

## ***Alfentanil Causes Less Postoperative Nausea and Vomiting than Equipotent Doses of Fentanyl or Sufentanil in Outpatients***

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**Background:** The relative potencies of alfentanil, fentanyl, and sufentanil as a risk factor for postoperative nausea and vomiting have not been determined. They were compared in a randomized study designed to obtain equipotent plasma concentrations of these three opioids at the beginning of the recovery period.

**Methods:** The study included 274 patients treated on an outpatient basis. The steady state opioid plasma concentration providing a predicted 50% reduction of the minimum alveolar concentration of isoflurane was used to determine the relative potency of the opioids. The opioids were prepared in equal volumes at concentrations of alfentanil 150 µg/ml, fentanyl 50 µg/ml, and sufentanil 5 µg/ml and were administered in vol/kg. Anesthesia was induced in a blinded fashion with a bolus of the study opioid (0.05 ml/kg) and 4–6 mg/kg thiopental and was maintained with isoflurane (0.6–1%) in a nitrous oxide–oxygen mixture with a continuous infusion of the study opioid (0.06 ml · kg<sup>-1</sup> · h<sup>-1</sup>). If necessary, up to five additional boluses of opioid (0.02 ml/kg) could be given. This opioid administration protocol was tested by pharmacokinetic simulations.

**Results:** The incidence of postoperative nausea and vomiting was not different in the postanesthesia care unit, but in the ambulatory surgery unit it was significantly lower for alfentanil compared with fentanyl and sufentanil (12, 34, and 35%, respectively  $P < 0.005$ ). Pharmacokinetic modeling showed that the end-anesthesia opioid plasma concentrations were approximately equipotent in the three groups. However, modeling does not support that the difference between groups in the postoperative period can be explained by a more rapid disappearance of alfentanil from the plasma.

**Conclusions:** Alfentanil, compared with approximately equipotent doses of fentanyl and sufentanil, is associated with a lower incidence of postoperative nausea and vomiting in outpatients. (Key words: Complication; emesis; narcotic.)

POSTOPERATIVE nausea and vomiting (PONV) is a frequent complication of anesthesia for outpatient surgery. In adults, the incidence of PONV after general anesthesia is approximately 10% in the postanesthesia care unit (PACU),<sup>1-3</sup> increasing to more than 40% if follow-up continues beyond the PACU period.<sup>3-5</sup> When patients are asked about problems associated with previous anesthesia, nausea and vomiting frequently are mentioned.<sup>6,7</sup> Because PONV is an important cause of delay of discharge and unplanned hospital admission<sup>8,9</sup> and an increasing number of surgical procedures are performed on an outpatient basis, requiring early ambulation,<sup>10</sup> the importance of reducing the incidence of PONV is clear.

Many risk factors for PONV have been identified.<sup>3,5,10-12</sup> Patient-related risk factors include younger age, female gender, history of PONV after previous anesthesia, and history of motion sickness. Some types of surgical procedures (e.g., middle ear surgery, laparoscopic procedures) are associated with greater incidences of PONV than others.<sup>12</sup> Anesthetic risk factors typically include longer duration of anesthesia, general *versus* regional anesthetic technique, use of inhalation anesthetics *versus* propofol, reversal of neuromuscular blockade, and use of opioids.<sup>3,5,11,13</sup> Three synthetic opioids, alfentanil, fentanyl and sufentanil, have been used in anesthetic practice for many years. However, their relative emetic potency has yet to be determined. Therefore, this prospective, randomized, double-blind study was designed to compare the incidences of PONV associated with an anesthetic protocol designed to obtain approximately equipotent end-anesthesia plasma concentrations of alfentanil, fentanyl, and sufentanil in outpatients.

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‡ Associate Professor of Anesthesiology. Received from the Department of Anesthesiology, Laval University, Quebec City, Canada. Submitted for publication November 3, 1998. Accepted for publication July 15, 1999. Support was provided solely from institutional and/or departmental sources. Presented in part at the annual meeting of the Canadian Anaesthetists' Society, Vancouver, British Columbia, Canada, June 8, 1997.

