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Reviews

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Clinical applications of fentanyl pharmacokinetics and pharmacodynamics: roles of fentanyl in anesthesia

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Introduction

Fentanyl, one of a series of synthesized opioids, is used extensively perioperatively. Its physiochemical and pharmacokinetic characteristics are unique. This article reviews the role of opioids in general anesthesia and discusses clinical applications of fentanyl pharmacokinetics to guide rational drug administration.

Inhalational agents in general anesthesia

During the 1960s, opioids were used only rarely in combination with inhalational agents. Ether, cyclopropane, or halothane was used with or without nitrous oxide, and most anesthesiologists were trained to use relatively "pure" inhalational anesthesia. There were good reasons to limit the combination of drugs in general anesthesia. The stages of surgical anesthesia were considered transient states between wakefulness and respiratory and circulatory depression and coma produced by the drugs. The stage of anesthesia suitable for surgery was reached only by adjusting the dose of inhalational agents guided by the degree of respiratory and circulatory depression or pupillary size [1]. Traditionally, general anesthetics were thought to act by perturbing the lipid bilayer portion of the nervous membrane, and the mechanisms of anesthetic actions of inhalational agents were considered to be nonspecific [2]. Ether had analgesic, hypnotic, and muscle-relaxant effects. Respiration and circulation were preserved reasonably well. Nitrous oxide provided additional analgesia and ease of induction. Thus, the combination of ether and nitrous oxide provided a satisfactory state of general anesthesia.

In 1981 isoflurane was introduced, and desflurane and sevoflurane were introduced in 1992 and 1994, respectively, in the United States. The low blood solubility of these newer inhalational agents was desirable because it facilitated the rapid induction of anesthesia, permitted precise control of anesthetic concentration during maintenance of anesthesia, and favored prompt recovery at the end of surgery. The quality of anesthesia produced by all inhalational anesthetics was thought to be similar. For example, Stoelting et al. [3] reported in 1970 that the concentration of volatile anesthetics (ether, halothane, methoxyflurane, and fluroxene) required to produce responses to verbal stimuli in 50% of patients (MAC-awake) was approximately 50%–60% of MAC (minimum alveolar concentration necessary to eliminate movement at skin incision) of each agent. Recently, Gaumann et al. [4] reported that the ratios between MAC-awake and MAC were 0.25 and 0.27 for isoflurane and enflurane, respectively, considerably lower than the values determined for halothane and ether. Thus, the hypothesis of a uniform ratio between MAC and MAC-awake values was challenged. Subsequent studies [5–7] showed that the MAC-awake values for isoflurane, sevoflurane, and desflurane were approximately one-third of MAC. If we assume MAC as an index that represents the analgesic effects of inhalational agents, the MAC-awake/MAC ratio may represent the relative analgesic potency of each inhalational agent, and the MAC/MAC-awake ratio may represent the relative hypnotic potency. Thus, ether and halothane may be more potent analgesic agents than isoflurane, sevoflurane, and desflurane, and these recent inhalational agents may be more potent hypnotics than ether or halothane. Subanesthetic doses

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of isoflurane produce more mental and physical sedation than equipotent doses of nitrous oxide [8], and awakening from halothane anesthesia is not slower than awakening from isoflurane anesthesia, in spite of the higher blood-gas coefficient value of halothane [4]. However, it should be noted that it is difficult to define analgesia in anesthetized patients. Although MAC is widely used as an indicator of anesthetic adequacy of inhalational agents, recent work has demonstrated that precollicular decerebration does not alter MAC of isoflurane in rats, suggesting that the forebrain is not a major site of action of isoflurane in blocking motor responses [9]. Some animal studies have demonstrated that lack of movement in response to noxious stimuli appears to result from anesthetic action in the spinal cord [10]. The spinal cord also influences the cardiovascular system. A recent study suggests that cardiovascular responses to noxious stimuli may be primarily mediated by the subcortical structures at least in goats [11]. These studies suggest that the subcortical structures including the spinal cord are important as sites of anesthetic action to prevent both motor and cardiovascular responses to noxious stimuli. Thus, the sites of blocking motor responses or cardiovascular responses to painful stimuli may not be the sites identified with conscious perception of pain, nor the sites responsible for producing hypnotic effects [9].

