Dose Response Effects of Insulin Glargine in Type 2 Diabetes

Zhihui Wang, MD², Maka S. Hedrington, MD¹, Nino Gogitidze Joy, MD¹, Vanessa J. Briscoe, PhD, NP², M. Antoinette Richardson, RN¹, Lisa Younk, BS¹, Wendell Nicholson, BS², Donna B. Tate, MS¹ and Stephen N. Davis, MBBS¹,²

¹Department of Medicine, University of Maryland School of Medicine, Baltimore, and ²Department of Medicine, Vanderbilt University, Nashville, TN

Please address all correspondence to:
Stephen N. Davis, MBBS, FRCP, FACP
Email: sdavis@medicine.umaryland.edu

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Objective- To determine the pharmacokinetic and pharmacodynamic dose response effects of insulin glargine administered subcutaneously in individuals with type 2 diabetes mellitus (T2DM).

Research Design and Methods - Twenty obese T2DM individuals (10M/10F, age 50±3 years, BMI 36±2 kg/m2, HbA1c 8.3±0.6%) were studied in this single center, placebo controlled, randomized, double-blind study. Five subcutaneous doses of insulin glargine (0, 0.5, 1.0, 1.5, 2.0 u/kg) were investigated on separate occasions using the 24 hr euglycemic clamp technique.

Results - Glargine duration of action to reduce glucose, NEFA and β-hydroxybutyrate levels, was close to or longer than 24 hrs for all four doses. Increases in glucose flux revealed no discernable peak and were modest with maximal glucose infusion rates of 9.4, 6.6, 5.5 and 2.8 μmol/kg/min for the 2.0, 1.5, 1.0 and 0.5 u/kg doses, respectively. Glargine exhibited a relatively hepato-specific action with greater suppression (p<0.05) of endogenous glucose production (EGP) as compared to little or no increases in glucose disposal.

Conclusion - A single subcutaneous injection of glargine at a dose of 0.5 u/kg or greater can acutely reduce glucose, NEFA and ketone body levels for 24 hrs in obese insulin resistant T2DM. Glargine lowers blood glucose by mainly inhibiting EGP with limited effects on stimulating glucose disposal. Large doses of glargine have minimal effects on glucose flux and retain a relatively hepato-specific action in T2DM.
Type 2 diabetes (T2DM) is a condition of relative or absolute insulin deficiency. Consequently, insulin replacement becomes a common and essential therapy in these individuals. Insulin therapy in T2DM can range from a single injection to basal-bolus replacement regimens with multiple daily injections. Insulin glargine is a soluble long-acting insulin analog that is widely used in clinical practice for basal insulin replacement.

Numerous studies have investigated the clinical efficacy of insulin glargine in both type 1 and type 2 diabetes (1-3). Glargine has been found to lower HbA1c, provide effective basal insulin replacement and reduce the risk of hypoglycemia (1-3). Despite the widespread use of glargine in clinical practice, there are relatively few studies investigating the pharmacokinetic (PK) and pharmacodynamic (PD) characteristics of the insulin. Two studies have investigated subcutaneous doses of 0.3 and 0.35 u of glargine in type 1 DM (4, 5). Other studies also utilizing a 24 hr glucose clamp technique have compared the PK and PD of single doses of glargine (0.5 u/kg and 0.8 u/kg) in patients with T2DM (6, 7). These studies provide valuable information about single doses of glargine in patients with diabetes. Klein, et. al. have also compared three doses of glargine (0.4, 0.8, and 1.4 u/kg) in T2DM during 24 hr clamp studies using the biostator (8). However, as the biostator has been reported to limit maximal glucose infusions during a glucose clamp and also produce a wide variation of blood glucose concentrations around the target glucose value (9) we reasoned that further information regarding the dose response characteristics of insulin glargine in patients with T2DM would also be useful. The aim of the present study was to use the 24 hr euglycemic clamp technique to determine the PK and PD of differing large, single subcutaneous doses of glargine (similar to those used in clinical practice when treating obese insulin resistant T2DM). Isotope dilution methods were used to determine glargine’s effects on endogenous glucose production and glucose disappearance.

