Glargine and Glycemia: Pitfalls and Perils

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Abstract:

Keywords:

1. INTRODUCTION

Patients in critical care can exhibit varying degrees of metabolic distress. As a result, treatment is tailored to individuals and requires high clinical effort. These variable requirements are evident in patients requiring accurate glycemic control (AGC). AGC involves targeting of blood glucose (BG) to a desired range to mitigate the effects of hyperglycemia, while controlling risk of hypoglycemia.

The implication of AGC is that patients have unfulfilled insulin requirements caused by low sensitivity or compromised endogenous production. Of interest to this paper is the use of the long-acting insulin analogue Glargine as exogenous basal insulin.

Glargine is an insulin analogue with an extremely long action period (22-26 hours), characterised by a unique flat peak (Campbell et al., 2001). Due to these unique characteristics, medical care providers may use the drug to supplement basal insulin requirements for patients with persistent hyperglycemia. This approach is may typically be used taken when a patient is transferred to a less acute ward, where constraints on nursing resources may make intensive glycemic control impractical. The kinetics and action of glargine in these patients has not be fully defined. In particular action profiles may show significant variations between patients, and the long-acting nature of glargine can create additional isuues in typical clinical practice. Additionally, glargine may have higher efficacy than other forms of insulin [REF]. This paper presents several case studies which illustrate a number of areas for concern w with glargine use. These examples were collected from observations during the pilot study of STAR in Christchurch Hospital medical ICU.

2. METHODS

2.1 Clinical Data

Glycemic control data was obtained from 4 patients who took part in the STAR Accurate Glycemic Control pilot trial in Christchurch hospital. Threeof these patients were administered one or more doses of glargine. The patients presented here typically transferred on and off STAR as dictated by changes in clinical condition and insulin requirements. Additional data was extracted from patient records to enable idenfitication of insulin sensitivity during these periods off intensive glycemic control.

2.2 ICING and Glargine Models

Insulin sensitivity was fitted using the clinically validated ICING model (Lin et al., 2011) and the Glargine Compartment Model. Table I lists the population constants of the ICING model defined in Equations 1-6.

$$\dot{G} = -p_G G(t) - S_I G(t) \frac{Q(t)}{1+\alpha_G Q(t)} + \frac{P(t) + EGP_b - CNS + PN(t)}{V_g} \quad (1)$$

$$\dot{I} = -\frac{n_L I(t)}{1+\alpha_I I(t)} - n_K I(t) - \left(I(t)-Q(t)\right) n_I + \frac{u_{ex}(t)}{V_I} + \left(1-x_L\right)\frac{u_{en}(G)}{V_I} \quad (2)$$

$$\dot{Q} = \left(I(t)-Q(t)\right) n_I - n_C \frac{Q(t)}{1+\alpha_G Q(t)} \quad (3)$$

$$\dot{P}_1 = -d_1 P_1 + P(t) \quad (4)$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1 \quad (5)$$

$$u_{en} = \max\left(16.67, \frac{14G(t)}{1+0.0147G(t)} - 41\right) \quad (6)$$

where G(t) [mmol/L] is the total plasma glucose, I(t) [mU/L] is the plasma insulin and interstitial insulin is represented by Q(t) [mU/L]. Exogenous insulin input is represented by $u_{ex}(t)$ [mU/min] and endogenous insulin production is estimated with u_{en} [mU/min], modeled as a function of plasma glucose concentration determined from critical care patients with a minimum pancreatic output of 1U/hr. P_1 [mmol] represents the glucose in the stomach and P_2 [mmol] represents glucose in the gut. Enteral glucose input is denoted P(t) [mmol/min].

Sensitivity to insulin is observed in the SI parameter. This lumped parameter formulation means that SI tracks physiological changes in sensitivity to insulin and accounts for mis-modelled dynamics. In particular supra-physiologic patterns in SI during glargine usage could indicate areas where the dynamics of this therapy are not fully captured.

The Glargine Compartment model captures the kinetics of Glargine from injection to appearance in plasma. Glargine has four states: precipitate, hexameric, monomeric / dimeric, and local interstitium (Wong et al., 2008b, Wong et al., 2008a). The resulting compartment model is defined in Equations 7-12.

