

# Nocturnal Administration of Very Low Dose Glucagon in Patients with Type 1 Diabetes Reduces Episodes of Nocturnal Hypoglycemia

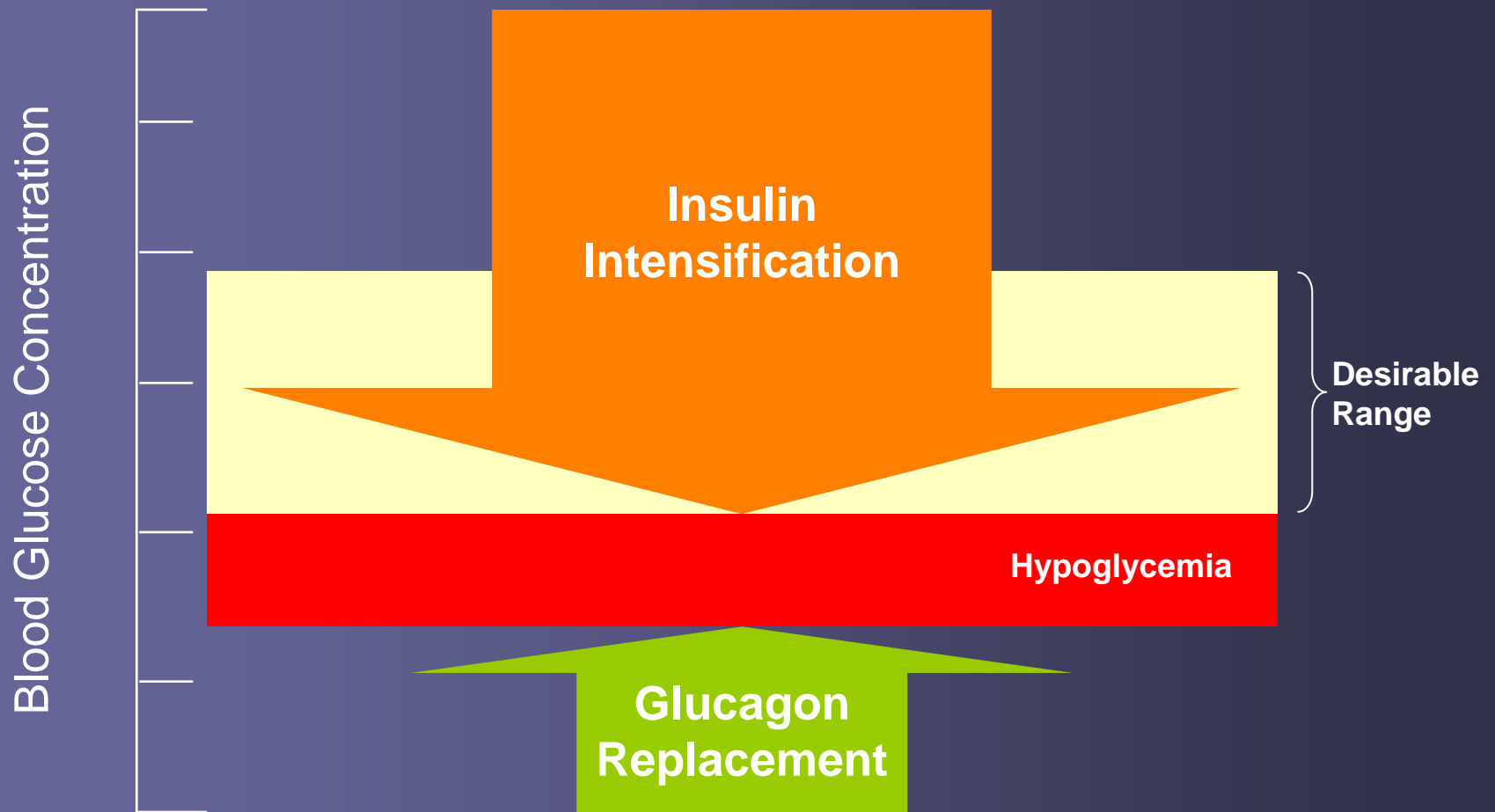
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# Rationale for Very Low Dose Glucagon (VLDG)

