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# Inhaled human insulin: Coup or caution?

**W**ITH THE APPROVAL in adults of the first inhaled human insulin (IHI) preparation, Exubera, by the US Food and Drug Administration (FDA) in January 2006, medicine takes a big step into the emerging era of inhaled therapeutic proteins.

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Indeed, IHI extends the spectrum of inhaled drugs, which has traditionally included bronchodilators, mucolytics (eg, acetylcysteine), antibiotics such as tobramycin, and, in special circumstances (eg, cardiopulmonary resuscitation without intravenous access), lidocaine. Though surely novel, IHI is not the first inhaled therapeutic protein. Recent predecessors have included DNAase in cystic fibrosis<sup>1</sup> and inhaled recombinant alpha-1 antitrypsin, the latter studied in a pilot trial that was curtailed over concerns about hypersensitivity pneumonitis ascribed to minute amounts of nonhuman protein.<sup>2</sup>

The introduction of IHI will surely exert profound effects on clinical practice, both on the need to more fully understand and characterize the effects of IHI on the lung and on clinical management, especially regarding the assessment of potential users and the follow-up of those using IHI. My goal in this editorial is to anticipate and discuss these effects of inhaled human insulin.

## ■ CAUTIONS AND CONTRAINDICATIONS

As nicely discussed by Davidson et al in this issue of the *Cleveland Clinic Journal of Medicine*.<sup>3</sup> Exubera achieved FDA approval on the strength of compelling evidence of effi-

cacy in controlling type 1 and type 2 diabetes mellitus, as shown primarily by glycosylated hemoglobin measures and by several other diabetes-related outcome measures.<sup>4</sup>

At the same time, important concerns about the pharmacokinetics and pharmacodynamics of Exubera and its pulmonary effects in patients with chronic lung diseases prompted major exclusions and cautions regarding the use of Exubera in the medication guide accompanying the drug.<sup>5</sup> To clarify recommended conditions and exclusions for using Exubera, the medication guide states:

- “Exubera is not recommended for people that have chronic lung disease (such as asthma or chronic obstructive pulmonary disease or emphysema).”<sup>5</sup>
- “Exubera should not be used at all by people with unstable or poorly controlled lung disease.”<sup>5</sup>

Also, regarding smoking, the medication guide states:

- “Do not use if you smoke, start smoking, or if you quit smoking less than 6 months ago.”<sup>5</sup>

Furthermore, the medication guide states that lung function testing is needed both before beginning Exubera in prospective users and afterward, and that serial lung function assessment thereafter may be performed at the discretion of the managing health care provider. Specifically:

- “You need to have lung tests before you start Exubera, and after you start Exubera, you may need to have lung tests again later as directed by your healthcare provider.”<sup>5</sup>

Features underlying the proscription against use in patients with chronic lung disease include evidence that Exubera is associat-

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ed with a slightly increased rate of decline in forced expiratory volume in 1 second (FEV<sub>1</sub>) in patients with chronic obstructive pulmonary disease (COPD), a finding that was based on studies of relatively few patients with COPD followed for up to 1 year.<sup>4</sup> Notably, no longer-term studies were available at the time of submission regarding the effect in patients with COPD, and no studies addressed the impact in patients with interstitial lung disease. Also, in the context that insulin is a growth factor,<sup>6</sup> the FDA requested data regarding the occurrence of lung cancer in Exubera users; as was presented in the submission,<sup>4</sup> a slight excess incidence of lung cancer in Exubera users compared with controls failed to achieve statistical significance and did not exceed the modeled predicted rate of lung cancer.

## ■ QUESTIONS AND CONCERNS

These proscriptions and recommendations regarding the use of Exubera raise several important questions and concerns.

**Will Exubera harm people with undiagnosed lung disease?** In the context that diabetes mellitus afflicts approximately 18 million Americans and that complete compliance with the medication guide recommendation to assess lung function in all prospective Exubera users is unlikely, concern arises about what happens when Exubera is used in patients with undiagnosed COPD, asthma, interstitial lung disease, or lung cancer.