In 1994 Zbinden et al. [12] examined blood pressure and heart rate responses to various noxious stimuli under isoflurane–air anesthesia and reported that isoflurane as a sole agent was unable to suppress hemodynamic responses to painful stimuli. Thus, deeper levels of isoflurane anesthesia depressed prestimulation blood pressure to unacceptable levels, yet failed to prevent hypertension or tachycardia in response to noxious stimuli. Yasuda et al. reported that desflurane anesthesia at 0.83 MAC or 1.24 MAC did not abolish the cardiovascular response to tetanic stimuli [13]. Furuya et al. studied the responses of plasma epinephrine, norepinephrine, and other stress hormones in elderly patients undergoing abdominal surgery with sevoflurane–nitrous oxide anesthesia and reported profound elevation of these stress hormones immediately after extubation [14]. Roizen et al. [15] studied the ability of halothane–N_2O anesthesia to attenuate hemodynamic responses to skin incision, defining MAC-BAR as the concentration of halothane required to block the "adrenergic" reaction to skin incision in 50% of patients. MAC-BAR for halothane was 1.5 MAC, including the contribution of 60% N_2O. The dose-related effect of halothane–N_2O to block the hemodynamic response to noxious stimuli reported by Roizen et al. contradicts the findings of Zbinden. Recently, Segawa et al. [16] reported that the release of norepinephrine and epinephrine due to noxious surgical stimulation increased in proportion to isoflurane concentration. This observation also contradicts the MAC-BAR concept of Roizen and suggests that the suppression of the blood pressure response to noxious stimulation by anesthetics may be the result of suppression of the response of vascular smooth muscle and myocardium to catecholamines. Thus, although hemodynamic responses are the most commonly used clinical criteria to judge the depth of anesthesia with inhalational anesthetics, and thus adjust the dosage, a scientific basis for this approach is less clear.

Opioids in general anesthesia

In clinical practice, anesthesiologists generally add opioids to obtain hemodynamic stability at clinically acceptable concentrations of inhalational anesthetics. Several investigators [17–21] have now quantified the decrease of inhalational anesthetic MAC at relatively low opioid concentrations (Fig. 1). For example, isoflurane MAC decreased 39% at a steady-state fentanyl concentration of 1 ng·ml^{-1} and 63% at a steady-state fentanyl plasma concentration of 3 ng·ml^{-1} [18]. Katoh reported sevoflurane MAC decreased 50% and 59% at steady-state fentanyl concentrations of 2 and 3 ng·ml^{-1}, respectively [19]. A fentanyl plasma concentration range of 1–3 ng·ml^{-1} also decreases Ec_{50} of propofol (plasma concentration of propofol that suppresses movement response to surgical incision in 50% of patients) by 40%–60% [20]. Daniel et al. [22] and Katoh [23] recently reported that at a fentanyl concentration of 1–3 ng·ml^{-1}, the dose requirements of isoflurane–N_2O, sevoflurane–oxygen, or sevoflurane–N_2O required to prevent cardiovascular responses to surgical incision (MAC-BAR) were substantially

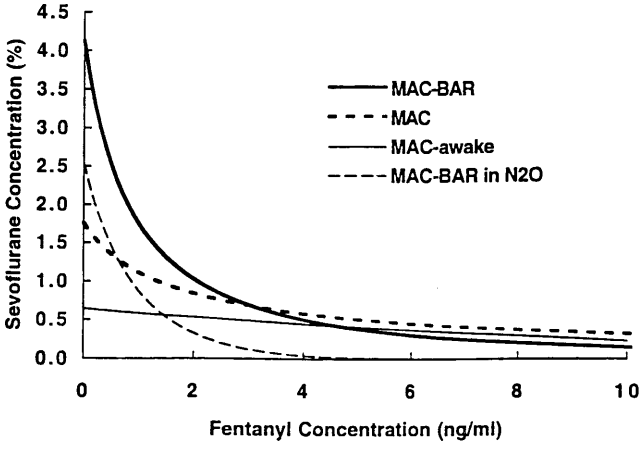

Fig. 1. Reduction in MAC-BAR, MAC, and MAC-awake of sevoflurane by increasing concentrations of fentanyl (from Katoh et al. [23], with permission)

reduced. Increasing fentanyl plasma concentration higher than 3 ng·ml^{-1} produced little further reduction in MAC and MAC-BAR. Thus, a fentanyl plasma concentration range of 1–3 ng·ml^{-1} represents a convenient therapeutic window to be used in general anesthesia with either inhalational agents or propofol. It is of interest that this range of fentanyl plasma concentration is also a therapeutic window of analgesia in conscious patients [24]. During the studies on MAC-BAR [12,13,23], it became apparent that blood pressure was unacceptably low when concentrations of inhalational agents were increased without using fentanyl to prevent the hemodynamic responses to incision. Thus, combined use of a low-dose opioid and inhalational agents (or intravenous hypnotic agents) appears to be a safer method of administering general anesthesia for surgery than general anesthesia without opioids.