## Type 1 Diabetes Mellitus



# Hypoglycemia in type 1 diabetic patients

Key factor limiting glucose control

Intensive insulin therapy is the gold standard

- Reduces vascular complications up to 70%

Intensive insulin therapy carries significant risks

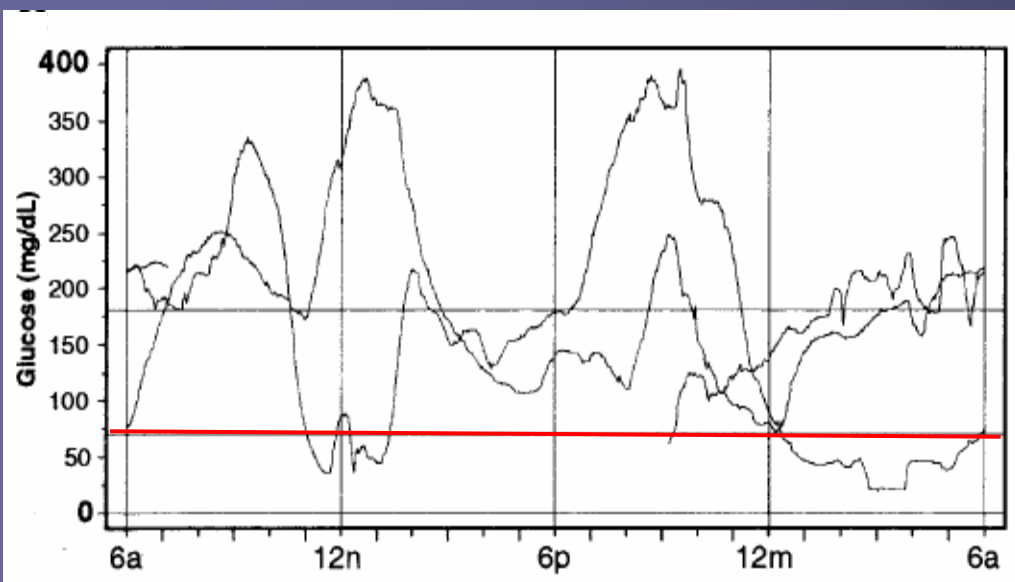
- *3x increased risk* of severe hypoglycemia
- More than 50% of episodes occur at night

Fear of hypoglycemia is a major factor limiting insulin intensification

# Background incidence of hypoglycemia

## Type 1 diabetes, 2005

60 subjects with T1DM were continuously monitored for an average of 12 days. Hypoglycemia was defined as a glucose of  $<70$  mg/dL for  $\geq 10$  minutes.



The average patient with T1DM had 2.1 episodes daily, lasting 1.1 hours (total of 2.3 hours/day).

60% of episodes were nocturnal

# Testing the hypothesis

Would replacement with VLDG decrease hypoglycemia?

Three clinical trials have now been completed in 37 subjects with T1DM.

- All subjects were  $\geq 18$  years old treated with CSII, had DM for  $\geq 10$  years and HbA1c  $\leq 8.0$

In these studies VLDG was administered as a SC infusion. Subjects generally served as their own controls.

- 20-fold dose range studied
- >130 infusions administered, ranging from 2 to 12 hours in duration

Isley, W., et al , 66<sup>th</sup> Scientific Sessions, ADA, 2006

Edelman, S.V. et al., 42<sup>nd</sup> Annual Meeting of EASD, 2006

Welles, B et al., 6<sup>th</sup> Annual Diabetes Technology Meeting, 2006

# Testing the hypothesis

## Preliminary results

- Confirmed that subjects with longstanding T1DM have a deficient glucagon response in the face of hypoglycemia
- Identified a range of doses that will bring glucagon levels into the mid to high physiological range
- Demonstrated that VLDG can delay or prevent insulin-induced hypoglycemia
- Demonstrated that VLDG can decrease the number of hypoglycemic episodes and their duration

# Single center pharmacology study

DIO-103

## Objectives

- Assess safety and tolerability of 3 different doses of VLDG administered nocturnally for 6, 9 or 12 hours
- Obtain pharmacokinetic profile of VLDG
- Assess pharmacodynamic effects: glucose AUC, excursions, incidence of hypoglycemia\*, time spent with hypoglycemia, FBG

Enable dose selection for future studies to be performed under fully outpatient conditions and under conditions of insulin intensification

Determine duration of action needed for development of an extended release formulation

\*Definition of hypoglycemia is glucose  $\leq 70$  mg/dL

# DIO -103 study design

Single center, single blind study, n=6

**Screening** – T1DM >10 yrs, CSII, HbA1c  $\leq$  8.0

**2 week Run-in-Period** - insulin adjustments based on weekly 72 hr CGM and SBMG

**Glucagon Assessment Period** – weekly 72 hour CMG with 3 consecutive nocturnal infusions; no bedtime snack

**Latin square randomization**

**Total control infusions = 6**

**Total VLDG infusions = 54**

	6 hrs	9 hrs	12 hrs
control			√
2 ng/kg/min	√	√	√
4 ng/kg/min	√	√	√
8 ng/kg/min	√	√	√

# Demographics

n = 6

Baseline Characteristic	Mean
Age (years) (range)	46.2 (29 – 51)
Gender F / M (% / %)	4 / 2 (67 / 33)
Duration of T1DM (years) (range)	27.8 (12 to 39)
HbA1c (%) (range)	6.52 (6.1 to 7.1)

# Safety

All glucose levels <50 mg/dL and >300 mg/dL were captured as an adverse event and treated as per protocol.

