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## Plasma Concentration of Fentanyl with Xenon to Block Somatic and Hemodynamic Responses to Surgical Incision

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**Background:** Although anesthesia with xenon has been supplemented with fentanyl, its requirement has not been established. This study was conducted to determine the plasma concentrations of fentanyl necessary to suppress somatic and hemodynamic responses to surgical incision in 50% patients in the presence of 0.7 minimum alveolar concentration (MAC) xenon.

**Methods:** Twenty-five patients were allocated randomly to predetermined fentanyl concentration between 0.5 and 4.0 ng/ml during 0.7 MAC xenon anesthesia. Fentanyl was administered using a pharmacokinetic model-driven computer-assisted continuous infusion device. At surgical incision each patient was monitored for somatic and hemodynamic responses. A somatic response was defined as any purposeful bodily movement. A positive hemodynamic response was defined as a more than 15% increase in heart rate or mean arterial pressure more than the preincision value. The concentrations

of fentanyl to prevent somatic and hemodynamic responses in 50% of patients were calculated using logistic regression.

**Results:** The concentration of fentanyl to prevent a somatic response to skin incision in 50% of patients in the presence of 0.7 MAC xenon was  $0.72 \pm 0.07$  ng/ml and to prevent a hemodynamic response was  $0.94 \pm 0.06$  ng/ml.

**Conclusions:** Comparing these results with previously published results in the presence of 70% nitrous oxide, the fentanyl requirement in xenon anesthesia is smaller than that in the equianesthetic nitrous oxide anesthesia. (Key words: Computer-assisted continuous infusion;  $Cp_{50}$ ; opioid.)

BECAUSE the minimum alveolar concentration (MAC) of xenon is 71%,<sup>1</sup> anesthesia with xenon must be supplemented with other anesthetic agents or techniques. It has been achieved with the administration of fentanyl and muscle relaxants.<sup>2,3</sup> Previous clinical studies suggested that the requirement for fentanyl during xenon anesthesia is minimal. For example, only 20% of the surgical patients in one study required fentanyl to maintain blood pressure within 20% of the baseline value during 70% xenon anesthesia at incision.<sup>2</sup> In addition, no patients had intraoperative recall, awareness, or hypertension during 0.8 MAC xenon anesthesia with 2.5  $\mu$ g/kg fentanyl.<sup>3</sup> However, the fentanyl requirement in xenon anesthesia has not been fully established.

Somatic and hemodynamic responses to surgical incision are clinical endpoints for assessing depth of anesthesia. Patient movement is easily defined and observed, and, in its absence, recall of intraoperative events by nonparalyzed patients is rare. In clinical anesthesia, the endpoints used in anesthetizing surgical patients frequently are hemodynamic variables, such as arterial blood pressure and heart rate. Therefore, it is important to establish the therapeutic concentrations of fentanyl needed to block somatic and hemodynamic responses to incision if it is to be used with xenon in clinical anesthesia. This study was designed to determine the concentration of fentanyl necessary to suppress somatic and

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hemodynamic responses to surgical incision in the presence of xenon.

## Materials and Methods

After approval from the Institutional Human Studies Committee of Teikyo University, we obtained informed consent from 25 adult patients classified as American Society of Anesthesiologists physical status I or II undergoing elective lower abdominal surgery. They were to undergo at least 5-cm skin incisions on the abdomen. Patients scheduled for laparoscopic surgery were excluded because of the small initial skin incision. Other exclusion criteria included history of cardiac and pulmonary abnormalities, neurologic disease, hypertension, and use of medications that might affect blood pressure, heart rate, or MAC values of inhaled anesthetics.

