Ultradian variation of blood glucose in ICU patients receiving insulin infusions


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INTRODUCTION:
Treatment of hyperglycemia with an insulin infusion protocol (IIP) has improved outcomes in intensive care unit (ICU) patients [1, 2]. While morning glucose has been reported, little is known about variation of blood glucose for patients on IIP causing uncertainty about the optimal treatment of ICU patients [3-5]. Our objectives were to test if morning glucose represented whole day glucose and to determine whether glucose varied over the course of the day. In ICU patients receiving IIP, glucose was lower in the early morning, correlated poorly with average glucose, and varied with an ultradian pattern.

METHODS:
In this prospective single-center observational study in the ICUs of a university tertiary care hospital we recorded all glucose measurements in two cohorts of ICU patients receiving IIP targeting blood glucose 80-110 mg/dL. Supplementary details are available in the on-line appendix (available at http://care.diabetesjournals.org).

RESULTS:
Between 5/20/06-8/6/06, 141 ICU patients were treated with IIP and 8 of these received insulin for two periods resulting in 149 patient episodes. The average duration of insulin use for an episode was 115±9 hours (range 5-604). Forty-one percent of the glucose measurements (n=11,670) made during this period were in the target range (80-110 mg/dL; Fig.1A). In preliminary data acquired between May 2004 and June 2005 the proportion of measurements in the target range increased initially and then stabilized (Fig.1). Twenty-six percent of the patients experienced at least one glucose value <60 mg/dL and 2.7% had a glucose value <40 mg/dL.

The IIP was designed to control glucose within 8 hours [1] and slightly more glucose measurements beyond 8 hours (42%; n=10766) were in range (p=0.014, Fig.1B). The mean and median of this positively skewed, non-Gaussian distribution (p<0.0001: KS test) were 118.5 and 112 mg/dL respectively. The 0600 hour measurements were also positively skewed (Fig.1B; KS test, p<0.0001). At 0600 hours glucose was lower than at the remaining times (112±1.4 mg/dL (n=477) vs 119±0.3 mg/dL (n=10,364); p<0.0001) and more of the 0600 values were in the target range (47%). The correlation between 0600 glucose measurement and average glucose for the consecutive 23 hours was weak (Fig. 1C; r²=0.07, p<0.0001, n=472).

A plot of average glucose with time of day from the 149 patient episodes revealed an ultradian pattern (Fig.1D, open circles). Mean glucose was steady overnight with an 0700 nadir after which glucose values rose, peaking at 1100 and again at 2200 hours. Mean blood glucose values were described after 0800 hours by a sine wave with period of 10.6 hr and amplitude of 3 mg/dL. A second independent cohort of glucose measurements (n=12,922) made from 201 patient episodes between 8/30/06 and 10/31/06 confirmed the ultradian pattern (Fig.1C; solid circles). Insulin infusion rates were collected with the second cohort showing a similar partially sinusoidal ultradian pattern (Fig.1D; solid squares; hourly n=647-731) that was phase-shifted by 1.2 hours. Median and mean blood glucose values of the combined data varied similarly (Fig.1E).
CONCLUSIONS:
Interest in blood glucose control in the critically-ill increased following the demonstration that targeting normoglycemia in a surgical ICU improves outcome [1]. However, debate continues over the optimal target glucose and how to best achieve it using IIP. Our major findings are that glucose is the lowest in the morning, 0600 glucose correlates poorly with daily glucose, and glucose fluctuates with an ultradian pattern in ICU patients on IIP. Furthermore we report that only a minority of glucose values were in the target range despite established IIP use, that glucose values were not normally distributed, and that insulin use was also ultradian.

Our data illustrate complex variability in blood glucose which may complicate achievement of optimal control. The single randomized trial in which IIP improved mortality, only reported mean ± standard deviation 0600 (103±19 mg/dL) glucose values [1]. Assuming a normal distribution, we calculate that 55% of all glucose values in that study would have been in the target range [1]. We found 47% of glucose values in range at 0800 hours but only 42% if all values were considered- similar to the 22-52% reported previously [6-8]. Since glucose is lowest at 0800 (Fig.1B,C) it remains unclear what proportion of the day glucose must be in the target range to improve outcome [9, 10].