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## Materials and Methods

The protocol was approved by an institutional review board. Over a 4-month period, every eligible patient was contacted by phone the day before surgery and given a complete explanation of the study. Included were patients between the ages of 18 and 65 yr, classified as American Society of Anesthesiologists physical status I or II, and scheduled for an elective surgical procedure during general anesthesia on an outpatient basis. Exclusion criteria were pregnancy, breast feeding, intake of any antiemetic drug within 24 h before surgery, allergy to any of the study medications, and morbid obesity. Patients were met the morning of surgery, their questions about the protocol were answered, and a written informed consent was obtained.

### Preparation and Administration of Opioids

The steady state plasma opioid concentration providing a predicted 50% reduction of the minimum alveolar concentration (MAC) of isoflurane (ISOMAC<sub>50</sub>) was used to determine the relative potency of alfentanil, fentanyl and sufentanil. ISOMAC<sub>50</sub> values for alfentanil, fentanyl, and sufentanil are 50, 1.67, and 0.145 ng/ml, respectively.<sup>14</sup> These figures translate to a potency ratio of alfentanil:fentanyl:sufentanil of 0.033:1:11.5. To compare emetic potencies, the opioids were administered using an anesthetic protocol designed to obtain equipotent plasma concentrations intraoperatively and, most importantly, at the beginning of the recovery period. Identical volumes of different dilutions of the study opioids were prepared in 60-ml syringes and were administered in vol/kg doses to ensure the double-blind nature of the study. The dilutions of the three opioids were determined using standard pharmacokinetic calculations,<sup>14</sup> and the pharmacokinetic parameters for opioids reported by Scott and Stanski<sup>15</sup> for alfentanil and fentanyl and by Hudson *et al.*<sup>16</sup> for sufentanil (Appendix). The opioids were prepared in equal volumes of 20 ml at a concentration of 150 µg/ml alfentanil, 50 µg/ml fentanyl, and 5 µg/ml sufentanil. The opioid-administration protocol consisted of a bolus of 0.05 ml/kg given at the time of induction of anesthesia followed by a fixed-rate infusion at 0.06 ml · kg<sup>-1</sup> · h<sup>-1</sup> throughout the surgical procedure. If the anesthetic depth was judged to be insufficient, up to five additional 0.02-ml/kg boluses could be administered. Boluses and infusions of opioids were given using a volumetric syringe pump.

Each patient was assigned by a computer-generated random table to one of three groups to receive one of

the three study opioids. The opioid syringes were identified only by the patient enrollment number. All investigators were unaware of the content of the opioid syringes, except for the research assistant who prepared the opioid syringes and who was involved neither in the management of anesthesia nor in data collection.

### Anesthetic Protocol

Patients were given no premedication. At arrival in the operating room, an intravenous infusion of lactated Ringer's solution was started *via* a large-bore antecubital vein. Monitoring included two-lead electrocardiography, noninvasive blood pressure measurement, nasopharyngeal temperature measurement, oxygen saturation measurement, capnography, and train-of-four stimulation of the ulnar nerve at the wrist. Anesthesia was induced by the initial bolus of the study opioid and 4–6 mg/kg thiopental, and a neuromuscular blocking agent was given to facilitate tracheal intubation. Minute ventilation was adjusted to keep the end-tidal carbon dioxide pressure between 35 and 40 mmHg. Anesthesia was maintained with isoflurane (0.6% end-tidal) in a nitrous oxide–oxygen mixture (60–40%) and the continuous infusion of the study opioid. If the anesthetic depth was judged to be insufficient, additional boluses of the study opioid were administered and isoflurane could be increased to 1.0%. No patient received any prophylactic antiemetic drug as part of the anesthetic technique. Ten minutes before the end of surgery, the opioid infusion was discontinued. Residual neuromuscular blockade was antagonized with 40 µg/kg neostigmine and 10 µg/kg glycopyrrolate, if indicated. Nitrous oxide and isoflurane were then discontinued, and the trachea was extubated when the patient was awake. If a gastric tube had been used, it was aspirated and removed at that time. Patients were then transferred to the PACU for standard care and monitoring for at least 60 min. After that, patients were observed in the ambulatory surgery unit (ASU) and were discharged from the hospital when they scored at least 9 on the Chung postoperative recovery scale.<sup>17</sup> In the PACU and the ASU, pain was treated with 30–60 mg ketorolac intravenously, followed, if necessary, by 1.0 mg/kg intramuscular meperidine. No other opioid was used in the postoperative period. Patients who experienced PONV were treated with 10 mg metoclopramide intravenously, followed, if necessary, by 0.625–1.25 mg droperidol intravenously.