TABLE I
CONSTANTS USED IN SYSTEM MODEL OF EQUATIONS (1)-(6)

Model var.	Description	Numerical value [typical range]
p_G	Endogenous glucose clearance	0.006 min^{-1}
S_I	Insulin sensitivity	[1x10^{-7}-1x10^{-2}] L/(mU.min)[a]
α_G	Saturation of insulin-dependent glucose clearance and receptor-bound insulin clearance from interstitium	1/65 L/mU
d_1	Rate of glucose transfer between the stomach and gut	-ln(0.5)/20
d_2	Rate of glucose transfer from the gut to the bloodstream	-ln(0.5)/100
P_{max}	Maximum disposal rate from the gut	6.11 mmol/min
EGP_b	Basal endogenous glucose production (unsuppressed by glucose and insulin concentration)	1.16 mmol/min typically
CNS	Non-insulin mediated glucose uptake by the central nervous system	0.3 mmol/min
V_G	Glucose distribution volume	13.3 L
n_I, n_C	Rate of transport between plasma and interstitial insulin compartments	0.0075 min^{-1}
α_I	Saturation of plasma insulin clearance by the liver	1.7x10^{-3} L/mU
V_I	Insulin distribution volume	4.0 L
x_L	First-pass hepatic insulin clearance	0.67
n_K	Clearance of insulin from plasma via the renal route	0.0542 min^{-1}
n_L	Clearance of insulin from plasma via the hepatic route	0.1578 min^{-1}

[a]Insulin sensitivity (SI) is identified from clinical data in the range shown.

$$\dot{p}_{gla}(t) = \frac{-k_{prep,gla} p_{gla}(t)}{1+\frac{k_{prep,gla}}{r_{dis,max}} p_{gla}(t)} + u_{p,gla}(t) \quad (7)$$

$$\boldsymbol{u_{p,gla}(t) = \alpha_{gla} u_{total,gla}(t)} \quad (8)$$

$$\boldsymbol{\dot{x}_{h,gla}(t) = -\left(k_{1,gla} + k_d\right) x_{h,gla}(t) + \frac{k_{prep,gla} p_{gla}(t)}{1+\frac{k_{prep,gla}}{r_{dis,max}} p_{gla}(t)}} \quad (9)$$

$$\boldsymbol{u_{h,gla}(t) = u_{total,gla}(t)\left(1-\alpha_{gla}\right) - u_{m,gla}(t)} \quad (10)$$

$$\boldsymbol{\dot{x}_{dm}(t) = -\left(k_2 + k_d\right) x_{dm}(t) + k_{1,gla} x_{h,gla}(t) + u_{m,gla}(t)} \quad (11)$$

$$\boldsymbol{\dot{x}_i(t) = -\left(k_3 + k_{di}\right) x_i(t) + k_2 x_{dm}(t)} \quad (12)$$

where $p_{gla}(t)$ [mU] is the total Glargine in precipitate form, $x_{h,gla}(t)$ [mU] is the total Glargine in hexameric form, $x_{dm}(t)$ [mU] is the total Glargine in monomeric / dimeric form and $x_i(t)$ [mU] is the total Glargine in the (local) interstitium. The exogenous Glargine is represented by $u_{p,gla}(t)$ [mU] in the precipitate form, $u_{m,gla}(t)$ in the monomeric / dimeric form and $u_{h,gla}(t)$ in the hexameric form. All other terms and values are defined in Table 2, based on an extensive validation study (Wong et al., 2008b, Wong et al., 2008a).

Glargine release from precipitate to hexameric form is a saturable process. The maximum dissolution rate, $r_{dis,max}$ [mU/min], gives Glargine its unique kinetic profile and is defined:

$$\boldsymbol{r_{dis,max} = r_{dis,max}\left(\alpha_{gla} u_{total,gla} < U_{tres}\right) + \frac{Br_{dis,max} \alpha_{gla} u_{total,gla}}{U_{tres}}\left(\alpha_{gla} u_{total,gla} \geq U_{tres}\right)} \quad (13)$$

where $Br_{dis,max}$ [mU/min] is the baseline precipitate dissolution rate and U_{tres} [mU] is the dosage threshold. The volume of the Glargine injected also has an effect on the kinetics in the form of a diffusive loss from the hexameric and monomeric /dimeric states. The rate of this diffusive loss k_d [min^{-1}] is defined:

TABLE II
CONSTANTS USED IN SYSTEM MODEL OF EQUATIONS (7)-(12)