Unless all potential IHI users undergo pulmonary function testing before use, a special concern is the possibility of prescribing Exubera for a patient with COPD in whom the diagnosis is unknown to both patient and provider. This concern about failure to detect COPD before prescribing Exubera is highlighted by the observation that only a minority of the estimated 16 million Americans with COPD are aware of their diagnosis.<sup>7</sup> As a result, the pool of prospective Exubera users with undiagnosed COPD who could experience accelerated decline in FEV<sub>1</sub>, albeit reportedly minimal and reversible on cessation of the drug, is potentially very large. Similar lines of reasoning likely apply to asthma and interstitial lung disease.

**Who will perform the pulmonary func-**

**tion tests?** To the extent that physicians do comply with recommendations to perform baseline and serial lung function testing in all potential IHI users, the introduction of Exubera will likely greatly increase the demand for lung function testing, thereby affecting pulmonary function laboratories, pulmonary function technicians, and pulmonologists.

Internists, family physicians, endocrinologists, and support personnel who are seeing diabetic patients and are prescribing IHI may consider beginning to perform spirometry themselves, thereby requiring them to learn how to perform spirometry, how to monitor and ensure the quality of testing, and how to interpret spirometry results.

## ■ WHAT STEPS SHOULD BE TAKEN?

Given these issues about a drug that is clearly an exciting prospect and that is likely to be widely used, what steps should be taken?

**Postmarketing surveillance.** Now that the drug will be available, I believe that rigorous postmarketing surveillance studies regarding the pulmonary effects of Exubera are essential. Such studies—initiated, hopefully, with enthusiasm by the manufacturers of the current and future IHI preparations and then carefully monitored by the FDA—must address questions such as:

- What is the prevalence of Exubera use in patients with undiagnosed COPD, asthma, interstitial lung disease, and lung cancer?
- In these patients, what are the short-term and long-term effects on pulmonary function, symptoms, functional status, and survival?
- What is the incidence of lung cancer among Exubera users and does it exceed expected rates?

Furthermore, to the extent that there is any excess rate, I believe that end points should be established with “stopping rules” that would mandate further inquiry and investigation.

Overall, although some of these issues were certainly addressed with the submission and FDA review of the drug,<sup>4</sup> the current data on pulmonary toxicity are sparse, especially in chronic diseases such as COPD and asthma,

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where IHI could be used long-term.

**Spirometry for prospective users.** I would underscore the imperative that all prospective Exubera users undergo spirometric testing (to measure FEV<sub>1</sub>, forced vital capacity [FVC], and the FEV<sub>1</sub>/FVC ratio). Only with uniform testing will the large number of patients with undiagnosed COPD be detected and counseled appropriately regarding the use of IHI.

**Spirometry training for health care providers.** At the same time, such a mandate to perform spirometric testing invites further investigation regarding spirometric testing and the adequacy of interpreting the results of spirometric testing in settings other than pulmonary function laboratories (eg, outpatient internal medicine, endocrinology practices<sup>8–10</sup>), as well as the cost-effectiveness of various strategies for assessing the lung function of prospective IHI users. I expect and hope that the introduction of this drug will spawn a flurry of important studies addressing these and other issues.

Regarding the impact of IHI on health care practices, pulmonary function laboratories should anticipate and prepare for increased demands as the drug becomes available. At the same time, clinicians who will be prescribing and evaluating prospective Exubera users—internists, family physicians, and endocrinologists—and their nurses and

office personnel should undertake spirometry training and commit to excellent performance and quality control of this simple but rigorous office procedure. In integrated health care systems, my hope is that the introduction of IHI will prompt pulmonologists and pulmonary function technicians to organize spirometry training for colleagues who plan to perform office-based spirometry in their practices.

**Quality control.** Also, as in large trials,<sup>11,12</sup> programs to monitor and ensure the quality of spirometric testing should be organized. Insurers and health plans should draft policies that encourage pulmonary function assessment of prospective users.

Finally, and perhaps most importantly, people with diabetes who wish to use IHI should insist on assessment of their lung function both before and intermittently during their use of Exubera, and they should be mindful of the recommended conditions for its use.

Overall, the advent of IHI is exciting and offers diabetic patients an important new therapeutic option. At the same time, the introduction of this drug requires broad and creative collaborations between government, industry, insurers, clinicians, and patients in order to ensure that this novel drug is used optimally and safely. Whether IHI represents a coup or a caution hangs in the balance. ■

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