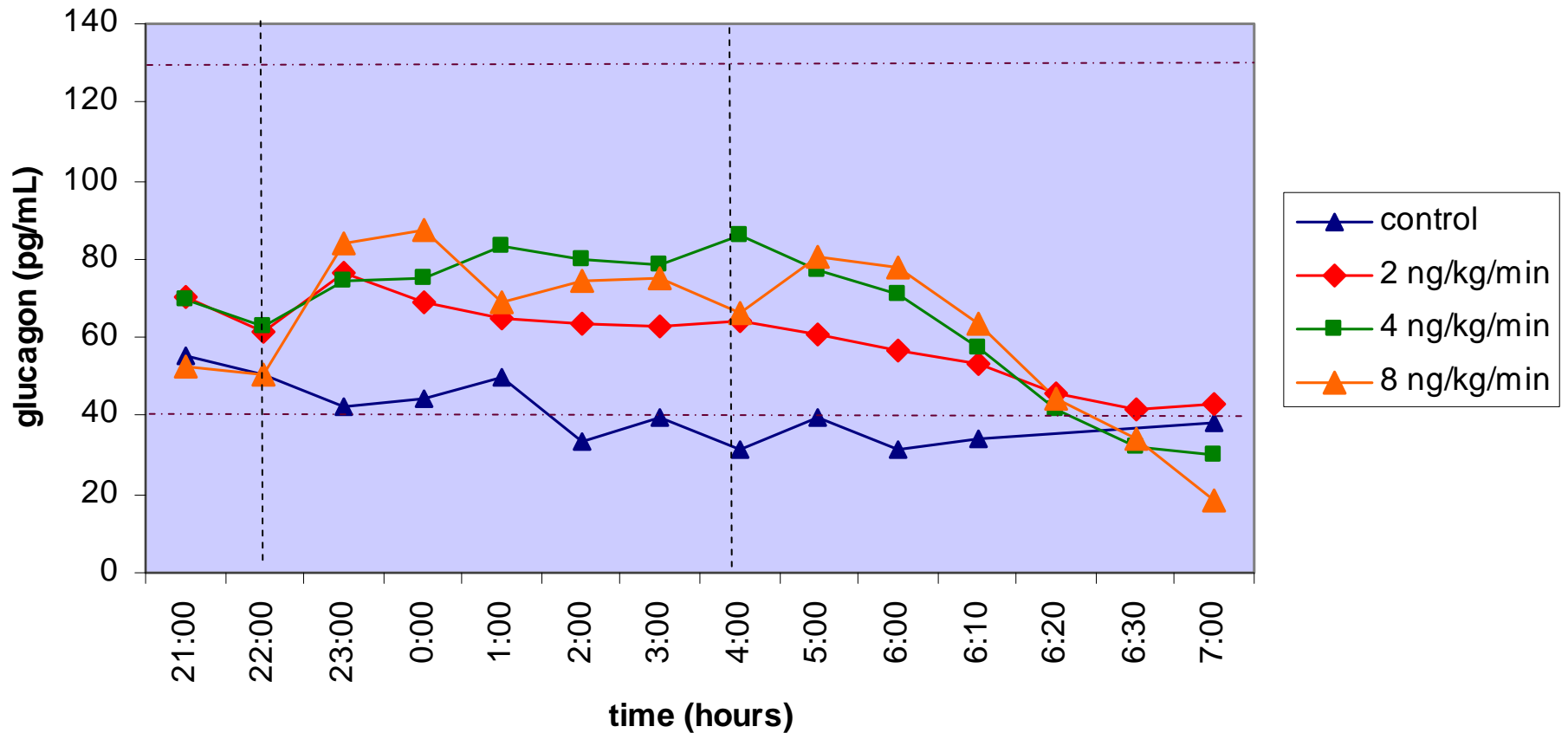
During the infusions, the following events occurred:

- Subject 06 had 6 episodes of hypoglycemia, 2 on control infusion
- Subjects 02 and 04 each had 1 episode of hypoglycemia
- Subject 05 had one episode of hyperglycemia

No drug related adverse events of any kind were reported.