Model var.	Description	Numerical value
$k_{prep,gla}$	Glargine precipitate dissolution rate	0.0216 min^{-1}
$alpha_{gla}$	Fraction of glargine as precipitate	0.9462
$k_{1,gla}$	Hexamer dissociation rate	0.0062 min^{-1}
D	Diffusion constant for hexameric and dimeric/monomeric states	9.00x10^{-5} cm^2/min
k_2	Dimeric/monomeric insulin transport rate into interstitium	0.0106 min^{-1}
k_3	Interstitium transport rate into plasma	0.0618 min^{-1}
k_{di}	Rate of loss from interstitium	0.029 min^{-1}
V_x	Subcutaneous insulin distribution volume	11.38 L
B_{r_dismax}	Baseline glargine precipitate dissolution rate	2.3134 mU/min
Q_D	Hexameric–dimeric equilibrium constant	1.50x10^{-2} ml^2/mU^2
U_{tres}	Dosage threshold	2.01x10^3 mU

$$k_d = \frac{3D}{r} \quad (14)$$

$$r = \left(\frac{3V_{inj}}{4\pi}\right)^{1/3} \quad (15)$$

where r [cm] is the radius of the depot formed by the subcutaneous injection and D [cm^2/min] is the diffusion constant for the hexameric and monomeric /dimeric states.

Finally the initial quantity of the Dimeric/Monomeric state in solution is found by solving the following derived from (Wong et al., 2008a):

$$Q_D V_{inj} \left(\frac{U_m}{V_{inj}}\right)^3 + u_m - u_{total}(1 - \alpha_{gla}) = 0 \quad (16)$$

2.3 Glargine Interventions

Glargine was prescribed as determined by the physician in charge, with doses conservatively chosen as half the previous daily IV insulin usage. Glargine was given in addition to IV Actrapid insulin for highly resistant patients, or as the sole exogenous insulin for stable but mildly resistant patients.

3. RESULTS

Clinica case A: Clinical nutrition requirements

Figure 1 presents the clinical course of glargine usage for Patient A, and highlights several areas where glargine negatively influenced glycemic control.A 30U dose of glargine was given at XXX hours. Enteral nutrition was halted soon after. The long-acting nature of glargine meant the action of insulin persisted for many hours, and in the presence of the nutrition stoppage led to a hypoglycemic incident, with BG dropping to 2.6mmol/L during the peak of the glargine action period and remaining low for the duration of the dose. Similar periods of lower BG happened three times for this patient around hours XX, XX and XX, with the low BG severity limited A) by the presence of parenteral nutrition, and B) by the duration of the nutrition stoppage. It is also interesting to note the transition on/off AGC.

Additionally, differences in glycemia are observed between AGC (0-160 hrs, 427-463 hrs) and glargine-only periods. The patient was initially controlled under STAR and met the stopping criteria. Due to apparent stability, glargine was then used to meet the patient's basal insulin requirement, leading to BG fluctuating over a wider range. After a hypoglycemic event was followed by sustained hyperglycemia STAR was restarted, and BG was rapidly brought down to normal glycemic levels.

Clinical cases B & C: Glargine kinetics and efficacy

Patients B amd C (Figures 2 and 3) illustrate the uncertainty surronding the appearance and efficacy of glargine in interstitium. Patient B was dosed with 50U of glargine due to a high insulin requirement. This relatively conservative glargine dose resulted in moderate hypoglycemia, requiring intervention with IV dextrose to correct.

Patient C was initially dosed with 60U of glargine to assist with an extended period of mild hyperglycemia whilst receiving maximum permitted IV insulin under the STAR protocol. This first dose was followed by two 100U doses, where the last of these doses preceeded a moderate hypoglycemic event. The effect of the glagine dose differed

