J Anesth (2005) 19:277–281
DOI 10.1007/s00540-005-0341-1

Journal of
Anesthesia

Insulin secretion and glucose utilization are impaired under general anesthesia with sevoflurane as well as isoflurane in a concentration-independent manner

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Abstract
Purpose. The dose-dependent effects of sevoflurane and isoflurane anesthesia on glucose tolerance were compared in humans.
Methods. A prospective, randomized clinical study was conducted in 30 patients. The 30 patients were divided randomly into three sevoflurane anesthesia groups (0.5, 1.0, and 1.5 minimum alveolar concentration [MAC]) and three isoflurane anesthesia groups (0.5, 1.0, and 1.5 MAC). Induction of anesthesia was accomplished by inhalation of the volatile agent and nitrous oxide. After induction, anesthesia was maintained at the designated MAC for 15 min without surgical stimulation. The intravenous glucose tolerance test (IVGTT) was performed in these 30 patients while they were under general anesthesia and again several days after surgery in 5 of these patients while they were awake, as a control.
Results. The insulinogenic index (change in concentration of immunoreactive insulin/change in glucose concentration), the acute insulin response, and rates of glucose disappearance were significantly lower in all anesthesia groups than in the control group. However, the insulinogenic index, acute insulin response, and the glucose disappearance rate did not differ significantly among the six anesthesia groups.
Conclusion. Sevoflurane anesthesia impairs glucose tolerance to the same degree as does isoflurane anesthesia. Glucose intolerance during sevoflurane or isoflurane anesthesia is independent of agent and dosage up to 1.5 MAC.

Key words Intravenous glucose tolerance test · Sevoflurane · Isoflurane

Introduction

Both the necessity of glucose infusion during anesthesia and the effects of inhaled anesthetics on insulin secretion remain controversial. Several studies have shown that volatile anesthetics, such as halothane [1] and enflurane [2], impair glucose tolerance in dogs. A study of the effects of isoflurane in humans [3] has shown impaired insulin secretion in response to intravenous glucose administration. However, these studies did not eliminate the possible effects of surgical stimulation, which differed among the studies.

Sevoflurane is a relatively new anesthetic whose effects on insulin secretion and glucose tolerance are poorly understood. Insulin secretion and glucose tolerance during sevoflurane anesthesia have been studied in pigs [4] and in humans during surgery [5]. In addition, studies in human subjects have shown that isoflurane-nitrous oxide anesthesia has dose-independent effects on insulin secretion [6].

We hypothesized that sevoflurane would affect glucose utilization and insulin secretion in the same fashion as does isoflurane, and that the impairment of glucose metabolism by sevoflurane/isoflurane would not be dose-dependent. In this study, we examined the effects of sevoflurane anesthesia on glucose utilization and insulin secretion in response to intravenous glucose administration in human subjects in the absence of surgical stimulation.

Methods

Subjects

This study was approved by the Ethics Committee of Jikei University. Informed consent was obtained from all patients before participation in this study. The subjects were 30 patients without metabolic or endocrine disorders (American Society of Anesthesiologists' classification I or II) who were scheduled to undergo elective minor surgery (plastic or orthopedic surgery). The patients were randomly assigned to receive sevoflurane anesthesia (n = 15) and isoflurane anesthesia (n = 15).

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Received: January 24, 2005 / Accepted June 9, 2005

Table 1. Patient characteristics

		Isoflurane			Sevoflurane		
MAC	Control	0.5	1.0	1.5	0.5	1.0	1.5
n	5	5	5	5	5	5	5
Sex ratio (F/M)	2/3	4/1	3/2	4/1	5/0	4/1	4/1
Age (years)	24.6 ± 3.6	38.6 ± 10.4	29.2 ± 9.4	38.2 ± 7.6	37.8 ± 7.8	37.6 ± 10.2	33.4 ± 7.8
Weight (kg)	56.7 ± 10.1	55.6 ± 13.0	52.9 ± 10.2	58.5 ± 5.9	53.6 ± 10.3	54.7 ± 10.6	57.1 ± 5.6
Height (cm)	167.4 ± 11.7	157.3 ± 11.3	163.8 ± 11.6	160.6 ± 6.8	157.1 ± 2.9	159.5 ± 12.3	159.0 ± 5.1
BMI ($kg \cdot m^{-2}$)	20.1 ± 1.1	22.4 ± 5.0	19.5 ± 1.2	22.7 ± 2.1	21.7 ± 3.9	21.8 ± 5.4	22.7 ± 3.4

Data values are presented as means ± SD. There were no statistically significant differences between groups
BMI, body mass index

Five patients in each group received 0.5, 1.0, or 1.5 minimum alveolar concentration (MAC) of the anesthesia. The patients' characteristics are shown in Table 1.

