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Hemodynamics and Emergence Profile of Remifentanil *versus* Fentanyl Prospectively Compared in a Large Population of Surgical Patients

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This study was sponsored by GlaxoWellcome Inc., Research Triangle Park, NC, USA, under protocol number USAA4001.

Study Objective: *To compare the responses to, and hemodynamics associated with surgical stress, recovery profiles, and anesthesiologists' satisfaction following balanced general anesthesia using either remifentanil or fentanyl in a large-scale population.*
Design: *Prospective, 1:1 single blind, randomized, controlled effectiveness study in which patients received either remifentanil or fentanyl in combination with a hypnotic-based anesthesia regimen of either isoflurane or propofol.*
Setting: *Multicenter study including 156 hospitals and ambulatory surgery facilities.*
Patients: *2,438 patients (1,496 outpatients and 942 inpatients), 18 years of age or older, scheduled for elective surgeries under general endotracheal anesthesia, with an expected duration of unconsciousness ≥ 30 minutes.*
Interventions: *Patients were randomized to receive either intravenous (IV) remifentanil (0.5 μg/kg/min for induction and intubation, with the infusion rate decreased to 0.25 μg/kg/min after intubation) or IV fentanyl (administered according to anesthesiologists' usual practice) as the opioid during surgery. Concomitant hypnotic drugs were either propofol and/or isoflurane (with or without nitrous oxide) titrated according to protocol. Transition analgesia with either morphine or fentanyl was given to the remifentanil patients and, at the anesthesiologists' discretion, in the fentanyl patients.*
Measurements: *Vital signs, adverse events, and emergence profiles were assessed and recorded. Recovery profile was assessed by recording time spent in the postanesthesia care unit and step-down recovery unit, number and timing of adverse events, timing and dosage of rescue medications, and time to eligibility for discharge (to home or to hospital room).*

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Received for publication August 21, 2000; revised manuscript accepted for publication May 21, 2001.

Journal of Clinical Anesthesia 13:407–416, 2001

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0952-8180/01/$–see front matter
PII S0952-8180(01)00292-6

Anesthesiologists' satisfaction with the anesthetic regimen was assessed at the end of surgery.
Main Results: *Remifentanil-treated patients exhibited lower systolic and diastolic blood pressures (by 10–15 mmHg) and lower heart rates (by 10–15 bpm) intraoperatively compared to the fentanyl-treated patients. This difference promptly disappeared on emergence. Remifentanil-treated patients responded to verbal command, left the operating room, and (for outpatients) were discharged home sooner than fentanyl-treated patients. Anesthesiologists rated the predictability of response to intraoperative titration, assessment of hemodynamic profiles, and the quality of anesthesia higher in the remifentanil-treated patients.*
Conclusions: *This study confirms previous observations on the hemodynamic properties associated with remifentanil and extends these to a wider context than previously reported. These characteristics provide clinicians with an alternative in opioid-based anesthesia.*

Keywords: Remifentanil; hemodynamics; recovery; fentanyl; anesthesia.

Introduction

Remifentanil hydrochloride (Ultiva) is a short-acting opioid of the phenylpiperidine class. The phenylpiperidines are more potent than alkaloid opiates, provide pure mu-opioid receptor agonist effects, and find wide usage in general anesthesia and conscious sedation techniques.[1,2] Remifentanil possesses an ester bond on a side chain from the phenylpiperidine ring unlike other members of this class (*e.g.,* alfentanil, sufentanil, and fentanyl). This ester bond is readily hydrolyzed by nonspecific plasma and tissue enzymes. Remifentanil has a terminal half-life of 8 to 20 minutes,[3] and a context-sensitive half-time of approximately 3 minutes.[4] The principal metabolite of remifentanil is the deesterified carboxylic acid GR90291, which has no clinically observable opioid properties.[5] Like other anesthetic agents, age influences pharmacokinetic-pharmacodynamic relationships for remifentanil.[6,7]

Hemodynamic stability and absence of somatic responses may be achieved by inducing profound anesthetic states; however, this usually carries the penalties of slow emergence and delayed recovery. The effectiveness of intravenous opioid anesthetic regimens must, thus, be compared during both the intraoperative and recovery stages of anesthesia.[8] This study was designed as a Phase IV prospective trial in a large surgical population to investigate whether the desired intraoperative characteristics of remifentanil, in comparison with fentanyl, could be obtained while achieving a fast, predictable recovery from anesthesia.

Materials and Methods

Ethical and Regulatory Considerations

This study complied with the Declaration of Helsinki (as amended) and was approved by the institutional review board of each of the participating institutions. All patients provided written informed consent.

Overview of Study Design

Anesthesiologists first participated in an open-label, remifentanil-based balanced infusional technique on ten patients to gain experience using the drug. In the next phase of the study, two balanced anesthetic regimens were compared using a parallel-group, 1:1 randomized, controlled single-blind design. The treatment groups differed in that the opioid used was either remifentanil or fentanyl in combination with other hypnotic drugs (see below). Patients were further stratified into those having inpatient or outpatient procedures to distinguish findings based on surgery and recovery processes. An additional arm of this study involving patients undergoing craniotomy is reported elsewhere.[9] Investigators (n = 110 and n = 49 for outpatients and inpatients, respectively, but not mutually exclusive) consisted of anesthesiologists recruited from both academic and community hospitals who had prior clinical experience using both remifentanil and fentanyl as components of balanced anesthesia and were aware of how these two opioids differ pharmacologically. No attempt was made to blind the anesthesiologist to the anesthetic regimen received by the patient.