**RESEARCH DESIGN AND METHODS**

**Subjects.** This single center randomized, double-blind, five period study was approved by the Vanderbilt University Institutional Review Board. Twenty individuals (10M/10F, aged 50±3 years, diabetes duration 8±1 yrs, BMI 36±2 kg/m², HbA1c 8.3±0.6%) were studied. None had major complications of diabetes, were non-smokers and had normal renal and hematologic function. Some individuals had mild elevations of hepatic transaminases suggestive of non-alcoholic steatohepatosis that were less than 1.5 times the upper normal limit. All study subjects were receiving varying combination therapy for glucose control. All study subjects were receiving metformin, and this was combined with sulfonylureas (6 patients), exenatide (6 patients), insulin (14 patients) (either glargine, detemir, humalog, novolog, 70-30 mixtures). Insulin dosages ranged from 11 to 70 units per day. (see Online Appendix Table 1 available at http://care.diabetesjournals.org).

**Experimental Design and Euglycemic Clamps.** The study consisted of five separate experiments, each lasting 26 hrs and separated by 6-8 weeks. In each experiment, individuals received subcutaneously into the abdomen, either 0.5, 1.0, 1.5 or 2.0 u/kg of glargine or an identical placebo injection (0 u/kg) in a randomized, double-blind fashion. Each limb of the study consisted of N=12 individuals.

Exenatide was withheld 24 hrs and oral medications, long and intermediate-acting insulins were withheld 60 hrs before each study. Individuals continued their normal weight maintaining diet and
Dose Response Glargin

participated in no exercise for three days before each experiment. Glucose control was maintained if necessary with short-acting insulin on the day before each study. Individuals were admitted to the Vanderbilt General Clinical Research Center at approximately 5 PM before an experiment. A hand vein was cannulated in a retrograde fashion and maintained in a heated box (55ºc) so that arterialized blood could be sampled (10). In addition, a vein in the contralateral arm was cannulated so that insulin, 20% dextrose and glucose tracer could be administered. An IV insulin infusion was started to control glucose during a standardized evening meal, a 2100h snack and was constantly adjusted overnight to maintain plasma glucose between 5.0-6.0 mmol/L. After a 9-hr overnight fast, a primed (10µCi in 10 min) continuous infusion (0.092 µCi/min) of [3-3 H] glucose was started at time -120 min and continued throughout the experiment. Plasma glucose was maintained at euglycemia during the 120 min isotope equilibration period by continuing the overnight insulin infusion. At time 0 min, a dose of glargine was administered subcutaneously into the abdominal area. The overnight insulin infusion was discontinued 45 min after the glargine injection. During the clamp period, plasma glucose concentrations were measured every 15-30 min, and a 20% dextrose infusion was used, when necessary, at a variable rate to maintain the plasma glucose concentration at the target value of 5.5 mmol/L (11). Blood for experimental parameters was sampled every 30 min to 2 hr throughout the study. The glucose clamp study was ended 24 hr after subcutaneous injection of glargine.

Tracer Calculations. Rates of glucose appearance (Ra), endogenous glucose production (EGP), and glucose utilization (Rd) were calculated according to the method of Wall, et al. (12). EGP was calculated as the total glucose production minus the exogenous glucose infusion rate. The total glucose production comprises EGP and any exogenous glucose which was infused to maintain the desired euglycemia. In order to maintain a constant specific activity, (and reduce underestimates of glucose kinetics), isotope delivery was increased commensurate with increases in exogenous glucose infusion.

Calculations. Pharmacodynamic parameters of insulin action were calculated as follows: 1) end of action: time at which plasma glucose was consistently (for at least 60 min) over 7.0 mmol/L (126 mg/dl).

