An Analysis of Dosing Equivalence of Insulin Detemir and Insulin Glargine: More Evidence?

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Abstract

Current guidelines for the management of type 2 diabetes call for the use of basal insulin when glycemic targets are not achieved. Previous studies have demonstrated noninferiority of insulin detemir, dosed once or twice daily, and insulin glargine, dosed once daily. In this issue of *Journal of Diabetes Science and Technology*, Dr. Allen King provides additional data of his previously published randomized, double-blinded, crossover trial in which both insulins were restricted to once-daily use. In this trial of 29 patients, 24-hour continuous glucose monitoring profiles (published previously) and dosing requirements (in this publication) were shown to be statistically equivalent between the two insulins. The shortcomings of this trial are its short duration, small number of patients, and potential interference from endogenous insulin. Longer trials with more patients, studying once-daily use of these medications, will help better determine if any significant differences exist.

J Diabetes Sci Technol 2010;4(1):155-157

Current guidelines for the management of type 2 diabetes call for the use of basal insulin when glycemic targets are not achieved, despite the use of oral antihyperglycemic medications.[1,2] Controversy remains in the medical literature regarding the comparative efficacy of insulin detemir and insulin glargine, both of which have demonstrated superiority over neutral protamine Hagedorn insulin. While two published studies have demonstrated noninferiority of insulin detemir and insulin glargine, both studies were designed to dose insulin detemir twice daily if predinner glucose levels were elevated, whereas insulin glargine was only dosed once daily regardless of predinner glucose levels.[3,4] A third study is underway with a similar design,[5] but does not address the comparative efficacy of once-daily administration of these two basal insulins.

In this issue of *Journal of Diabetes Science and Technology*, Dr. Allen King provides further important details of his previously published trial that provides important data in addressing this issue.[6,7] In this randomized, double-blinded, crossover trial, once-daily insulin detemir was compared with insulin glargine in 29 patients with type 2 diabetes under relatively good glycemic control (average hemoglobin A1c 7.1%). Several design features help provide new information about the use of both of these basal insulins. First, both insulins were restricted to once-daily use in the evening at 8 pm, whereas previous comparison trials allowed for twice-daily usage of insulin detemir. No mealtime insulins were administered in the trial. Second, the crossover design allowed for the patients to serve as their own controls, i.e., each patient used both forms of insulin in the trial. Third, continuous

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Abbreviations: (AUC) area under the curve, (CGM) continuous glucose monitoring

Keywords: continuous glucose monitoring, detemir, glargine, insulin dosing, type 2 diabetes

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glucose monitoring (CGM) was used to more closely assess the effect of the insulins for the 24-hour period following titration to the appropriate dose. Finally, per the protocol, patients consumed the dinner meal at 6 pm, followed by the dose of basal insulin 2 hours later.

In this trial, the 24-hour glucose profiles were published previously and shown to be statistically equivalent in this group of 29 patients **(Figure 1)**,.[6] In this month's publication, Dr. King provides further information regarding the dosage requirements, which were found to also be equivalent between the two insulin regimens **(Figure 2)**. These data are in contrast to data from a previous trial in which the dose of insulin detemir (0.52 U/kg), particularly when dosed twice daily (1.00 U/kg), far exceeded the dose of insulin glargine (0.44 U/kg).[3] In King's trial, the amount of insulin required to achieve control was 0.26 U/kg for both regimens, noting that only 3 of the 29 individuals required more than the 0.4-U/kg dosing. Some patients required more insulin detemir than insulin glargine, and vice versa, but 16 of the 29 patients achieved similar glucose control on the same insulin dose, regardless of type.

There are several items of interest in King's trial. This trial provided additional data that suggest noninferiority of one product over the other. In the 29 patients studied in this trial, insulin detemir and insulin glargine provided a similar duration of action, similar efficacy, and similar potency on the basis of the statistically equivalent 24-hour glucose profile and the equivalent dosing figure.

One must remember, however, that this trial was small, involving only 29 patients, and that all glucose data were generated from two 24-hour periods, one for each insulin type per patient. Interestingly, it does not appear from the 24-hour glucose profile chart that there was any particular time of day in which deviation between the two insulins occurred, suggesting a similar duration of action.