All patients fasted overnight before the study and were brought to the operating room without receiving premedication.

Anesthesia

Anesthesia was induced with the designated volatile agent and nitrous oxide. Tracheal intubation was facilitated by $0.15\,mg \cdot kg^{-1}$ intravenous vecuronium. Anesthesia was maintained with sevoflurane or isoflurane at the designated MAC and 66% nitrous oxide in oxygen at $6\,l \cdot min^{-1}$ for 15 min. The end-tidal concentration of sevoflurane or isoflurane was measured by the infrared absorption method (Capnomac Ultima; Datex, Helsinki, Finland). Normocapnia was maintained by controlled mechanical ventilation at an end-tidal carbon dioxide pressure ranging from 35 to 40 mmHg. Body temperature was measured with a rectal thermistor probe and maintained at 36.4 ± 0.47°C with a heating pad. Lactated Ringer's solution was infused at a rate of $5\,ml \cdot kg^{-1} \cdot h^{-1}$. No glucose was administered until the performance of the intravenous glucose tolerance test (IVGTT), which was conducted before any incision was made.

IVGTT

We modified the standard IVGTT described by Pfeifer et al [7]. Glucose (20 g as 50% dextrose in water) was administered intravenously over 3 min. Blood samples were obtained immediately before and 1, 3, 5, 10, 20, and 30 min after the intravenous administration of glucose to measure plasma levels of glucose and insulin. Zero time was defined as the moment when the glucose injection was completed.

Several days after the surgery, an IVGTT was performed again in five of the 30 patients while they were awake, to serve as a control (control group). They were receiving a normal diet and received no intravenous infusions or pain medications. They received only wound disinfection and rehabilitation. The IVGTT was performed at the same time as in the anesthesia study.

Analytical methods

Plasma glucose concentration was measured by the glucose oxidase method. The plasma insulin concentration was determined with radioimmunoassay.

Calculated values and statistics

The glucose disappearance rate from 10 to 30 min after each glucose load was calculated by the least-squares method, from decreases in plasma glucose levels, and transformed to natural logarithms [3]. The acute insulin response to glucose was calculated as the mean of the changes in insulin levels from the zero-time level at 1, 3, and 5 min after glucose administration. The insulinogenic index was calculated by dividing the area under the insulin-time curve by the corresponding area under the glucose-time curve from 0 to 5 min.

Statistical analysis was performed with the Tukey-Kramer test for intergroup comparison. The demographic variables and the baseline values were examined by one-way analysis of variance. Statistical significance was defined as $P < 0.01$. All data values are presented as means ± SD.

Results

The mean plasma glucose and insulin concentrations are shown in Figs. 1 and 2, respectively. Zero-time glucose and insulin values were comparable in all anesthetic groups. However, zero-time glucose values in all anesthetic groups were significantly higher than those in the control group, and zero-time insulin values in all anesthetic groups were significantly lower than those in

Table 2. Changes in acute insulin response, insulinogenic index, and glucose disappearance rate

	MAC	Acute insulin response (μU/ml)	Insulinogenic index (ΔIRI/ΔBS)	Glucose disappearance rate (%/min)
Control		96.9 ± 32.3	0.348 ± 0.129	2.28 ± 0.41
Isoflurane	0.5	19.6 ± 18.0*	0.053 ± 0.045*	1.40 ± 0.16*
	1.0	28.2 ± 13.5*	0.060 ± 0.023*	1.51 ± 0.20*
	1.5	16.0 ± 10.1*	0.063 ± 0.031*	1.23 ± 0.16*
Sevoflurane	0.5	21.7 ± 15.8*	0.050 ± 0.031*	1.49 ± 0.20*
	1.0	26.4 ± 19.6*	0.055 ± 0.043*	1.29 ± 0.13*
	1.5	21.1 ± 16.9*	0.040 ± 0.031*	1.57 ± 0.30*