Analytical Methods. Plasma glucose concentrations were measured in triplicate using the glucose oxidase method with a glucose analyzer (Beckman, Fullerton, CA). Subcutaneously administered insulin glargine (A21-Gly-B31-Arg-B32-Arg-insulin) precipitates at the injection site from which it is gradually liberated into the blood stream in three equivalently bio-active forms; insulin glargine, A21-Gly-insulin, A21-Gly-des-B30-Thr-insulin, plus A21-Gly-B31-Arg-insulin, a minor metabolite of unknown biological potency (13). The virtually complete sequence homology among insulin glargine, its metabolites, and insulin facilitates the immunoassay of the former compounds with methods developed for the assay of human insulin (14, 15). However, these assays can only measure total immunoreactive insulin in human plasma. Consequently, the contribution of insulin glargine and its metabolites to total plasma insulin can not be calculated unless each glargine component is known to react equally in the immunoassay and endogenous insulin can be discounted. An insulin radioimmunoassay (#PI-12K, Millipore, St. Charles, MO) which employs recombinant human insulin as reference was utilized in the present study. The sensitivity of the assay is 0.05 ng (1.25 u I.U.)/ml and the inter-assay coefficient of variation (CV) at 0.8 ng (20 u I.U.), 2.28 ng (57 u I.U.), and 6.0
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ng (150 u I.U./ml is 3, 7 and 9%, respectively.

C-peptide was determined by radioimmunoassay using an RIA kit (#HCP-20HK, Millipore, St. Charles, MO). The sensitivity of the assay is 0.1 ng/ml and the CV at 0.34 ng/ml and 1.41 ng/ml is 8.5 and 5%, respectively.

Plasma glucagon concentrations were measured using a modification of the method of Aguilar-Parada, et al. (16) with an interassay CV of 12%. Plasma non-esterified fatty acid (NEFA) concentrations were determined using the WAKO kit (Ho RJ 1970). Plasma β-hydroxybutyrate was measured using the method of Lloyd, et al. (17).

Statistical Analysis. Results were expressed as mean±SE, and were analyzed for statistical comparisons using one and two-way ANOVA. P<0.05 was accepted as significant differences between dosage. Calculations and statistical analyses were performed using SPSS (SPSS 16.0, SPSS Inc., Chicago, Illinois). Group differences were tested by LSD multiple comparison test.

The linear trapezoidal rule was used to calculate the area under curve (AUC) for plasma glucose, GIR, and plasma insulin.

RESULTS

Plasma Glucose Levels. Following placebo injection, plasma glucose levels increased to 8.7 ±0.3 mmol/L at 24 hrs (Figure 1). Following 0.5 u/kg of glargine, plasma glucose was maintained under 6.1 mmol/L until 18 hrs and then increased progressively (p<0.05) to a peak of 7.2±0.7 mmol/L at 24 hrs. In contrast, with higher doses of glargine (1.0, 1.5, 2.0 u/kg), plasma glucose levels were maintained at 5.7±0.3, 5.6±0.2 and 5.3±0.1 mmol/L at 24 hrs which were significantly reduced (p<0.05) compared to placebo.

Insulin, C-peptide, Glucagon Levels. The final 2 hrs of IV insulin administration were similar in each group (2.1±0.6, 1.9±0.3, 1.9±0.6, 2.1±0.2, 2.3±0.5, u/hr for placebo 0.5, 1.0, 1.5, 2.0 u/kg respectively). During the placebo (time control no exogenously administered insulin studies), basal insulin levels fell slowly and continuously over a 24 hr period from 132±18 to 94±4 pmol/L (Figure 1). Following glargine administration, insulin levels were significantly increased (p<0.05) compared to placebo (Figure 1) and followed a physiologic pattern (i.e smooth slow decrease over 24 hrs) similar to placebo. Larger doses of glargine produced stepwise increases (p<0.05) in mean insulin levels only up to 1.0 u/kg (137±23, 216±14, 254±25, 259±27 pmol/L for 0.5, 1.0, 1.5 and 2.0 u/kg, respectively). No glargine dose produced a discernable peak in insulin concentration. Inter-individual CV’s for insulin levels were 45, 51, 54 and 46% for the 0.5, 1.0, 1.5 and 2.0 u/kg glargine doses, respectively. There were no differences in average plasma insulin levels between the 1.0, 1.5 and 2.0 u/kg doses.