During the 1960s, opioids were not considered an exciting subject for investigation or an appropriate area for innovation. Few would have predicted the dramatic developments that occurred in cardiac anesthesia in subsequent years. Cardiac surgery was in its infancy in the 1960s. Challenges generated by patients with valvular heart disease who required correction of their anatomic lesion dramatically changed the importance of opioids [25]. Lack of myocardial depression by morphine anesthesia allowed for circulatory stability and conditions suitable for operation in patients with cardiac cachexia associated with valvular heart disease. However, the lack of circulatory depression turned out to be disadvantageous in relatively robust patients undergoing coronary artery surgery. Hypertension associated with opioid anesthesia and surgical stimulation was not completely controlled by increasing the dose [26]. Respiratory depression associated with opioid anesthesia was both a disadvantage and an advantage. Following opioid anesthesia for cardiac surgery, tracheostomy was common in the late 1960s, but it was soon learned that endotracheal intubation was well tolerated following opioid anesthesia. At that time, early extubation or rapid awakening was considered undesirable in cardiac surgical patients because of hypothermia, excessive bleeding from the chest tube, residual neuromuscular blockade, and circulatory instability. In the past 10 years, the mortality rate from cardiac surgery has decreased. Hypothermic cardiopulmonary bypass was modified by normothermia or tepid hypothermia. Myocardial preservation improved, and blood loss to the chest draining tube lessened. Thus, in the United States, the stage was set for early extubation, aggressive pain management, early mobilization, and early hospital discharge. Although cost containment has forced the pendulum to shift to early extubation from previous overnight ventilation, it has recently been demonstrated that this technique is safe and cost-effective and can improve resource utilization [27]. The anesthetic regimen of early extubation anesthesia requires a balanced anesthesia with low-dose opioid, propofol, and inhalational agents. Recent developments in pharmacokinetics, pharmacodynamics, and drug interactions among opioids, inhalational agents, and propofol improved the dosing regimen and thus contributed to the success of modern balanced anesthesia to meet the challenge to provide satisfactory anesthesia for cardiac surgery, ambulatory surgery, and anesthesia for high-risk or elderly patients.

Classical pharmacokinetics versus three-compartment pharmacokinetic models

Knowledge of pharmacokinetics should guide anesthesiologists to administer eliminate opioids rationally. However, classical pharmacokinetic parameters, such as volume of distribution, elimination half-time, or clearance, are difficult to interpret in anesthetic practice and rarely help anesthesiologists in guiding dosing. In 1991 Shafer and Varvel [28] used a pharmacokinetic simulation based on a three-compartment model of opioids and pointed out that comparing the elimination half-times of fentanyl and sufentanil did not predict recovery from drug effects. The elimination half-time of sufentanil is longer than that of fentanyl (562 *vs* 475 min), yet computer simulations of recovery curves of plasma concentrations following termination of infusion found faster recovery from sufentanil than from fentanyl. The long elimination half-life of sufentanil results primarily from a large "slow" compartment with low clearance. During infusion, the slow-distribution compartment acts as a reservoir that continues to fill over many hours. Thus, when infusion is terminated, the compartment continues to fill and thereby helps to reduce the plasma (and effect site) concentrations. Thus, a single classical pharmacokinetic parameter is uninterpretable in the practice of anesthesia, and three-compartment models that integrate all pharmacokinetic parameters are necessary to predict the changes in opioid plasma or effect site concentrations [28]. In 1992 Hughes et al. [29] examined the influence of the duration of drug infusion on the decrease in plasma (and effect site) concentrations of drugs after the discontinuation of infusion. The time required for the plasma drug concentration to decrease by 50% was determined using a three-compartment model and was designated as the "context-sensitive half-time," where "context" refers to the duration of infusion (Fig. 2). These simulations demonstrate that the elimination half-life is of no value because it does not characterize intercompartmental disposition of