### Measurements

Patients were observed for emetic symptoms during PACU and ASU stays. Data were collected by a nurse unaware of the patient study groups. *Vomiting* was defined as the forceful expulsion of any amount of gastric content, *retching* as expulsive efforts without expulsion of any material, and *nausea* as the subjective sensation of the need to vomit. Patients were asked about their general state of comfort, but no direct question about nausea was asked. The following day the same information about the 24-h period after discharge was obtained during a phone interview.

### Pharmacokinetic Modeling

The opioid preparation and administration protocol was tested using pharmacokinetic simulations using the STANPUMP and STELPUMP programs developed by Steven L. Shafer (Department of Anesthesia, Stanford University, Stanford, CA) and by Johan Coetzee and Ralph Pina (Department of Anaesthesia, University of Stellenbosch, South Africa), respectively (STANPUMP and STELPUMP are available at <http://pkpd.icon.paloalto.med.va.gov>). These simulations were run at the end of the study for the mean age and weight of patients enrolled in each group and using the mean number of additional boluses actually received in each group. One additional bolus (0.02 ml/kg) was administered 10 min after induction (at the time of skin incision), and the remaining fraction of additional bolus was administered at 20 min. The infusions were run for the actual mean duration of anesthesia. Then the infusions were discontinued, but the pharmacokinetic simulations were continued for a total of 450 min to include in the modeling the postoperative disappearance of the opioids from the plasma. To allow easier comparison of the opioids in terms of equipotency, the absolute plasma concentration numbers obtained from these simulations were normalized to ISOMAC<sub>50</sub> equivalents (the plasma concentration of the opioid divided by its ISOMAC<sub>50</sub> value).

### Statistical Analysis

The primary endpoint of the study was the risk of experiencing at least one emetic episode (nausea or retching or vomiting) during the first 24 h after surgery. From a previous study, we estimated the incidence of PONV in our population during the 24-h postoperative period at 40%.<sup>2</sup> Using type I ( $\alpha$ ) and type II ( $\beta$ ) errors of 0.05 and 0.2 respectively, and considering a 50% difference in the incidence of PONV as the minimal relevant difference, we calculated that a sample of 90 patients per

**Table 1. Patient Demographic Characteristics**

	Alfentanil	Fentanyl	Sufentanil
Number of patients	91	84	99
Age (yr)	37 ± 10.8	38 ± 12.3	38 ± 12.5
Sex (M/F)	44/47	44/40	54/45
Weight (kg)	71.0 ± 16.6	69.9 ± 16.7	69.9 ± 13.9
ASA Physical Status (I/II)	76/15	65/19	78/21
Menstrual cycle (1–8 days) (% of female patients)	21	25	31
History of motion sickness (%)	17	16	17
History of PONV (%)	15	20	24

Data are mean ± SD, or percentages (%). There were no significant differences between the three groups for all variables.

ASA = American Society of Anesthesiologists; PONV = postoperative nausea and vomiting.

group would be necessary. Data are reported as the mean ± SD or as percentages. Continuous parametric variables were analyzed using one-way analysis of variance and the Tukey–Kramer multiple comparisons test, if appropriate. Nonparametric variables were compared with the chi-square test and the Kruskal–Wallis test with the Dunn multiple comparisons test. A probability level less than 0.05 was considered significant.