The protocol was designed to be similar to that of the study by Glass *et al.*<sup>4</sup> to make a comparison valid. Using a computer-generated random-number table, patients were allocated randomly to a predetermined target fentanyl plasma concentration of 0.5, 1, 2, or 4 ng/ml. Fentanyl was administered using a pharmacokinetic model-driven computer-assisted continuous infusion device capable of administering intravenous drugs to achieve constant target plasma concentrations. The device consisted of a Dyna-Book 433 laptop computer (Toshiba, Minato-ku, Tokyo, Japan) and a Harvard PHD2000 Syringe Pump (Harvard Apparatus, Holliston, MA). The pharmacokinetic parameters used in computer-assisted continuous infusion for administration of fentanyl were based on a study by Shafer *et al.*<sup>5</sup> To ensure rapid equilibration between the plasma and effect compartments, infusion was adjusted for the first 6 min to achieve a concentration of fentanyl twice the predetermined target concentration according to the half-time ( $k_{ec}$ ) for equilibration between the blood and the brain (6.6 min).<sup>6</sup> Thereafter, the target concentration of fentanyl was returned to the value for the patient.

No patient received premedication. After the patients were in the operating room, monitoring with an electrocardiograph, pulse oximetry, and a noninvasive blood pressure cuff was begun. A venous catheter was inserted into one arm for administration of drugs, and the computer-assisted continuous-infusion for administration of fentanyl was started. After preoxygenation and denitrogenation with 100% oxygen for 3 min, anesthesia was induced with inhalation of 70% xenon with continuous infusion of fentanyl, as previously.<sup>7</sup> After a loss of con-

sciousness, the trachea was sprayed with 2.5 ml topical lidocaine, 4%, and tracheal intubation was facilitated with 1 mg/kg succinylcholine administered intravenously. Immediately after tracheal intubation, a 20-gauge arterial line was inserted into a radial artery at the wrist for continuous blood pressure measurement and for blood sampling. The transducer (Life Kit DX-360R; Nihon Kohden, Shinjuku-ku, Tokyo, Japan) was placed at the level of the patient's right atrium and was calibrated by opening the stopcock to atmospheric pressure. Before the study, the arterial catheter tubing and transducer were inspected carefully to ensure that there were no air bubbles and that there was an optimum dynamic response.<sup>8</sup> This was calculated before each study by performing the flush test after placement of the intra-arterial catheter. The tracing obtained during several fast flushes was recorded on the computer. Natural frequency and amplitude ratio were calculated to determine the damping coefficient, as described by Gardner.<sup>8</sup> The inspired concentration of xenon was adjusted to maintain the measured end-tidal concentration at 0.7 MAC in the closed-circuit anesthesia. The MAC values of xenon were adjusted to the patient's age using the Mapleson formula.<sup>9</sup> Respiratory gases were sampled at the Y connector, and inspired oxygen and expired carbon dioxide concentrations were monitored continuously using an infrared gas monitor (PM8050; Dräger, Rubeck, Germany), which was calibrated just before each anesthetic with a tank standard. The xenon concentration was monitored continuously with an AZ720 xenon monitor (Anzai Medical, Minato-ku, Tokyo, Japan), which used the absorption of a characteristic X-ray for the measurement. It was calibrated before each case using an 80% xenon–20% oxygen mixture analyzed to  $\pm 0.02\%$  accuracy (Nihon-Sanso, Minato-ku, Tokyo, Japan). The effective working range for this monitor was 1–100%, with an error of  $\pm 1\%$  and a 90% response time of less than 1 s. Patients' lungs were ventilated mechanically to normocapnia, and body temperature was maintained at more than 35.5°C during the period of the study. No patient received drugs other than those stated.

