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Inhaled insulin—what went wrong

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Insulin therapy is essential for all patients with type 1 diabetes and becomes necessary for a sizable proportion of patients with type 2 diabetes. Considerable resistance to the use of insulin is observed in the latter group, however, primarily because of the need for subcutaneous injection. Even in patients with long-standing type 1 diabetes, who seem to have adapted to multiple daily injections, the availability of a noninvasive insulin delivery system could enhance acceptance of intensive insulin therapy. Various alternative means of insulin administration have been explored, including nasal, oral, transdermal, and rectal routes. Inhalation seemed a particularly attractive option, as the lung provides an appealing alternative to subcutaneous systemic administration, given its large available surface area for drug absorption and ease of accessibility.

In January 2006, the US FDA approved the first formulation of inhaled insulin (Exubera®; Pfizer Labs, New York, NY) for clinical use in nonsmoking adults with type 1 or type 2 diabetes without pulmonary disease. Approval of Exubera® provided the first noninjectable insulin delivery option since the discovery of insulin in the 1920s. Given the premise that a noninjectable formulation of insulin would be highly desirable, inhaled insulin was expected to be a blockbuster product and marketing was aggressive. However, in October 2007—after 11 years of development and 1 year of clinical use—Exubera® was withdrawn from the market because sales were well below expectations. Despite the fact that Exubera® cost millions of US dollars to develop and market, the new technology had "failed to gain acceptance by patients and physicians."[1] Within a short period of time, other pharmaceutical companies abandoned their inhaled insulin development programs. In retrospect, many factors contributed to the failure of inhaled insulin to be embraced by patients and health-care providers, some of which were unique to Exubera®. These factors included cost, efficacy, safety, patient eligibility, and convenience.

Inhaled insulin was on average around 30% more expensive than injectable insulin. In order to justify this higher cost, patients, health-care providers and those responsible for paying (i.e. insurance companies and national health systems) had to be convinced that inhaled insulin had clear advantages over injectable insulin. In terms of efficacy, however, inhaled insulin was only as good as, but no better than, subcutaneous insulin. We performed a meta-analysis that combined data from 16 open-label trials of inhaled insulin (4,023 patients, age range 18–80 years). Among patients with type 1 or type 2 diabetes, there was a small, but statistically significant, decline in HbA_{1c} levels from baseline that favored subcutaneous insulin over inhaled insulin (–0.08%).[2] As expected, inhaled insulin lowered HbA_{1c} levels more than did oral antidiabetic agents (–1.80%), but much less so when compared with oral antidiabetic agents titrated to glycemic efficacy (–0.20%). In short-term studies, no increased risk of weight gain or severe hypoglycemia was observed with inhaled insulin as compared with subcutaneous insulin.

FDA approval of Exubera® was initially delayed because of concerns about potential pulmonary toxicity after long-term use. Indeed, pulmonary toxicity was a key reason why health-care providers did not support the use of inhaled insulin. In the pre-marketing trials, inhaled insulin was associated with mild to moderate, nonprogressive dry cough.[2] A small decrease in certain pulmonary function testing parameters was also observed, which did not progress over 2 years of pre-marketing trials.[2] Frequent pulmonary function testing became necessary during the clinical use of inhaled insulin.

As insulin is a growth factor, an additional safety concern was that systemic administration by inhalation might result in an increased incidence of lung cancer. In long-term surveillance of the pre-marketing clinical trials, 6 of 4,740 Exubera®-treated patients (0.13%) and 1 of 4,292 comparator-treated patients (0.02%) developed lung cancer. In addition, there has

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been one post-marketing report of primary lung cancer in a patient treated with Exubera®.[3] All the patients diagnosed with lung cancer had a previous history of cigarette smoking, and there are too few cases to determine whether these cancers were linked to Exubera®. Nevertheless, this finding was a significant blow to the concept of inhaled insulin. Evidence of a decline in pulmonary function and concerns about the development of lung cancer, coupled with the burden of frequent monitoring of pulmonary function, dissuaded many health-care providers from prescribing inhaled insulin.

In light of these safety concerns, inhaled insulin was approved for use only in non-smoking patients without chronic lung disease who had a forced expiratory volume ≥70% of that predicted for age, sex and height. On the basis of these requirements, however, it has been estimated that inhaled insulin would be considered inappropriate in approximately 40% of all patients with diabetes mellitus. Furthermore, the proportion of ineligible patients would increase to two-thirds after 7 years of use.[4]

A key premise behind the development and marketing of inhaled insulin was the ease of administration compared with subcutaneous insulin; however, the first inhaled insulin was anything but convenient. First, the steps required for the preparation and delivery of this insulin formulation were so many and so complicated that a mnemonic had to be devised by the manufacturer. Second, the inhalation device had high maintenance requirements (weekly cleaning, bimonthly replacements of internal valve, etc.). Third, the dosing was in mg rather than IU. The conversion between mg and IU was so complicated that patients were advised to carry and use a laminated conversion card. Dosing was also inflexible as the inhaled powder came in blisters of 1 mg or 3 mg (corresponding to 3 IU and 8 IU, respectively), which made administration of small or large doses very challenging. Fourth, the inhalation device was very bulky, which made it difficult to convince patients to exchange small, pen-like injection devices for inhaled insulin. Finally, inhaled insulin had to be coadministered with subcutaneous long-acting insulin, which would require patients to learn, and health-care providers to teach, two different methods of insulin delivery.

The lack of convenience afforded by inhaled insulin might at first seem surprising, as inhaled insulin rated highly in patient preference surveys both as a theoretical treatment option and among patients who were randomly allocated to inhaled insulin in the pre-marketing trials.[2,5] At least two possible explanations can account for this discrepancy. First, the trials recruited patients who were interested in the use of inhaled insulin. As a consequence, those patients who received inhaled insulin were naturally more satisfied than those who did not. Second, inhaled insulin was compared with syringes and vials of regular insulin. The landscape of injectable insulin has changed dramatically over the past decade. Most patients now use either high-accuracy insulin pumps or pen-like devices with needles that are thinner, shorter, sharper, and much less painful than those previously used.

The introduction of a new class of medications or technology is generally a welcome addition to our existing armamentarium against diabetes mellitus. In general, new products are prized and are often quickly embraced over older, well-established and effective products, despite our limited ability to judge the merits of new products in relation to long-term effectiveness and safety in clinical use.[6] Aggressive marketing campaigns to physicians and direct-to-consumer advertisement also contribute to early widespread use of new products. Nevertheless, when alternatives exist that are safe, tested and effective, the merits of introducing a new product need to be weighed carefully against the standard of care. Inhaled insulin was a rare occasion in clinical practice when the response of patients and health-care providers to a new technology was in line with the unfavorable aspects of the product, and in opposition to the perceived need and aggressive marketing by the manufacturer. Perhaps we, the consumers, have learned our lesson after all.[6]

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Competing interests

The authors declared no competing interests.

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