* $P < 0.01$ versus control

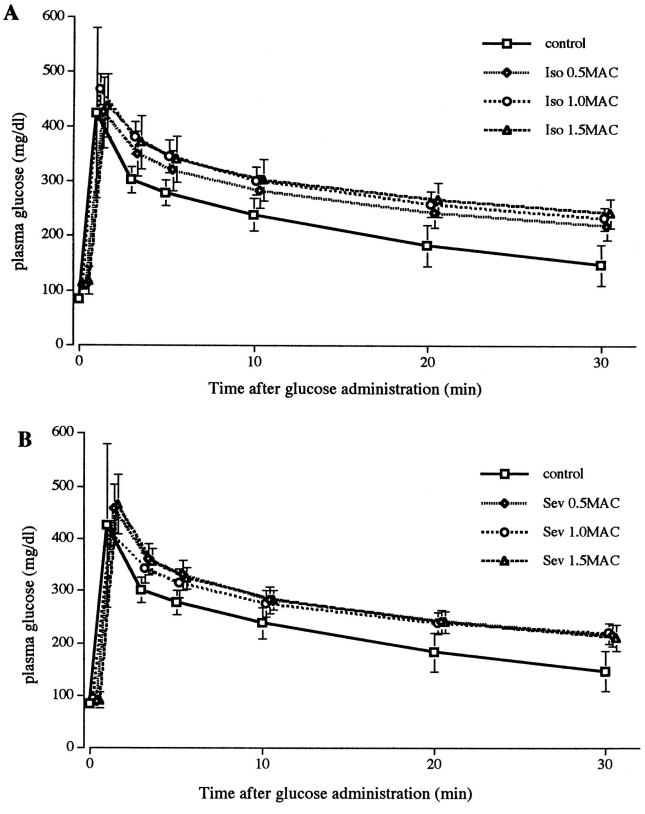

Fig. 1. Changes in plasma glucose concentrations. **A** Isoflurane (*Iso*); **B** sevoflurane (*Sev*). *MAC*, minimum alveolar concentration

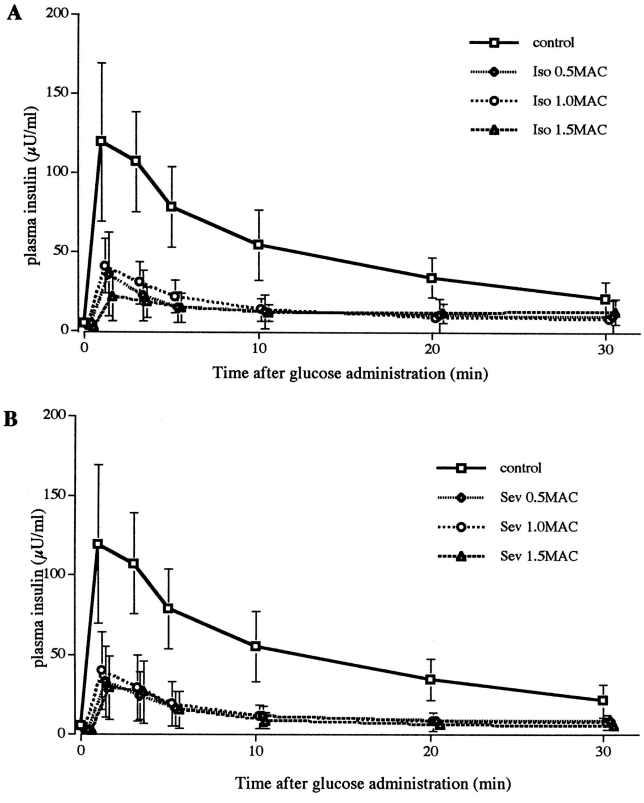

Fig. 2. Changes in immunoreactive insulin levels. **A** Isoflurane; **B** sevoflurane

the control group. During IVGTT, neither plasma glucose levels nor insulin levels differed significantly among the anesthetic groups. However, plasma glucose and insulin values in all anesthetic groups were significantly higher and significantly lower, respectively, than those in the control group.

Neither the acute insulin response nor the insulinogenic index differed significantly among the anesthetic groups (Table 2). Both the acute insulin response and the insulinogenic index were significantly lower in the anesthetic groups than in the control group.