For approximately 30 min after tracheal intubation the patients were left unstimulated, except for positioning, preparation, and draping. The xenon concentration remained stable at the target end-tidal concentration for at least 15 min before surgical incision. Blood samples were taken from the arterial line 5 min before and after incision. The hemodynamic data were displayed continuously on the cardiac catheter monitor (RMC-1100; Nihon Kohden, Shinjuku-ku, Tokyo, Japan) and recorded

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by a high-frequency thermal array chart recorder (WS-180G; Nihon Kohden, Shinjuku-ku, Tokyo, Japan). The data also were stored digitally in a computer system (Winkey; Sanyo, Minato-ku, Tokyo, Japan) using software (Hyperterminal Version 1.2; Hilgraeve, Monroe, MI) and were recorded every 10 s on paper. A person who was blind to the fentanyl concentration analyzed these hemodynamic data. We confirmed that patients could not respond to the verbal command just before surgical incision. If a patient responded to a command, the response was treated as indicating positive somatic and hemodynamic responses to incision. A blood sample was taken as a postincision sample, and the patient received propofol immediately. During surgical incision each patient was monitored for somatic and hemodynamic responses. A somatic response was considered to be any purposeful bodily movement.<sup>10</sup> The patients were monitored for somatic response for 1 min after surgical incision by an observer who was blind to the fentanyl concentration used; coughing, chewing, and swallowing were not considered to be positive purposeful movements. If patients did not move in response to incision, residual neuromuscular blockade was assessed by train-of-four stimulation of the ulnar nerve. We confirmed that the train-of-four ratio returned to almost 1.0, and first-twitch height at skin incision was not different from that recorded before administration of succinylcholine. A positive hemodynamic response was defined as a more than 15% increase in heart rate or mean arterial pressure greater than the preincision value. The preincision value was defined as the mean value of the 2- and 1-min measurements before skin incision. All patients received approximately  $10 \text{ ml} \cdot \text{kg}^{-1} \cdot \text{h}^{-1}$  of Ringer's lactate solution for the duration of the study. The total duration of these procedures was approximately 45 min.

The blood samples were allowed to clot for 15 min, and then the plasma was separated and frozen at  $-70^{\circ}\text{C}$  until assayed. Plasma fentanyl concentrations were measured by gas chromatography-mass spectrometry in an outside laboratory.<sup>11</sup> The lower detection limit was 0.2 ng/ml. The pre- and postincision concentrations of fentanyl were compared to ensure that a steady concentration was maintained. Only paired samples that had concentrations within  $\pm 35\%$  of each other were included in the statistical analysis.

### Statistical Analysis

The plasma concentrations ( $C_p$ ) of fentanyl necessary to prevent somatic and hemodynamic responses to incision in 50% of patients were defined as  $C_{p50}$  and  $C_{p50\text{-BAR}}$ .

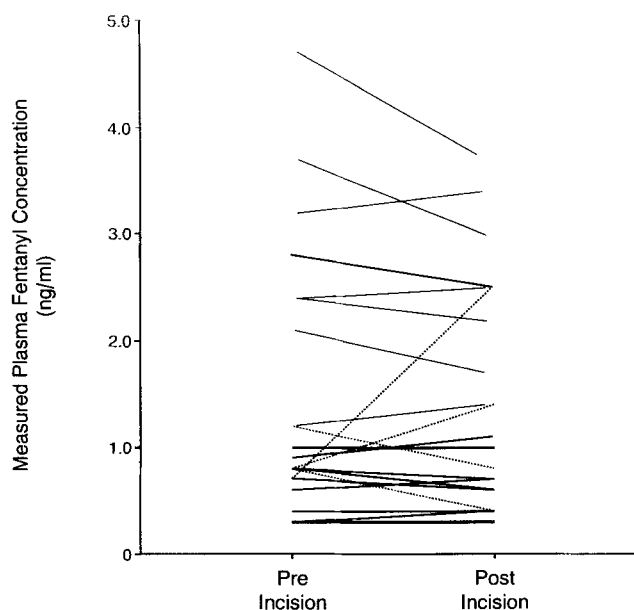


Fig. 1. Measured pre- and postincision fentanyl concentrations for all patients ( $n = 25$ ). Solid lines represent the patients ( $n = 20$ ) in whom the pre- and postincision plasma fentanyl concentrations were within 35% of each other. Actual differences in concentrations of fentanyl between preincision and postincision samples used for data analysis ranged from  $-25.0$  to  $+25.0\%$ . Dashed lines represent the patients in whom differences between the pre- and postincision plasma fentanyl concentrations exceeded 35% and were not included in the calculation of the  $C_{p50}$  and  $C_{p50\text{-BAR}}$ .