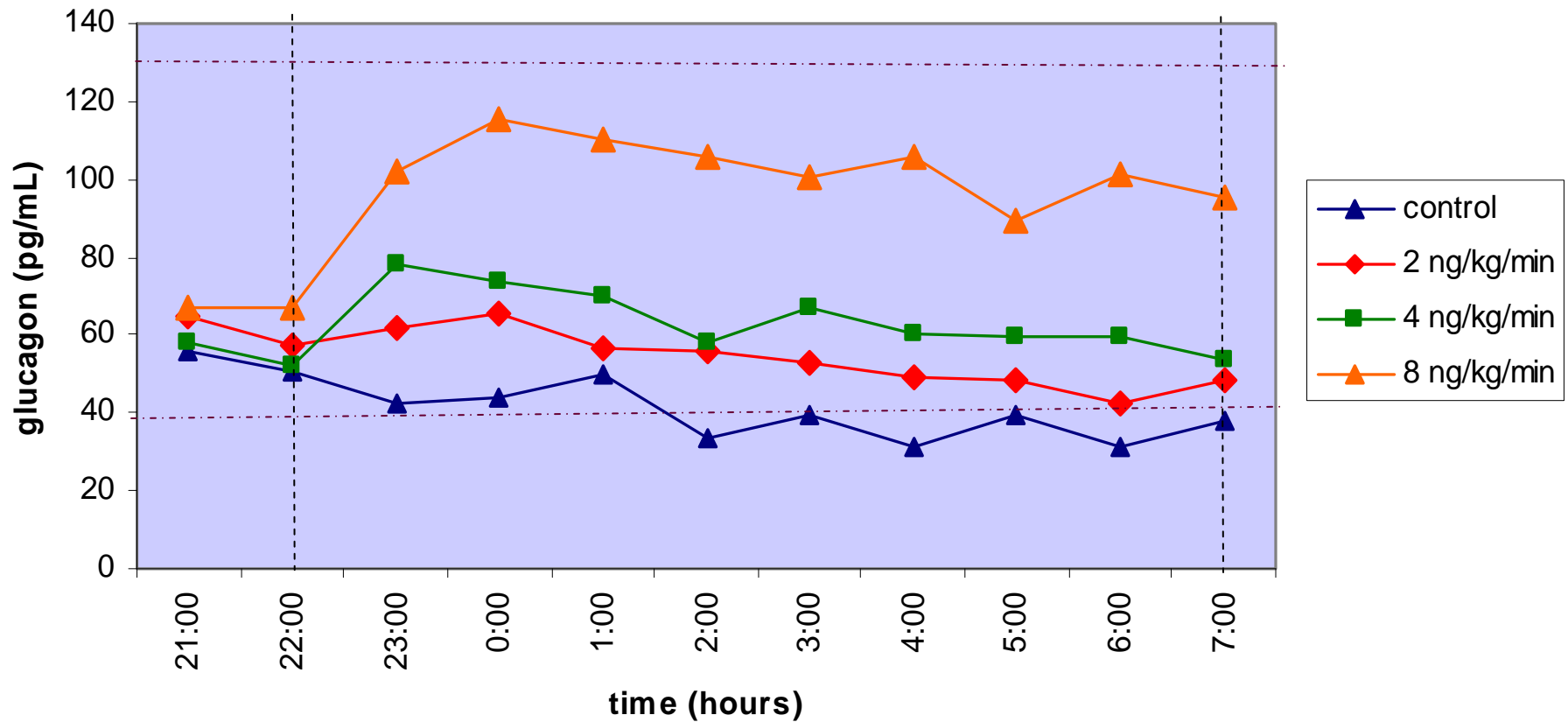
# Glucagon levels during 6 hour infusions