Difficulty in achieving tight glucose control has been attributed to patient instability and variability of glucose intake [11] however; the ultradian pattern of blood glucose demonstrated here may also explain some of the difficulty. Because a mean glucose rise of 20 mg/dL increases mortality by 30% [12], even the modest peak to trough ultradian variation (~12 mg/dL; Fig.1C,D) we observed may significantly impact mortality and morbidity.

This study cannot determine the mechanism of the ultradian variation. The falls in glucose from peaks at ~1100 and 2300 hours despite no increase in insulin indicate a decreased insulin requirement, possibly reflecting increasing insulin sensitivity or decreased glucose load. Likewise the rise in glucose at 0900 and 2100 hours occurred with little change in insulin. Nursing shift changes (Fig.1C; broken vertical lines), changes in nutritional support, and medication administration are factors that may influence these observations. Interestingly, patients with type 2 diabetes have a similar ultradian pattern of blood glucose [13]. Recently, a circadian pattern of glucose values was observed in Australian ICU patients when glucose values were pooled over four hour periods. The apparently lower frequency of glucose variation may reflect the lower sampling rate or the impact of low use of IIP in Australian ICUs [14].

While we included medical, cardiac, neurosurgical, trauma, general surgical ICU patients, further studies are required to determine if the findings may be extended to other patient populations at other institutions.

In conclusion, glucose is lower in the morning than during the remainder of the day. Blood glucose varies during the day in ICU patients receiving insulin. Consideration of this ultradian variation when treating hyperglycemia may help reduce the frequency of hypo- and hyperglycemic episodes.

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REFERENCES


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**FIGURE LEGEND**

**Figure 1.** Blood glucose variation in ICU patients receiving IIP. A, category plot of the percentage of measurements in described blood glucose ranges in ICU patients receiving IIP for hyperglycemia. The measurements (n= 655, 1374, 2508, 1547, and 11707) were collected over two week periods in May 2004, August 2004, November 2004, and June 2005, and between 5/20/06 and 8/6/06 from 19, 38, 57, 31, and 141 patients respectively. B, The histograms show blood glucose values after 8 hours of IIP in 141 patients pooled (top trace), at 0600 hours (bottom trace), and pooled data excluding 0600 hours (middle trace). All data is positively skewed. The target range is described by vertical broken lines and the Gaussian functions fit to all data up to modal value are given by the unbroken curves. The fitted Gaussian curves have mean and standard deviations of 100±16, 95±15, and 100±16 mg/dL for upper, middle and lower histograms respectively. C, plot of 0600 glucose (n=472) versus average measured glucose for consecutive 23 hours shows low correlation ($r^2=0.07$). D, time averaged data from the 149 patient episodes shows a ultradian variation in the mean glucose (upper plot, open circles; hourly n= 407-493) against time. Glucose peaked at 1100 and 2200 hours and was described from 0800 hours by a sine wave with a mean value of 120 mg/dL, an amplitude of 3 mg/dL, and a period of 10.6 hr. The mean glucose of the second cohort of measurements plotted against time also displayed a ultradian pattern (solid circles; hourly n=482-624) and was described from 0800 hours by a sine wave with a mean value of 120 mg/dL, an amplitude of 3 mg/dL, and a period of 10.1 hr. Insulin infusion rates, collected contemporaneously with the second cohort, were also ultradian and fitted to a sine wave from 0800 hours which had a mean value of 3.4 IU/hr, an amplitude of 0.09 IU/hr, a period of 10.4 hr and a phase-delay of 1.2 hours (solid squares; hourly n=647-731). E, Plots of median (solid squares) and mean (open circles) blood glucose versus time of the pooled data from the two cohorts showed similar ultradian variation. This graph shows combined data from 350 patient episodes and each point represents between 889 and 1092 measurements. The sine waves fitted to median and mean data have mean values of 113 and 120 mg/dL, amplitudes of 2.3 and 3.0 mg/dL, and periods of 10.7 and 10.3 hours, respectively.
Figure 1

Ultradian glucose variation in ICU patients

A

B

C

D

E