing hypoglycemia. Serial blood samples are taken after administration for the determination of total insulin and glucose concentrations. In addition, blood samples should be assessed for C-peptide, a polypeptide co-secreted in equimolar amounts with insulin from the β-cells of the pancreas. C-peptide levels may be used to estimate the endogenous insulin (i.e., the subjects' own insulin) and therefore to calculate the exogenous insulin (i.e., delivered insulin) by subtraction of endogenous from the measured (total) insulin in blood (15). C-peptide levels will decline in healthy fasting subjects following insulin administration, showing a suppression of endogenous insulin secretion. The rate and extent of suppression of endogenous insulin may depend upon the rate and extent of exogenous insulin appearance in blood after absorption, hence the contribution of endogenous insulin to the total measured insulin may be different for different routes of insulin administration. Using non-corrected insulin levels can confound the accurate measurement of bioavailability, i.e., the absorbed fraction of inhaled insulin versus SC insulin. The most accurate determination of bioavailability is accomplished after the C-peptide correction routine.

**Glucose clamp studies**

Larger doses of insulin may be administered to healthy fasting subjects by the use of a "glucose clamp" experimental technique. In this method, subjects are titrated with a low-dose insulin and glucose infusion in order to obtain a pre-determined blood glucose level. Insulin is then administered by inhalation or SC injection and the baseline glucose blood level is maintained using a variable glucose infusion. The insulin pharmacodynamic response is represented by the glucose infusion rate necessary to maintain the starting blood glucose level, i.e., to counteract the natural efforts of the absorbed insulin to reduce the blood glucose. Comparison of the total infused glucose in the inhaled and SC administration treatment arms of the study then determines bioeffectiveness.

Ideally, glucose clamp studies should be conducted on patients with diabetes. The most scientifically rigorous experiments involve subjects with type 1 diabetes, as these subjects are C-peptide negative, i.e., do not secrete endogenous insulin, and lack the influences of hormonal and non-hormonal counteracting mechanisms that potentially may affect the observed pharmacodynamic response to administered insulin. These disadvantages exist in experiments involving healthy subjects, even when adopting a glucose clamp technique. For the evaluation of the AERx insulin Diabetes Management System (IDMS), Professor Thomas Pieber's group conducted a study in type 1 subjects. In this study (16), reported at the 2000 ADA conference, patients were given four different doses of pulmonary insulin, which were compared to a single administration of SC regular insulin. In addition to system efficiency of the AERx IDMS (discussed in the Comparison of System Efficiency section), the study results showed a clear dose response curve for inhaled insulin (both for pharmacokinetics and pharmacodynamics parameters) and a level of intra-subject variability comparable to that seen after SC administration.

**Meal Challenge Studies**

Another method for determining system efficiency involves patients with diabetes who are provided with a standard meal shortly after insulin is administered. Blood samples are collected for insulin and glucose analysis at baseline and then at regular intervals post meal. Pharmacokinetic parameters are determined as normal, but the primary pharmacodynamic endpoint is determined by the extent to which the anticipated blood glucose excursion is blunted relative to another route of insulin administration.

**Comparison of System Efficiency**

As described above, there are a number of study designs that can be used to determine the overall efficiency of inhaled insulin systems. Thus, it is important that retrospective comparisons between the various insulin inhalation systems are made using studies that at least have reasonably similar experimental designs. Ideally, of course, a comparison of two systems should be evaluated in the same experiment; this will be possible only after one or both systems are commercially available. Data are now available for the Inhale system and AERx IDMS in separate studies involving glucose clamp and meal challenge study designs. The comparative data for system efficiency are shown in Table 1.
Table 1: Comparison of Efficiencies for Inhalation Delivery Systems

<table>
<thead>
<tr>
<th>Glucose clamp study</th>
<th>Bioavailability (%)</th>
<th>Bioeffectiveness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhale system¹</td>
<td>N/A</td>
<td>10 (9-12)²</td>
</tr>
<tr>
<td>AERx iDMS³</td>
<td>13 (10-16)</td>
<td>13 (10-15)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Meal challenge study</th>
<th>Bioavailability (%)</th>
<th>Bioeffectiveness (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhale system⁴</td>
<td>≈11⁵</td>
<td>≈13⁶</td>
</tr>
<tr>
<td>AERx iDMS⁷</td>
<td>16 (15-17)</td>
<td>17 (15-19)</td>
</tr>
</tbody>
</table>

¹ Heise et al (17). Study in 18 healthy subjects
² 95% confidence intervals estimated from SD in Heise et al (17)
³ Brunner et al (16). Study in 17 patients with type 1 diabetes. All inhaled insulin doses included.
⁵ Mean bioavailability calculated from dose-normalized population means for area under plasma insulin versus time curves in Gelfand et al (18)
⁶ System efficiency estimated from ratio of insulin doses in Gelfand et al (18), where the reduction in post-prandial hyperglycemia was comparable for inhaled and SC insulin

From Table 1, it can be seen that the recently reported efficiency of inhaled insulin in the glucose clamp studies shows the AERx iDMS and the Inhale system to be at least comparable. While the study designs were not identical (Brunner et al used type 1 patients whereas Heise et al used normal healthy subjects) there is a suggestion of a numerical advantage for the AERx System. This seems to be substantiated by comparison of the meal challenge studies.

