J. H. DeVries

Mealtime inhaled insulin lowers fasting glucose: a look at possible explanations

Received: 5 August 2005 / Accepted: 10 August 2005 / Published online: 5 November 2005
© Springer-Verlag 2005

Abbreviations FPG: fasting plasma glucose

To the Editor: Recently, two Phase 3 Exubera inhaled insulin trials in type 1 diabetes and a Phase 2 AERx inhaled insulin trial in type 2 diabetes were reported. No overall difference in HbA_{1c} was noted, but fasting plasma glucose was lower in the inhaled insulin group in all three trials. What is the explanation behind the observation that inhaled insulin administered at mealtime lowers fasting glucose—a finding now reported three times?

In the first fully reported Phase 3 Exubera study, 203 patients were randomised to Exubera as mealtime insulin with ultralente as basal insulin, and 193 patients to premeal human insulin with NPH insulin as basal insulin. At the end of the 6-month trial, HbA_{1c} was similar in the two treatment groups, and fasting plasma glucose (FPG) was 1.3 mmol/l lower in the Exubera/ultralente group [1]. At first sight, it seems that the different basal insulins could explain the lower FPG in the Exubera/ultralente group. However, the finding of a lower FPG was replicated in the second reported Phase 3 study, which randomised 163 patients to premeal inhaled insulin and 165 patients to human insulin, with both arms using NPH as basal insulin, injected twice daily at similar dosages. The results revealed that the FPG at endpoint was 2.2 mmol/l lower in the inhaled group. The authors state that ‘it is possible that (1) the FPG decrease with inhaled insulin relates to IAbs functioning as a repository that slowly releases insulin... or (2) the inhalation of insulin may increase insulin sensitivity or reduce endogenous glucose release...’ [2]. Also, in the first fully reported AERx Phase 2 study, 107 type 2 diabetes patients were randomised to either inhaled or human insulin as mealtime insulin, both groups using NPH

at similar dosages as basal insulin. Again, no difference in HbA_{1c} was found, but fasting serum glucose at endpoint was 1.9 mmol/l lower in the AERx group [3].

A difference in the contribution made by the ‘tail’ of dinner-time inhalation and human insulin injection to nocturnal glucose homeostasis is also unlikely, as the duration of action of Exubera is very similar to, or even slightly shorter than that of human insulin [4]. The possibility that ‘the inhalation of insulin may increase insulin sensitivity or reduce endogenous glucose release’ comes from trials in dogs [5, 6]. In a first trial, inhaled insulin as compared with insulin infused in the portal vein increased non-hepatic glucose clearance for up to 3 h [5]. In a second trial, the amount of glucose needed to maintain euglycaemia over 6 h was 20% higher in the inhaled group than in the group that received subcutaneous insulin, despite similar insulin AUCs [6]. In all, it therefore seems unlikely that either basal insulin supplementation or the pharmacodynamic properties of inhaled insulin can account for the difference in fasting glucose noted with the use of inhaled insulin. The possibility that inhaled insulin could have a larger bioefficacy than injected insulin, or even increase insulin sensitivity over a longer period of time than its duration of action, lacks a theoretical explanation but warrants further study in humans.

Patients participating in inhaled insulin studies are, of course, fully aware of and probably attracted to the novelty of pulmonary insulin delivery. Those randomised to the inhaled group may have perceived this outcome of the randomisation process as the preferred one, and some disappointment may have occurred in those randomised to continuation of their old regimen. This may result in better overall adherence to the treatment regimen in the inhaled group vs the control group, possibly translating into a lower fasting glucose in the inhaled group. A study effect as large as 0.75% HbA_{1c} has recently been reported in type 1 diabetes, so a difference of 1.3–2.2 mmol/l in FPG seems well within reach [7]. However, an argument against a study effect is that in none of the many trials investigating

J. H. DeVries (✉)
Department of Internal Medicine, Academic Medical Center,
PO Box 22660, 1100DD Amsterdam, the Netherlands
e-mail: j.h.devries@amc.uva.nl

rapid-acting insulin analogues—an equally new treatment modality in their day of registration studies—noted a lower FPG in the intervention group [8].

