British Journal of Anaesthesia 1994; 73: 322–325

Effect of fentanyl on awakening concentration of sevoflurane

T. KATOH, T. UCHIYAMA AND K. IKEDA

Summary

This study was designed to determine if fentanyl altered MAC-awake (the end-tidal concentration of sevoflurane associated with eye opening to verbal command) in 30 healthy, ASA I patients. During anaesthesia, no other anaesthetics or drugs were given with the exception of sevoflurane. After surgery, end-tidal anaesthetic concentration was maintained constant for at least 15 min. If patients failed to respond to command, the end-tidal concentration was decreased and again maintained constant for 15 min. The anaesthetic concentration midway between the value permitting the response and that just preventing the response was recorded as MAC-awake. Fentanyl was administered at predicted plasma concentrations of 1 and 2 ng mg^{-1} using a computer-controlled continuous infusion and plasma concentrations of fentanyl were measured at the time of MAC-awake measurements. MAC-awake of the control group in which fentanyl was not administered was mean 0.67 (SD 0.12)% or 0.36 (0.03) MAC, being significantly higher than that of the fentanyl 2-ng ml^{-1} group (0.57 (0.09)% or 0.30 (0.04) MAC). In the fentanyl 1-ng ml^{-1} group, MAC-awake (0.65 (0.10)% or 0.34 (0.05) MAC) did not differ from that in the control group. Logistic regression analysis showed that increasing plasma concentration of fentanyl and increasing age significantly reduced the MAC-awake of sevoflurane. Because the reduction was very small relative to the overall scatter of the MAC-awake, a low plasma concentration of fentanyl did not significantly reduce the MAC-awake of sevoflurane. (*Br. J. Anaesth.* 1994; **73**: 322–325)

Key words

Anaesthetics volatile, sevoflurane. Analgesics opioid, fentanyl. Potency, anaesthetic, MAC.

Sevoflurane was first used clinically in 1987 and it has become a widely used agent in Japan. At present, no single anaesthetic drug is used to provide all the necessary components of general anaesthesia. Therefore, it is important to define the properties of the interaction between the drugs that are used in combination. Sevoflurane has a potent hypnotic action but its analgesic potency is low [1]. Fentanyl may be used in combination with sevoflurane as it produces a dose- and concentration-dependent decrease in MAC for other inhalation anaesthetics [2, 3]. This may, however, delay rapid recovery from anaesthesia, which is one of the advantages of sevoflurane. This study was designed to determine if fentanyl administered during operation by means of a pharmacokinetic model-drive infusion pump (computer-controlled continuous infusion) altered MAC-awake, the end-tidal anaesthetic concentration associated with eye opening to verbal command.

Patients and methods

With local Ethics Committee approval and informed patient consent, we studied 30 patients (22–62 yr) of both sexes, all ASA I, who were undergoing elective oral or nasal surgery. Patients were excluded if they had undergone any other surgery. They were monitored routinely, fasted for at least 8 h before surgery and received no premedication. Anaesthesia was induced with sevoflurane and oxygen. Vecuronium 0.02 mg kg^{-1} was administered for precurarization and neuromuscular block with suxamethonium 1.5 mg kg^{-1} was followed by tracheal intubation. Fentanyl was administered using an infusion pump (TFV-2200, Nihonkoden, Tokyo, Japan) with a serial port communicating with a microcomputer. We used pharmacokinetic simulation and infusion algorithms to calculate the infusion rate (every 6 s) required to immediately obtain and then maintain a set plasma concentration. The microcomputer was programmed with the fentanyl kinetic variable set reported by Shafer and colleagues [4].

Thirty patents were allocated to three groups according to predicted fentanyl plasma concentrations of 0, 1 or 2 ng ml^{-1}. The infusion was started after induction of anaesthesia and continued to the end of anaesthesia. Throughout surgery, anaesthesia was maintained with sevoflurane and 50% nitrogen in oxygen, but with no other drugs. End-tidal concentrations of sevoflurane and carbon dioxide were measured continuously using an infrared multigas anaesthetic analyser (Capnomac Ultima, Datex, Helsinki, Finland). Gas samples were collected with a Teflon catheter placed at the tracheal end of the tracheal tube at a rate of 200 ml min^{-1}. The anaesthetic concentration was varied to facilitate surgery. Anaesthetists and an observer were blinded as to how much fentanyl was given to each patient.