### Results

Interviewed by phone, 289 patients agreed to be included in the study. When these patients were met on the morning of surgery, 10 were excluded because of planned postoperative hospital admissions or because they decided to undergo surgery during regional anesthesia. Therefore, 279 patients signed a written informed consent and were included in the study. Among these patients, five did not complete the protocol, because of either technical problems with the infusion pump (four patients) or severe intraoperative hypertension necessitating protocol discontinuation (one patient). The number of patients completing the protocol and included in the analysis was 274 (alfentanil, 91; fentanyl, 84; sufentanil, 99). Five of these patients required an unplanned hospital admission, although none of those was related to PONV (causes were surgical bleeding, two patients; severe pain, two patients; and further medical investigation, one patient). Thus, the analysis of the data collected after PACU stay included 269 patients (alfentanil, 90; fentanyl, 82; sufentanil, 97). Table 1 shows patient

ALFENTANIL, FENTANYL, SUFENTANIL, AND PONV

**Table 2. Anesthetic and Surgical Data**

	Alfentanil	Fentanyl	Sufentanil
Number of patients	91	84	99
Type of surgery (%)			
Orthopedics	26	29	31
Eye	7	6	11
ENT	28	29	27
General	11	11	10
Gynecologic	18	19	15
Other	10	7	5
Laparoscopic surgery (%)	16	17	15
Neuromuscular blockade reversal (%)	59	50	62
Intraoperative gastric tube (%)	26	27	21
Duration of anesthesia (min)	58 ± 26	61 ± 28	64 ± 32
Total volume of opioids (ml)	9.36 ± 3.36	9.07 ± 4.07	8.63 ± 3.44
Additional boluses (number)	1 (1-3)	1 (0-2)	1 (0-2)*

Data are mean ± SD, or percentages (%), except for number of additional boluses where data are median and 25th-75th centile.

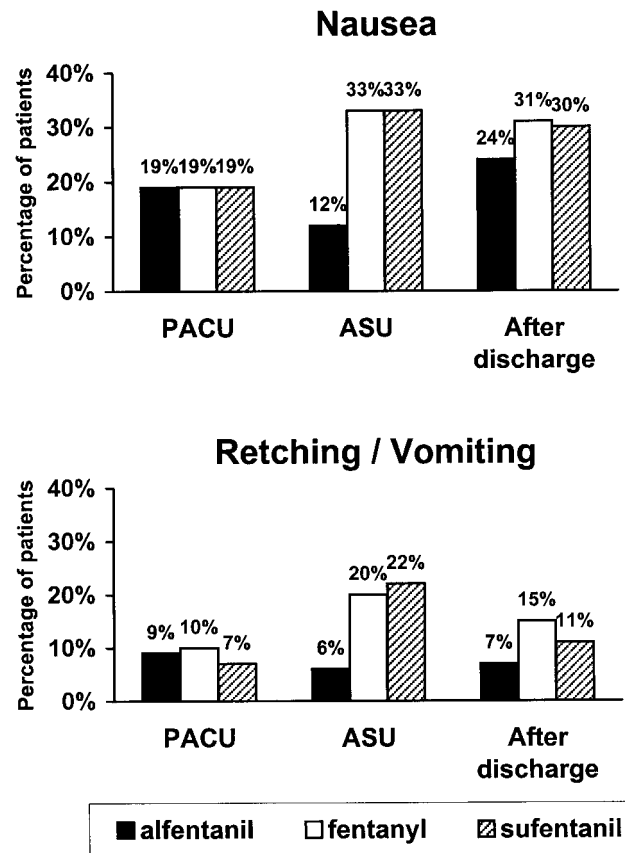
\* *P* < 0.05, alfentanil versus sufentanil. There were no significant differences between the three groups for all other comparisons.