Might insulin antibody formation following inhaled insulin result in the ‘morning low’ syndrome? With the advent of purified human insulin, antibody formation to insulin injected subcutaneously has virtually disappeared as a clinical issue. Only with the use of implantable insulin delivery devices that deliver insulin intraperitoneally are patients with symptoms attributable to insulin antibodies encountered. The first systematic study of this phenomenon noted increased insulin antibody levels in 11 of 25 (44%) patients treated with intraperitoneal insulin. Four of these 11 developed nocturnal hypoglycaemia, despite lowering the insulin infusion rate to 0.5 U/h ($n=2$) or even stopping nocturnal insulin infusion ($n=2$). Two of these patients showed large increases in daily insulin requirements [9]. Another study reported that the development of insulin antibodies was associated with higher mean glucose values, higher postprandial glucose values and increased daily insulin requirements. Interestingly, two patients showed nocturnal falls in blood glucose despite stopping nocturnal insulin delivery, and in one of these patients, free insulin levels increased at night-time, from an average of 15 μ U/ml during the day to 77 μ U/ml at 24.00 h and 39 μ U/ml at 04.00 h [10].

Recently, pooled data from seven Phase 2/3 Exubera studies on the antibody response to inhaled insulin have been reported. More insulin antibody formation was observed in patients receiving inhaled insulin vs subcutaneous insulin, with larger antibody responses observed in type 1 than in type 2 diabetes patients. Antibody binding was not correlated with HbA_{1c}, insulin dose requirements, hypoglycaemia rate or pulmonary function [11]. Also, the authors of the second Phase 3 Exubera trial noted that ‘no correlation between insulin binding and FPG has been observed to date’, although exact data were not reported. Moreover, the fact that the difference in fasting glucose was seen in type 2 diabetes, where less antibody formation is seen than in type 1, argues against a possible role for insulin antibody formation acting as a depot from which release during the night could lower fasting glucose.

In conclusion, the finding that mealtime inhaled insulin consistently lowers fasting plasma glucose is both intriguing and unexplained.

Acknowledgements I would like to thank professor J. B. Hoekstra for critically reading the manuscript.

Duality of Interest I have no conflict of interest in respect to this work.

References

1. Quattrin T, Belanger A, Bohannon NJ, Schwartz SL (2004) Efficacy and safety of inhaled insulin (Exubera) compared with subcutaneous insulin therapy in patients with type 1 diabetes: results of a 6-month, randomized, comparative trial. *Diabetes Care* 27:2622–2627
2. Skyler JS, Weinstock RS, Raskin P et al (2005) Use of inhaled insulin in a basal/bolus insulin regimen in type 1 diabetic subjects: a 6-month, randomized, comparative trial. *Diabetes Care* 28:1630–1635
3. Hermansen K, Ronnema T, Petersen AH, Bellaire S, Adamson U (2004) Intensive therapy with inhaled insulin via the AERx insulin diabetes management system: a 12-week proof-of-concept trial in patients with type 2 diabetes. *Diabetes Care* 27:162–167
4. Rave K, Bott S, Heinemann L, Sha S, Becker RH, Willavize SA et al (2005) Time-action profile of inhaled insulin in comparison with subcutaneously injected insulin lispro and regular human insulin. *Diabetes Care* 28:1077–1082
5. Edgerton DS, Neal DW, Scott M et al (2005) Inhalation of insulin (Exubera) is associated with augmented disposal of portally infused glucose in dogs. *Diabetes* 54:1164–1170
6. Cherrington AD, Neal DW, Edgerton DS et al (2004) Inhalation of insulin in dogs: assessment of insulin levels and comparison to subcutaneous injection. *Diabetes* 53:877–881
7. DeVries JH, Snoek FJ, Kostense PJ, Heine RJ (2003) Improved glycaemic control in type 1 diabetes patients following participation per se in a clinical trial—mechanisms and implications. *Diabetes Metab Res Rev* 19:357–362
8. Siebenhofer A, Plank J, Berghold A et al (2004) Meta-analysis of short-acting insulin analogues in adult patients with type 1 diabetes: continuous subcutaneous insulin infusion versus injection therapy. *Diabetologia* 47:1895–1905
9. Olsen CL, Chan E, Turner DS et al (1994) Insulin antibody responses after long-term intraperitoneal insulin administration via implantable programmable insulin delivery systems. *Diabetes Care* 17:169–176
10. Jeandidier N, Boivin S, Sapin R et al (1995) Immunogenicity of intraperitoneal insulin infusion using programmable implantable devices. *Diabetologia* 38:577–584
11. Fineberg SE, Kawabata T, Finco-Kent D, Liu C, Krasner A (2005) Antibody response to inhaled insulin in patients with type 1 or type 2 diabetes. An analysis of initial phase II and III inhaled insulin (Exubera) trials and a two-year extension trial. *J Clin Endocrinol Metab* 90:3287–3294