Glargine administration significantly inhibited (p<0.05) the release of C-peptide as compared to placebo (Figure 1). Incremental AUC C-peptide levels were significantly lower during the 1.0, 1.5 and 2.0 u/kg doses compared to 0.5 u/kg (p<0.05). There were no differences in incremental AUC C-peptide values following 1.0, 1.5 and 2.0 u/kg glargine doses. Plasma glucagon levels were significantly reduced (p<0.05) as compared to placebo by all glargine doses (Online Appendix Figure 1).

Glucose Kinetics. Glucose infusion was not required following placebo. The incremental area under the curve (AUC) for the glucose infusion rate to maintain euglycemia was 64±23, 149±46, 213±70 and 247±60 µmol/kg for 0.5, 1.0, 1.5, 2.0 u/kg, respectively. All were significantly increased (p<0.05) compared to placebo and the incremental AUC during the 1.0, 1.5 and 2.0 u/kg doses were increased (p<0.05) as compared to the
0.5 u/kg dose. The peak glucose infusion rates were (2.8±0.9, 5.5±1.5, 6.6±2.0 and 9.4±2.0 µmol/kg/min) in the 0.5, 1.0, 1.5 and 2.0 u/kg doses, respectively. All peak glucose infusion rates were significantly increased (p<0.05) following glargine administration as compared to placebo. Peak infusion rates were also higher (p<0.05) in the 1.0, 1.5 and 2.0 u/kg doses as compared to 0.5 u/kg. Glucose infusion rates at the end of the 24 hr study for the four glargine doses in increasing order were 0.2±0.17, 1.8±1.0, 3.0±1.6 and 3.7±1.1 µmol/kg/min, respectively.

Endogenous glucose production was suppressed during the placebo time control (Figure 2). Glargine at 0.5 u/kg produced similar suppression of EGP as compared to placebo. Glargine doses of 1.0, 1.5 and 2.0 u/kg produced greater suppression (p<0.05) of EGP as compared to placebo. Glucose rates of disappearance were not significantly increased by any of the glargine doses as compared to placebo (Figure 2). Endogenous glucose production was suppressed by a relatively greater amount (p<0.05) during placebo and all glargine doses as compared to the respective changes in glucose disappearance (Table 1).

**Intermediary Metabolism.** Plasma NEFA levels were suppressed (p<0.05) in a stepwise fashion with increasing doses of glargine. Blood β-hydroxybutyrate followed a similar pattern with a significantly greater reduction (p<0.05) of the ketone body with increasing doses of glargine (Online Appendix Figure 1).

**DISCUSSION**

This present study has examined the pharmacokinetic and pharmacodynamic dose response effects of single subcutaneous injections of insulin glargine in obese T2DM. Our study demonstrates that over a dose range of 0.5 to 2.0 u/kg. Glargine lowers plasma glucose by a relatively hepatospecific mechanism. In obese insulin resistant T2DM all the glargine doses exerted metabolic effects throughout the 24 hr clamp study. Circulating plasma insulin levels increased modestly despite large SC glargine doses (>200 units). Peak insulin levels plateaued following the 1.5 and 2.0 u/kg dose at 259±27 pmol/L which was barely double the insulin values following the 0.5 u/kg dose. The glucose infusion rates needed to maintain euglycemia were also modest with peak values of ≥ 9 µmol/kg/min required after the largest 2.0 u/kg dose.