BAR (blockade of adrenergic or cardiovascular responses), respectively. Using the preincision fentanyl concentration, the  $C_{p50}$  and  $C_{p50\text{-BAR}}$  values for fentanyl were determined using SAS/STAT Software (release 6.04; SAS Institute, Cary, NC) from the following equation:

$$P = 1/1 + e^{-(ax + b)}$$

where  $P$  is the probability of no response,  $x$  is the fentanyl concentration, and  $a$  and  $b$  are parameters to be determined.  $C_{p50}$  and  $C_{p50\text{-BAR}}$  are then given by  $-b/a$ .<sup>12</sup> Data are reported as the mean  $\pm$  SD.

### Results

In 20 of 25 patients studied, the fentanyl concentration postincision was maintained within 35% of preincision the preincision value (fig. 1). These 20 patients were used in the determination of  $C_{p50}$  and  $C_{p50\text{-BAR}}$ . Actual differences in concentrations of fentanyl between preincision and postincision samples used for data analysis ranged from  $-25$  to  $+25\%$ . Of these 20 patients, three were men and 17 were women. Average age was  $47 \pm 9$

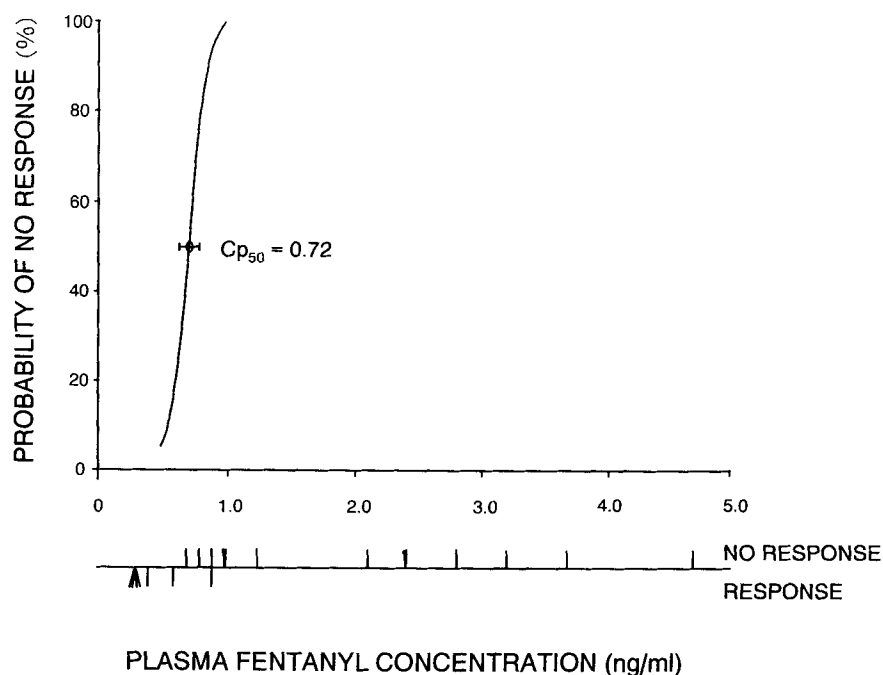


Fig. 2. The tick-mark plot shows the response–no response (movement) *versus* plasma fentanyl concentrations. Each mark indicates the plasma fentanyl concentration and response to surgical incision. From these data, the predicted probability of no response (movement) plasma fentanyl concentration obtained using logistic regression is plotted in the upper graph. The bar indicates  $\pm 1$  SD of the estimate of the plasma fentanyl concentration producing a 50% probability of no movement at surgical incision.

yr (range, 25–57 yr), and weight was  $57 \pm 10$  kg (range, 46–86 kg). The average time between the pre- and postincision fentanyl samples was  $8.6 \pm 4.5$  min. Two of these 20 patients responded to verbal commands before skin incision.

