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Optimal dose and duration of glucose administration during fasting period preceding surgery in rabbits

Hideki Kamuro[1,2], Naruyasu Komorita[1], and Ryo Ogawa[3]

[1]Osaka Laboratories, Pharmaceutical Research Division, Yoshitomi Pharmaceutical Industries, 2-25-1 Shodai-Ohtani, Hirakata, Osaka 573-1153, Japan
[2]Department of Pharmacology and [3]Department of Anesthesiology, Nippon Medical School, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8602, Japan

Abstract

Purpose. We examined preoperative glucose administration to establish what dose and cutoff point were optimal for suppression of lipolysis and prevention of hypo- or hyperglycemia.

Methods. Rabbits were preoperatively fasted and simultaneously received glucose at a constant rate of 0, 0.1, 0.2, 0.3, or 0.4 g·kg^{-1}·h^{-1} in fluid infusion for 3 h. Plasma glucose, immunoreactive insulin activity, nonesterified fatty acids, and ketone bodies were measured 0, 1.5, 3 and 4 h after the start of infusion, and hepatic glycogen content was assessed 1 h after cessation of infusion.

Results. Fluid infusion without glucose decreased plasma glucose. Glucose administration at more than 0.2 g·kg^{-1}·h^{-1} caused hyperglycemia (>200 mg·dl^{-1}) in the infusion period; the differences were significant compared with the value at zero time or in the 0 g·kg^{-1}·h^{-1} group ($P < 0.01$). The highest dose also raised plasma immunoreactive insulin activity, which was significantly higher than in the 0 g·kg^{-1}·h^{-1} group ($P < 0.01$) at the midpoint of the infusion period. Plasma nonesterified fatty acids increased in all groups. The changes were, however, significantly reduced in both the 0.3 and 0.4 g·kg^{-1}·h^{-1} groups ($P < 0.05$ and $P < 0.01$, respectively) by the end of infusion. All these effects of glucose supply, including suppression of lipolysis, disappeared regardless of dose within 1 h after the cessation of infusion.

Conclusion. These results suggest that the optimal dose for preoperative glucose infusion, in order to preserve carbohydrate or fat metabolism, is 0.1–0.2 or 0.3 g·kg^{-1}·h^{-1}, respectively, and indicate that administration should not be discontinued until the start of surgery.

Key words: Preoperation, Glucose supply, Plasma glucose, Plasma nonesterified fatty acids

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Introduction

Glucose infusions are widely used in clinical practice, and many patients are given glucose as an energy substrate perioperatively to counteract fasting. There has been considerable controversy regarding glucose administration during the intraoperative period, since glucose easily exacerbates carbon dioxide production and intracellular lactic acidosis caused by surgical stress [1]. However, in many circumstances, intraoperative glucose administration may be advantageous to inhibit catabolism and improve fat and carbohydrate metabolism [2–4]. Our previous animal study also showed that intraoperative glucose supplementation is effective in preventing hepatic glycogen depletion, and indicated further that the optimal dose to avoid glucose overloading was 0.1–0.2 g·kg^{-1}·h^{-1} [5]. These findings confirm the necessity of intraoperative glucose infusion in clinical settings.

In the preoperative setting, meanwhile, risks such as carbon dioxide production originating from surgical stress can be ruled out. Moreover, preoperative administration may be more rational for the prevention of accelerated catabolism during surgery than intraoperative administration. Infants and women, in particular, tend to fall into hypoglycemia as their hepatic glycogen runs low [1,6]. Preoperative glucose administration may therefore be necessary in some and possibly in many fasting patients to maintain energy metabolism. Some clinical studies have suggested that preoperative infusion of glucose is useful to maintain energy metabolism during the fasting state [7,8]. However, there is no consistent agreement as to the appropriate dose, nor is it clear how long glucose administration should be continued.

This experimental study in rabbits, whose glucose tolerance is considered to be nearly the same as that of humans [9], was undertaken to find the optimal dose for preoperative glucose infusion, and to examine whether

infusion should be continued until surgery, with particular reference to catabolic inhibition in the anesthesia induction stage.