ENT = ear, nose, throat.

characteristics. There were no differences among the three groups with respect to age, sex, weight, physical status, period of menstrual cycle, history of emesis after a previous anesthesia, or history of motion sickness. Table 2 shows anesthetic and surgical data. The three groups were comparable for the type of surgery, reversal of neuromuscular blockade, use of a gastric tube intraoperatively, duration of anesthesia, and total volume of study opioid received. Patients in the alfentanil group received more additional boluses than in the sufentanil group (*P* < 0.05). The total doses of opioids received were 1,401 ± 504 μg, 454 ± 204 μg, and 43 ± 17 μg in the alfentanil, fentanyl, and sufentanil groups, respectively.

In the PACU, there was no difference in the incidence of nausea and of retching or vomiting among the three opioid groups (fig. 1). However, in the ASU, the incidence of nausea was significantly lower in the alfentanil group than in the fentanyl and sufentanil groups (*P* < 0.01 for both comparisons; fig. 1). The incidence of retching or vomiting in the ASU also was significantly lower in the alfentanil group than in the fentanyl group (*P* < 0.05) and the sufentanil group

(*P* < 0.01). The relative risk and the absolute reduction in risk for PONV between alfentanil and fentanyl were 0.35 (95% confidence interval, 0.19-0.65) and 23% (95% confidence interval, 11-35), respectively, and were 0.36 (95% confidence interval, 0.19-0.67) and 22% (95% confidence interval, 9-34) between alfentanil and sufentanil, respectively. After discharge from the hospital, the incidences of nausea and of retching or vomiting were not different among the three groups (fig. 1). Over the 24-h postoperative period, the incidence of PONV (nausea or retching or vomiting) in the alfentanil group was significantly



**Fig. 1.** Incidence of nausea (top) and of retching or vomiting (bottom) for each of the three groups in the postanesthesia care unit (PACU), in the ambulatory surgery unit (ASU), and after discharge from hospital. In the PACU, no difference among the three opioid groups was present, neither for nausea nor for retching or vomiting. In the ASU, the incidences of nausea and of retching or vomiting were significantly lower with alfentanil compared with fentanyl (*P* < 0.05) and sufentanil (*P* < 0.01; *n* = 91, 84, and 99 for the alfentanil, fentanyl, and sufentanil groups, respectively, in the PACU; *n* = 90, 82, and 97 for the alfentanil, fentanyl, and sufentanil groups, respectively, in the ASU and after discharge).

**Table 3. Postoperative Pain Control and Discharge Times**

	Alfentanil	Fentanyl	Sufentanil
Analgesic medication (% of patients)			
Ketorolac	67	68	60
Meperidine	31	20	11*
Discharge times (min)			
PACU	79 ± 23	80 ± 30	80 ± 28
ASU	175 ± 66	187 ± 80	186 ± 74

Data are mean ± SD, or percentages (%).

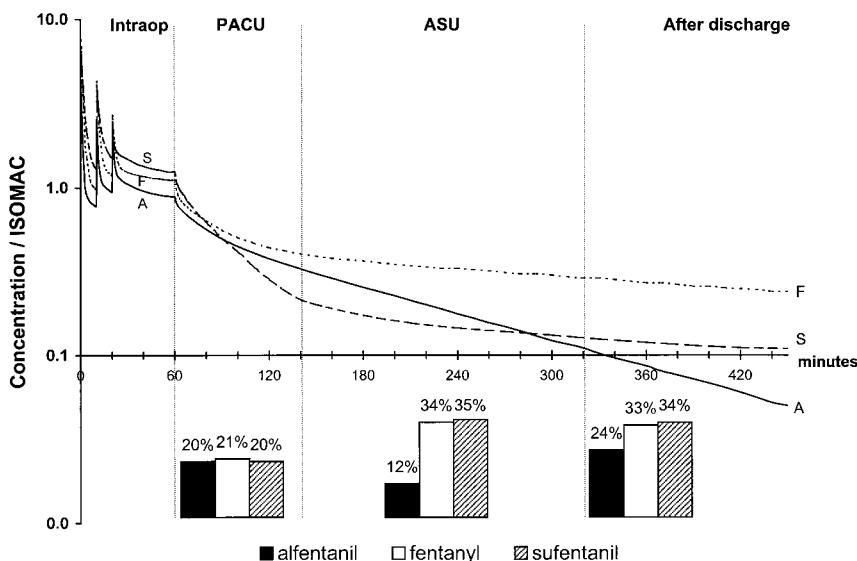
\*  $P < 0.05$ , sufentanil versus alfentanil. There were no significant differences between the three groups for all other comparisons.