The much lower than expected amount of insulin (0.26 U/kg) also warrants discussion. Perhaps this effect was related to endogenous insulin production in these type 2 diabetic patients. Another consideration is the impact of the 6 pm dinnertime on these patients. Perhaps this dinnertime promoted earlier digestion and overall improved glycemic control in the early morning hours, enabling a lower basal insulin dose. Finally, use of a CGM device to titrate insulin dosing may have also been a key factor in the lower dose. Several CGM data
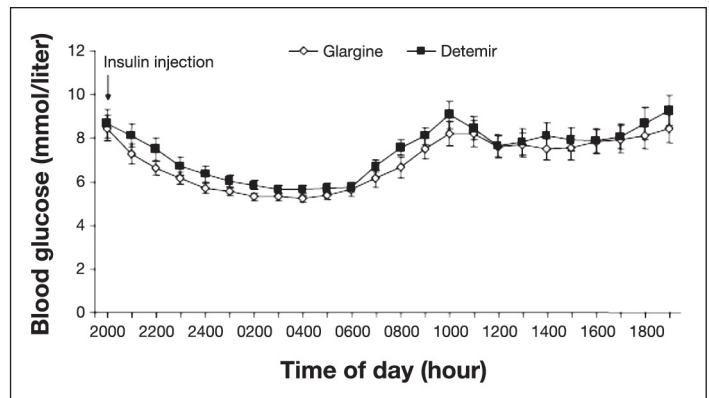
Figure 1. The 24-hour glucose profiles. Each point represents the treatment group's mean glucose for each hour and standard error of 29 subjects treated with once-daily insulin detemir or glargine starting at 20:00 hours. The basal period is from 24:00 hours to 06:00 hours. Reprinted with permission from *Diabetes Obesity and Metabolism*.[6]
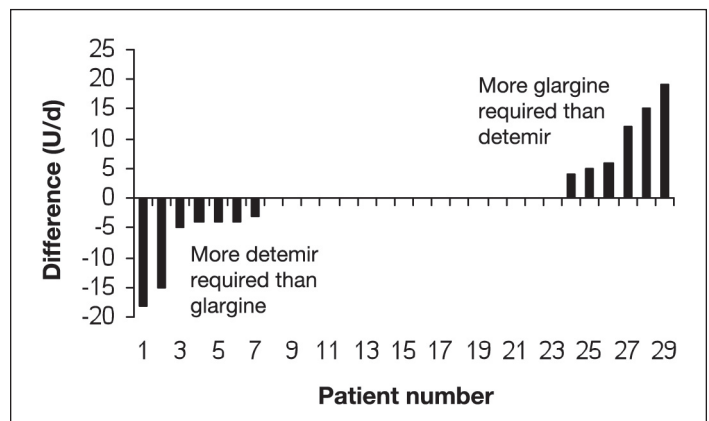
Figure 2. Comparison of once-daily evening dose of either insulin detemir or glargine to achieve the target basal glucose (<120 mg/dl between the hours of 12 MN and 6AM) in 29 subjects with type 2 diabetes in a crossover, double blind, randomized prospective trial using continuous glucose monitoring for titration and for evaluation of the response. Note that 16 of 29 required no alteration in dosage when switched from glargine or detemir to the other.

points were used throughout the 2400 to 0600 hours in order to titrate insulin to achieve the target 70- to 120-mg/dl range, whereas other trials used a single fasting glucose level for titration. It should also be noted that previously published comparison trials also had a lower fasting glucose goal for titration at <108 mg/dl, for which more insulin would be required.

The main shortcoming of this trial was its short duration. Once patients were titrated to the correct dose to achieve the fasting glycemic target of 70–120 mg/dl, they were only studied for 24 hours prior to crossing over to the other insulin. Although CGM data were used, the number of data points to derive equivalency was very small to what could be achieved in a longer trial.

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A short trial of this nature also excludes any effect that insulin-induced insulin resistance could play, as this phenomenon takes weeks to months to develop.[8]

Another shortcoming was the small patient group (*n* = 29). In reviewing the area under the curve (AUC) for CGM readings over 24 hours in the original publication, there was a trend toward significance favoring the glargine group [AUC was 2932.2 mg h/dl for glargine and 3114.5 mg h/dl for detemir (point ratio 0.941, 90% confidence interval: 0.885, 1.001)]. Dosing equivalency, as claimed in this trial, depends on equivalent glycemic control. If the trial had involved a larger number of patients for a longer period of time, the trend toward significance may have indeed achieved statistical significance, in which case it could be assumed that a higher dosage of insulin detemir would have been needed to maintain the same level of control. The clinical significance of this difference would be uncertain.

Another alleged shortcoming is the potential role of endogenous insulin in the patients, which may have played a role in the lower than expected insulin dosages to achieve glycemic control. Dr. King provided some data about C-peptide levels in the studied patients, but this information was obtained retrospectively and was not timed to make an accurate assessment of the degree of endogenous insulin at the time of the investigation. The use of sulfonylureas, glucagon-like peptide-1 agonists, and dipeptidyl peptidase 4 inhibitors in these patients suggests that endogenous insulin production may have been present. If endogenous insulin were present, then differences between the two insulins would potentially be blunted.

Overall, this trial provided much needed information about the comparative use of once-daily insulin detemir and insulin glargine, and it suggests noninferiority and equivalency in the duration of action, efficacy, and dosing. However, more data are needed before definitive conclusions can be made. Longer trials with more patients, studying once-daily use of these medications, will help better determine if any significant differences exist between these two medications.

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