

# The Need for Faster Insulin: Problem Solved?

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## Abstract

Considerable progress in treatment of diabetes has been made in the nearly 100 years following the discovery of insulin, and advances in insulin therapy have improved convenience, quality of life, overall glycemic control (A1C), and risk of hypoglycemia. An unmet need remains for a mealtime insulin that can faithfully reproduce the metabolic profile that ensues following meal ingestion in healthy persons. A number of “ultra-fast” insulin programs have been initiated, and Afrezza® (insulin human; Inhalation Powder, MannKind Corporation, Danbury, CT) stands as the first such product to be approved by the US FDA. Afrezza is unique as an “ultra-ultra” fast insulin, faster than any other entrant except IV insulin. The benefits and limitations of the Afrezza profile are discussed in this analysis.

## Keywords

pulmonary insulin, ultrafast insulin, Afrezza, insulin pharmacokinetics

The advent of insulin therapy for treatment of diabetes was one of the great medical accomplishments of the previous century, saving thousands from an agonizing death of progressive inanition or a rapid demise from the metabolic meltdown of ketoacidosis. Since then, incremental advances such as intermediate-acting insulins, highly purified animal-derived insulins, synthetically derived human insulins, rapid-acting analog insulins (RAIs), and long- and ultra-long acting insulins have brought improvements in convenience, quality of life and, if applied in a conscientious program of overall diabetes management, improvements in both overall glycemic control (A1C) and risk of hypoglycemia.

However, as has been noted previously,<sup>1</sup> current “rapid”-acting analog insulins are not absorbed quickly enough to mimic the metabolic response observed in following a meal challenge in healthy individuals. From a practical perspective, it has been demonstrated that RAIs provide best postprandial glucose excursion control if they are administered 15 to 20 minutes before a meal,<sup>2</sup> necessitating the inconvenience of anticipating meal intake and dosing insulin accordingly. Until a faster, more physiologic insulin profile has been achieved, persons with diabetes will continue to face challenges as they attempt to balance insulin dose quantity and timing against meal content and size, perpetually trying to avoid excessive upward glycemic excursions in the early postprandial period and hypoglycemia risks in the later postmeal stages.

Several efforts at developing “ultra-rapid” insulins have been undertaken,<sup>3</sup> and one such product, Afrezza® (insulin human; Inhalation Powder, MannKind Corporation, Danbury, CT) has been approved by the US FDA. Heinemann and colleagues have

reviewed the pharmacokinetics and pharmacodynamics of this novel inhaled insulin product,<sup>4</sup> and it is clear that this product fulfills the criteria that one might use to distinguish an ultra-rapid-acting insulin from RAI. To wit, the time to maximum insulin concentration following a dose of Afrezza varies by study between 8 and 15 minutes as compared to more than 50 minutes for RAIs (Heinemann et al, Table 1).<sup>4</sup> Although the return to baseline for Afrezza is relatively prolonged (180–240 minutes), it is still considerably faster than the 280 minutes required for insulin lispro (Heinemann et al, Table 1).<sup>4</sup> Looking at the shape of the time-exposure curves, it is clear that great majority of Afrezza exposure occurs in the first 80–100 minutes following dosing, roughly twice as fast as insulin lispro (Heinemann et al, Figure 1).<sup>4</sup>

Comparing Afrezza exposure to the insulin pharmacokinetic profile following a meal that occurs in healthy subjects,<sup>5</sup> it appears that Afrezza is actually non-physiologically “ultra-ultra” fast, particularly on the decay side of the curve. This novel profile has the attractive property of allowing insulin dosing to occur right at the time of meal initiation (rather than having to wait 15 minutes or more between RAI dosing and meal start) while also reducing the risk of late postmeal hypoglycemia.<sup>6</sup> On the negative side, however, this “ultra-short” duration of insulin exposure and subsequent

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insulin action can lead to runaway hyperglycemia in the late postmeal period, necessitating the use of a second dose of Afrezza in nearly 40% of subjects.<sup>7</sup> The good and the bad of this property is that insulin dosing can be more readily controlled with respect to its temporal properties at the expense of requiring persons with diabetes to face the inconvenience of choosing and administering a dose of insulin at yet additional time of day.