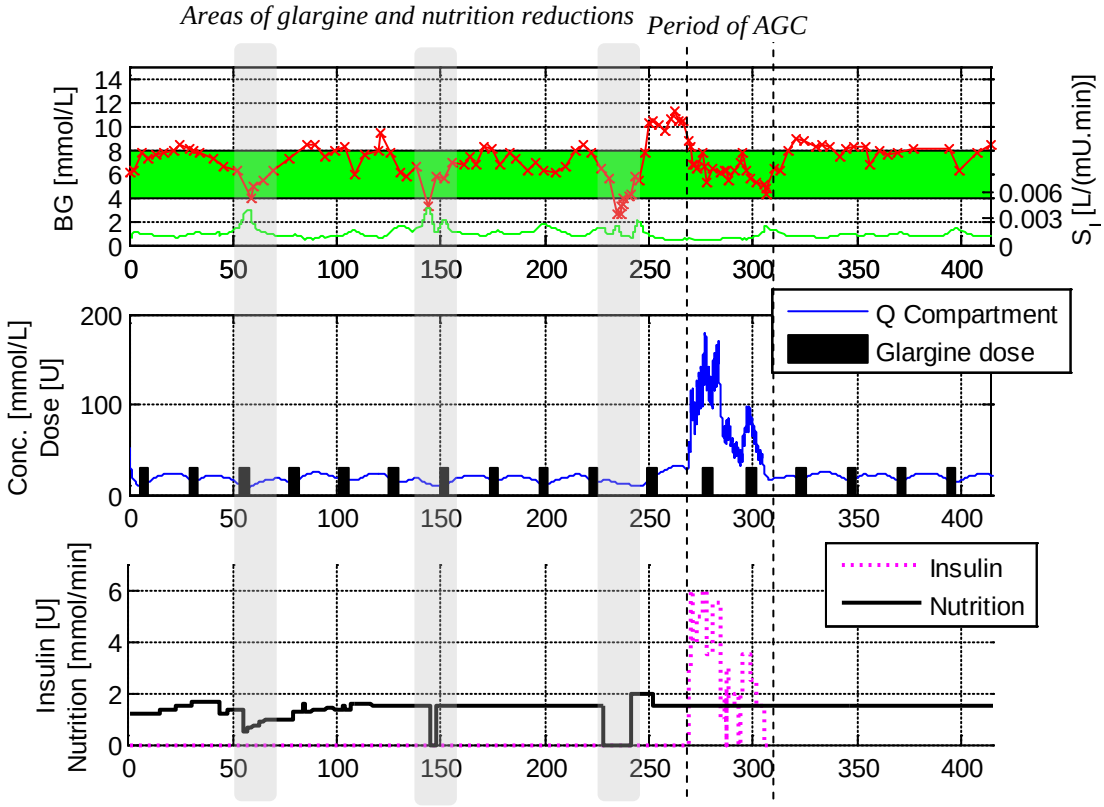

Figure 1. Patient with regular 30U glargine doses who experienced periods without nutrition, the longest of which led to severe hypoglycaemia.

