Evaluation of Unit Equivalency of Insulin Glargine to Insulin Detemir in an Acute Care Setting

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Elizabeth A. Cook, PharmD, AE-C, BCACP, CDE¹,
Taylor Gill, PharmD, BCPS, AAHVP²,
and Scott Taylor, PharmD, MSc, BCPS²

Abstract

Background: Insulin glargine and insulin detemir are the most commonly prescribed basal insulins in the United States. While these analogs chemically differ, clinical trials have established no significant difference in efficacy. However, controversy remains as to whether the 2 agents are comparable with regard to unit equivalency. **Objectives:** To determine the ratio of glucose lowering between insulin detemir and insulin glargine. **Methods:** This institutional review board-approved, single-center, retrospective, case-crossover study was conducted in patients with diabetes mellitus with inpatient admissions between June 30, 2014, to July 1, 2015. Patients must have received both insulin detemir and insulin glargine on either the same or separate hospital visits. A blood glucose-lowering ratio for both insulin glargine and insulin detemir was calculated for each patient based off of up to 5 days of fasting blood glucose values and the total number of units of insulin administered. **Results:** Fifty-two patients were included in this study. No significant difference was found in the blood glucose-lowering ratio between insulin glargine (0.23 mg/dL/unit) as compared with insulin detemir (0.16 mg/dL/unit; $P = .08$). **Conclusion:** No difference was found in the blood glucose-lowering ratio between insulin glargine and insulin detemir. The results of this study suggest that conversion between insulin glargine and insulin detemir using a 1:1 ratio in an acute care setting may be appropriate.

Keywords

antihyperglycemics, diabetes, type 2 diabetes, insulin, internal medicine, pharmacokinetics, pharmacodynamics

Introduction

Insulin detemir and insulin glargine are 2 commonly prescribed basal insulin analogs for the treatment of type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). These agents have increased in popularity among clinicians due to the many advantages they carry over older formulations of basal insulin, such as neutral protamine Hagedorn (NPH) insulin. The newer basal insulin analogs offer longer durations of action, more stable plasma glucose profiles, and reduced interpatient variability compared with NPH insulin.^{1,2}

In insulin glargine, the asparagine residue at position A21 is replaced with glycine and 2 arginine molecules are added to the C-terminus of the insulin β -chain.³ The presence of arginine molecules reduces insulin glargine's solubility at physiologic pH, delaying absorption at the injection site and prolonging the duration of action compared with NPH insulin.³ Insulin detemir differs in that an acyl group is bonded through covalent attachment to the amino acid

sequence of human insulin.⁴ Additionally, the fatty side chain of insulin detemir reversibly binds to albumin, resulting in increased self-association at the injection site.⁴

While insulin glargine and insulin detemir differ with regard to their chemical profiles, clinical trials have established that there is no significant difference in the 2 agents' clinical efficacy or safety.² Current prescribing information for insulin detemir, issued by Novo Nordisk, suggests that conversion between insulin detemir and insulin glargine can be performed on a one unit to one unit basis.⁵ Prescribing information for insulin detemir indicates that this agent may be administered once or twice daily, with no further

¹University of Texas at Tyler, Tyler, TX, USA

²Via Christi Hospitals, Wichita Inc, Wichita, KS, USA

Corresponding Author:

Elizabeth A. Cook, University of Texas at Tyler Ben and Maytee Fisch College of Pharmacy, 3900 University Boulevard, WTB 256, Tyler, TX 75799, USA.