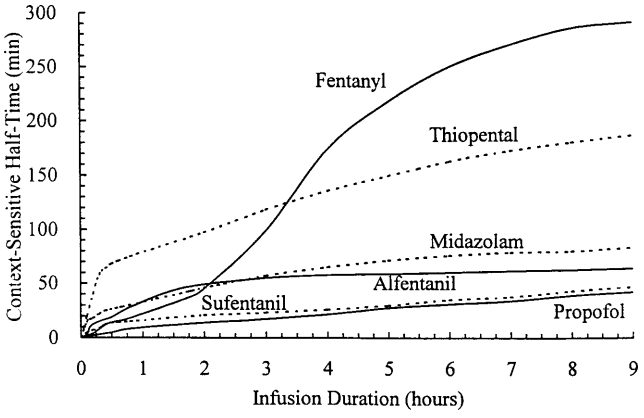

Fig. 2. Context-sensitive half-time as a function of infusion for each of the pharmacokinetic models simulated. *Solid* and *dashed line* patterns are used only to permit overlapping lines to be distinguished (from Hughes et al. [29], with permission)

intravenous anesthetic drugs during dosing periods relevant to anesthesia. These two articles influenced anesthesiologists enormously, providing them with a new insight into and description of drug behavior, and have led to improved understanding in clinical pharmacological practice. For example, if one examines a graph in Hughes's articles, it is apparent that fentanyl, a short-acting drug, becomes long-acting if continuous infusion continues beyond 2 h. It can be interpreted that the plasma fentanyl concentration rises when an infusion of fentanyl is continued at the same rate. Therefore, the infusion rate of fentanyl must be reduced stepwise to maintain a constant plasma concentration.

Accuracy of prediction of fentanyl plasma concentrations with three-compartment models

The usefulness of a pharmacokinetic model lies in its ability to predict concentrations of drug in the blood or at the effect sites. Plasma concentrations of drugs can be measured, but not the effect site concentration. Therefore, the concentration at the effect site is calculated from the plasma concentration using a blood–effect site equilibrium half-time. The half-time of equilibrium between blood and brain is 6.4 min when EEG changes are used as effects of fentanyl [30]. Thus, equilibrium between blood and brain is reached within 20–30 min during fentanyl infusion. This pharmacokinetic characteristic of fentanyl makes it easy to titrate fentanyl doses to the effects desired. Since blood concentrations of fentanyl can be measured, the ability of a pharmacokinetic model to predict plasma concentration can be tested by comparing the measured values (C_m) against predicted values (C_p). Performance error (%PE) is defined as $\%PE = (C_m - C_p)/C_p \times 100$. A positive value indicates underestimation, and a negative value indicates overestimation of the measured values. The absolute valve of PE is termed the absolute performance error (APE) and represents the overall predictive accuracy; PE represents the prediction bias. Three pharmacokinetic programs for fentanyl are available in Stanpump [31]: McClain and Hug's, Scott and Stanski's, and Shafer's. These are subsequently referred as McClain's, Scott's, and Shafer's models. Shafer et al. [31] found that the median values of the APE of these three models, which were used to run the computer-controlled infusion pump, were 61%, 33% and 21%, for McClain's, Scott's, and Shafer's models, respectively. One of the authors (K.S.) used these three models as simulators to predict fentanyl plasma concentrations during surgeries of various durations and found that McClain's program underestimated plasma concentrations when infusion was prolonged. The APE values of Scott's and Shafer's models were approximately 30%, but Shafer's program tended to overestimate the value of fentanyl plasma concentrations [32].

Influence of age on the pharmacokinetics and pharmacodynamics of fentanyl

There is a general belief that elderly patients require lower amounts of opioids for analgesia [33], implying that opioid pharmacokinetics are altered or the pharmacodynamic sensitivity of the brain to opioids is increased in the elderly. Yet, there are surprisingly few unambiguous data demonstrating definite age-related changes in pharmacokinetics or pharmacodynamics. In 1982 Bentley et al. [34], comparing classical pharmacokinetics in four elderly and five younger patients, reported that clearance was decreased in the elderly patients, but subsequent investigators were not able to find age differences in pharmacokinetic parameters [35,36]. However, differences in fentanyl concentrations in arterial blood were detected 2–4 min after a bolus infusion of fentanyl [35]. Scott et al. [36] firmly established that the fentanyl serum concentrations required to produce slowing of the spectral edge of the EEG were significantly (approximately 50%) decreased in elderly patients as compared with younger patients. However, it is uncertain whether EEG slowing reflects the analgesic effect of fentanyl, because EEG slowing occurs at much higher fentanyl plasma concentrations ($7\,ng \cdot ml^{-1}$) than those required for analgesia ($1–2\,ng \cdot ml^{-1}$). We compared fentanyl plasma concentrations required to produce effective postoperative pain relief in elderly and younger patients. The