Materials and methods

Forty-six male Japanese white rabbits, weighing between 2.35 and 2.80 kg and aged about 3 months, were randomly assigned to five groups of 8–11 animals each. The animals were allowed access to food and water until the start of glucose and fluid infusion, and then they were fasted for the experimental period lasting 4 h. They were restrained and locally anesthetized at the right external femoral portion with 30–40 mg lidocaine. A polyvinyl chloride cannula filled with heparinized saline (ϕ 1.5 mm) was then inserted and remained in the femoral artery for drawing of blood samples at each testing point. Fluid infusion was carried out for 3 h at a constant flow rate of 20 ml·kg^{-1}·h^{-1} in the form of an ear intravenous drip injection of Ringer's acetate solution either without glucose (0%) or containing 0.5, 1.0, 1.5, or 2.0 w/v% of glucose, which corresponded to the following glucose doses: 0, 0.1, 0.2, 0.3, and 0.4 g·kg^{-1}·h^{-1}. The start of the infusion was designated zero time.

One milliliter of arterial blood was withdrawn from the femoral artery into a heparinized syringe at 0, 1.5, 3, and 4 h. Blood samples were kept on ice, after which plasma was obtained by centrifugation (3000 rpm for 15 min) at 4°C and frozen (−20°C) until analysis. Immediately after the last blood sampling, the rabbits were anesthetized with 50 mg·kg^{-1} sodium pentobarbital by bolus injection into the auricularis vein, subjected to laparotomy, and sacrificed by bleeding. The liver was obtained from each animal for the measurement of glycogen content.

All of the biochemical analyses described below were performed in duplicate. Plasma glucose concentrations were measured enzymatically by the glucose-oxidase method using a commercially available kit (Glucose B-Test: Wako Pure Chemical Co., Tokyo, Japan). Plasma immunoreactive insulin activities were determined by enzyme immunoassay using a commercially available kit (Insulin-EIA Test: Sanyo Kasei Co., Kyoto, Japan). Plasma nonesterified fatty acids and ketone bodies (acetoacetic acids and β-hydroxybutyric acids) were measured enzymatically using a commercially available kit (NEFA C-Test: Wako Pure Chemical Co., Ketone Test: Sanwa Chemical Co., Nagoya, Japan). Hepatic glycogen content was determined by a method previously reported [5]. The frozen liver samples and the purified glycogen (Wako) used as standards were solubilized with 30% (w/v) KOH by boiling at 100°C for 30 min. Glycogen was precipitated by the addition of 99% ethanol and hydrolyzed by 2 N H_2SO_4 in a boiling water bath for 2 h. After 2 N NaOH neutralization, the amount of glycogen was calculated from the glucose value determined in the hydrolyzed glycogen sample using the method cited above.

All values are expressed as means ± SD. Statistical significance was assessed using analysis of variance (one-way ANOVA) and multiple comparison (Dunnett) tests between the 0 g·kg^{-1}·h^{-1} group and the other groups. The values after the start of infusion and at zero time were also compared by repeated one-way ANOVA and Dunnett tests. Probability values less than 0.05 were considered significant.

Results

Figure 1 shows the time course of change in plasma glucose concentrations. Plasma glucose decreased only in the group receiving a glucose-free infusion (3 h after start of infusion; $P < 0.01$), which was similar to the change observed in fasting animals not receiving infusions in our preliminary study. The plasma glucose level did not differ from the values at zero time in the 0.1 and 0.2 g·kg^{-1}·h^{-1} groups. However, glucose administration at a dose of more than 0.2 g·kg^{-1}·h^{-1} caused hyperglycemia (>200 mg·dl^{-1}) frequently during infusion, with significant differences compared with the value at zero time or the dose of 0 g·kg^{-1}·h^{-1} ($P < 0.01$). One hour after the end of infusion, however, plasma glucose