ASU = ambulatory surgical unit; PACU = postanesthesia care unit.

lower than in the fentanyl group ( $P < 0.05$ ), but the difference with the sufentanil group was not significant. The numbers of patients who received an antiemetic drug were distributed in a pattern similar to the incidence of PONV: There was no difference in the PACU (alfentanil 15%, fentanyl 17%, sufentanil 18%), but significantly fewer patients in the alfentanil group received an antiemetic drug in the ASU (8% vs. fentanyl 27% and sufentanil 26%;  $P < 0.01$  for both comparisons). The number of patients that received ketorolac for postoperative pain control was not different among the three groups, but fewer patients in the sufentanil group required supplemental meperidine ( $P < 0.05$ , table 3). Duration of stay in the PACU and the ASU were not different among the three groups (table 3).

### Pharmacokinetic Modeling

The results of the pharmacokinetic simulations are presented in figure 2. The infusions were discontinued at 60 min, the mean duration of anesthesia. The mean number of additional boluses actually received in each group and entered in the simulation was 1.84, 1.48, and 1.16 for alfentanil, fentanyl, and sufentanil, respectively. These computer simulations predicted that, at the end of anesthesia, opioid plasma concentrations would be 44.2, 1.85, and 0.18 ng/ml, which translated into ISOMAC<sub>50</sub> equivalents of 0.88, 1.11, and 1.24 for alfentanil, fentanyl, and sufentanil, respectively. During the PACU period, although the plasma concentrations of the three opioids decreased rapidly, the sufentanil plasma concentration decreased more rapidly than the two others. At 20 min in the PACU period, the plasma concentrations of the three opioids were equipotent (0.56, 0.63, 0.62 ISOMAC<sub>50</sub> equivalents for alfentanil, fentanyl, and sufentanil, respectively). Thereafter, for the second half of the PACU period and until the end of the ASU period, the sufentanil ISOMAC<sub>50</sub> equivalents remained lower than the alfentanil and fentanyl equivalents, in which decay was the slowest. At the beginning of the ASU period, alfentanil, fentanyl, and sufentanil ISOMAC<sub>50</sub> equivalents were 0.33, 0.40, and 0.21, respectively. After patients were discharged from the ASU, plasma concentrations of the study opioids, with the possible exception of fentanyl, were very low. The differences in the incidence of PONV among the three groups were not linked to relative opioid plasma concentration at any stage of the postoperative period (fig. 2).



**Fig. 2.** (Top) Pharmacokinetic modeling of the plasma concentration (expressed as concentration/ISOMAC<sub>50</sub> on the y-axis) of alfentanil (A), fentanyl (F), and sufentanil (S) during the intraoperative, the postanesthesia care unit (ASU) periods and after discharge from the ASU. The x-axis is time (minutes) from the induction of anesthesia. (Bottom) The incidence of postoperative nausea and vomiting (nausea, retching, or vomiting) during the postanesthesia care unit and the ASU period and after discharge from the ASU.

## Discussion

The objective of this prospective, randomized, double-blind study was to investigate whether alfentanil, fentanyl, and sufentanil used as part of a balanced anesthetic technique would be associated with different risks of PONV in the 24-h period after outpatient surgery. To obtain meaningful results, each of the three study drugs were administered using an anesthetic protocol designed to obtain approximately equipotent plasma concentrations at the beginning of the recovery period. No difference in the incidence of PONV was observed between patients who received fentanyl or sufentanil. However, patients who received alfentanil experienced significantly less PONV than patients who received fentanyl or sufentanil, although this difference was not present at all stages of the postoperative period. Indeed, there was no difference among the three groups in the PACU. However, in the ASU, a significantly lower incidence of nausea and retching or vomiting was observed in the alfentanil group. After discharge, the lower incidence in the alfentanil group was not statistically significant.