Seven patients moved in response to skin incision

(fig. 2). All patients who moved showed a positive hemodynamic response. Three patients who did not move showed 15% or greater increases in mean arterial pressure or heart rate. Therefore, 10 patients showed positive hemodynamic responses (fig. 3).

For a somatic response,  $Cp_{50}$  of fentanyl in the pres-

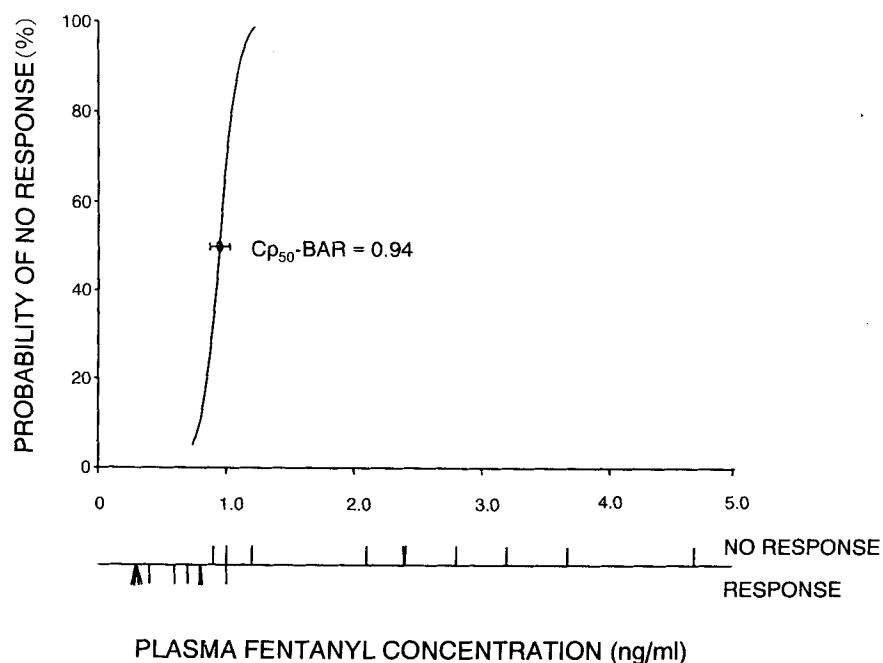


Fig. 3. The tick-mark plot shows the response–no response (hemodynamic) *versus* plasma fentanyl concentrations. Each mark indicates the plasma fentanyl concentration and response to surgical incision. From these data, the predicted probability of no response (hemodynamic) plasma fentanyl concentration obtained using logistic regression is plotted in the upper graph. The bar indicates  $\pm 1$  SD of the estimate of the plasma fentanyl concentration producing a 50% probability of no hemodynamic response at surgical incision.

ence of 0.7 MAC xenon was determined to be  $0.72 \pm 0.07$  ng/ml, and the  $Cp_{50}$ -BAR was  $0.94 \pm 0.06$  ng/ml (figs. 2 and 3).

## Discussion

We determined the plasma concentration of fentanyl (in the presence of 0.7 MAC xenon) necessary to prevent somatic and hemodynamic responses to skin incision in 50% of patients, after the plasma and effect-site concentrations were in equilibrium ( $0.72$  and  $0.94$  ng/ml, respectively). A previous study reported that  $Cp_{50}$  and  $Cp_{50}$ -BAR of fentanyl in the presence of 70% nitrous oxide (approximately 0.7 MAC)<sup>8</sup> were 3.26 and 4.17 ng/ml,<sup>4</sup> both of which are considerably greater than the results obtained in the current study. The concentration of fentanyl necessary to prevent a somatic response in 50% of patients at 0.7 MAC isoflurane or sevoflurane was approximately 0.8 ng/ml,<sup>13,14</sup> which is similar to our results with xenon. However, the concentration of fentanyl necessary to prevent a hemodynamic response in 50% of patients at 0.7 MAC sevoflurane was approximately 1.8 ng/ml,<sup>15</sup> which is considerably greater than in the current study. Therefore, we have demonstrated that the fentanyl requirement in xenon anesthesia is similar to or less than that using equianesthetic nitrous oxide, sevoflurane or isoflurane. These findings confirm previous studies<sup>2,3</sup> that suggested that the requirement for fentanyl during xenon anesthesia is minimal. Although the specific mechanism of the difference in fentanyl requirements was not identified in the current study, there are at least three explanations for this difference.