Criteria for Patients Entering the Study

To imitate the ordinary clinical setting as closely as possible, the selection criteria for patients taking part in this study were consistent with U.S.-approved labeling for remifentanil (Ultiva, GlaxoWellcome Inc., Research Triangle Park, NC). All patients who met inclusion criteria were approached by the investigators for participation in the study. Men and women, 18 years of age and older, could enter the study. There was no restriction based on American Society of Anesthesiologists (ASA) physical status; however, because all the cases were elective, it was anticipated that fewer ASA IV patients would be enrolled. The anesthetic plan included general anesthesia with endotracheal intubation and an expected duration of unconsciousness $\geq$30 minutes.

Premedication and Induction

Premedication was unrestricted except that preoperative opioids were not permitted. Baseline measurements of heart rate (HR) and blood pressure (BP) were obtained just before induction so as to capture any pharmacological effects of premedication.

Investigators began induction with IV fluid loading and preoxygenation according to their usual practice. For fentanyl-treated patients, investigators administered this opioid intravenously before, during, or after induction, at his or her discretion. For subjects receiving remifentanil, an intravenous infusion of 0.5 μg/kg/min was started simultaneously with the administration of either thiopental or propofol. Remifentanil infusions could be reduced at any time in the event of hypotension. For patients who weighed more than 30% above the ideal body weight (IBW), the remifentanil dose was calculated according to IBW, not actual weight. Muscle relaxants, oxygen, isoflu-

rane, and nitrous oxide were administered at each investigator's discretion.

Maintenance

For patients assigned to receive fentanyl, dose and titration during maintenance was performed according to each investigator's usual practice. For patients assigned to remifentanil, the infusion rate was initially reduced to 0.25 μg/kg/min after intubation was completed. Titrations (up or down) of the remifentanil infusion rate were permitted in anticipation of a stressful stimulus, when anesthesia was perceived to be too light or deep, or to maintain hemodynamic stability. Light anesthesia was classified as somatic (purposeful movement, swallowing, grimacing, or eye opening), autonomic (tearing, sweating, or mydriasis), hyperdynamic (a clinically relevant increase in BP or HR), or anticipated changes in the magnitude of surgical stimulation. Upward titration was either a 1 μg/kg bolus dose or a 25% to 100% incremental increase in the infusion rate (*i.e.,* initially, 0.0625–0.25 μg/kg/min), up to a maximum infusion rate of 2 μg/kg/min. After two upward titrations, investigators were permitted to increase the hypnotic agent (see below). Reducing the hypnotic agent was the initial treatment for hypotension; if hypotension persisted, reduced doses of remifentanil (in decrements of 25%–100% at 2-minute intervals) and administration of vasopressor agents were permitted. Definitions for hemodynamic and respiratory parameters requiring treatment were prospectively defined. Hypotension was defined as a systolic blood pressure <80 mmHg that was medically untoward or a systolic blood pressure that was treated with pharmacologic drugs and was medically untoward. Hypertension was defined as a systolic BP >180 mmHg or a diastolic BP >100 mmHg that was medically untoward. Bradycardia was defined as a HR <40 bpm and treated with pharmacologic drugs. Respiratory depression was defined as a respiratory rate ≤8 breaths/minute, and apnea as a respiratory rate of zero lasting for 15 seconds or more.

Concomitant hypnotic drugs were either propofol or isoflurane with or without nitrous oxide at the investigator's discretion. The recommended dose of isoflurane initially was 0.2% to 0.8% inspired, pursuing end-tidal concentrations of 0.2% and 0.4%, in the presence and absence of nitrous oxide, respectively. Target infusion rates for propofol depended on whether nitrous oxide was used and the age of the patient: with nitrous oxide and for patients over and under 55 years of age, target propofol infusion rates were 50 to 75 and 50 to 100 μg/kg/min, respectively. Without nitrous oxide and for patients over and under 55 years of age, target infusion rates for propofol were 75 to 100 and 100 to 150 μg/kg/min, respectively.

Emergence

Investigators were advised to down-titrate propofol at approximately 10 to 15 minutes after intubation, to assist in rapid emergence. The remifentanil group received either morphine sulfate 10 to 15 mg intravenously (IV), 20 to 30 minutes before the last suture, or fentanyl 1 to 2 μg IV, 10 to 20 minutes before the last suture. The timing of the last dose of fentanyl in the fentanyl-treated group was entirely at the investigator's discretion.

Remifentanil infusions were discontinued with the last suture or, in closed procedures, with the last surgical manipulation; investigators were warned to clear the infusion lines to avoid residual drug administration. In both treatment groups, the discontinuation of propofol, isoflurane, and nitrous oxide, and the reversal of muscle relaxants was at the investigator's discretion.