Although the intraoperative use of opioids is a well-known risk factor for PONV,<sup>3,5,11,13</sup> little is known about the relative emetic potencies. Studies comparing the incidence of PONV after the use of various opioids as part of a general anesthetic technique are difficult to perform and have failed to show any strong evidence of differences among the commonly used synthetic opioids. Previous studies yielded conflicting results and have limitations. They concluded either the absence of difference among the opioids tested,<sup>18-21</sup> an increase in incidence of PONV with fentanyl compared with alfentanil<sup>22,23</sup> or sufentanil,<sup>24</sup> or an increase in incidence of PONV with alfentanil compared with fentanyl.<sup>25,26</sup> However, many of these studies included only women undergoing short-duration gynecologic procedures.<sup>19,21-26</sup> Also, the postoperative observation period either was not clearly defined or was limited to a few hours, and the assessment of PONV was only a secondary end point in most of these studies.<sup>18,19,21-23,25,26</sup> Other studies were unable to rule out a type II error in the conclusions because of the limited number of patients included.<sup>18,20</sup> Finally, and most importantly, the equipotency rate between the opioids was not based on objective markers of potency but was either chosen according to the authors' experience<sup>21-26</sup> or calculated *a posteriori* from the total dose of opioids received by the patients.<sup>19,20</sup> Therefore, no study has compared the incidence of PONV associ-

ated with alfentanil, fentanyl, and sufentanil in the general outpatient population in an anesthetic protocol based on an objective marker of potency and using the pharmacokinetic characteristics of these opioids to administer them in equipotent doses.

The anesthetic protocol was designed to allow the administration of clinically equipotent doses of the study opioids throughout most of the intraoperative period and, most importantly, to obtain equipotent plasma concentration at the beginning of the postoperative period. ISOMAC<sub>50</sub>, an objective measure of the anesthetic potency of opioids in a balanced anesthetic technique, was used to determine the relative potency of alfentanil, fentanyl, and sufentanil.<sup>14</sup> The administration of the study opioids in equipotent dosage also was complicated by their different pharmacokinetic characteristics. The administration of a single intravenous bolus of the study opioid at the induction of anesthesia, followed by an inhalation agent, would not yield equipotent plasma concentrations of the different opioids at the end of anesthesia. With such a protocol, every opioid might not be given an "equal chance." Therefore, in this study, the opioids were administered in a double-blind manner by a bolus, followed by an infusion. The administration of smaller additional boluses was also permitted if the anesthetic depth was judged to be inadequate. This blinded administration protocol probably allowed the patients in the three groups to receive clinically equipotent amount of opioids, although the computer simulations suggest that the plasma concentration of alfentanil at the end of anesthesia was slightly lower than for sufentanil (fig. 2). It must also be recognized that there is great variability in pharmacokinetic parameters of opioids, and only plasma sampling for opioid assay at the end of surgery could have provided firm data regarding opioid equipotency at the beginning of the postoperative period.

The influence of opioids on PONV is probably more related to the plasma concentrations at the time emetic symptoms occur than to the intraoperative concentrations. Therefore, the postoperative period is the most important part of the pharmacokinetic modeling in the interpretation of our results. Figure 2 shows that the patterns of opioid plasma concentration decay are markedly different for alfentanil, fentanyl, and sufentanil. In the PACU, the plasma concentrations of the three opioids were quite equipotent and the incidence of PONV was identical for the three groups. This suggests that the opioid drug used during anesthesia was not a critical factor in the occurrence of PONV in the PACU. How-