Email: ecook@uttyler.edu

specification about when to use either dosing method.⁵ To date, Sanofi Aventis has not issued any statements regarding conversion of insulin glargine to insulin detemir.⁶

Lack of information from Sanofi Aventis regarding the conversion of the 2 agents has led to pharmacokinetic studies examining the dosing of insulin detemir in individuals with T1DM and T2DM. In 24-hour isoglycemic clamp studies conducted in patients with T1DM, the duration of action of insulin detemir was found to be dependent on the mg/kg dose administered, with those individuals receiving ≤ 0.4 units/kg/day of insulin detemir failing to achieve 24-hour basal glycemic coverage, potentially warranting twice-daily dosing.^{7,8} In similar studies conducted in patients with T2DM, there has been conflicting evidence regarding the glycemic efficacy between the 2 products, with some trials purporting that there is no difference between the 2 agents.⁹ Others contrast this opinion, remarking that insulin glargine has a longer duration of action when administered at doses equivalent to insulin detemir.¹⁰

These findings have spurred a number of clinical trials in outpatient care settings exploring whether insulin glargine and insulin detemir are equivalent with regard to dosing equivalency and frequency. These studies have shown that higher daily doses of insulin detemir, compared with insulin glargine, may be needed to achieve equivalent glycemic control in patients with diabetes.¹¹⁻¹⁷ A literature review performed by Wallace and colleagues ascertained that patients with diabetes treated with insulin detemir required anywhere from 14.8% to 77.2% more insulin to achieve hemoglobin A1c values comparable with those seen in patients treated with insulin glargine.¹⁸

While there is an abundance of literature comparing insulin glargine with insulin detemir in an outpatient setting utilizing hemoglobin A1c as a marker of glycemic control, very little data are currently available comparing the equivalency of their effects on fasting blood glucose (FBG) in an acute care setting. Acute illness may provoke stress-induced hyperglycemia, a factor that is not often encountered in chronic disease management in ambulatory settings.^{19,20}

In most instances in the hospital setting, insulin is the preferred treatment for glycemic control.²¹ A randomized control trial conducted by Umpierrez and colleagues determined that inpatient basal-bolus treatment improved overall glycemic control and reduced complications in patients who had just undergone general surgical procedures compared with sliding scale alone.²² Regimens composed of basal plus bolus insulin or basal insulin alone are preferred for non-critically ill patients with adequate oral intake, and use of sliding scale alone is strongly discouraged.²³

The tertiary teaching center where this research was conducted had historically maintained both insulin glargine and insulin detemir on formulary, with usage split between the 2 agents as 60% and 40%, respectively. As a therapeutic and cost savings initiative, the institution streamlined the

long-acting basal insulin products on formulary, retaining insulin detemir alone. Additionally, an auto-substitution policy was implemented to convert all patients prescribed insulin glargine to insulin detemir on a one unit per one unit basis, starting on July 1, 2015. The authors initiated this study to determine whether changes in patient's glycemic control may result when transitioning from utilizing insulin detemir to insulin glargine.

The purpose of this study is to explore the unit equivalency of insulin detemir to insulin glargine in an acute care setting. Should a difference be found between the blood glucose-lowering capabilities of the 2 basal insulins, the authors aimed to derive a unit ratio for conversion between the 2 agents.

Methods

Study Design and Sample

This retrospective case-crossover study was conducted at a tertiary teaching center with a total of 805 beds distributed among 3 facilities. The initial pool of patients eligible for inclusion were identified electronically by the following criteria in the electronic health record: ≥ 18 years of age, diagnosis of T1DM or T2DM, and receipt of both insulin glargine and insulin detemir in the same or separate hospital stays during the time period of July 1, 2014, to June 30, 2015. Patients were permitted to be included in this study regardless of whether they were prescribed insulin or any other injectable or oral antihyperglycemic agent in an outpatient setting prior to hospital admission.

To control for medications that could possibly influence glycemic control, patients were manually reviewed and excluded if they had received total parenteral nutrition, intravenous dextrose, and corticosteroids. Patients were excluded if they received doses of antihyperglycemics other than mealtime insulin, including corrective insulin. Patients were also excluded if they were admitted under the diagnosis of diabetic ketoacidosis or were admitted to any of the surgical or intensive care units in the facilities. Therefore, patients eligible for inclusion were managed by internal medicine or family medicine teaching teams, composed of an attending physician, medical residents, and ancillary physician extenders.