An aspect of insulin replacement therapy that is often overlooked is the fact that achieving a perfect reproduction of the peripheral insulin time-exposure profile that obtains following a meal in a healthy subject is still inherently non-physiologic. Heinemann et al<sup>4</sup> suggest that an advantage of pulmonary drug delivery is that it avoids “first pass” metabolism. This may indeed be an advantage for many drugs that are usually delivered through the gastrointestinal tract, but in the case of insulin, the normal physiologic milieu would be most faithfully reproduced by a system that delivers insulin to the liver via the portal vein. Pulmonary insulin delivery still requires that non-physiologically elevated peripheral insulin levels need to be achieved in order to provide adequate hepatic insulin exposure. Given that extremely rapid suppression of hepatic insulin production that occurs following intravenous insulin dosing,<sup>8</sup> it may be that Afrezza is effective in this regard not due to avoidance of “first pass” metabolism but rather due to its extremely rapid absorption and high but transient peak blood levels that occur as a result of this absorption profile. This hypothesis is supported by the finding that Afrezza results in much faster suppression of endogenous glucose production in humans when compared to either a different (slower) inhaled insulin product (Exubera®, Pfizer, New York, NY) or to subcutaneously administered RAI.<sup>9</sup>

Another property of Afrezza worthy of mention is the relatively coarse dose increment that is available. The product is delivered in doses that are equivalent to multiples of 4 units of RAI. This raises concerns about the constraints in dosing flexibility that this increment engenders, and one might predict that it would lead to undue postmeal hyperglycemia (due to underdosing to avoid late postmeal hypoglycemia) or late hypoglycemia (due to overdosing while trying to achieve optimum glycemic control). In point of fact, the clinical data do not support these fears, possibly because of the ultra-short duration of insulin exposure following Afrezza dosing.

Safety of insulin delivered through the pulmonary route remains as an incompletely answered question. However, as demonstrated in bronchial washing studies in humans, Afrezza is rapidly cleared from the lung,<sup>10</sup> reducing the likelihood of local accumulation of insulin that could, in theory, lead to clinically relevant stimulation of insulin-like growth factor receptors.

Risk of lung cancer during treatment with inhaled insulin was considered during the FDA Endocrinologic and Metabolic Advisory Committee hearing regarding the Afrezza application

for marketing authorization on April 1, 2014.<sup>11,12</sup> During the Afrezza development program, 4 cases of lung cancer following Afrezza exposure (2 during the Afrezza treatment and 2 between 2 and 4 years after exposure to Afrezza) were documented during clinical trials whereas no cases were seen in the control arms.

Previous data from the Pfizer Exubera experience were also cited at the hearing during discussion of the FUSE (follow-up study of Exubera) results. In this study, approximately one-third of all Exubera clinical trial subjects were followed during and after Exubera clinical trial participation, representing more than 10 000 person-years of exposure for both Exubera and control groups. Lung cancer incidence and mortality were increased approximately 3-fold in the Exubera group compared to the control group; all but one of the cases of lung cancer were observed in former smokers. It is important to recognize the limitations of these data: they represent a small number of cancer cases derived from randomized but open label studies, and, along with the mild pulmonary symptoms attributable to Exubera exposure (eg, cough), there may well have been substantial detection bias. Further, as noted above, the extremely rapid transit of Afrezza from the lung to the blood may limit the applicability of Exubera results to the Afrezza risk profile.

The potential concerns about the theoretical risk of inhaled insulin inducing mitotic disease can only be dispelled with long term exposure studies, but animal toxicology and the paucity of compelling clinical data do not support these concerns. Nonetheless, use of Afrezza in current or former smokers or in persons with chronic obstructive pulmonary disease or asthma is not advisable.

All pulmonary insulin development programs to date have demonstrated small, reversible declines in standard pulmonary function studies (FEV1 and DLco). This author considers these to be physiologic rather than pathologic changes, potentially due to reversible insulin pharmacodynamic effects on alveolar interstitial fluid levels and/or pulmonary microcirculatory dynamics.

As discussed by Heinemann and colleagues,<sup>4</sup> Afrezza offers unique pharmacokinetic and pharmacodynamic profiles which have potential to allow persons with diabetes to more closely tailor their insulin therapy to the fast moving demands of glucose excursions. On the down side, the dosage interval available for Afrezza is relatively coarse, but, as discussed above, this may not represent a major problem. More significant is the tendency for Afrezza to be too short acting, necessitating the use of additional routine dosing episodes in order to avoid runaway hyperglycemia after meals. However, the ultra-ultra-fast absorption and action of Afrezza lend themselves perfectly to delivery of “rescue” doses of insulin in the face of unexpected hyperglycemia. The noninvasive, convenient inhalation device, coupled with the lack of need for constant refrigeration, add to the appeal of Afrezza for this use. Longer term safety data will be needed

to reassure the more timid prescribers but the current data package is comforting in this regard.

In summary, Afrezza offers a new, novel route of insulin delivery with flexibility of dosing based on its very fast onset and very short duration of exposure. Coupled with promising data that demonstrate reduced rates of late postmeal hyperglycemia, Afrezza can be considered to be another useful tool in the diabetes treatment armamentarium.

### Abbreviations

RAIs, rapid-acting analog insulins.

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