Measurements

Age, gender, ethnic origin, ASA physical status, and baseline vital signs were recorded. Systolic BP, diastolic BP, and HR were monitored throughout the procedure. The prospectively defined time-points of interest for analysis were 1) loss of consciousness; 2) 1 and 5 minutes after intubation; 3) first incision or trocar insertion; and 4) skin closure. The first postanesthetic care unit (PACU) measurement was also recorded.

Postoperative event timing was relative to the last suture or surgical manipulation. Events recorded were extubation, response to a verbal command, discharge from the operating room, arrival in the PACU, eligibility for and actual discharge from the PACU, and (for outpatients) eligibility for and actual discharge from the hospital.

Intravenous agents were quantified as total amounts administered and rounded to integers. Total isoflurane administration was calculated as minimum alveolar concentration (MAC)-hours using 1.15% as the minimum alveolar concentration. Before patient discharge from the PACU, anesthesiologists completed a global assessment questionnaire of their satisfaction with the anesthetic regimen, which consisted of a 5-point rating scale ranging from 1, equaling poor, to 5, equaling excellent. Specifically, they evaluated the predictability of response to intraoperative titration, the intraoperative hemodynamic profile, and overall quality of anesthesia.

Statistical Considerations

Intent-to-treat and safety populations were prospectively defined. The safety population included all patients who were exposed to any amount of remifentanil or fentanyl; the intent-to-treat population included all patients exposed to any amount of remifentanil or fentanyl who were evaluable for response to intubation.

Hemodynamic assessments, including BP and HR measurements at each of the defined time-points, were compared between treatment groups (remifentanil- *vs.* fentanyl-treated anesthesia), separately for inpatients and outpatients. Continuous variables were described as mean ± standard deviation (SD) for comparison of treatments at each time-point. For each endpoint, Cox regression analyses were used to assess treatment differences by comparing the ratio of hazard functions. For global assessment ratings, treatment differences were assessed using

Cochran-Mantel-Haenszel Chi-square test for ordinal data, stratifying by clinical setting. To examine the overall predictability of recovery, risk ratios and 95% confidence intervals for these variables were calculated. A p-value $<$ 0.05 was prospectively defined as statistically significant. The power calculations for this study were based on hemodynamic changes and 3% differences in patient satisfaction with their anesthetic, on the basis of findings from a previous study.[11] The number of patients enrolled in this study provided >90% power to demonstrate a 5-minute difference in recovery profile, if it were to exist.

Adverse Event Monitoring

Patients were assessed for adverse events up until the time of discharge to hospital room (inpatients) or to home (outpatients). Investigators were instructed to report all adverse events at any time and regardless of whether or not they were thought to be related to the study procedures or test medications. According to protocol guidelines, an adverse event was to be recorded for any event of hypotension, hypertension, bradycardia, or tachycardia. Spontaneous reports of nausea and vomiting by patients were always recorded as adverse events. Nausea and vomiting were rated as mild, moderate, or severe. Time to cessation of emetic symptoms was also recorded. Postoperative pain was considered to be an adverse event when the investigator assessed it as unexpectedly severe. Summary statistics were used for adverse event frequency analysis because small-sized differences in drug tolerability may have clinical significance without approaching statistical significance.

Results

Demographics

For inpatients, the safety and intent-to-treat populations were 477 and 465 for remifentanil and fentanyl, respectively. For outpatients, the safety population was 752 and 744 for remifentanil- and fentanyl-based regimens, respectively. For one outpatient, the surgical procedure was emergently canceled, and the intent-to-treat populations were 751 and 744 for remifentanil and fentanyl, respectively. Demographic characteristics of these populations were comparable between treatment groups, although there were predictable differences in ASA status and age between inpatients and outpatients (*Table 1*).

Concomitant Anesthetic Use

Remifentanil-treated patients received less concomitant anesthetic drugs during maintenance of anesthesia. This was true for both inpatients and outpatients (*Table 2*).

Hemodynamics in Remifentanil- versus *Fentanyl-based Anesthesia*

Median baseline, loss of consciousness, and first postoperative hemodynamic measurements were similar between the treatment groups for both outpatients and inpatients. Median systolic BP (*Figure 1*), diastolic BP (*Figure 2*), and HR (*Figure 3*) were all lower intraoperatively for remifentanil- than for fentanyl-treated patients. This difference was also consistent for both inpatients and outpatients ($p < 0.05$ for between treatment group comparisons, for all intraoperative measurements). Investigators reported more ephedrine use in the remifentanil group (10% outpatients, 23.1% inpatients) than in the fentanyl group (3.9% outpatients, 9.7% inpatients). More labetalol and esmolol were used in the fentanyl group (labetalol: 3.1% outpatients, 7.1% inpatients; esmolol: 12% outpatients, 4.3% inpatients) compared to the remifentanil group (labetalol: 0.7% outpatients, 3.4% inpatients; esmolol 0.3% outpatients, 1.3% inpatients). Use of atropine, glycopyrrolate, and phenylephrine did not differ.