The glucose disappearance rates in all anesthetic groups were significantly lower than those in the control group, but did not differ significantly among the anesthetic groups (Table 2).

Discussion

The mechanism by which inhalation anesthetics inhibit insulin secretion remains unclear. Previous studies have shown that insulin secretion from pancreatic β cells is

directly inhibited by halothane [1], enflurane [2], and isoflurane [8], although in vitro studies of sevoflurane have not been performed. The results of the present clinical study suggest that sevoflurane anesthesia impairs glucose tolerance in humans to the same degree as does isoflurane anesthesia. Previous studies have shown that levels of stress hormones, such as epinephrine, norepinephrine, and cortisol, which influence insulin output, are not increased during sevoflurane anesthesia [4]. Therefore, sevoflurane may directly inhibit insulin secretion. Fundamental research on the mechanism of sevoflurane action is necessary.

Few studies of the dose-dependent effects of volatile anesthetics on glucose-stimulated insulin secretion have been performed. In vitro, glucose-stimulated insulin secretion is inhibited by halothane in a concentration-dependent fashion [9]. Saho et al. [4] have also reported that insulin secretion is inhibited by sevoflurane in a dose-dependent manner in pigs. However, this observed inhibition may have been due to their use of only the insulinogenic index as an index of insulin secretion, because zero-time insulin values differed among their various MAC groups. Their data suggest that basal insulin secretion decreases during sevoflurane anesthesia in a dose-dependent manner. In the present study, we used the acute insulin response, which is an absolute value, and found no differences among the anesthetic groups in zero-time values. Therefore, we believe our data more accurately reflect insulin secretion during anesthesia. Additionally, previous studies used successive IVGTTs, which are known to induce the Staub-Traugott effect [10,11], which is the acceleration of glucose tolerance after repetitive intravenous glucose loads. Consequently, the extent to which the Staub-Traugott effect is modified by anesthetics and by the depth of anesthesia is unknown. Therefore, estimating glucose tolerance using successive IVGTTs is difficult. We believe our present findings suggest that glucose intolerance during sevoflurane or isoflurane anesthesia is independent of the dose up to 1.5 MAC, which is the standard clinical dose. In addition, other investigators have suggested that insulin secretion is inhibited by isoflurane in a concentration-independent fashion [6].

In the present study, the zero-time glucose values in the anesthesia groups were significantly higher than those in the control group, and the zero-time insulin values in the anesthesia groups were significantly lower than those in the control group. It has been shown that plasma catecholamine concentrations increased significantly following tracheal intubation [12]. In addition, plasma catecholamines were increased after rapid increases in sevoflurane or isoflurane concentrations under tracheal intubation [13]. Therefore, we believe these differences were likely induced by tracheal intubation. General anesthesia in our subjects was maintained for 15 min before IVGTT was performed. The effects of tracheal intubation lasted for at least 15 min. Although levels of catecholamines and cortisol were not measured in our study, zero-time glucose and insulin values did not differ among the anesthesia groups. Therefore, the insulinogenic index, the acute insulin response, and the glucose disappearance rate in all anesthesia groups were comparable.

A possible limitation of our study was the small number of patients in each group. Because each group comprised only five patients, a type II error may have occurred. However, if the experiments were to have been performed for 80% statistical power, at least 250 patients would have been necessary. In addition, each anesthesia group comprised 15 patients and clearly showed impaired glucose metabolism.

Data in the present study may have been affected by nitrous oxide, but, to our knowledge, no studies have examined the effect of nitrous oxide on glucose tolerance. However, in previous studies [5,6,14], nitrous oxide was used as an anesthetic. Nitrous oxide was used to prevent the patient from becoming awake, especially with 0.5 MAC of inhaled anesthetics.

In conclusion, sevoflurane anesthesia impairs glucose tolerance to the same degree as does isoflurane anesthesia. Glucose intolerance during sevoflurane or isoflurane anesthesia is independent of dosage up to 1.5 MAC. Further studies are needed to determine the extent of glucose intolerance during surgical stimulation.

Acknowledgments. We thank Dr. Mitsuyoshi Urashima, Division of Clinical Research and Development, The Jikei University School of Medicine, for his statistical advice. We also thank Associate Professor Masao Okazaki, Medical Information Center, The Jikei University School of Medicine, for his editorial advice.

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