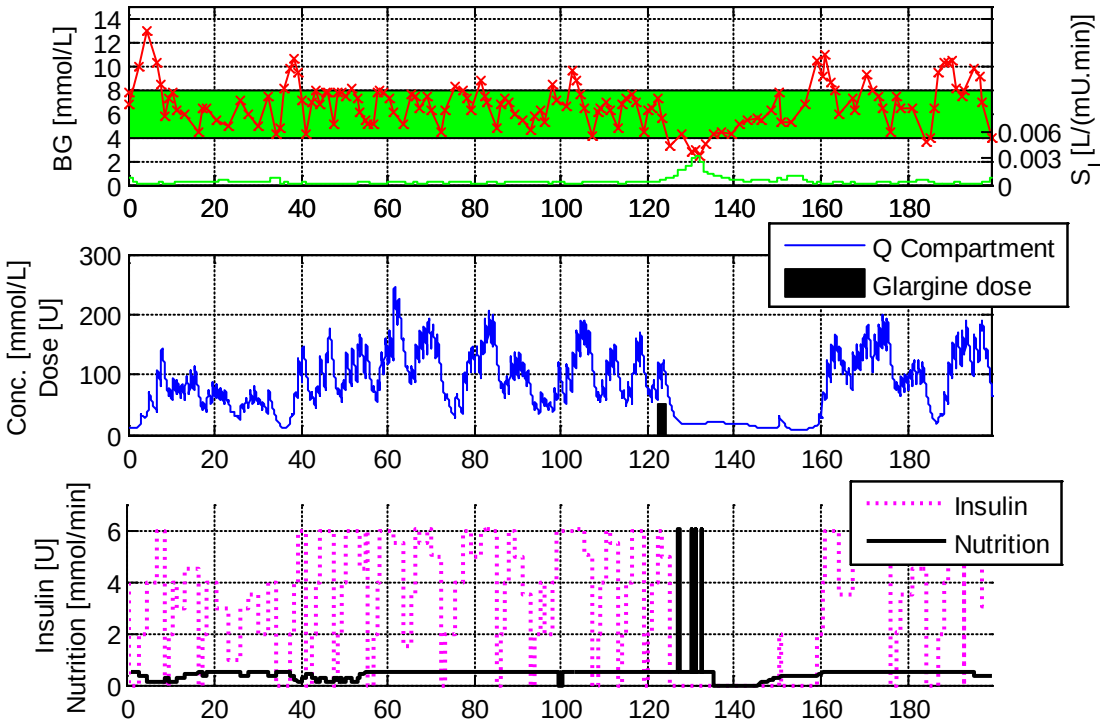

Figure 2. Patient with a single dose of glargine, with mismodelling of the dynamics is exhibited as a peak of insulin sensitivity.

appeared to differ between each individual dose in this case.

Mis-modelling of the glargine dose would appear as changes in fitted insulin sensitivity, Although the insulin sensitivity peak is confounded by potential changes in patient condition, the 50U dose given to Patient B appeared much more strongly than expected by the models in literature, where the relatively sharp peak conflicts with the expected flat action profile. In contrast, the first glargine dose given to Patient C approximates the expected appearance profile, whilst the two

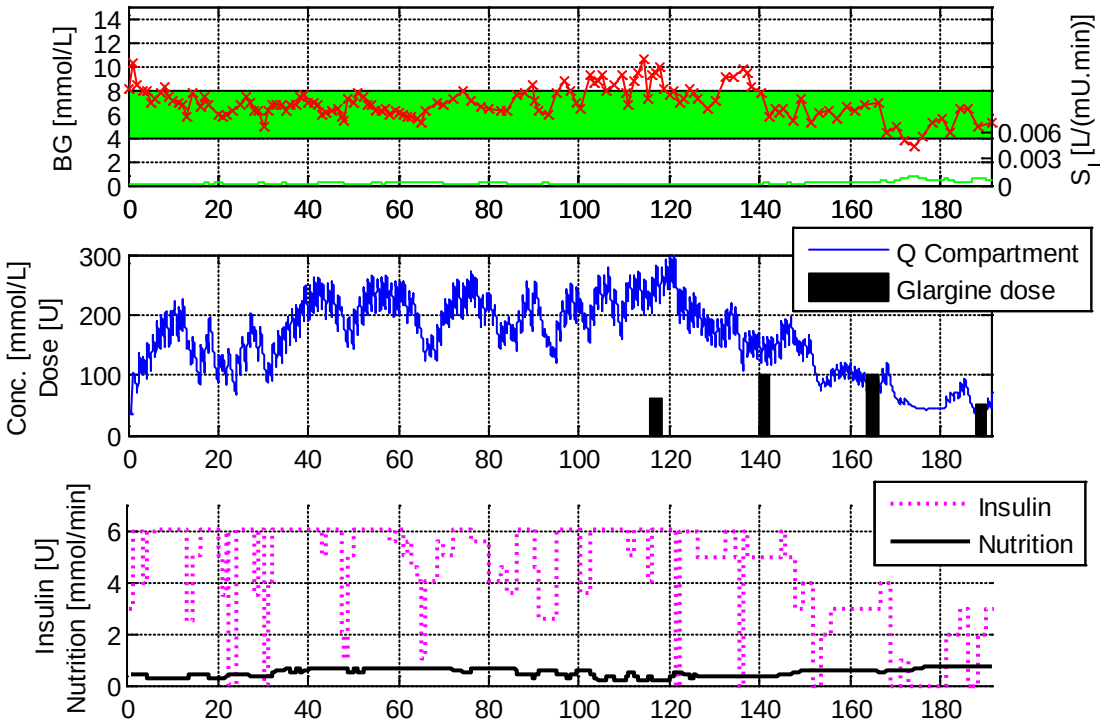

Figure 3. Patient with three doses of glargine, with differing levels of appearance between doses.

100U doses were correlated with a rise in fitted insulin sensitivity. This rise in insulin sensitivity may be due to change in patient condition or the action profile of glargine, and cannot be further resolved in this case..