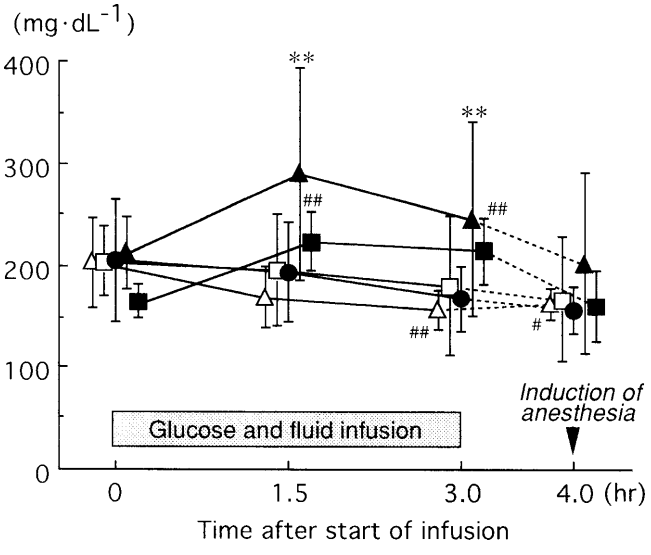

Fig. 1. Time course of change in plasma glucose concentrations. **Significantly different from 0 g·kg^{-1}·h^{-1} group, $P < 0.01$. #,##Significantly different from the value at zero time, $P < 0.05$ and $P < 0.01$, respectively. Rates of infusion of glucose (g·kg^{-1}·h^{-1}): *open triangles*, 0 ($n = 9$); *open squares*, 0.1 ($n = 8$); *filled circles*, 0.2 ($n = 11$); *filled triangles*, 0.3 ($n = 9$); *filled squares*, 0.4 ($n = 9$)

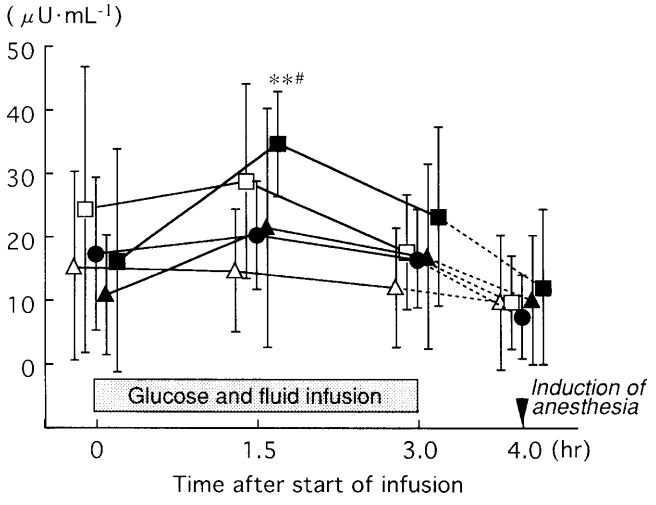

Fig. 2. Time course of change in plasma immunoreactive insulin activities. **Significantly different from $0\,g\cdot kg^{-1}\cdot h^{-1}$ group, $P < 0.01$. #Significantly different from the value at zero time, $P < 0.05$. Rates of infusion of glucose ($g\cdot kg^{-1}\cdot h^{-1}$): *open triangles*, 0 ($n = 9$); *open squares*, 0.1 ($n = 8$); *filled circles*, 0.2 ($n = 11$); *filled triangles*, 0.3 ($n = 9$); *filled squares*, 0.4 ($n = 9$)