Anesthesiologists Ratings

Anesthesiologists rated the predictability of response to intraoperative titration and assessment of hemodynamic profile as excellent in 54% and 47%, respectively, in the remifentanil group compared to 20% and 23%, respectively, in the fentanyl-treated group ($p < 0.001$). The overall quality of anesthesia was rated as excellent in 55% of remifentanil patients *vs.* 22% of fentanyl-treated patients ($p < 0.001$). Remifentanil patients were rated significantly better than fentanyl patients on all aspects of the assessment of quality of emergence, a finding that was consistent in all clinical settings. Anesthesiologists rated patient comfort during emergence as excellent in 59% of remifentanil-treated patients compared to 28% of fentanyl-treated patients ($p < 0.001$). Hemodynamic profile and level of consciousness during emergence were rated as excellent in 54% and 60%, respectively, of remifentanil patients compared with 25% and 19%, respectively, of fentanyl patients ($p < 0.001$). The overall quality of emergence from anesthesia was rated as excellent in 54% of remifentanil patients *versus* 20% of fentanyl patients ($p < 0.001$).

Adverse Events

Adverse cardiovascular events as defined in the protocol (medically untoward or requiring treatment) are reported in *Table 3*. Major morbidities were rare and no differences were recorded between treatment groups.

Recovery with Remifentanil- versus *Fentanyl-based Anesthesia*

Times to extubation did not differ between the treatment groups. The log rank test for the Kaplan-Meyer analysis for outpatients did give a p-value of 0.041, relating principally to the absence of criss-crossing of the plots. However, the size of the differences was too small to be clinically significant (*Figure 4*).

Responses to verbal command were significantly earlier for outpatients and inpatients who were administered

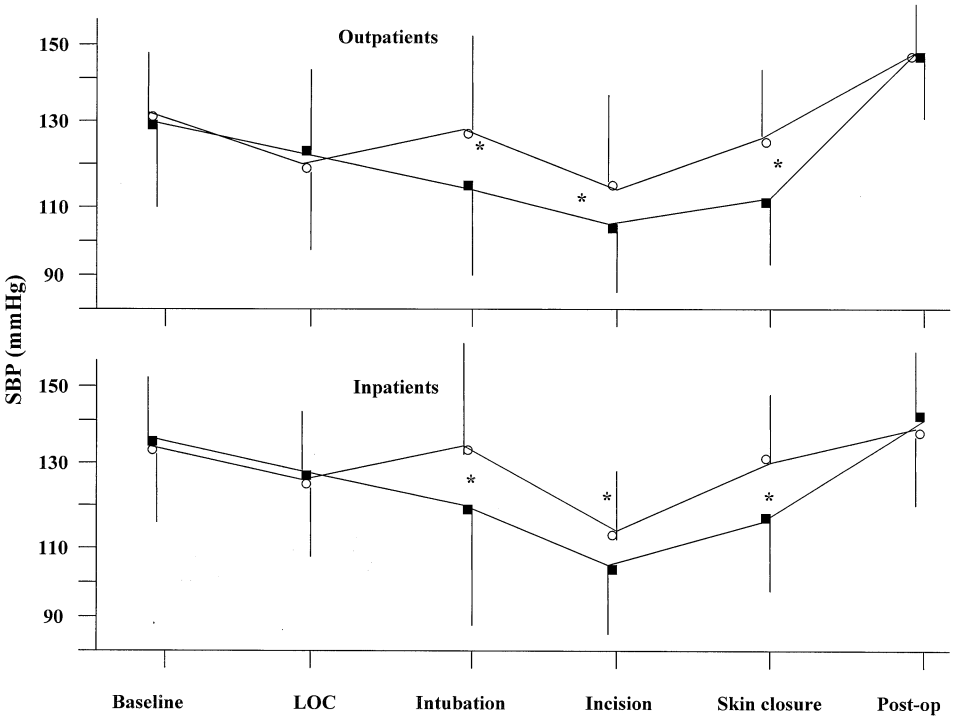

Figure 1. Mean ± SD systolic blood pressure (SBP; mmHg) before induction (baseline) and at loss of consciousness (LOC), intubation, incision, skin closure, and first assessment after emergence (Postop) for outpatients (upper panel) and inpatients (lower panel). Solid squares: remifentanil. Open circles: fentanyl. *$p < 0.05$, unpaired, one-tailed *t*-test with one degree of freedom.

remifentanil compared to those receiving fentanyl. The risk ratio analysis showed that remifentanil outpatients were 1.43 (95% C.I.: 1.28, 1.59, $p < 0.001$) times more likely to respond sooner to a verbal command than fentanyl outpatients. For inpatients, the risk ratio for this comparison was 1.36 (95% C.I.: 1.19, 1.56, $p < 0.001$). *Figure 4* shows the time to 90% of patients responding to verbal command in each treatment group.

Remifentanil outpatients had shorter times to operating room discharge than did the fentanyl-treated outpatients; the risk ratio was 1.13 (95% C.I.: 1.02, 1.26, $p = 0.021$), although the size of the difference between median discharge times was small (8.0 *vs.* 9.0 min). For inpatients, times to discharge from the operating room were similar for the two treatment groups (median = 10 minutes, both groups). PACU discharge times did not vary between the treatment groups.