Clinical case D: Patient insulin sensitivity variation

Patient D (Figure 4) illustrates the dynamic changes in insulin requirement. This patient was well controlled under the STAR protocol, with BG measures within the 4.4-8.0mmol/L target over the entire period, and would have been a likely candidate for glargine usage, particularly over the last few days of ICU stay. For the first 4 days patient condition is stable, with moderate to high insulin requirement. At the end of the 5th day, insulin requirement is dramatically reduced, and is removed altogether on the 6th. Glargine doses given on the 4th-6th day would have likely resulted in greater risk of hypoglycemia, given the very rapid rise in sensitivity to insulin, coupled with the long-last, non-reversible effect of glargine.

4. DISCUSSION

The clinical case studies presented here indicate that adequately considering nutritional requirements is of critical importance for safe usage of glargine in critical care. Patient A (Figure 1) was regularly dosed with glargine, but nutrition was inconsistent, leading to a major hypoglycemic incident. Enteral nutrition was stopped three times during the glargine-only period, with the severity of the outcome determined by the length of the stoppage and the presence of parenteral nutrition. As it was not an isolated event, this case study indicates that nutrition intake must be carefully monitored to ensure adequate safety, and that adequate nutrition is supplied throughout the entire ~24-hour action period of glargine.

The contrast between controlled and uncontrolled glycemia for Patient A displayed the propensity for uncontrolled BG to be persistently hyperglycemic when a patient has an unfulfilled exogenous insulin requirement. Sensitivity to changes in nutrition was displayed after the major hypoglycemic incident, as the restart rate was approximately 20% higher than the rate prior to stoppage, and led to exacerbated hyperglycemia. AGC was required to bring BG back under control, and was able to do so rapidly. However, after STAR was stopped for the second time, BG rose again and persisted in the mild hyperglycemic range. This sensitivity to nutrition suggests that AGC protocols should be designed to take nutrition into account, either through direct control (such as STAR) or by design for use with specific rates. The BG profile suggests insulin requirement might be preferred over BG stability as a stopping criteria for AGC, requiring metabolic self-sufficiency before control is completely stopped. This case also highlights the integrated nature of the insulin-glucose-nutrition system can result in complex clinical interactions.

Uncertainty in both the pharmacokinetics and pharmacodynamics will make prospective dosing of glargine difficult. Peaks in the observed insulin sensitivity profile indicate the model is not completely capturing either the kinetics or the dynamics in Figure 2, contrasting with the profile of Figure 3. Figure 3 also suggests the profile can vary between dose, not just between patient, so prior behavior is potentially not indicative of future response.

A final cautionary note warns that patient condition can change dramatically over a few hours, having a large effect

