

Counterpoint: No Time to Inhale: Arguments Against Inhaled Insulin in 2007

Much of the storied history of insulin has revolved around attempts to make its administration easier for patients who have to inject it to survive. The search for alternative routes of administration began almost immediately after its discovery—insulin was administered by inhalation, with modest effectiveness, and then within several years of its first administration by subcutaneous injection (1). The now almost unimaginable use of 20-gauge needles, sharpened by hand, and glass syringes that had to be sterilized regularly made the development of less painful and more convenient injections highly desirable. Moreover, before the development of intermediate- and long-acting formulations of insulin in the 1930s, four to five daily injections of the available rapid-acting formulation were required if patients wanted to avoid hyperglycemia and accompanying polyuria and polydipsia.

The introduction of “protamine insulin” in 1936 (2), followed by protamine zinc insulin, NPH, and the lente series of insulins, made it possible to maintain generally asymptomatic levels of glucose control, based on the longer-acting profile of the formulations, with only two injections per day. Although more convenient for patients with type 1 diabetes, the intermediate-acting insulins, and long-acting insulins that followed, had the unintended consequence of distracting attention from the more physiologic administration of insulin by multiple injections (3). When the glycohemoglobin assay became widely available in the early 1980s (4), it was clear that the chronic glycemic control achieved with these nonphysiologic, albeit convenient, regimens was far from normal. More importantly, the elevated levels of chronic glycemia were strongly associated with all of the long-term complications of diabetes that resulted in severe morbidity and premature mortality (5).

It took almost 60 years after the introduction of intermediate-acting insulins to establish the long-term benefits of intensive therapy. As defined in the Diabetes Control and Complications Trial

(DCCT), intensive therapy included at least three injections per day or continuous subcutaneous insulin administration with an external pump (6). The need to frequently administer rapid- or very-rapid-acting insulin in order to achieve near-normal glucose control and delay or prevent the long-term complications once again placed a major burden on patients with type 1 diabetes. However, this time the burden was not owing to limited insulin formulations; rather, the demands of therapy arose from strong evidence that individuals with type 1 diabetes could live a healthier and longer life if they injected more frequently. The development of a whole range of insulin formulations to provide basal and bolus delivery, along with increasingly sharp small gauge needles, disposable syringes, and insulin delivery devices (e.g., insulin pens, pumps), has made injection therapy more tolerable; however, the need to frequently inject insulin remains a burdensome feature of the modern therapy of type 1 diabetes.

Now, the latest innovation in insulin delivery, inhaled insulin, promises to free type 1 diabetic patients from frequent injections, although the provision of basal insulin will still require injections. The development of inhaled insulin is based on the technology used to deliver pulmonary medicine for respiratory diseases. The limited, ~10%, absorption of the insulin powder from the respiratory tract has been solved by delivering doses that are 10-fold larger than would be given by the subcutaneous route. Concerns regarding potential pulmonary toxicity (insulin is a potent growth factor, and there are insulin receptors in the pneumocyte, raising the specter of potential changes in the alveolar or bronchiolar structure that could interfere with gas exchange) have been addressed through studies in animals and long-term (generally 2-year) studies in patients with diabetes. Only modest changes in DLCO have been observed, and the increased anti-insulin antibody titers generated with inhaled insulin have been found not to adversely affect the availability or biologic activity of insulin (7,8).

Given the enthusiasm of investigators

and manufacturers of inhaled insulin, and the uniform approval of the patients who use it, why would anyone object to its use? My primary objection to inhaled insulin is not that it is unsafe or that it will cost more than injected insulin. I do not find fault with the obscenely large inhaler that must be carried everywhere. Patients who have inhaled insulin have coped with these barriers and continue to inhale. My primary objection is that the level of glycemic control achieved in the clinical trials using inhaled insulin has been substandard. The recent excellent meta-analysis by Ceglia et al. (7), which reviewed seven controlled clinical trials in >1,500 type 1 diabetic patients, noted that all of the efficacy trials were noninferiority studies. Thus, the investigators only needed to demonstrate that the inhaled insulin was no worse than an active comparator, usually preprandial injections of rapid- or very-rapid-acting insulin. This level of proof is apparently satisfactory to the U.S. Food and Drug Administration (FDA), as evidenced by its approval of inhaled insulin in January 2006; however, given the critical importance of long-term near-normal glycemia, the level of control achieved by the comparator and inhaled insulin must be scrutinized. As noted in the meta-analysis, the A1C achieved with preprandial inhaled insulin in type 1 diabetic patients was slightly higher than with subcutaneous insulin regimens. More worrisome was that none of the long-term inhaled insulin regimens achieved a mean A1C as low as that in the DCCT, even though the baseline A1C value was substantially lower in the inhaled insulin studies than in the DCCT. The failure of the comparator therapy in the inhaled insulin studies to reach the A1C levels achieved in the DCCT is peculiar, considering that they had access to the very-rapid-acting and newer very-long-acting insulin analogs that were not available during the DCCT.

The data presented to the FDA during the approval process showed that during two 24-week studies in >200 subjects with type 1 diabetes using inhaled insulin, the mean A1C at study end was 7.5% in one study and 7.7% in the other. A1C

<7% was achieved by only 22% of the type 1 diabetic patients at 24 weeks (9). By contrast, in the DCCT, 65% of the intensively treated subjects had an A1C \leq 7% at ~24 weeks, and ~50% maintained an A1C \leq 7% over the 6.5 years of the study (6,10). The most successful of the published trials, to date, with inhaled insulin in type 1 diabetic patients has not been able to lower mean A1C to <7.5%, compared with the DCCT intensive therapy mean of ~7.1% over 6.5 years (7,10).

Whether inhaled insulin is capable of achieving as low a level of chronic glycemia as subcutaneous regimens remains to be seen. The relatively low absorption of inhaled insulin, requiring doses of 50–100 units to absorb 5–10 units, may be the limiting factor. Relatively small differences in absorption from dose to dose (e.g., absorbing 8% of 100 units on one day and 12% on another would result in a range of 8–12 units) might preclude “tight” glucose control with inhaled insulin. Moreover, the attenuated insulin profile with inhaled insulin compared with the very-rapid-acting analogs may be associated with more hypoglycemia if doses are increased to achieve intensive therapy goals.

What of type 2 diabetes? Whereas physiologic insulin replacement in the insulin-deficient type 1 diabetic patient requires frequent injections, it is not clear if the type 2 diabetic patient with relative insulin deficiency requires frequent preprandial insulin (11). Most type 2 diabetic patients require more basal insulin, combined with metformin or another oral agent, to achieve intensive therapy goals (12). In a sense, inhaled insulin for type 2 diabetic patients is a “distraction” (13). The manufacturer has suggested that inhaled insulin may be an alternative for type 2 diabetic patients who refuse to use

insulin. In those relatively infrequent patients who are terrified of “the needle” (often because their health care provider has been threatening them with insulin for years), perhaps it will be useful. However, here again, the clinical trial data have not supported inhaled insulin as an effective means of normalizing chronic glycemia (7).

This new delivery method is sufficiently appealing that patients and physicians may be tempted to sacrifice control for convenience and recreate the clinical experience of the 1930s, when the simple nonphysiologic regimens utilizing twice-per-day regimens with intermediate-acting insulins resulted in poor diabetes control and long-term complications. Inhaled insulin may turn out to be a wonderful addition to our therapeutic arsenal, combining patient convenience and comfort with acceptable glycemic control. However, until inhaled insulin is shown to achieve the chronic glycemic levels that effectively prevent or delay complications, patients would be well advised not to inhale.

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