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Table 1 Patient characteristics and anaesthetic details (mean (SD or range)) in the control and fentanyl groups. * $P < 0.05$ compared with control group

	Control	Predicted fentanyl concn (ng ml^{-1}) 1	2
No. of patients	10	10	10
Age (yr)	43.2 (22–62)	42.1 (22–59)	39.0 (00–00)
Weight (kg)	56 (14)	52 (10)	54 (12)
Total duration of sevoflurane administration (min)	161 (48)	141 (52)	152 (62)
Plasma fentanyl concentration (ng ml^{-1})	0	0.86 (0.16)	1.86 (0.41)
MAC-awake (%)	0.67 (0.12)	0.65 (0.10)	0.57 (0.09)*
MAC-awake (MAC multiple)	0.36 (0.03)	0.34 (0.05)	0.30 (0.04)*

After surgery, mechanical ventilation was performed to maintain end-tidal carbon dioxide concentration at 4.8–5.3 kPa during the study. We ensured that the end-tidal plateau of the capnogram exceeded 3 s. The end-tidal concentration was decreased to a predetermined concentration, initially 1.0%, and kept constant for at least 15 min to ensure equilibration with cerebral anaesthetic partial pressure. After the 15-min equilibration period, patients were asked at frequent intervals to open the eyes. If they failed to do so, the end-tidal concentration was decreased by 0.2% and again kept constant for 15 min. The process was repeated until an end-tidal concentration was reached at which patients responded to command. The concentration midway between the value permitting the response (open eyes on request) and that just preventing the response, was defined as MAC-awake. Rectal temperature ranged from 36.0 to 37.0 °C in all patients.

Blood samples were obtained from the femoral artery at the time when patients responded to command and immediately placed on ice. Plasma was separated and frozen at −70 °C until assayed. The plasma concentration of fentanyl was measured by gas chromatography–mass spectrometry (HP-model 5989, Hewlett Packard Co, CA, USA). The lower limit of quantitation of the assay was 0.5 ng ml^{-1} [5].

To compensate for the effect of age on anaesthetic requirements [6], we computed the ratio of MAC-awake to the age-adjusted sevoflurane MAC for each patient. One-way analysis of variance was used to compare variables between groups. $P < 0.05$ was considered significant.

We also estimated MAC-awake, MAC-awake reduction of sevoflurane by fentanyl and the effect of age on MAC-awake using a multiple independent variable logistic regression model [3]:

$$P(\text{no response}) = \frac{1}{1+e^{-z}}$$

$$Z = \beta_0+\beta_1X_1+\beta_2X_2+\beta_{12}X_1X_2+\beta_3X_3$$

where X_1 = measured plasma concentration of fentanyl; X_2 = end-tidal sevoflurane concentration; X_3 = patient age; β_0 = regression intercept constant; β_1 = coefficient for fentanyl; β_2 = coefficient for sevoflurane; β_{12} = coefficient for the product of the measured fentanyl and end-tidal sevoflurane concentrations (interaction coefficient); β_3 = coefficient for age. The likelihood ratio test was applied to determine the independent variables to be removed from the model. MAC-awake for given age and plasma concentration of fentanyl was determined by setting the probability of no response to 0.5 and solving for sevoflurane concentration as a function of the measured concentration of fentanyl and age:

$$X_2 = \frac{-(\beta_0+\beta_1X_1+\beta_3X_3)}{\beta_2+\beta_{12}X_1}$$

Table 2 Coefficient estimates for the logistic regression model. Constant = Regression intercept constant; Sevoflurane = end-tidal sevoflurane concentration; Age = patient age; Fentanyl = plasma concentration of fentanyl

Variable	Coefficient	SE	*P*
Constant	28.8118	8.0097	0.0003
Sevoflurane (%)	−33.2452	8.7764	0.0002
Age (yr)	−0.1449	0.0559	0.0095
Fentanyl (ng ml^{-1})	−1.9663	0.8057	0.0147

Results

Patient age, body weight and total duration of administration of sevoflurane did not differ between groups (table 1). The mean MAC-awake of patients not receiving fentanyl (0.67 (SD 0.12)% or 0.36 (0.03) MAC) differed from that of patients with a mean plasma concentration of fentanyl of 1.86 (0.41) ng ml^{-1} (0.57 (0.09)% or 0.30 (0.04) MAC), but not significantly from that of patients with a mean plasma concentration of fentanyl of 0.86 (0.16) ng ml^{-1} (0.65 (0.10)% or 0.34 (0.05) MAC). The logistic model was fitted to 99 data sets of observed response, measured plasma fentanyl concentration, end-tidal sevoflurane concentration and patient age. The independent variable for interaction between sevoflurane and fentanyl was removed from the model by the likelihood ratio test. The coefficient estimates are shown in table 2. Logistic regression analysis showed that plasma fentanyl concentration and age significantly reduced the MAC-awake of sevoflurane (fig. 1).