Postoperative nausea rates were similar for the two treatment groups. For outpatients, 22.7% of remifentanil-treated and 22.3% of fentanyl-treated patients reported nausea. Among inpatients, rates of nausea were 31.9% for remifentanil-treated *versus* 29.7% for fentanyl-treated patients. Severity of nausea did not differ between the remifentanil and fentanyl groups in either inpatients or outpatients. Mean scores for both groups were mild (60%), moderate (35%), and severe (5%). The 95% confidence intervals for median time to resolution of nausea always included 1.0 and were not statistically significant.

Among outpatients, the incidence of vomiting was similar for the two treatment groups (10% for remifentanil- *vs.* 9.9% for fentanyl-treated patients). Fewer inpatients vomited after fentanyl than remifentanil treatment (15.5% *vs.* 12.5%, $p = 0.031$).

Postoperative pain of unexpected severity was rare, being reported by 0.4% *versus* 0.5% of outpatients and 1.0% *versus* 0.2% of inpatients, after remifentanil- and fentanyl-treated regimens, respectively. These small treatment differences did not approach statistical significance. There was no difference in postoperative analgesic use.

Median time for eligibility to be discharged to home was earlier for remifentanil- than fentanyl-treated outpatients (risk ratio 1.14; 95% CI: 1.02, 1.27; $p = 0.019$). However, the size of this difference was modest (median 131 minutes *vs.* 137 minutes for remifentanil- and fentanyl- treated patients, respectively).

Discussion

We compared hemodynamics and recovery outcomes observed during and after remifentanil- *versus* fentanyl-based balanced anesthesia regimens in a large-scale, multicenter, randomized, single-blind study. This is the largest study to date (2,438 patients) comparing intraoperative and recovery profiles of two phenylpiperidine opioids. Inpatients and outpatients were studied separately because of predictable demographic differences in age, ASA status, and type and duration of surgery. Statistically significant differ-

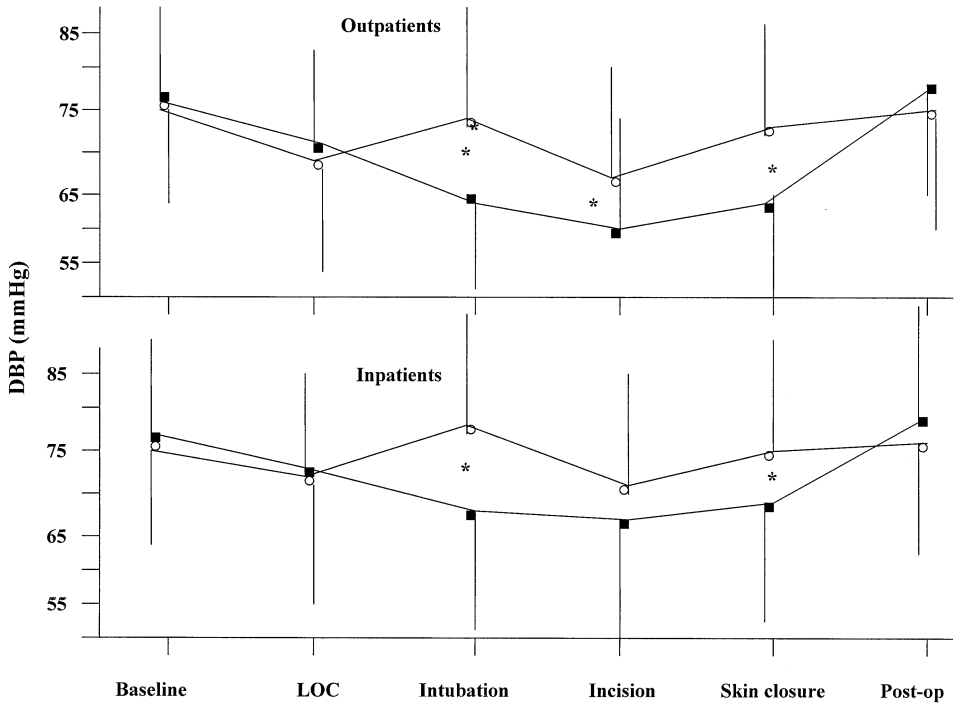

Figure 2. Mean ± SD diastolic blood pressure (DBP) before induction (baseline) and at loss of consciousness (LOC), intubation, incision, skin closure, and first assessment after emergence (Postop) for outpatients (upper panel) and inpatients (lower panel). Solid squares: remifentanil. Open circles: fentanyl. $*p < 0.05$, unpaired, one-tailed *t*-test with one degree of freedom.

