The evidence for insulin lispro

The review article by Anuradha L. Puttagunta and Ellen L. Toth[1] concerning insulin lispro in the treatment of diabetes mellitus contravenes a number of methodological principles for evidence-based educational messages. For example, Table 1 of their article was adapted from another publication,[2] apparently without critical evaluation. Of the 10 studies reported in that table, 7 were reported only in abstract form. Abstracts do not provide sufficient detail for full critical appraisal, and without such appraisal there is little basis for determining the validity of the findings. In addition, the fourth and fifth studies[3,4] presented in the table are both subsets of the third study.[5] Although this limitation is mentioned in a footnote, the reader might infer more evidence than there really is.

None of the 3 randomized controlled trials[6–8] included in Table 1 of the article was blinded. Because hypoglycemic episodes constitute an adverse effect that is often subjectively interpreted, lack of blinding in clinical trials might lead to systematic bias in the reporting of such events.

Table 1 accompanying this letter provides a more detailed synopsis of the published information comparing insulin lispro with regular insulin.[6,7,9–12] Another report, that of Pfutzner and associates,[8] covers a subset of the patients studied by Anderson and colleagues,[6] so it has not been included.

Of the 6 studies summarized in our Table 1, only 2 showed a significant difference in the incidence of hypoglycemic episodes,[6,7] and for one of these, there was no significant difference after a longer follow-up period.[7]

Only one study demonstrated a significant difference in the incidence of severe hypoglycemic episodes,[10] although there was no difference in the overall frequency of hypoglycemic episodes. In addition, only one study (which used infusion) demonstrated a difference in levels of hemoglobin A_{1c}.[12] In this trial, the only double-blind one, there was no significant difference in incidence of hypoglycemic episodes.

A recent meta-analysis of all available trials comparing insulin lispro with regular insulin (involving a total of 2361 patients with insulin-dependent and non-insulin-dependent diabetes mellitus) found no statistically significant difference between these products with regard to incidence of hypoglycemic episodes or level of hemoglobin A_{1c}.[13] Postprandial blood glucose levels were lower in the insulin lispro groups, but the clinical significance of this difference must be questioned, given that it did not translate into a reduction in the incidence of hypoglycemic episodes or levels of hemoglobin A_{1c}.

For some patients, insulin lispro may provide an advantage over regular insulin in terms of convenience (since it can be taken closer to mealtime). However, readers must examine the evidence and decide for themselves if there is a clinical advantage

Table 1: Summary of published trials comparing insulin lispro and regular insulin

Study	Blinded	No. of patients	Duration, mo	Type of insulin;* no. of hypoglycemic episodes per patient		Type of insulin;* no. of severe hypoglycemic episodes per patient		Type of insulin;* level of hemoglobin A_{1c}, %	
				Lispro	Regular	Lispro	Regular	Lispro	Regular
Anderson et al[6]	No	1008 IDDM	3	5.6 over 30 d	6.3 over 30 d	NS		NS	
Garg et al[7]	No	39 IDDM	12	4.7 over 6 mo	16.8 over 6 mo	NS		NS	
				NS over 12 mo					
Anderson et al[9]	No	722 NIDDM	3	NS		NS		NS	
Holleman et al[10]	No	199 IDDM	3	NS		36 over 3 mo	58 over 3 mo	NS	
Vignati et al[11]	No	379 IDDM 328 NIDDM	2	NS		NS		NS	
Zinman et al[12]†	Yes	30 IDDM	3	NS		NS		7.66	8.00

Note: IDDM = insulin-dependent diabetes mellitus, NIDDM = non-insulin-dependent diabetes mellitus, NS = nonsignificant difference.
*Multiple daily doses unless specified otherwise.
†Regular insulin and insulin lispro administered by infusion.

with regard to hypoglycemia and long-term glucose control.

James McCormack, PharmD
Ken Bassett, MD, PhD
Therapeutics Initiative
University of British Columbia
Vancouver, BC

Disclosure: None declared.