n=6 at each dose level



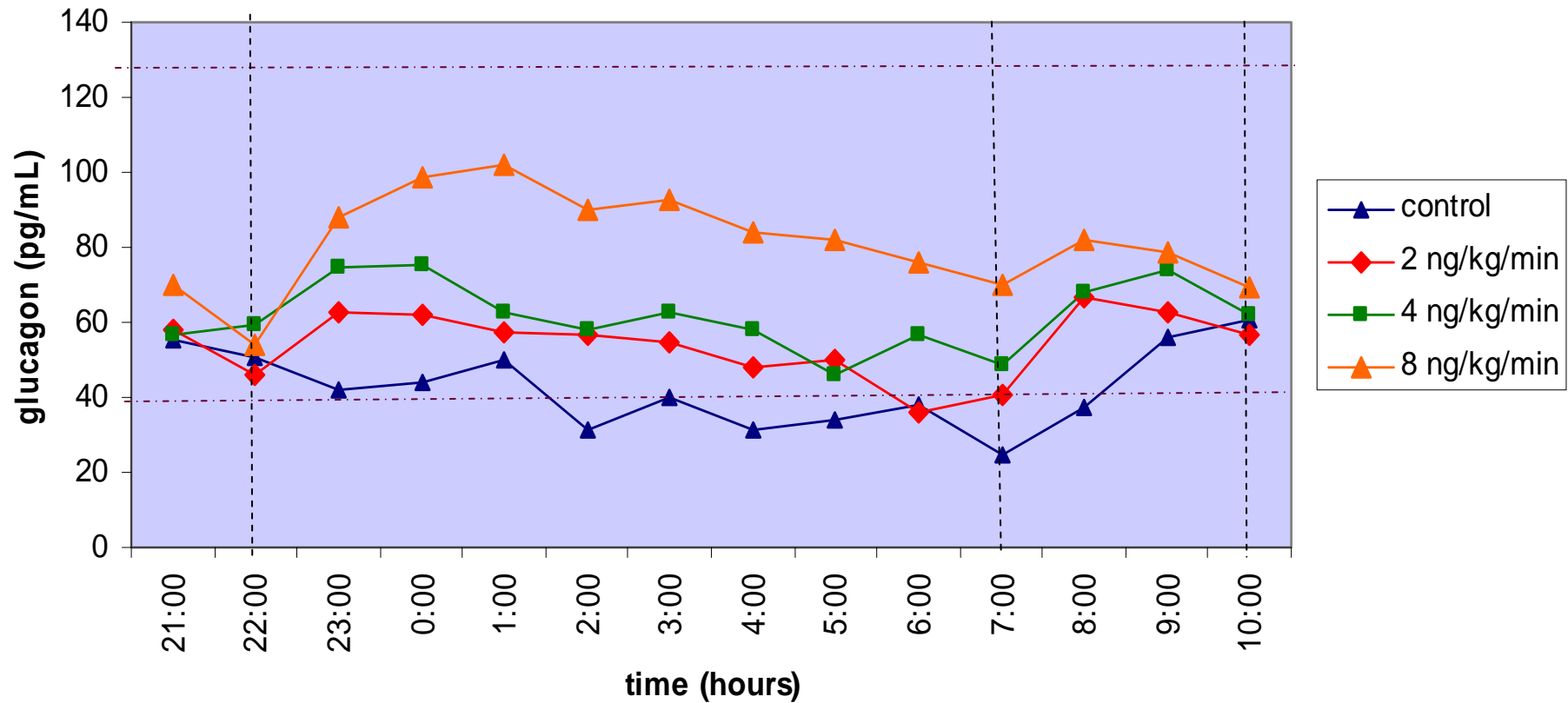
# Glucagon levels during 9-hour infusions

n=6 at each dose level



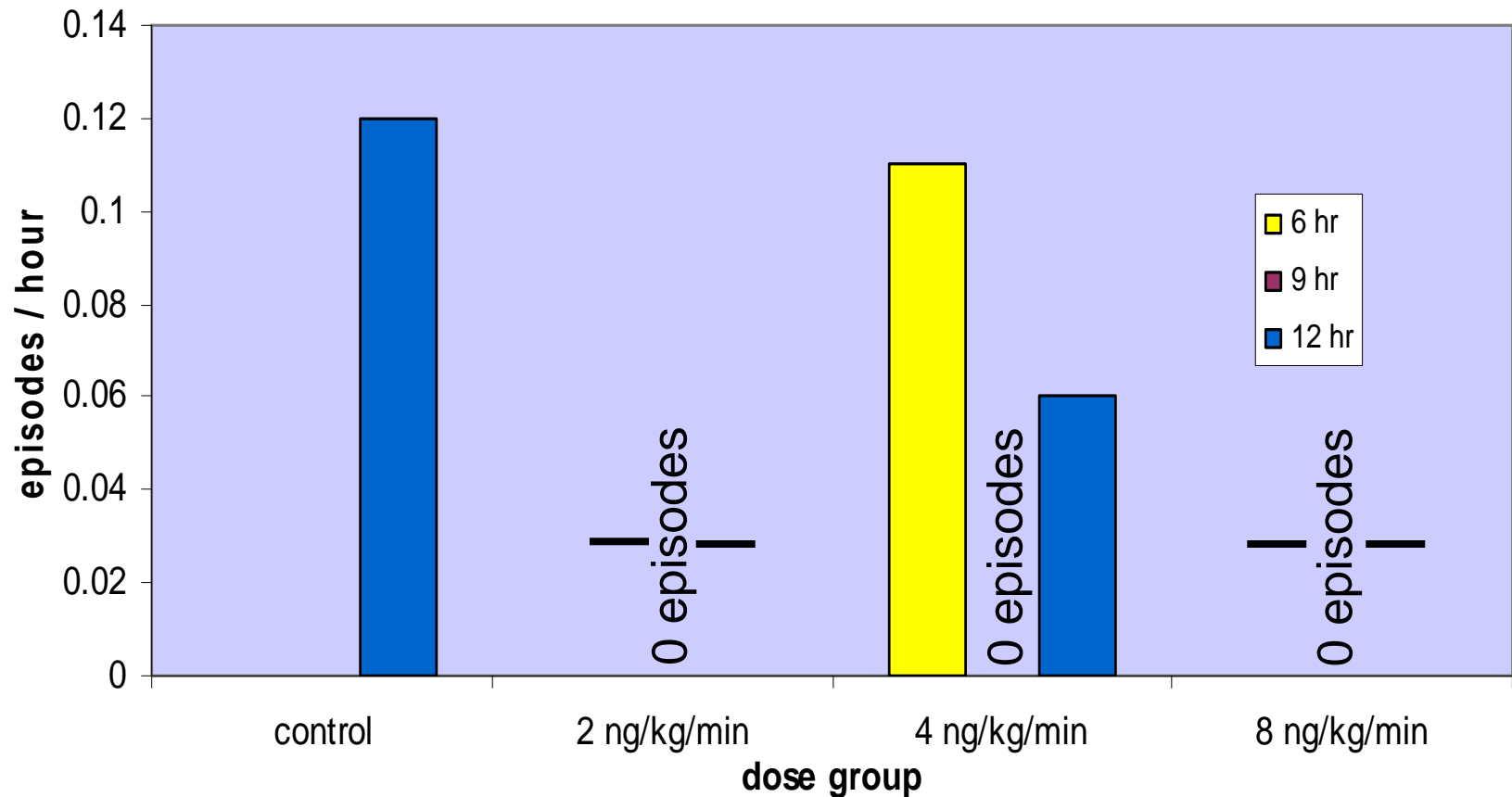
# Glucagon levels during 12-hour infusions