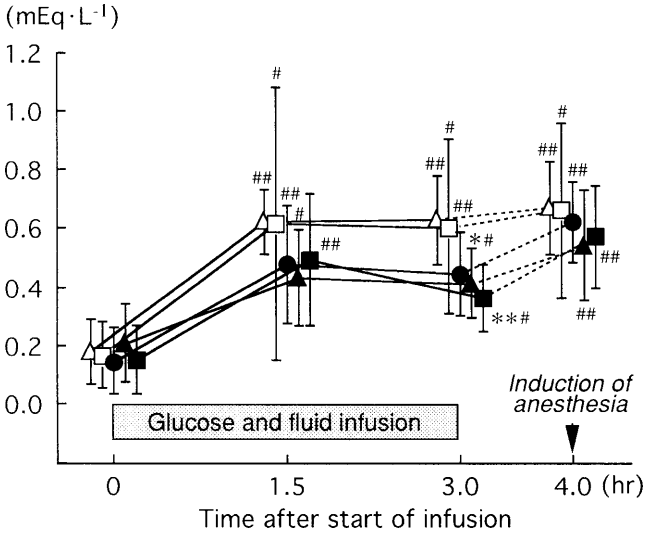

Fig. 3. Time course of change in plasma nonesterified fatty acid concentrations. *.**Significantly different from $0\,g\cdot kg^{-1}\cdot h^{-1}$ group, $P < 0.05$ and $P < 0.01$, respectively. #,##Significantly different from the value at zero time, $P < 0.05$ and $P < 0.01$, respectively. Rates of infusion of glucose ($g\cdot kg^{-1}\cdot h^{-1}$): *open triangles*, 0 ($n = 9$); *open squares*, 0.1 ($n = 8$); *filled circles*, 0.2 ($n = 11$); *filled triangles*, 0.3 ($n = 9$); *filled squares*, 0.4 ($n = 9$)

decreased in all groups receiving glucose and reached low levels similar to those in the $0\,g\cdot kg^{-1}\cdot h^{-1}$ group.

Figure 2 illustrates the time course of changes in plasma immunoreactive insulin concentration. The plasma immunoreactive insulin level did not change in the groups given doses of glucose of $0.3\,g\cdot kg^{-1}\cdot h^{-1}$ or lower. In the $0.4\,g\cdot kg^{-1}\cdot h^{-1}$ group, the values at 1.5 h were significantly greater than those at zero time ($P < 0.05$) or those in the $0\,g\cdot kg^{-1}\cdot h^{-1}$ group ($P < 0.01$). However, insulin activity in this group recovered before the cessation of infusion.

The time course of changes in plasma nonesterified fatty acid levels is shown in Fig. 3. The concentrations rose in all groups after the start of infusion during fasting, although the levels in the 0.3 and $0.4\,g\cdot kg^{-1}\cdot h^{-1}$ groups were significantly lower than those in the $0\,g\cdot kg^{-1}\cdot h^{-1}$ group at 3 h ($P < 0.05$ and $P < 0.01$, respectively). However, the values for nonesterified fatty acids tended to increase after the end of infusion, particularly in the groups receiving high doses of glucose, and eventually reached a similar level in all groups.

As shown in Fig. 4, the plasma levels of total ketone bodies (and both acetoacetic acids and β-hydroxybutyric acids) did not change during infusion, though slight increases were observed after the end of infusion in all groups.

The glycogen content of the liver 1 h after the end of infusion was around $40\,mg\cdot g^{-1}$, regardless of the dose of glucose, with no significant differences among groups (Fig. 5).