Plasma glucose was maintained at or below 7.0 mmol/L for ≥ 23 hrs following the 0.5 u/kg and for 24 hrs with the 1.0, 1.5 and 2.0 u/kg doses. Additionally, NEFA, β-hydroxybutyrate and C-peptide levels were all suppressed, relative to placebo for 24 hrs. This indicates that in this present group of obese, insulin resistant type 2 patients that single SC glargine doses of 0.5 u/kg or higher can have a time action profile close to or longer than 24 hrs. As this present study investigated the effects of a single sc dose of glargine, we cannot determine whether repeated doses of glargine at 0.5 u/kg given over a longer period would also have resulted in a longer duration of action. This is a possibility as Porcellati, et al. have demonstrated extended duration of action of glargine at a dose of 0.3 u/kg following one week of repeated daily use in a group of T1DM (18). Luzio, et al. have also used the 24 hr euglycemic clamp technique to investigate 0.5 u/kg of glargine in T2DM individuals (19). In their study, glargine at 0.5 u/kg had a 24 hr duration of action. However, the T2DM individuals investigated by Luzio, et al. were very different from the present study cohort as they were less obese, had better glycemic control and were all maintained on oral hypoglycemic agents. Thus, the subjects would have been predicted to be less insulin resistant and also appeared to have less advanced T2DM. Supporting this is the finding that the maximal glucose
infusion rate in the study of Luzio, et al. was 
\( \simeq 9 \text{ pmol/kg/min} \) which was equivalent to the 
largest glucose infusion rate occurring in this 
study following a four-fold higher dose of 
glargine (2.0 u/kg).

Due to the fact that glargine can have 
a variable activation time (18) we decided, a 
priori, to maintain the overnight infusion of 
insulin for 45 minutes in all studies. This 
extends why there was a small increase in 
plasma glucose levels following glargine 
administration at the start of the clamp 
studies. Additionally, as the initial period of 
the clamps would have reflected both SC 
glargine and IV insulin administration we did 
not report plasma insulin levels until 2 hrs 
into the clamp studies. The insulin profiles 
from each of the injected doses did not 
display any demonstrable peak. Additionally, 
the elevations in circulating plasma insulin 
were dramatically truncated and were not 
proportional to the linear increases of the SC 
injected insulin glargine. Thus, insulin 
levels were only \( \simeq 30 \text{ pmol/L (5µU/ml)} \) 
higher than placebo following the 0.5 u/kg 
dose. Insulin levels increased \( \geq 80 \text{ pmol/L (14µU/ml)} \) 
between the 0.5 and 1.0 u/kg 
doses. Thereafter, there was only a mean 
non-significant 38 pmol/L (6µU/ml) 
increase between the 1.0 to 1.5 u/kg doses and 
no difference in insulin levels between the 1.5 
and 2.0 u/kg doses. In fact, the mean 
maximal insulin levels following the 1.5 and 
2.0 u/kg doses were equivalent at only 312- 
318 pmol/L (52-53 µU/ml). It is also worth 
noting that based on work by Ciaraldi, et al 
(20) that this level of glargine has similar 
binding to skeletal muscle IGF-1 receptors as 
comparable levels of human insulin. This 
provides reassurance that glargine levels at even very high clinical 
doses do not have increased mitogenic 
potential. When interpreting the insulin 
levels, some additional points may warrant 
consideration. The circulating insulin levels 
will represent a combination of exogenous 
and endogenous insulin. The endogenous C-
peptide area under the curve was suppressed 
by a greater amount for the 24 hr study 
following the largest doses of glargine as 
compared to placebo or the 0.5u/kg dose. 
Thus, it may be assumed that the suppressed 
endogenous insulin levels may have 
contributed a relatively lower amount to the 
total plasma insulin level during the higher 
dose glargine clamp studies. Additionally, 
measurement of insulin levels following SC 
glargine administration is complicated by 
circulating metabolites of the molecule that 
both have differential metabolic effects and 
abilities to cross react in a conventional 
insulin immunoassay. Thus, the presented 
plasma insulin levels following glargine may 
represent an overestimate of the total 
circulating glargine species present in the 
plasma (13). Nevertheless, what is evident 
from this study is that the chemical 
formulation of the glargine molecule 
dramatically limits absorption of insulin from 
the subcutaneous tissue and acts as a buffer to 
limit circulating insulin levels (19, 21). We 
believe that the formulation of insulin 
glargine is a major determinant of the 
molecule’s pharmacokinetic profile as the 
interindividual CV of insulin levels in the 
present study ranged from 45-54\% and are 
similar to previously reported values with 
non-analog extended action insulins (22).