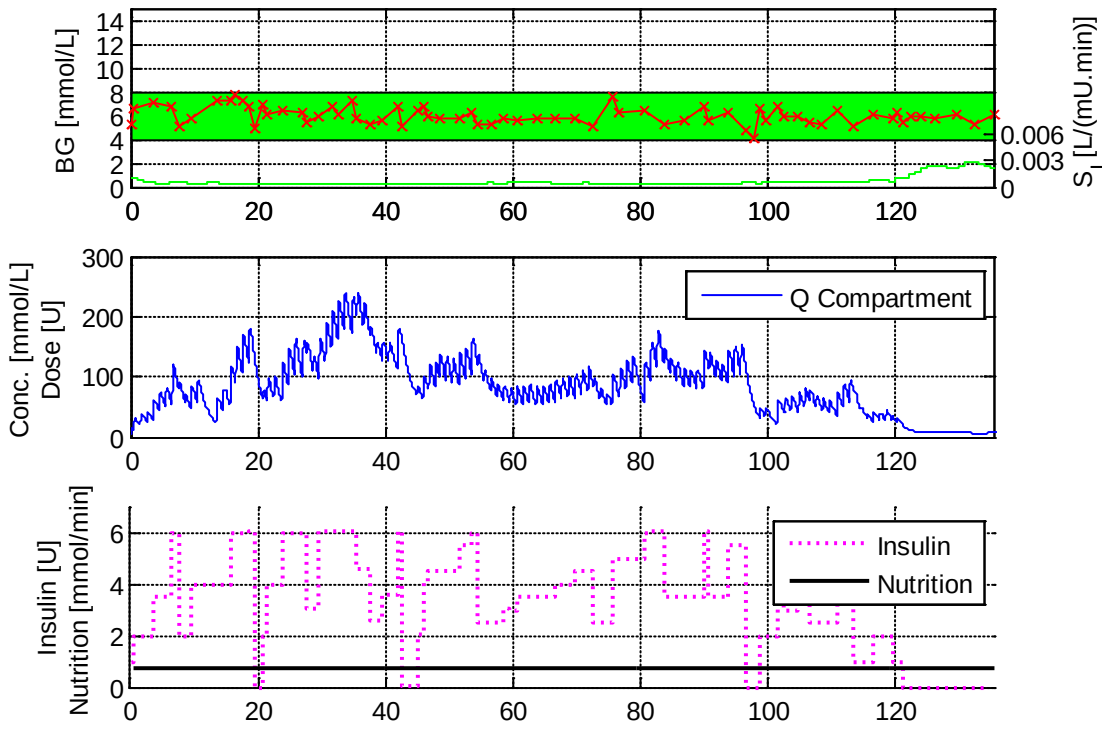

Figure 4. Patient displaying the significant changes in insulin requirement, shown by a steady rise in insulin sensitivity.

on a patient's apparent insulin requirement. The long action period and non-reversible nature of glargine presents a potential problem with patients similar to Figure 4, where a sudden rise in insulin sensitivity removed all requirement for exogenous insulin to maintain normoglycemia over the course of several hours. Such a patient would be at risk of severe hypoglycemia if previously dosed with glargine during the stable period of high insulin requirement. Glargine is typically used when a patient requires additional insulin under AGC, or is deemed stable and thus no longer requires such intense observation. Thus, this case study displays the potential for longer acting insulin analogues to put patient safety at risk when metabolic conditions quickly change.

With these clinical results showing hypoglycemia in each of the patients dosed with glargine during the STAR trial, safety is clearly an issue. Despite conservative dosing (half of the prior daily insulin requirement) two cases resulted in severe hypoglycemia (< 2.2 mmol/L). It is also important to note that none of the severe hypoglycemic events can be attributed to failing of AGC, as in each case either exogenous insulin was previously stopped by the protocol or AGC had been discontinued. These episodes suggest more research is required to investigate the effects of glargine in an intensive care population.

A potential solution to utilize glargine safely in intensive care may be to use glargine in conjuction with a specifically designed low-effort AGC protocol that may employ faster-acting insulins. With more information on glargine in intensive care populations, a conservative low-dose glargine regimen could be used to replace a patient's basal insulin requirement while the AGC protocol responds to intra-day variability. Taking advantage of the extended timescale of glargine has the potential to reduce effort, with risk addressed by an effective AGC protocol.

5. CONCLUSIONS

Clinical results from glargine usage during the STAR pilot trial suggest that use of glargine in the ICU can present unaddressed risks, compounded by uncertainty on the behavior of glargine in this population. Extended timescales increase the potential for changes in patient condition to negatively affect safety, while reducing the tolerance for clinical events such as nutrition stoppages. Further research appears necessary to set the stage for prospective dosing to reduce the risks associated with the long action insulin analogue.

6. REFERENCES

CAMPBELL, R. K., WHITE, J. R., LEVIEN, T. & BAKER, D. 2001. Insulin glargine. *Clinical Therapeutics,* 23**,** 1938-1957.

LIN, J., RAZAK, N. N., PRETTY, C. G., LE COMPTE, A., DOCHERTY, P., PARENTE, J. D., SHAW, G. M., HANN, C. E. & GEOFFREY CHASE, J. 2011. A physiological Intensive Control Insulin-Nutrition-Glucose (ICING) model validated in critically ill patients. *Comput Methods Programs Biomed,* 102**,** 192-205.

WONG, X., CHASE, J., HANN, C., SHAW, G., LOTZ, T., LIN, J. & LE COMPTE, A. 2008a. A Subcutaneous Insulin Pharmacokinetic Model for Computer Simulation in a Diabetes Decision Support Role: Model Structure and Parameter Identification. *Journal of Diabetes Science and Technology (JoDST),* 2**,** 658-671.

WONG, X., CHASE, J., HANN, C., SHAW, G., LOTZ, T., LIN, J. & LE COMPTE, A. 2008b. A Subcutaneous Insulin Pharmacokinetic Model for Computer Simulation in a Diabetes Decision Support Role: Validation and Simulation. *Journal of Diabetes Science and Technology (JoDST),* 2**,** 672-680.