n=6 at each dose level



# Episodes / hour of nocturnal hypoglycemia

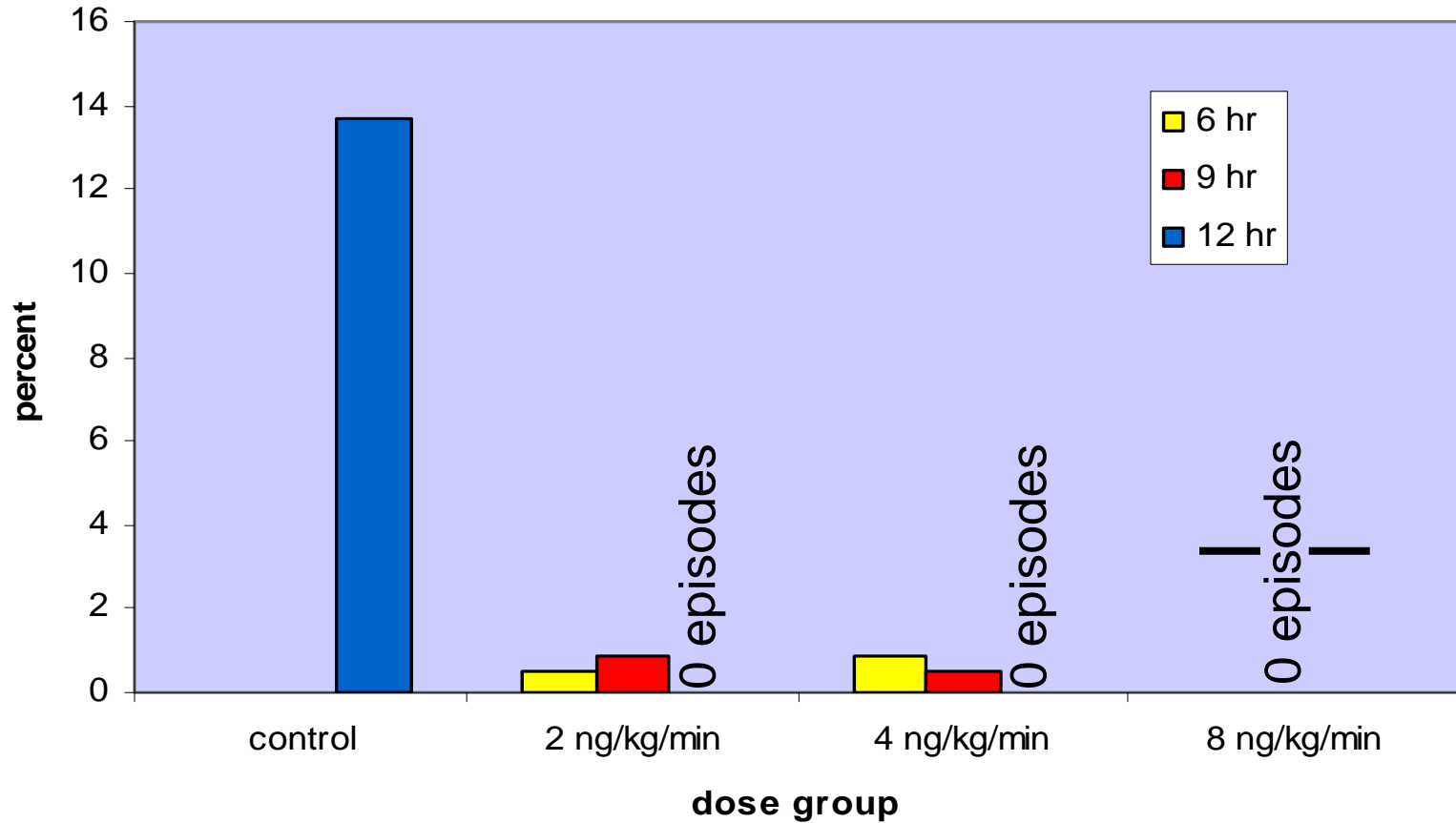
Median number 2200 to 0700 hours



An episode was defined as lasting  $\geq 10$  minutes

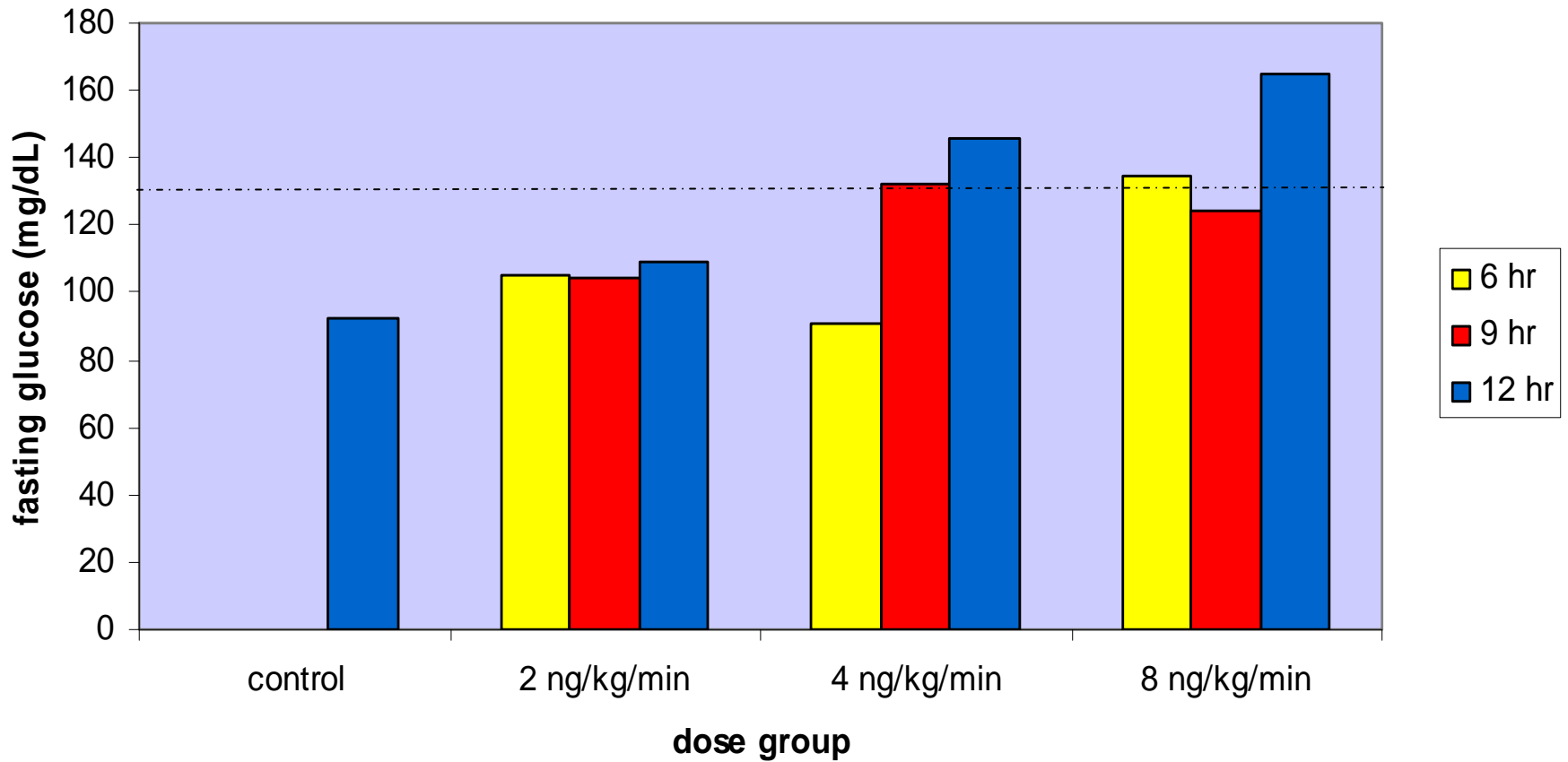
# Duration of nocturnal hypoglycemia

Median % time between 2200 and 0700 hours



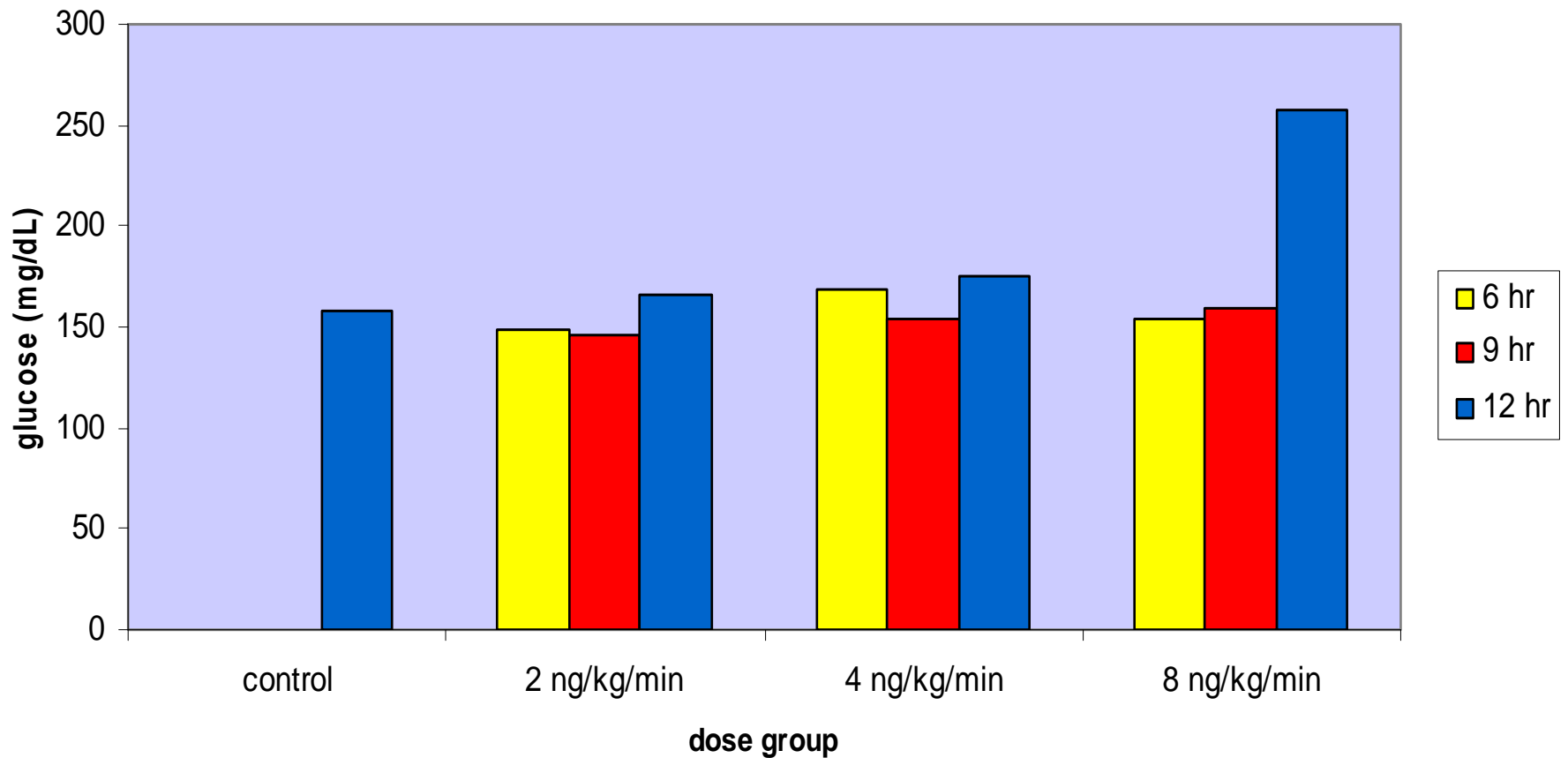
# Fasting glucose

Median level at 0700 hours



# Peak glucose

Median during 2200 and 0700 hours



# Summary and conclusions

- Nocturnal infusion of VLDG in doses of 2 to 8 ng/kg/min resulted in glucagon levels in the low to mid-physiological range
- No safety signal was detected
- The amount and duration of hypoglycemia detected while on control infusion was comparable to that reported in the literature
- Treatment with VLDG appeared to lower the duration of nocturnal hypoglycemia.

# Summary and conclusions (cont.)

- The improvements in nocturnal hypoglycemia must be balanced with overall glycemic control.
- Doses of 4 to 8 ng/kg/min infused for between 6 and 9 hours may maximize ability to prevent hypoglycemia without causing excessively high glucose levels.
- A larger trial of longer duration in patients undergoing insulin intensification is planned. A single nightly injection of an extended release formulation will be administered.

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