Glargine lowered plasma glucose by a 
relatively hepato-specific mechanism. At 
each dose level, endogenous glucose 
production was suppressed by a greater 
amount as compared to any relative increase 
in glucose disposal (Rd). In fact, none of the 
glargine doses increased Rd by a significantly 
greater amount as compared to placebo. 
Contributing to the relatively hepato-specific 
action was glargine’s effect on glucagon and 
NEFA levels. Glucagon is known to be a 
significant contributor to basal EGP (23). 
Thus, glargine’s effects to suppress glucagon 
during the glucose clamps could also have
been a contributory mechanism for the relative hepato-specific action. Additionally, glargine’s effects to reduce circulating NEFA levels would also have effects to lower EGP. The reduced β-hydroxybutyrate levels following glargine administration also support the molecules hepatic action. Conversion of NEFA to ketone bodies occurs largely in the liver and this was significantly reduced during the present studies. During fasting, EGP falls as glycogen stores are utilized (22). Furthermore, physiologically endogenous basal insulin has a relatively hepato-specific effect. This can be clearly seen in the placebo experiments. However, what the present studies have demonstrated is that insulin glargine doses up to 2.0 u/kg (with injected insulin doses > 200 units) also lower fasting glucose in T2DM in a “physiologic” hepato-specific manner.

Although the doses of glargine used in T1DM practice are usually quite low (<0.5 u/kg), the amount of glargine used in managing T2DM is often considerably higher. Therefore in this present study, we have studied the acute 24 hr PK and PD effects of large doses of glargine (0.5 – 2.0 u/kg) in T2DM. We should point out that the study was performed in the southeastern USA where there is a very high prevalence of T2DM and accompanying obesity. Our study population had a mean BMI of 36±2 and was clearly obese. Additional studies investigating the PK and PD dose response characteristics of glargine using lower doses of the insulin in less obese individuals would also be useful. Additionally, we should also mention that in this study, glargine was administered in the morning, which occurs in clinical practice but not as commonly as evening dosage. Furthermore, the pharmacodynamics of glargine may be influenced by the time of administration. The dawn phenomenon with its attendant changes in plasma glucose and insulin sensitivity can occur 4-8 hrs after evening dosage but ~ 20 hrs following a morning injection. Thus the pattern of glucose kinetics might have been altered if glargine had been administered in the evening.

In summary, this study has investigated the pharmacokinetics and pharmacodynamics of large doses (0.5-2.0 u/kg) of insulin glargine in obese T2DM. A single subcutaneous injection of glargine can have a duration of action of at least 24 hrs. Very large doses result in modest increases in glucose flux with no discernable peak action. This appears due to the limited, peakless and continuous release of the insulin from the subcutaneous tissue. Glargine lowers plasma glucose by a predominantly hepato-specific action (i.e. inhibiting endogenous glucose production) with minimal effects on stimulating glucose disposal.

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REFERENCES


Table 1. Pharmacodynamic effects of subcutaneous injections of glargine in type 2 DM.