differences in mean values were small (14%), and there were large (fivefold) interindividual differences in both groups. It appears that pharmacodynamic sensitivity may increase in some elderly patients, but the changes are not uniform. In many elderly patients (37%), the pharmacodynamic requirements of opioids for analgesia were equal to or higher than the mean value in younger patients [32]. Therefore, the dose of fentanyl required for analgesia must be titrated individually, especially in the elderly.

Effects of total body weight on the pharmacokinetics of fentanyl

Currently available three-compartment pharmacokinetic models of fentanyl are not weight-adjusted. Thus, the predicted value of fentanyl plasma concentration, with the same dose per kilogram, for 100-kg patients is double that for 50-kg patients, because a computer calculates plasma concentrations using the same non-weight-adjusted model for both 50-kg and 100-kg patients, resulting in doubling of the dose. Shafer [31] scaled volumes and clearance of his model to body weight, but the weight-adjusted model did not result in improvement of APE. Accordingly, Shafer recommended that, for simplicity, non-weight-adjusted models be used for patients weighing 40–90 kg. We modified the predicted values of fentanyl concentration (Cp) using the following formula: modified values = Cp $\times$ 69/total body weight (kg). We found improvement of APE in a group of patients that included obese patients [37]. Therefore, body weight is certainly an important factor in determining doses of fentanyl.

Designing a fentanyl infusion scheme

Respiratory depression may occur in conscious patients at fentanyl plasma concentrations higher than 2–3 ng·ml^{-1} [38]. The fentanyl plasma concentration required for postoperative analgesia is approximately 1.5 ng·ml^{-1} [24]. Therefore, if analgesic effects of fentanyl without respiratory depressant effects are desired, it would be reasonable to aim for fentanyl plasma concentrations of 1–1.5 ng·ml^{-1} at extubation [39]. During surgery with inhalational anesthetics or with intravenous agents such as propofol, we now know that fentanyl plasma concentrations of 1–3 ng·ml^{-1} effectively attenuate movements and hemodynamic cardiac responses to surgical stimuli. Increasing fentanyl plasma concentrations above 3 ng·ml^{-1} has little additional attenuating effect.

Ausems et al. [40] defined Cp_{50} of alfentanil in the presence of 66% nitrous oxide for various surgical stimuli. The highest concentrations were required at endotracheal intubation. The concentration of alfentanil required for skin closure was less than that required for skin incision or spontaneous ventilation. This finding allows the opioids to be titrated gradually downwards toward the end of surgery [41]. Using a graph from Shafer's study [28], one realizes that a decrease in fentanyl plasma concentration of approximately 30% occurs over 40–60 min, if fentanyl infusion is terminated after 4 h (Fig. 3). If the fentanyl plasma concentration is required to decrease to 1.5 ng·ml^{-1} during a period of 40–60 min, one can easily calculate that the fentanyl plasma level should be 2.1 ng·ml^{-1} (1.5/0.7) when the infusion is terminated after 4 h. Therefore, the fentanyl plasma concentration should be approximately 2 ng·ml^{-1} toward the end of surgery, and the fentanyl infusion should be discontinued 40–60 min before the expected extubation.