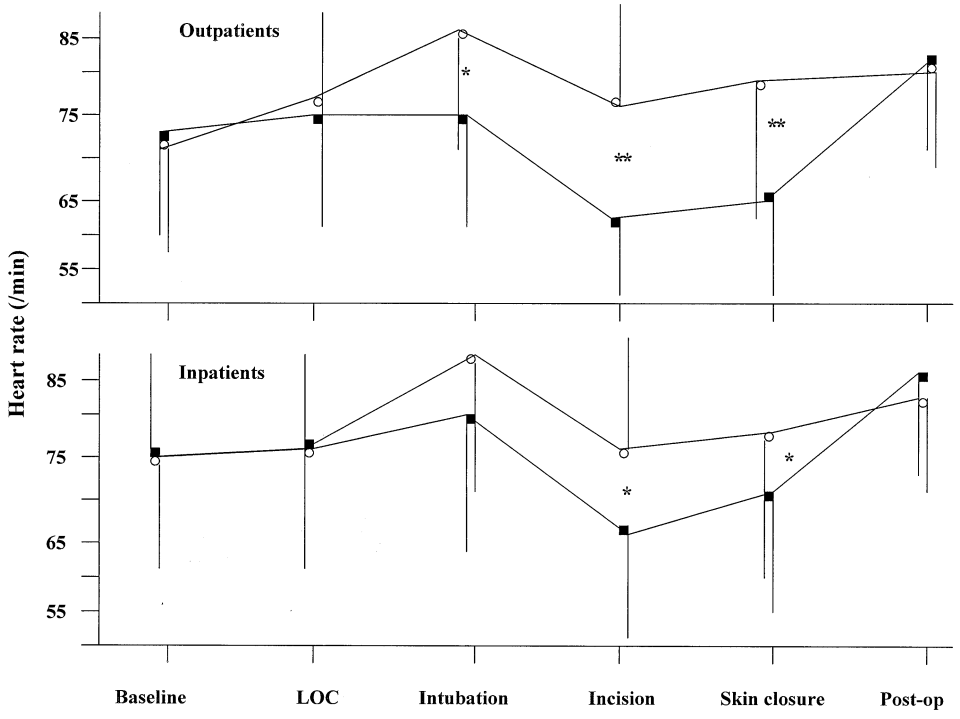

Figure 3. Mean ± SD heart rate before induction (baseline), loss of consciousness (LOC), intubation, incision, skin closure, and first assessment after emergence (Postop) for outpatients (upper panel) and inpatients (lower panel). Solid squares: remifentanil. Open circles: fentanyl. $*p < 0.05$, $**p < 0.025$, unpaired, one-tailed *t*-test with one degree of freedom.

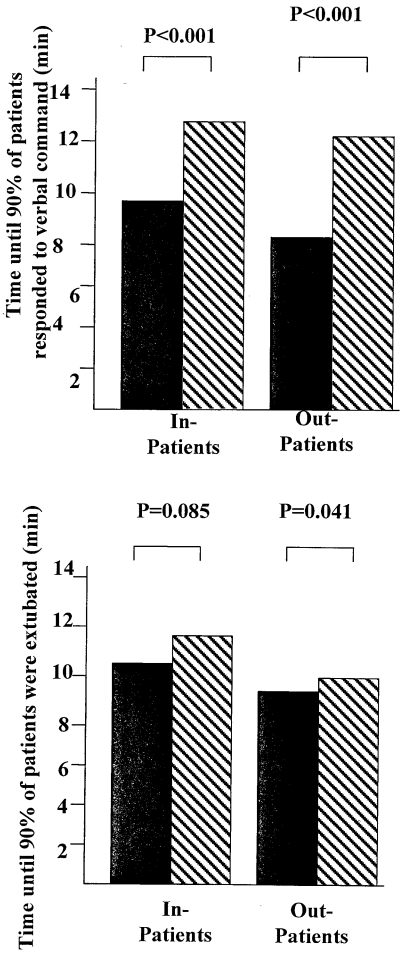

Figure 4. Time until 90% of patients were extubated (upper frame) and responded to verbal command (lower frame) for inpatients and outpatients administered either a remifentanil- or a fentanyl-based anesthetic regimen. An unadjusted log rank test was used, giving the *p* values shown. Solid bars: remifentanil; striped bars: fentanyl.

ences between remifentanil and fentanyl were observed for intraoperative hemodynamic parameters, time to response to verbal command, operating room discharge time, and, for outpatients, time to eligibility for discharge home. Lack of differences in actual times to outpatient discharge may be attributable to as yet unresolved system issues that are characteristic of many facilities (*e.g.,* nursing staff, lack of immediately available patient escort). These system issues would then obscure the benefits of accelerated recovery and discharge. The earlier response to verbal command observed here is similar to previous reports[1,9] and is consistent with the rapid clearance of remifentanil by esterases.

Reliable hemodynamic stability with remifentanil during periods of intraoperative stress was achieved without any increase in significant adverse events. Perioperative morbidity and mortality was exceedingly rare in both treatment groups. Although more episodes of hypotension and bradycardia were observed in the remifentanil group, the need for treatment was not extraordinary for clinical practice.