<table>
<thead>
<tr>
<th></th>
<th>0 u/kg</th>
<th>0.5 u/kg</th>
<th>1.0 u/kg</th>
<th>1.5 u/kg</th>
<th>2.0 u/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma glucose at end of study (mmol/L)</td>
<td>8.7±0.8</td>
<td>7.2±0.7*</td>
<td>5.7±0.3*†</td>
<td>5.6±0.2*†</td>
<td>5.3±0.1*†</td>
</tr>
<tr>
<td>Maximum Glucose infusion rate (µmol/kg/min)</td>
<td>0.3±0.3</td>
<td>2.6±0.9*</td>
<td>5.5±1.5*†</td>
<td>6.8±2.0*†</td>
<td>9.5±2.1*†</td>
</tr>
<tr>
<td>Glucose infusion rate at end of study (µmol/kg/min)</td>
<td>0.0±0.0</td>
<td>0.2±0.2</td>
<td>1.87±1.0*</td>
<td>3.0±1.6*†</td>
<td>3.7±1.1*†</td>
</tr>
<tr>
<td>Suppression of Endogenous Glucose Production (%)</td>
<td>28±4‡</td>
<td>45±6*‡</td>
<td>71±10*‡</td>
<td>61±12*‡</td>
<td>80±15*‡</td>
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<tr>
<td>Increase in glucose disposal rate (%)</td>
<td>(-2.3)±4.0</td>
<td>4.0±3.8</td>
<td>10±7</td>
<td>12±10</td>
<td>24±18</td>
</tr>
</tbody>
</table>

* p<0.05 compared to 0 u/kg (placebo)
† p<0.05 compared to 0.5 u/kg Glargine
‡ p<.05 compared to increase in glucose disposal rate

FIGURE LEGENDS

Figure 1
Effects of single injections of insulin glargine (0, 0.5, 1.0, 1.5 and 2.0 u/kg) on plasma glucose. Insulin and C-peptide levels in overnight fasted type 2 DM. Plasma glucose levels at 24 hrs are significantly increased (p<0.05) in the placebo and 0.5 u/kg dose groups.

Plasma insulin levels are significantly increased (p<0.05) compared to placebo following all doses of glargine. 1.0, 1.5 and 2.0 u/kg doses of glargine are increased (p<0.05) compared to 0.5 u/kg dose.

Plasma C-peptide levels are significantly decreased (p<0.05) as compared to placebo. Incremental area under the curve values following 1.0, 1.5 and 2.0 u/kg doses are also significantly lower (p<0.05) than 0.5 u/kg dose.

Figure 2
Effects of single injections of insulin glargine (0, 0.5, 1.0, 1.5 and 2.0 u/kg) on endogenous glucose production, glucose rate of disappearance and glucose infusion rates in overnight fasted type 2 DM. Rates of endogenous glucose production are significantly suppressed by a greater amount (p<0.05) following 1.0, 1.5 and 2.0 u/kg as compared to placebo. Rates of glucose disposal are similar following placebo and all doses of glargine.

Glucose infusion rates are significantly increased (p<0.05) following all doses of glargine as compared to placebo. Incremental area under the curve values for 1.0, 1.5 and 2.0 u/kg doses were also significantly increased as compared to the 0.5 u/kg dose.
Figure 1

- Placebo
- 0.5U/Kg dose
- 1.0U/Kg dose
- 1.5U/Kg dose
- 2.0U/Kg dose

Plasma glucose (mmol/L)

Insulin (pmol/L)

C-Peptide (nmol/L)

Time (hours)
Figure 2

- Placebo
- 0.5U/Kg dose
- 1.0U/Kg dose
- 1.5U/Kg dose
- 2.0U/Kg dose

**Rate of Disappearance (μmol/kg/min)**

**Endogenous Glucose Production (μmol/kg/min)**

**Glucose infusion Rate (μmol/kg/min)**

**Time (hours)**

0 2 4 6 8 10 12 14 16 18 20 22 24