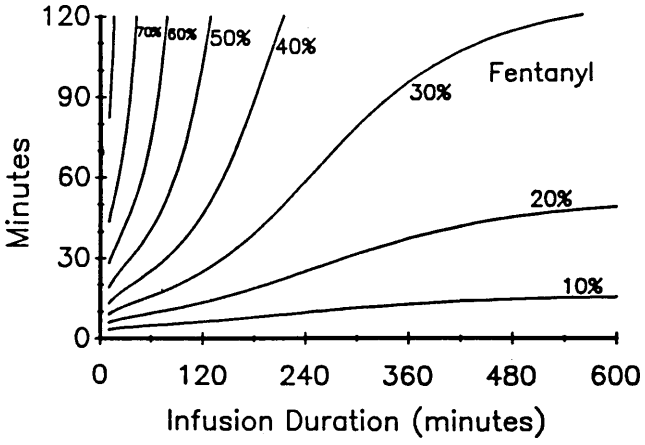

Fig. 3. Recovery curves for fentanyl showing the time required for decreases of a given percentage from the maintained intraoperative effect site concentration after termination of infusion (from Shafer et al. [28], with permission)

How can we design a dosing scheme of fentanyl for major surgery lasting 5 h to produce concentrations of 1–3 ng·ml^{-1} during surgery, 2 ng·ml^{-1} toward the end of surgery, and 1–1.5 ng·ml^{-1} at extubation? One way is to use a computer-assisted continuous infusion pump (CACI) or a target-controlled infusion system (TCI). However, these devices have not yet been approved by the US Food and Drug Administration. Another way of designing an infusion scheme is to use a computer simulation. Stanpump [31] is a software program containing three-compartment pharmacokinetic programs for various anesthetic agents that is available without charge from S.L Shafer, M.D., of Stanford University, Stanford, CA, USA. The following is an example of an infusion scheme of fentanyl devised by one of the authors (K.S.). For major abdominal surgery lasting 5 h, we recommend a bolus of fentanyl at 2–5 μg·kg^{-1}

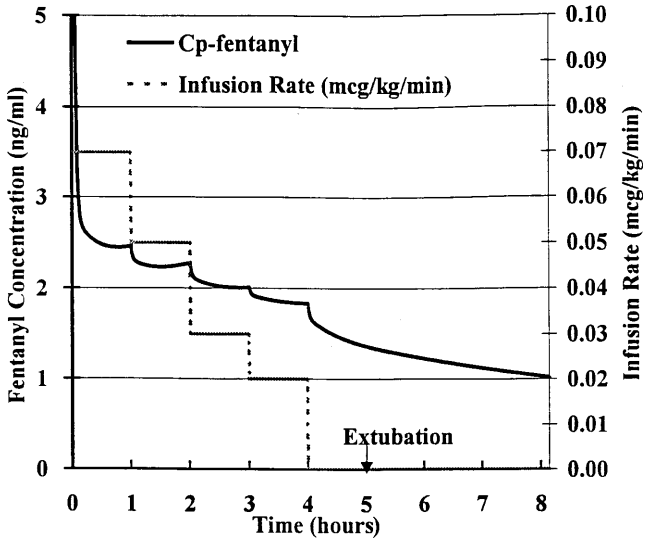

Fig. 4. Design of an infusion scheme for major surgery lasting 5 h. *Dashed lines* represent the infusion rate and *solid lines* represent Cp (predicted plasma concentration) of fentanyl

followed by hourly stepdown infusion at rates of 0.07, 0.05, 0.03, and 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The infusion is terminated 40–60 min before the expected time of the end of surgery (Fig. 4). For surgery lasting less than 2 h, the infusion scheme of fentanyl can be more flexible, because a decrease in plasma concentration of approximately 40%–50% is expected 30–40 min after termination. For surgery lasting more than 10 h, a lower infusion rate% 1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or 0.02 $\mu g \cdot kg^{-1} \cdot min^{-1}$ may be reasonable during the latter part of surgery. During the first half of surgery, one can use the same infusion scheme described for 5 h of surgery.

During balanced anesthesia, fentanyl is combined with inhalational agents or propofol. The authors prefer to maintain a constant fentanyl plasma concentration and vary the doses of inhalational agents or propofol as needed, because recovery from drug effects at the termination of administration is faster for inhalational agents or propofol. If remifentanil is used, one can vary the dose (plasma concentration) of remifentanil rather than varying the doses of propofol or inhalational agents. The context-sensitive half-time of remifentanil is 4 min and is not affected by the duration of infusion. Thus, the infusion rate of remifentanil is proportional to the remifentanil plasma concentration (and effect site concentrations), and recovery from the effects of remifentanil is rapid. Therefore, TCI is not needed for the infusion of remifentanil in clinical practice. It may be preferable to administer remifentanil to a high opioid concentration of 4–8 $ng \cdot ml^{-1}$ (which corresponds to 0.15–0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$) with just sufficient hypnotic agents to ensure unconsciousness [41].