ever, in the ASU, the plasma concentrations of the three opioids were much lower than during the PACU period and were not equipotent anymore. At the beginning of the ASU period, alfentanil, fentanyl, and sufentanil plasma concentrations were 0.33, 0.40, and 0.21 ISO-MAC<sub>50</sub>, respectively, and this difference persisted for most of the ASU period. Meanwhile, the incidences of PONV in both the fentanyl and the sufentanil groups were three times higher than in the alfentanil group. After discharge from the hospital, the plasma concentrations of opioids were very low (with the possible exception of fentanyl) and the incidence of PONV was not different among the three groups. In summary, the differences in the incidence of PONV among the three groups were not linked to the relative opioid plasma concentrations (ISOMAC<sub>50</sub> equivalent) at any stage of the postoperative period, and the lower incidence of PONV observed with alfentanil cannot be explained by a lower relative plasma concentration.

Postoperative pain can promote PONV and, although nausea and vomiting are side effects of opioids, adequate pain control with opioids can also relieve PONV.<sup>4,5,27,28</sup> These conflicting factors can complicate the study of PONV. In this study, postoperative pain was treated with a nonopioid drug (intravenous ketorolac) as a first line, followed, if necessary, by intramuscular meperidine (an opioid different from the study opioids). A lower degree of postoperative pain could have explained the lower incidence of PONV in the alfentanil group, but patients in the alfentanil group actually received more meperidine, thereby suggesting more postoperative pain. It is interesting to note that neither postoperative pain nor the administration of meperidine seems to have affected PONV adversely. It has also been suggested that opioids cause PONV by sensitizing the vestibular apparatus to the effect of movement, which has been identified as a frequent trigger for PONV.<sup>29</sup> The differences in incidence of PONV in the ASU could be related to differences in the time or magnitude of mobilization. However, considering the large number of patients included in this study, it is reasonable to assume that mobilization in the ASU was comparable among the three groups. Another possible explanation for the differences in the incidence of PONV is that pharmacodynamic differences exist among alfentanil, fentanyl, and sufentanil. However, neither the precise mechanism nor the receptor by which opioids induce emesis is well-known. Obviously, further pharmacodynamic studies are necessary to better understand the relative emetic effects of alfentanil, fentanyl and sufentanil.

In summary, the incidence of PONV in the ASU was significantly lower in patients who received alfentanil compared with approximately equipotent plasma concentrations of fentanyl or sufentanil. Pharmacokinetic modeling of the plasma concentration of opioids in the postoperative period does not support the hypothesis that the differences in the incidence of PONV among the three opioid groups are related to their different pharmacokinetic characteristics. This study suggests that the selection of an opioid can affect the incidence of PONV in outpatient surgery.

The authors thank H el ene Brassard, R.N., and Diane Paquet, R.N. (research assistant nurses), and Line Godin for secretarial assistance.

## Appendix 1

### Pharmacokinetic Parameters and Equations of Opioids

	Alfentanil	Fentanyl	Sufentanil
Target plasma concentration (C <sub>T</sub> ) (ng/ml)	50	1.67	0.145
Volume of distribution (per 70 kg) (l)*			
Peak effect (V <sub>d</sub> peak effect)	5.9	75	89
Central (V <sub>1</sub> )	2.19	12.7	17.8
Micro rate constants (min <sup>-1</sup> )†			
K <sub>10</sub>	0.0910	0.0492	0.0653
K <sub>12</sub>	0.656	0.380	0.272
K <sub>21</sub>	0.214	0.0960	0.102
K <sub>13</sub>	0.113	0.179	0.0723
K <sub>31</sub>	0.017	0.0077	0.0027

Loading dose (per 70 kg) = C<sub>T</sub> × V<sub>d</sub> peak effect. Maintenance infusion (per 70 kg) = C<sub>T</sub> × V<sub>1</sub> (K<sub>10</sub> + K<sub>12</sub> e<sup>-k<sub>21</sub>t</sup> + K<sub>13</sub> e<sup>-k<sub>31</sub>t</sup>).

\* From Glass *et al.*<sup>14</sup>

† From Scott *et al.*<sup>15</sup> and Hudson *et al.*,<sup>16</sup> as reported by Shafer *et al.*<sup>30</sup>

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