Meal challenge studies are relevant because they mimic the intended use of inhaled insulin, i.e., to counteract post-prandial hyperglycemia. In these studies, the AERx iDMS appears to be more efficient than the Inhale system. There were, however, bigger differences in the meal challenge studies. The study (18) involving the Inhale device was conducted on patients with type 2 diabetes and the time of insulin administration for inhaled and SC insulin was standardized to 10 min before the meal. Because type 2 subjects were investigated, the total insulin AUCs after inhaled and SC administration would have included a substantial contribution from endogenous insulin that is secreted in response to digestion of the meal. The insulin AUC in the control treatment arm, in which the subjects received the meal but no insulin was administered, was 50 - 60% of the total insulin AUCs in the drug treatment arms. In addition, the study did not adopt the recommended duration of 30 min between SC injection and starting ingestion of the meal, which takes into account the lag time before regular insulin begins to be well absorbed from the injection site. As inhaled insulin is absorbed faster than SC insulin, the use of a standard administration time close to the meal could have biased the post-prandial glucose data in favor of inhaled insulin. The study by Kipnes et al (19), which evaluated the AERx iDMS, avoided the issues described above. Type 1 (C-peptide negative) patients were investigated and insulin administration times were selected to account for the different pharmacokinetic profiles of inhaled and SC insulin. Thus, a standard meal was given immediately after pulmonary administration and 30 minutes after SC injection.

Manufacturing Efficiency

Manufacturing efficiency is the efficiency of converting insulin from an active pharmaceutical ingredient into a dosage form for use by a patient. This factor is not normally reported from studies measuring system efficiency, however it could have a significant impact on the commercial viability of an inhaled insulin product. For example, assume that the system efficiency of inhaled insulin relative to subcutaneous insulin was shown to be 12% in a typical clinical study described earlier. It is also reasonable to assume that the manufacturing process for SC insulin is extremely efficient (a liquid product, marketed for many years). Thus, if the efficiency of manufacturing the inhaled insulin drug product is 60% relative to an injection product, the overall system efficiency is actually 7% compared to SC insulin.

Aradigm, by adopting the liquid approach to formulation, is able to leverage the long history of the compounding process used for parenteral products as well as take advantage of form-fill-seal processes broadly implemented in the pharmaceutical industry. Thus, it is believed that the efficiency of manufacturing the liquid insulin product in the AERx System is very similar to SC insulin. System efficiency as measured in clinical studies is therefore very similar to the overall system efficiency when manufacturing losses are taken into account. In contrast, the production of respirable powders of insulin utilizes processes such as spray drying that are poorly efficient compared historically to liquid systems.

Spray drying is conducted after completing a similar compounding process used for insulin in the AERx iDMS and SC products. But instead of being filled into the final container, the liquid is subjected to an expensive spray drying process to form the bulk product. Expected yields for a scaled-up, conventional spray drying operation range from 50 - 80%, the lower value more typical for protein products. From there the finely powdered bulk product is directed into a feeder system and dispensed and packed into the final dosage form. Dry powder systems, therefore, require expensive manufacturing steps that are not found with liquid formulation systems and are expected to have a significantly lower manufacturing efficiency. As a result, the overall system efficiency for the commercial dry powder product should be less than that for a liquid based system.

Conclusions

System efficiency is an important factor in determining the viability of a delivery system to non-invasively administer insulin to patients with diabetes mellitus. A number of approaches to measuring system efficiency are possible, the most scientifically rigorous studies being conducted in diabetic subjects. Studies in type 1 subjects have demonstrated the mean system efficiency of the AERx iDMS is around 13 - 17%,
depending on the actual study design. Because of Aradigm’s liquid formulation approach, the efficiency of commercial scale manufacture should not influence the AERx System efficiency data obtained to date. The dry powder approach adopted by Inhalite leads to similar or slightly lower values for system efficiency. However, because of the complexity of the processes involved in the manufacture of respirable dry powders, there is a greater risk of manufacturing efficiency having a significant deleterious effect on the system efficiency of the commercial product.

References


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