Anesthesiologists rated remifentanil as superior to fentanyl for predictability of intraoperative titration, hemodynamic profile, and overall quality of anesthesia. Thus, hemodynamic changes associated with remifentanil did not affect the consistently excellent rating by anesthesiologists. Perception ratings could have been biased by the unblinded anesthesiologists. However, it would be difficult to extend this critique to the objective hemodynamic variables. In a subset of this Phase IV study previously reported for neurosurgical patients, blinded assessments conducted postoperatively by neurosurgeons yielded a similarly higher level of satisfaction with the overall quality of anesthesia and level of consciousness in the remifentanil- *versus* fentanyl-treated patients.[9]

Hemodynamic stability with remifentanil has been demonstrated previously under randomized, double-blind conditions.[8,10] When remifentanil-propofol and alfentanil-propofol regimens for total IV anesthesia in outpatient surgery were compared, remifentanil was associated with fewer hemodynamic responses to tracheal intubation and trocar insertion/skin incision.[8]

This study confirms that remifentanil does not increase time to resolution of postoperative nausea and vomiting when compared with fentanyl. Similar to other studies, the incidence of vomiting observed in this study was comparable for remifentanil.[1,8] This observation is consistent with the rapid termination of opioid-agonist effects of remifentanil and the fact that its principal metabolite (GI90291) is without clinically relevant opioid-agonist properties.[3]

The administration of relatively large amounts of almost any anesthetic regimen can achieve a stable intraoperative course (assessed by hemodynamic responses to stressful stimuli, *e.g.,* intubation, incision, and visceral manipulation).[11] However, the concern, especially in outpatients, is that administration of large amounts of anesthetic agents will delay postoperative recovery, impact PACU occupancy, and decrease the probability of same-day discharge. Here, we have shown that remifentanil was associated with 1) a desirable, stable intraoperative course, and 2) a predictable recovery from anesthesia that is without penalty. Although differences in recovery were statistically significant, they were small. Nonetheless, these differences did translate into meaningful outcomes as perceived by the patient. These assessments were validated using a 24-Hour Functional Ability Questionnaire developed to measure final recovery and satisfaction in this study.[12] The impact of these findings on patients' functional ability within the first 24 hours is reported by Fleisher *et al.*[13]

The rapid clearance of remifentanil and the consequent faster emergence led to an inferior postoperative pain profile in early clinical studies. A proactive pain management technique has been developed, with which these investigators were familiar. This large and heterogenous patient population exhibited postoperative pain frequencies comparable to the fentanyl-treated group. This further confirms the appropriateness of administer-

Table 1. Demographic Characteristics of Patient Populations in a 1:1 Randomized, Parallel-Group Comparison of Remifentanil- and Fentanyl-based Balanced Anesthesia for Outpatient and Inpatient and Surgical Procedures

	OutP		InP	
	Remi (%)	**Fent (%)**	**Remi (%)**	**Fent (%)**
Total patients	752 (100)	744 (100)	477 (100)	465 (100)
Male	291 (39)	296 (40)	221 (46)	222 (48)
Female	461 (61)	448 (60)	256 (54)	243 (52)
Age (yr; m ± SD)	42.3 ± 14.8	41.2 ± 14.9	48.9 ± 15.9	51.0 ± 16.4
Weight (kg; m ± SD)	79.4 ± 19.8	78.1 ± 19.3	80.9 ± 19.8	81.1 ± 17.5
Race:				
White	621 (83)	588 (79)	885 (81)	358 (77)
Black	83 (11)	91 (12)	74 (16)	77 (17)
Oriental	8 (1)	8 (1)	1 (<1)	2 (<1)
Hispanic	36 (5)	42 (6)	14 (3)	22 (5)
Other	4 (1)	15 (2)	2 (<1)	6 (1)
ASA status				
I	297 (40)	317 (43)	84 (18)	99 (21)
II	368 (49)	359 (48)	271 (57)	251 (54)
III	86 (11)	66 (9)	117 (25)	108 (23)
IV	1 (<1)	2 (<1)	5 (1)	7 (1)
Type of surgery				
Abdominal	138 (18)	124 (17)	220 (46)	198 (43)
Superficial	609 (81)	620 (83)	246 (52)	260 (56)
Other	5 (1)	0 (0)	11 (2)	7 (2)
Duration of anesthesia (min; mean ± SD)	69.0 ± 40.8	70.9 ± 45.6	135 ± 76	143 ± 85.8

Remi = remifentanil-based balanced anesthesia, Fent = fentanyl-based balanced anesthesia, OutP = outpatient, InP = inpatient, ASA = American society of anesthesiology, SD = standard deviation.

ing 10 to 15 mg of morphine 20 to 30 minutes, or 1 to 2 μg/kg fentanyl 10 to 20 minutes, before the anticipated time of last suture, without interference with the rapid recovery profile of remifentanil. Other strategies for postoperative pain management can also be considered.[14]

The findings in this study may be biased by the fact that equipotent doses of the two agents were not administered. Such studies, controlling the doses of both remifentanil and alfentanil and fentanyl have been reported before, and equipotent doses result in prolonged recovery times for the comparator opioid and the need for opioid antagonists.[10,15] In the development program for remifentanil, the potency ratio between remifentanil and alfentanil was estimated as 4:1 when these agents were administered as a maintenance infusion.[10] However, this study was critiqued because this caused more alfentanil to be administered than would normally be given clinically. These higher doses of alfentanil resulted in significantly slower emergence from anesthesia than seen with remifentanil. Similarly, doses of fentanyl and remifentanil administered to achieve similar intraoperative hemodynamics (approximate ratio of 2:1) resulted in a slower emergence from anesthesia for the fentanyl group.[15] Therefore, this study was designed to allow for doses of remifentanil and

Table 2. Concominant Drugs Used by Patients in the Subgroups Shown.