Point of care blood glucose (BG) measurements were obtained by nursing staff, with timing of measurements dictated via institutional protocols applying to all facilities encompassed within the hospital system. Basal, bolus, and sliding scale insulin dosing were exclusively managed by physicians or physician extenders. Protocols and electronic order sets were utilized for sliding scale insulin dosing, but adjustment of basal and/or bolus insulins was left to the discretion of the provider. Pharmacist-driven insulin dosing protocols were not in place, but recommendations could be

$$\frac{\left(\text{Fasting Blood Glucose the Day of} \right)}{\text{Basal Insulin Administration} \left[\frac{\text{mg}}{\text{dL}} \right]} - \frac{\left(\text{Fasting Blood Glucose the Day Following} \right)}{\text{Basal Insulin Administration} \left[\frac{\text{mg}}{\text{dL}} \right]}$$

Units of Basal Insulin Administered (units)

Figure 1. Fasting blood glucose to unit insulin ratio equation.

made to providers by those pharmacists rounding with medical teams or serving in an order entry capacity.

This study protocol was approved by the hospital systems Institutional Review Board/Human Subjects Research Committee requirements and was carried out in accordance with the Declaration of Helsinki.

Data Collection

Patients were identified electronically via documentation of both insulin glargine and insulin detemir orders that were verified between July 1, 2014, and June 30, 2015. Data were manually collected from the electronic health record and recorded utilizing a standardized data collection form. The BG prior to insulin administration, the units of each basal insulin administered, and the FBG measured on the morning following insulin administration were collected for a maximum of 5 days at the beginning of each patient's hospital stay. Data were collected for the first 5 days of hospitalization in patients who were admitted for longer than 5 days. Data were collected for the first 2 hospital visits if patients were admitted for >2 instances during the time period of the study. A unit ratio for each hospital stay was calculated utilizing the equation listed in Figure 1, which was developed by the researchers. This unit ratio was calculated for up to 5 hospital days and then converted to a single average dose of insulin glargine and insulin detemir for each patient. Patients were eligible for inclusion if they had received at least 1 day of insulin with the respective morning BG value, with a maximum of 5 days of insulin doses and BG values recorded. Demographic characteristics abstracted included age, sex, ethnicity, and T1DM or T2DM status.

Statistical Analysis

Data were analyzed using IBM-SPSS Version 22 (Chicago, IL). A paired samples Student's *t* test was used to evaluate continuous data, specifically the unit ratio of insulin detemir to insulin glargine. The a priori level of significance was designated as a 95% confidence interval, correlating to an α of .05.

Results

Between July 1, 2014, and June 30, 2015, a total of 158 patients were identified to have received both insulin

glargine and insulin detemir in the same or separate hospital stays during this time period as depicted in Figure 2. Of those patients identified, 52 patients were included in the final analysis following application of exclusion criteria (Figure 2). Of these patients, 59.6% were male and the mean age was 66 ± 12.8 years of age. Of note, 92.3% of individuals were diagnosed with T2DM. Demographic information is highlighted in Table 1.

The average dose of insulin required by patients was 112.4 units/day for insulin detemir and 117.17 units/day for insulin glargine. The average units/kg for insulin detemir and insulin glargine was 1.18 units/kg and 1.23 units/kg, respectively. No statistically significant difference was found in the BG-lowering capabilities of insulin detemir unit ratio (4.07 mg/dL/unit) as compared with insulin glargine unit ratio (2.86 mg/dL/unit; 95% confidence interval = -0.18 to 2.61 , $P = .08$).