References

1. Puttagunta AL, Toth EL. Insulin lispro (Humalog), the first marketed insulin analogue: indications, contraindications and need for further study. *CMAJ* 1998;158 (4):506-11.
2. Holleman F, Hoekstra JBL. Insulin lispro [review]. *N Engl J Med* 1997;337:176-83.
3. Vignati L, Anderson JH, Brunelle RL, Jefferson FL, Richardson M. Improvement of glycemic control with the rapidly absorbed lispro insulin analog in type I diabetes [abstract]. *Diabetologia* 1994;37(Suppl 1):A78.
4. Anderson JH, Vignati L, Brunelle RL, Boggs B. Therapy of type II diabetes with insulin lispro, a rapidly absorbed insulin analog [abstract]. *Diabetologia* 1994;37 (Suppl 1):A169.
5. Vignati L, Anderson J, Brunelle R. Efficacy of [Lys(B28), Pro(B29)] human insulin in a one year global randomized clinical trial [abstract]. *Diabetes* 1994;43(Suppl 1):78A.
6. Anderson JH Jr, Brunelle RL, Koivisto VA, et al. Reduction of postprandial hyperglycemia and frequency of hypoglycemia in IDDM patients on insulin-analog treatment. *Diabetes* 1997;46:265-70.
7. Garg SK, Carmain JA, Braddy KC, Anderson JH, Vignati L, Jennings MK, et al. Premeal insulin analogue insulin lispro vs Humulin insulin treatment in young subjects with type I diabetes. *Diabet Med* 1996;13:47-52.
8. Pfutzner A, Kustner E, Forst T, Schulze-Schleppinghoff B, Trautmann ME, Haslbeck M, et al. Intensive insulin therapy with insulin lispro in patients with type 1 diabetes reduces the frequency of hypoglycemic episodes. *Exp Clin Endocrinol* 1996;104(1):25-30.
9. Anderson JH, Brunelle RL, Keohane P, et al. Mealtime treatment with insulin analog improves postprandial hyperglycemia and hypoglycemia in patients with non-insulin-dependent diabetes mellitus. *Arch Intern Med* 1997;157:1249-55.
10. Holleman F, Schmitt H, Rottiers R, et al. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 1997;20:1827-32.
11. Vignati L, Anderson JH, Iversen PW. Efficacy of insulin lispro in combination with NPH human insulin twice per day in patients with insulin-dependent or non-insulin dependent diabetes mellitus. *Clin Ther* 1997;19:1408-21.
12. Zinman B, Tildesley H, Chiasson JL, Tsui E, Starck TR. Insulin lispro in CSII: results of a double-blind, cross-over study. *Diabetes* 1997;46:440-3.
13. Davey P, Grainger D, MacMillan J, et al. Clinical outcomes with insulin lispro compared with human regular insulin: a meta-analysis. *Clin Ther* 1997;19:656-74.

[One of the authors responds:]

I appreciate the concerns raised by James McCormack and Ken Bassett. It is difficult to write about an emerging literature, particularly when many of the articles are in abstract form.

The fact is, however, that there is a lot of interest in the new insulin analogues, of which there are now almost half a dozen either newly on the market or undergoing clinical testing.[1] This interest clearly indicates that we have not yet found the best means to replace physiologic insulin.[2]

As pointed out by McCormack and Bassett, one of the greatest hazards of present-day intensive therapy for diabetes is hypoglycemia, which

was of concern in the Diabetes Control and Complications Trial[3] and has also been discussed in a recent meta-analysis.[4] In the latter study, it was found that the odds ratio for hypoglycemia was 2.99 for intensive treatment (with regular insulin) relative to conventional treatment, and there was a significant relation (p = 0.005) with the degree of reduction in level of hemoglobin A_{1c}.

It is this context in which the information on hypoglycemia associated with insulin lispro must be interpreted. I hope that our paper was not misinterpreted as implying that hypoglycemia is not a risk with this therapy. However, the concept of a ratio between hemoglobin A_{1c} and hypoglycemia is an important one, particularly if the reduction in hypoglycemia for the same level of hemoglobin A_{1c} can be achieved with respect to severe hypoglycemia, coma or overnight hypoglycemia, as reported by Holleman and associates.[5]

In this era of evidence-based medicine, it can be difficult to express qualitative views, let alone to quote experience, so I dare say that McCormack and Bassett might also be sceptical of the extensive published and unpublished "evidence" that patients like insulin lispro and that they usually choose to continue taking this drug at the end of clinical trials because it gives them more flexibility and is more reliable in its effect on hypoglycemia. Hypertensive patients may not be able to assess whether a particular drug is more or less protective with regard to cardiovascular outcomes, but when it comes to the subjective experience of hypoglycemia, might diabetic patients know best?

Ellen L. Toth, MD
Associate Professor
Division of Endocrinology
Department of Medicine
University of Alberta
Edmonton, Alta.

Disclosure: None declared.

References

1. Bloomgarden ZT. American Diabetes Association annual meeting, 1997: obesity, diabetes prevention, and type 1 diabetes. *Diabetes Care* 1997;20:1913-7.
2. Zinman B. The physiologic replacement of insulin. An elusive goal. *N Engl J Med* 1989;321:363-70.
3. DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329: 977-86.
4. Egger M, Davey Smith G, Stettler C, Diem P. Risk of adverse effects of intensified treatment in insulin-dependent diabetes mellitus: a meta-analysis. *Diabet Med* 1997;14(11):919-28.
5. Holleman F, Schmitt H, Rottiers R, Rees A, Symanowski S, Anderson JH, et al. Reduced frequency of severe hypoglycemia and coma in well-controlled IDDM patients treated with insulin lispro. *Diabetes Care* 1997;20:1827-32.

Assessing osteoporosis risk

In reply to a letter from a participant in the BC Study of Osteoporosis Risk[1] David Kendler[2] states that the review of bone mineral density testing