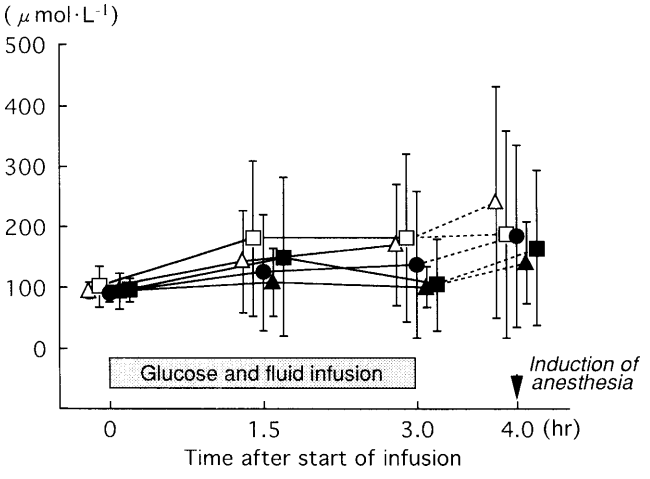

Fig. 4. Time course of change in plasma total ketone body concentrations. Rates of infusion of glucose ($g\cdot kg^{-1}\cdot h^{-1}$): *open triangles*, 0 ($n = 9$); *open squares*, 0.1 ($n = 8$); *filled circles*, 0.2 ($n = 11$); *filled triangles*, 0.3 ($n = 9$); *filled squares*, 0.4 ($n = 9$)

Discussion

The individual metabolic pathways of glucose and fat have been well known for a long time, and many investigators have reported on their reciprocal relation. The level of glucose in the blood is regulated by several organs (mainly the liver and pancreas) and by periph-

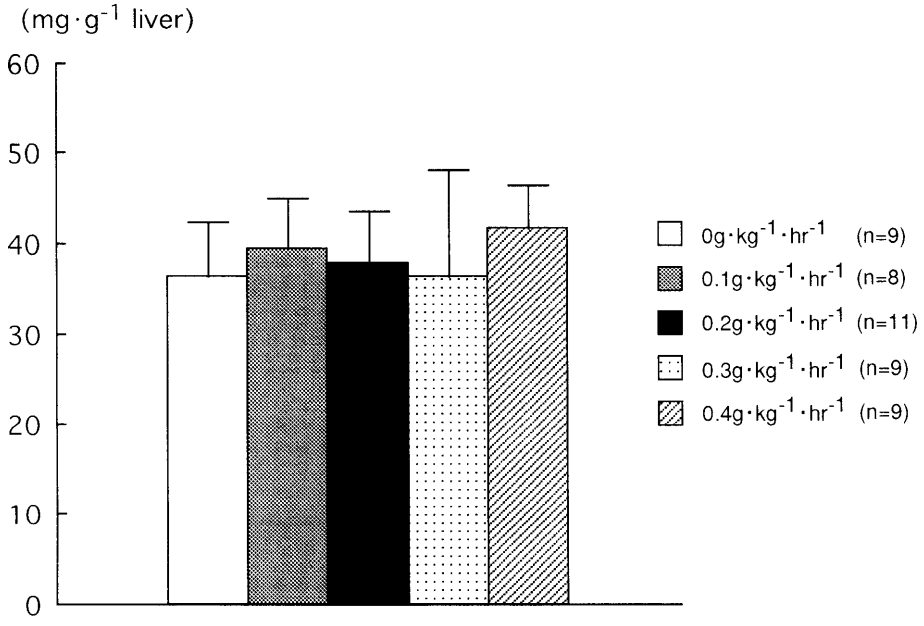

Fig. 5. Glycogen content in liver 1 h after cessation of infusion

eral glucose uptake. In intravenous administration of concentrated glucose solution, the capacity for glucose metabolism is generally held to be up to $0.5\,g\cdot kg^{-1}\cdot h^{-1}$ in a normal state [10]. On the other hand, it is also known that the glucose tolerance limit varies depending on physiological conditions. For example, it is often low during trauma, surgery, and other states. In a previous study we confirmed that alterations can be induced in the glucose tolerance limit by demonstrating that administration of no glucose caused an intraoperative increase in plasma glucose level [5], and in the present study by demonstrating that plasma glucose level does not change with infusion of $0.2\,g\cdot kg^{-1}\cdot h^{-1}$ glucose or less.