First, the mechanism of analgesic effects of xenon may differ from that of other anesthetics. Although xenon and nitrous oxide both produce an analgesic effect by inhibiting inhibits the excitatory *N*-methyl-D-aspartate receptors,<sup>16,17</sup> xenon, in contrast to nitrous oxide, directly inhibits the nociceptive stimulation-induced activity of spinal wide-dynamic-range neurons.<sup>18</sup> The mechanism of analgesic effects of xenon is described to be *via* suppression of spinal dorsal horn neurons<sup>19</sup> independent of  $\alpha_2$ -adrenergic or opioid receptors.<sup>20</sup> The direct antinociceptive action of xenon on the spinal cord is greater than that of nitrous oxide.<sup>18</sup> These differences in the mechanism of analgesic effects may explain the difference in fentanyl requirements between xenon and nitrous oxide.

Second, nitrous oxide augments sympathetic outflow, but xenon has not been reported to do so. The sympa-

thetic activation by nitrous oxide has been shown by elevated plasma catecholamine concentrations<sup>21</sup> and, more recently, by microneurography.<sup>22,23</sup> The sympathetic activation induced by nitrous oxide increases arterial blood pressure and heart rate.<sup>24</sup> In contrast, xenon decreases plasma catecholamine concentrations,<sup>25</sup> indicating that the drug produces a sympatholytic effect. Furthermore, heart rate (a good indicator of sympathovagal balance)<sup>26</sup> was significantly reduced during xenon administration in some, although not all, of the previous investigations.<sup>27,28</sup> To maintain stable hemodynamic variables, a larger dose of fentanyl may have been necessary to compensate for the increased sympathetic excitation by nitrous oxide.

Third, the study protocol was not exactly identical to those of the previous studies. For example, the MAC value of xenon was adjusted to age in our study but not in the previous studies<sup>4,13-15</sup>; Our patients were older than those in the previous studies.<sup>4,13-15</sup> McEwan *et al.*<sup>13</sup> and Glass *et al.*<sup>4</sup> used radioimmunoassay techniques for fentanyl concentration measurement; we measured fentanyl using gas chromatography-mass spectrometry.<sup>29</sup> The baseline hemodynamic variables were defined as mean preincision values in our study; they were measured before induction of anesthesia in the study of Glass *et al.*<sup>4</sup> These differences in the protocols may, at least partially, explain the differences in the fentanyl requirements among various inhaled anesthetics.

Our previous study showed a similar sevoflurane requirement between xenon and nitrous oxide to achieve stable hemodynamic responses to surgical incision.<sup>30</sup> In general, volatile anesthetics enhance activity of inhibitory  $\gamma$ -aminobutyric acid type A receptors; fentanyl acts on the opioid receptors.<sup>31</sup> The difference in the mechanism of actions between sevoflurane and fentanyl may explain the difference in their requirement, although the exact mechanism was not revealed in our investigations.

In conclusion, we determined that the  $Cp_{50}$  of fentanyl in the presence of 0.7 MAC xenon was  $0.72 \pm 0.07$  ng/ml for a somatic response, and the  $Cp_{50}$ -BAR was  $0.94 \pm 0.06$  ng/ml for a hemodynamic response. Compared with the results obtained in a previous study,<sup>4</sup> xenon needs the smaller concentrations of fentanyl than does the equianesthetic nitrous oxide to block somatic and hemodynamic responses.

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