Discussion

We have found that fentanyl decreased the MAC-awake of sevoflurane. There have been no previous reports on the effect of fentanyl on MAC-awake, although there are several studies on the effect of morphine. Our finding does not appear to agree with

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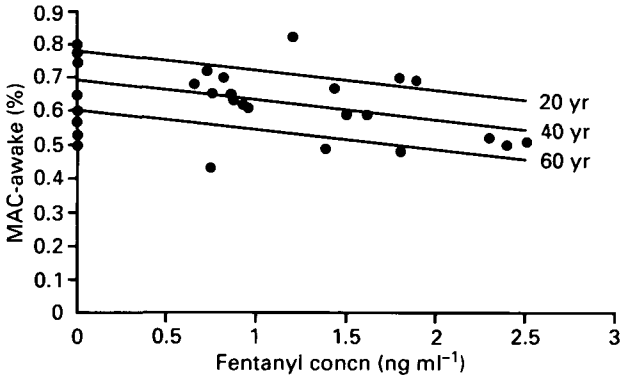

Figure 1 MAC-awake (end-tidal concentration on awakening from sevoflurane) reduction of sevoflurane by increasing concentrations of fentanyl and age. Lines = Logistic regression solution: MAC-awake = 0.87 − 0.00436*age(yr) − 0.0591*fentanyl concentration (ng ml^{-1}).

those from similar morphine studies. Gross and Alexander demonstrated that intraoperative administration of morphine did not alter the MAC-awake of isoflurane [7]. Watch, Lagueruela and White reported that the concentration of halothane at which children opened their eyes spontaneously was not affected by administration of morphine during operation [8]. We reported that MAC-awake during recovery from sevoflurane anaesthesia was not affected by analgesic doses of morphine [6]. In these three studies, morphine was administered 60 min before the end of anaesthesia at a dose of 0.1 mg kg^{-1}. These reports agreed that morphine did not affect the hypnotic effects of volatile anaesthetics. The different findings between the present fentanyl study and previous morphine studies may reflect methodological differences, although the differences in the pharmacological characteristics between the two agents is a possible explanation. In previous studies, low doses of opioid were given or the times between opioid administrations and MAC-awake determinations were long. The plasma concentration of opioid should be low when determining MAC-awake and sedative or hypnotic effects, therefore, may not be sufficient to delay awakening.

$C_{P,50}$-asleep for i.v. anaesthetics (the plasma concentration at which 50% of patients do not respond to verbal command) is a similar concept to MAC-awake for inhalation anesthetics. Fentanyl did not alter the $C_{P,50}$-asleep at an analgesic plasma concentration of 1.27 ng ml^{-1} [9]. In contrast, low doses of fentanyl (1.5 μg kg^{-1}) resulted in a small decrease in the dose of thiopentone (13%), whereas larger doses (3 μg kg^{-1}) resulted in a greater decrease in thiopentone requirements (34%) for induction of anaesthesia [10]. Even a dose of 1.5 μg kg^{-1} results in a peak plasma and effect compartment concentration exceeding 2.0 ng ml^{-1}. Thus at low but analgesic plasma concentrations, a hypnotic interaction between fentanyl and thiopentone appears minimal, but may be additive or synergistic at higher concentrations of fentanyl. In this study, MAC-awake was reduced from 0.36 to 0.30 MAC with a mean plasma fentanyl concentration of 1.86 ng ml^{-1} in the 2-ng ml^{-1} group but not with a mean plasma fentanyl concentration of 0.86 ng ml^{-1} in the 1-ng ml^{-1} group. Thus low concentrations of fentanyl did not significantly affect MAC-awake, while higher concentrations reduced MAC-awake. As seen in figure 1, MAC-awake reduction by fentanyl was small relative to the overall scatter. The small reduction with a large scatter might have prevented the detection of any MAC-awake reduction in previous studies where a small dose of opioid was administered. Logistic regression analysis revealed that an increasing plasma concentration of fentanyl decreased the probability of no response to verbal command in patients anaesthetized with sevoflurane. The present study extends this finding from thiopentone to sevoflurane anaesthesia.