Discussion

The results of this study suggest that there is no significant difference in the FBG-lowering capabilities measured in mg/dL unit ratio of insulin glargine to insulin detemir on a unit per unit basis in an acute care setting. This is one of the few studies conducted analyzing the mg/dL of FBG lowered per unit of insulin when comparing insulin detemir with insulin glargine in an acute care setting and studies exploring this clinical controversy have found similar results. A prospective crossover study conducted by Zhang and colleagues evaluated the efficacy and safety between insulin glargine and insulin detemir in individuals with T2DM. This study enrolled individuals admitted to the inpatient endocrinology ward, and carefully titrated the basal insulin products in a regimented manner to achieve goal FBG measurements, demonstrating that the basal insulin analogs were similar in efficacy.²⁴ An observational study conducted by Galindo and colleagues examined glycemic control in general medicine and surgery patients managed with either insulin glargine or insulin detemir. The researchers found that treatment with insulin glargine and insulin detemir resulted in similar inpatient glycemic control, with no differences in mortality, complications, or readmissions. However, patients treated with insulin detemir required a higher daily basal insulin dose and an increased likelihood of receiving twice daily dosing rather than once daily dosing to achieve glycemic control.²⁵

Figure 2. Study subject identification and data collection points.

^aTPN, total parenteral nutrition. ^bICU, intensive care unit. ^cDKA, diabetic ketoacidosis.

A strength of this study included the researchers' exclusion of those patients who received medications and nutritional support therapy that could have potentially influenced FBG measurements outside of basal-bolus insulin regimens. The case-crossover design is an added strength of this study as it may reduce the likelihood of confounding covariates interfering with the results. However, one factor that may have faulted the study based on this design was the lack of a washout period in those patients who received insulin glargine and insulin detemir in succession and those patients who may have been prescribed basal insulin at home prior to admission.

Limitations of this study included that it was retrospective in nature, relying on documentation from the electronic medical record system. This was also a single-center study with a relatively small sample size, which was limited by those patients who had received both basal insulin agents in the study time period. As the majority of the patient population was composed of those diagnosed with T2DM, the results are not necessarily generalizable to patients with T1DM as initially intended. Additionally, endogenous insulin secretion from those patients diagnosed with T2DM may potentially reduce the need for basal insulin compared with patients with T1DM. Varying pathology between T2DM and T1DM again comes into play with the high likelihood that those patients with T2DM may be insulin resistant, requiring larger doses of basal insulin to achieve FBG goals compared with T1DM patients.

The researchers made an effort to limit the study to patients who were medically stable by excluding those who were admitted to the intensive care unit or under the diagnosis of diabetic ketoacidosis, but no other controls

Table 1. Demographic Characteristics of Adults With Diabetes Mellitus.

Characteristics	Percentage (%) or Mean ($\pm$ SD)
Age (years)	66 ($\pm$ 12.8)
Sex	
Male	31 (60)
Female	21 (40)
Race	
White	41 (79)
African American	5 (10)
Hispanic	5 (10)
Asian	0 (1)
Other	1 (0)
Classification of diabetes	
Type 2 diabetes mellitus	48 (92)
Type 1 diabetes mellitus	4 (8)

were set in place to account for varying degrees of illness that could potentially influence glycemic control. With the exception of total parenteral nutrition administration, the researchers did not account for the patients' diets during their hospital stay, which may have also affected FBG measurements. Should this study be replicated on a larger scale, control for these confounding variables should be considered.

Conclusion

While studies in the outpatient setting have demonstrated that higher doses of insulin detemir may be necessary to achieve long-term glycemic control, this study suggests that the 2 agents may be equivalent with regard to the mg/dL reduction in FBG they are able to achieve in an acute care setting bearing in mind that generalization of the results is limited by the confounding variables discussed above. The authors hope to further investigate this matter by analyzing whether there may be potential cost benefits in switching between the 2 agents, through analysis of overall spending on basal insulin products following the formulary transition. While additional studies are needed to strengthen the body of literature on this subject, the researchers conclude that converting between insulin glargine and insulin detemir using a 1:1 ratio is indeed appropriate in an acute care setting.

Authors' Note

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Declaration of Conflicting Interests

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