If patients do not receive glucose during surgery, the blood concentration of nonesterified fatty acids rises from lipolysis in the adipose tissue, which results in hyperketonemia and ketoacidosis owing to the acceleration of β-oxidation of the nonesterified fatty acids [11]. These increases are caused by the compensatory utilization of fat and by abnormal energy metabolism. Clinical practice has therefore attempted to normalize the blood levels of nonesterified fatty acids and ketone bodies. In the present study, we sought to establish the glucose dose optimal for maintenance of normal carbohydrate and fat metabolism during the period of fasting before surgery. We simultaneously attempted to establish until what point administration should be continued. Since we gave priority to preventing rather than correcting metabolic disorders, animals were given free access to food and water until the start of glucose infusion.

Regarding the rate of administration, our results suggested that glucose infusion at a rate of 0.1–$0.2\,g\cdot kg^{-1}\cdot h^{-1}$ is appropriate in the preoperative setting, where importance is attached to preserving carbohydrate metabolism, since infusion of fluid without glucose decreased plasma glucose, and administration at a rate of $0.3\,g\cdot kg^{-1}\cdot h^{-1}$ or more caused hyperglycemia. When maintenance of fat metabolism is a primary purpose, however, an adequate rate of glucose administration is $0.3\,g\cdot kg^{-1}\cdot h^{-1}$, since this rate, as well as the maximum dose ($0.4\,g\cdot kg^{-1}\cdot h^{-1}$), was effective in suppressing increases in plasma levels of nonesterified fatty acids . The mechanism of this potential benefit was considered to be as described previously [11], that is, that glucose administration, not only in itself but also through insulin release, suppresses lipolysis by lipase. Our hypothesis that preventing metabolic disorders would be easier than correcting them was confirmed by the finding that glucose at a rate of $25\,g\cdot h^{-1}$ (approximately $0.4–0.5\,g\cdot kg^{-1}\cdot h^{-1}$) was necessary during surgery to decrease plasma levels of nonesterified fatty acids that were elevated before the surgery [12]. On the other hand, plasma levels of total ketone bodies scarcely changed during the infusion period, even without glucose supply, and there was no obvious correlation between plasma total ketone body concentration and glucose dose. It has been suggested that, in the glucose–fatty acids–ketone body cycle, ketone bodies (especially β-hydroxybutyric acids) are sensitive to and important indicators of carbohydrate and fat metabolism [11,13]. However, the increase in plasma ketone bodies is delayed compared with the increase in nonesterified fatty

acids, since ketone bodies are endogenously produced through increase in nonesterified fatty acids. We therefore suspected that the plasma concentration of nonesterified fatty acids was a better short-term indicator of disorder in carbohydrate and fat metabolism.

The hepatic glycogen content in all groups was the same, regardless of glucose dose; therefore, we now speculate that glycogen content does not change in the incipient fasting stage featured in this study.

In connection with the administration cutoff point, a matter of importance is the finding that the potential effect of the glucose supply disappeared even in the highest-dose group within 1 h after cessation of administration. It is well known that the increase in blood nonesterified fatty acids causes arrhythmia [14,15], which is a frequent occurrence in the induction stage of anesthesia [16], against which Collins recommends preoperative administration of fluid and glucose [17]. In principle, it should therefore be attempted to bring blood nonesterified fatty acid levels as close to normal as possible for the beginning of anesthesia. Consequently, we recommend, without citing an absolute duration, that the infusion of glucose should be continued until the induction of anesthesia. Based on observations from this study and from our previous study on the necessity of intraoperative glucose infusion, it seems logical to sustain glucose administration throughout the pre- and intraoperative period as a form of perioperative infusion therapy.

The tolerance limit of normal rabbits for intravenous glucose infusion is below $0.85\,g{\cdot}kg^{-1}{\cdot}h^{-1}$, nearly the same as the value for humans [9]. Consequently, if the results of this experimental study were extrapolated to clinical application, the optimal dose of preoperative glucose required to preserve plasma glucose level is judged to be $0.1–0.2\,g{\cdot}kg^{-1}{\cdot}h^{-1}$, with an increase up to $0.3\,g{\cdot}kg^{-1}{\cdot}h^{-1}$ if necessary in order to suppress lipolysis. Furthermore, it is suggested that glucose administration should be continued until the induction of anesthesia.

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