	Outpatients		Inpatients	
Concomitant Drug	**Remifentanil**	**Fentanyl**	**Remifentanil**	**Fentanyl**
With nitrous oxide				
Propofol (mg)	80 ± 25	109 ± 30*	57 ± 11	93 ± 33*
Isoflurane (MAC-hr)	0.39 ± 0.35	1.08 ± 0.80*	0.71 ± 0.58	1.91 ± 1.52*
Without nitrous oxide				
Propofol (mg)	103 ± 31	136 ± 44**	115 ± 30	1***
Isoflurane (MAC-hr)	0.59 ± 0.43	1.47 ± 1.18*	0.90 ± 0.64	2.16 ± 1.70*

Mean ± SD values are shown. The units of measurement for each drug are shown in parentheses.

*$p < 0.001$ Student's t test.

**$p = 0.08$.

***Only a single patient was studied in this category.

Table 3. Cardiovascular Adverse Events Compared for Remifentanil- and Fenatyl-based Anesthetic Regimens

	Outpatients		Inpatients	
Adverse Event Type	**Remifentanil (n = 752)**	**Fentanyl (n = 744)**	**Remifentanil (n = 477)**	**Fentanyl (n = 465)**
Hypotension	66 (8.8%)	20 (2.7%)	84 (17.6%)	31 (6.7%)
Hypertension	27 (3.6%)	35 (4.7%)	22 (4.6%)	42 (9.0%)
Bradycardia	14 (1.9%)	7 (0.9%)	13 (2.7%)	2 (0.4%)
Tachycardia	14 (1.9%)	11 (1.5%)	6 (1.3%)	19 (4.1%)

Adverse events occurring with a frequency >2% in any subgroup are shown, for sample sizes given at the top of each column.

fentanyl to be used as is recommended in a "real world setting." We chose the dose of remifentanil based on previous studies that provided maximal suppression of response to intubation (1 $\mu g/kg + 0.5\ \mu g \cdot kg^{-1} \cdot min^{-1}$) and intraoperative stimuli ($0.25\ \mu g \cdot kg^{-1} \cdot min^{-1}$).[8,11] Because our study was an effectiveness trial and not a pharmacodynamics study, anesthesiologists were permitted to use fentanyl according to whatever their usual practice may be, and remifentanil according to the recommendations of the package insert. This study design provides a realistic comparison of the use of these two opioids in the ordinary anesthetic situation. The advantage of our large-scale prospective Phase IV trial was that it allowed us to evaluate the effectiveness of two opioid-balanced anesthetic regimens in a manner that best reflects usual clinical practice, rather than how the agents may perform in a rigidly designed efficacy trial.

The decision to choose one opioid over another is influenced in part by cost benefits. Although anesthesia costs actually represent only a small fraction of total health care cost, they are highly visible and easy for administrators to scrutinize,[16] which is why drug acquisition costs are often the primary focus of cost-containment strategies in anesthesia.[17,18] The acquisition cost when calculated per milligram for remifentanil is $12.46 compared to a range of $2.11 (generic) to $23.12 for fentanyl based on the Average Wholesale Price (AWP) from the *2001 Redbook*.[19] However, acquisition costs may be offset if the amount of other drugs needed can be offset (*e.g.*, concomitant hypnotic agents, adjuvants, muscle relaxants, antiemetics, and antagonists). Indeed, in previous studies examining overall costs for outpatient anesthesia and neuroanesthesia, remifentanil was found less expensive to use compared to alfentanil or fentanyl.[20,21] Although not part of this study design, proper cost analysis should evaluate the total costs of all drugs including anesthetics, adjuvants, and antagonists, rather than evaluating individual drugs costs alone. Future studies to determine cost-effectiveness must also recognize any time savings realized in the operating room and recovery areas.

In conclusion, in diverse inpatients and outpatients, and in the hands of numerous anesthesiologists, remifentanil was associated with a consistently stable intraoperative course and somewhat faster emergence than fentanyl. Faster emergence was accompanied by earlier response to verbal command, earlier discharge from the operating room for outpatients, and earlier eligibility for discharge home for outpatients. There was a higher degree of satisfaction expressed by anesthesiologists. These results were not explicable in terms of faster extubation, nor in terms of earlier PACU discharge. Frequencies of postoperative nausea and vomiting were similar. The stable intraoperative hemodynamic findings associated with remifentanil in this study are consistent with those from earlier, more specialized, studies. This study established an effective postoperative pain management regimen without interfering with emergence. These recovery parameters correspond with the faster clearance of remifentanil and demonstrate that this opioid can deliver a stable intraoperative course without penalty in terms of recovery from anesthesia.

Acknowledgements

We thank the investigators, other advisory panel members (Kenneth Tuman, Michael Roizen, Peter Glass), Deborah Thompson (Project Leader), study site coordinators, and patients who took part in this study.

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