Our estimate of MAC-awake for sevoflurane in the control group of the present study was slightly higher than that obtained in our previous study (0.30 MAC) where the trachea was not intubated [6]. The MAC-awake in the previous study was similar to that obtained in the 2-ng ml^{-1} group of the present study. The presence or absence of a tracheal tube may explain the discrepancy. Under light anaesthesia, a tracheal tube often induces coughing which is a strong stimulus to awaken patients. Therefore, the MAC-awake for patients whose trachea is not intubated may be lower because of the absence of noxious stimulation which a tracheal tube creates. Fentanyl may block afferent nerve impulses resulting from stimulation of the pharynx, larynx and lungs during intubation. High concentrations of opioid receptors are present in the solitary nuclei and the nuclei of the 9th and 10th cranial nerves, associated with the visceral afferent fibres of these nerves originating in the pharynx, larynx and lungs [11]. These receptors provide a possible mechanism for the antitussive effects of fentanyl and may be one of the reasons why fentanyl reduced the MAC-awake of sevoflurane.

We chose to infuse fentanyl to a predicted plasma concentration of 1.0 and 2.0 ng ml^{-1}, because the MAC reduction of volatile anaesthetics by fentanyl was steep at concentrations less than 2.0 ng ml^{-1} and the further reduction by increasing the plasma fentanyl concentration to greater than 3 ng ml^{-1} was small [2, 3]. These plasma concentrations are sufficient for satisfactory postoperative analgesia [12]. If fentanyl produces the same degree of MAC reduction with sevoflurane as occurs with isoflurane or desflurane, it does not reduce both MAC and MAC-awake by comparable amounts.

Because we determined MAC-awake after surgery, the relief of postoperative pain produced by fentanyl may have resulted in decreasing MAC-awake. As fentanyl produces satisfactory postoperative analgesia at a concentration of 1 ng ml^{-1}, MAC-awake in the 1-ng ml^{-1} group should be significantly lower than that in the control group, if pain relief is a primary mechanism for reducing the MAC-awake of sevoflurane. Because the difference in MAC-awake between the control and 1-ng ml^{-1} group was not significant, we can conclude that the pain relief produced by fentanyl does not seem to be a primary reason for the reduction in MAC-awake.

A previous study suggested that i.v. fentanyl produced unconsciousness and amnesia, even when

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administered without other concomitant anaesthetics. At an estimated effect-site fentanyl concentration of 9.7 ng ml^{-1}, 50% of patients (six of 12) did not respond to command [13]. The predicted concentration of fentanyl permitting response to command in 50% of patients from the regression model is 11.7 ng ml^{-1} at 40 yr, being fairly close to the value obtained in the previous study. This finding suggests that fentanyl has a small hypnotic effect, and reduces MAC-awake of sevoflurane in a dose-related manner. This discussion, however, could be criticized for the lack of MAC-awake determinations at higher plasma concentrations of fentanyl in the present study.

The concentration of fentanyl at the effect site determines drug effect. Thus a stable plasma concentration for three times longer than $T_{\frac{1}{2}}k_{eo}$ (the half-time for equilibration between the plasma and effect compartment) should be maintained for equilibration between plasma concentration and effect-site concentration. The $T_{\frac{1}{2}}k_{eo}$ of fentanyl was reported to be about 6.4 min [14]. Constant plasma fentanyl concentrations should thus be maintained for at least 20 min. At 20 min, equilibration between plasma and brain concentrations should be 97%. We sampled blood once to measure the plasma concentration of fentanyl at the time of patient response. In previous studies assessing the drug interaction of fentanyl with other anaesthetics, plasma concentrations were measured twice at an interval of 20–30 min to confirm that stable plasma concentrations of fentanyl were maintained during infusion [2, 3]. In the present study, more than 120 min elapsed after the start of the infusion of fentanyl. Although at the first response to command, the plasma concentration predicted with other investigator's pharmacokinetic variables [15] was different from that based on the variables used in this study, each predicted concentration of fentanyl was stable for more than 30 min before MAC-awake determinations. Even with a simple constant rate infusion, the difference in plasma concentration of fentanyl between 100 min and 120 min after the start of infusion would be less than 15%. We felt justified in making the assumption that plasma concentrations of fentanyl were stable for 20 min before MAC-awake determinations for the reasons described above. The plasma concentrations measured at the time of MAC-awake determinations should reflect the effect-site concentration.

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