The ideal combination of opioids and inhalational anesthetics or hypnotics is that which provides adequate intraoperative anesthesia and allows for rapid recovery. According to Katoh and Ikeda [19], the drug interaction between sevoflurane and fentanyl for MAC-awake is not the same as that seen for MAC. At fentanyl plasma concentrations of 1–3 $ng \cdot ml^{-1}$, the MAC of sevoflurane is reduced significantly (approximately 50%), whereas fentanyl at this range of concentrations causes only a modest reduction (15%) in MAC-awake (Fig. 1). Thus, fentanyl may significantly reduce the anesthetic requirements of sevoflurane, at a relatively low concentration, but the fentanyl concentration in this range does not significantly delay awakening from sevoflurane anesthesia. This information provides clinicians with a guide for optimal dosing during surgery and awakening. If interactions between opioids and hypnotics are similar for both MAC reduction effects and MAC-awake reduction, the use of opioids in general anesthesia reduces some of the benefit, because awakening may be delayed. The differences in opioid–propofol interactions between $Cp_{50incision}$ (plasma concentrations of propofol that attenuate movement response to incision in 50% of patients) and $Cp_{50sleep}$ (plasma concentrations of propofol that induce sleep in 50% of patients) are less clear. Smith et al. [20] reported a significant reduction of $Cp_{50incision}$ at fentanyl concentrations in the range of 1–3 $ng \cdot ml^{-1}$, but the reduction in $Cp_{50sleep}$ was modest. Vuyk et al. [42], however, reported that alfentanil significantly decreased the Cp_{50} of propofol concentrations at which patients regained consciousness. Accordingly, they noted the possibility of delay in awakening from opioid–propofol anesthesia. Vuyk et al. calculated the time required for awakening from surgical anesthesia with an optimal combination of propofol and opioid. After 60 min of propofol–fentanyl anesthesia (50% probability of no response to surgical stimuli), 50% of patients are expected to respond to verbal stimuli at 12 min, when propofol concentration decreases from 3.42 to 1.70 $\mu g \cdot ml^{-1}$ and fentanyl plasma concentration decreases from 1.26 to 0.93 $ng \cdot ml^{-1}$. Recovery from propofol–fentanyl anesthesia is relatively rapid when the duration of infusion is not prolonged, but after surgical anesthesia lasting for 300 min, 19.6 min was needed until awakening in 50% of the patients, when propofol concentratio decreased from 3.72 to 1.68 $\mu g \cdot ml^{-1}$, and fentanyl blood concentration decreased from 1.11 to 0.94 $ng \cdot ml^{-1}$. If remifentanil is selected as an opioid during propofol anesthesia, awakening from surgical anesthesia in 50% of patients can occur 6.7 min after 300 min of remifentanil–propofol anesthesia [42]. With the use of desflurane–fentanyl anesthesia for surgery for repair of an abdominal aortic aneurysm lasting approximately 5 h, extubation was performed at fentanyl plasma concentrations of appro-

ximately 1.5 ng·ml^{-1}. Significant delay in awakening or serious respiratory depression was rare in this patient group, which included elderly patients and patients with chronic obstructive palmonary disease [39]. Fentanyl and desflurane or sevoflurane appear to be good combinations for major surgery, especially for elderly patients, because decrease in the effect site concentration of sevoflurane or desflurane after discontinuation is little affected by the duration of anesthesia, as compared with that seen after the use of isoflurane.

Conclusions

The pharmacokinetic characteristics of fentanyl are unique. The context-sensitive half-time of fentanyl is longer than that of sufentanil, alfentanil, or remifentanil if infusion is longer than 2 h. This means that recovery of drug effects of fentanyl following prolonged infusion is slower than that of sufentanil, alfentanil, or remifentanil. Therefore, understanding of pharmacokinetics based on a three-compartment model is essential in avoiding overdosing in prolonged cases.

The ideal combination of opioids and inhalation anesthetics or hypnotics is that which provides adequate intraoperative anesthesia and allows for rapid recovery. Relatively low blood concentrations of fentanyl (1–3 ng·ml^{-1}) allow reduction of doses of inhalation agents or hypnotic agents needed during the intraoperative period. Thus, the combination of low-dose fentanyl and inhalation agents/hypnotics provides balanced anesthesia with circulatory stability and rapid recovery from anesthesia.

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