Postoperative pain management in patients undergoing major surgery after remifentanil *vs* fentanyl anesthesia

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Purpose: To determine if morphine sulphate was an effective transition analgesic in patients receiving a remifentanil-based anesthetic regimen.

Methods: Open-label remifentanil or fentanyl was administered to 210 randomized patients undergoing inpatient surgery. Isoflurane and nitrous oxide was administered to all patients. Thirty minutes before the end of surgery, patients receiving remifentanil were randomized to receive morphine 0.15 $mg \cdot kg^{-1}$ (R/M15 group) or 0.20 $mg \cdot kg^{-1}$ (R/M20 group). Following extubation and prior to patient-controlled analgesia (PCA) initiation, 2 mg boluses of morphine were administered for moderate/severe pain. Efficacy endpoints were total morphine used in the post anesthesia care unit (PACU) and 24 and 48 hr postoperatively; postoperative pain; time to first morphine bolus; time to first PCA administration; and time to recovery endpoints.

Results: Mean total morphine used in PACU was not different among groups (15.5 mg, 16.5 mg and 13.3 mg in R/M15, R/M20 and F groups, respectively). Mean total 24 hr morphine use (58.1 mg, 56.93 mg and 53.6 mg in R/M15, R/M20 and F groups) and mean total morphine used at 48 hr were not different (69.8 mg, 64.7 mg and 62.1 mg in R/M15, R/M20 and F/I groups). Groups were similar with respect to pain severity ratings at all postoperative times. Patients in the fentanyl arm experienced faster times to some recovery endpoints than patients receiving either remifentanil regimen.

Conclusion: Morphine sulphate regimens of 0.15 or 0.20 $mg \cdot kg^{-1}$ administered 30 min before the end of surgery are equally effective transition regimens for inpatient procedures.

Objectif : Déterminer si le sulfate de morphine constitue un analgésique de transition efficace chez les patients qui reçoivent une anesthésie à base de rémifentanil.

Méthode : Des doses connues de rémifentanil ou de fentanyl ont été administrées à 210 patients de chirurgie ambulatoire répartis au hasard. Tous ont reçu de l'isoflurane et du protoxyde d'azote. Trente minutes avant la fin de l'opération, les patients qui recevaient du rémifentanil ont eu, de façon aléatoire, 0,15 $mg \cdot kg^{-1}$ (groupe R/M15) ou 0,20 $mg \cdot kg^{-1}$ (groupe R/M20) de morphine. Après l'extubation, et avant l'analgésie contrôlée par le patient (ACP), on a administré de la morphine en bolus de 2 mg pour contrer les douleurs de modérées à sévères. Les paramètres d'efficacité étaient la quantité totale de morphine utilisée à la salle de réveil et 24 et 48 h après l'opération, la douleur postopératoire, le temps écoulé avant l'administration du premier bolus de morphine, le temps écoulé avant la première dose d'ACP et le temps nécessaire pour satisfaire aux paramètres de la récupération.

Résultats : La consommation moyenne totale de morphine à la salle de réveil n'a pas présenté de différence intergroupe (15,5 mg, 16,5 mg et 13,3 mg pour les groupes R/M15, R/M20 et F, respectivement). La consommation moyenne totale de morphine à 24 h (58,1 mg, 56,93 mg et 53,6 mg pour les groupes R/M15, R/M20 et F) et à 48 h n'était pas différente entre les groupes (69,8 mg, 64,7 mg et 62,1 mg pour les groupes R/M15, R/M20 et F/I). Toutes les mesures postopératoires de la douleur ont montré des estimations similaires de sévérité. Les patients du groupe fentanyl ont connu une récupération plus rapide, pour certains paramètres, que les patients qui ont reçu l'un ou l'autre régime de rémifentanil.

Conclusion : Les doses de 0,15 ou de 0,20 $mg \cdot kg^{-1}$ de sulfate de morphine, administrées 30 min avant la fin de l'opération, constituent des régimes de transition d'efficacité égale pour des patients de chirurgie ambulatoire.

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POTENT opioids possessing shorter durations of action have recently been added to the therapeutic armamentarium available to the anesthesiologist. Remifentanil hydrochloride is the latest short-acting synthetic opioid to be introduced. Remifentanil is a selective μ-opioid receptor agonist having a methyl-ester linkage that makes it susceptible to metabolism by esterases in blood and other tissues.[1–3] The pharmacokinetic and pharmacodynamic profile of remifentanil suggests that this agent is highly titratable with a predictable offset of action.[3] Indeed, the rapid metabolism of remifentanil results in an ultrashort effective biological half-life of 10 min or less.[2]

The short-acting nature of remifentanil, which provides rapid recovery from anesthesia, also results in the potentially rapid appearance of postoperative pain. Thus, a transition analgesic regimen is needed before discontinuation of a remifentanil infusion. In an effort to define a better transition analgesic regimen, this study compared the analgesic efficacy and safety of two loading doses of morphine sulphate administered 30 min prior to the end of surgery in patients receiving remifentanil. Since fentanyl is a widely used opioid in balanced anesthesia with inhalational agents, this study also compared the anesthesia recovery profiles and morphine requirements of patients receiving remifentanil *vs* traditional fentanyl anesthesia with isoflurane and nitrous oxide. This is the first study to use fentanyl as a direct comparator with remifentanil and the first to evaluate transition analgesic requirements during the post-anesthesia care unit (PACU) period through patient-controlled analgesia (PCA) discontinuation.

Materials and methods

This multicentre (12 sites) study consisted of an open-label, randomized, parallel-group anesthesia phase; followed by a double-blind, randomized, parallel-group, active-control analgesia phase. Eligible patients were at least 18 yr old with American Society of Anesthesiologists I-III physical status. In addition, patients were eligible if they were scheduled for inpatient surgery under general anesthesia of at least one hour duration which required treatment with parenteral analgesics for postoperative pain and at least a 24 hr hospitalization. Written informed consent was obtained from eligible patients during the screening period at which time physical examination and medical history were evaluated.

Anesthetic protocol

ANESTHESIA PHASE. Study evaluation began upon the patient's arrival in the preoperative area. At this time, standard ASA monitors, including lead II ECG, finger pulse oximeter, and non-invasive BP cuff were placed. After baseline measurements were obtained, patients were premedicated with 0.025 $mg \cdot kg^{-1}$ midazolam *iv*. A second dose of 0.025 $mg \cdot kg^{-1}$ midazolam was administered if further sedation was required.

Intraoperative heart rate (HR), oxyhemoglobin saturation (S_pO_2), end-tidal carbon dioxide partial pressure ($P_{ET}CO_2$), and systolic and diastolic blood pressure (SBP and DBP) were measured by an automated measuring device were continuously monitored. During induction anesthesia, patients' lungs were ventilated with oxygen 100% for three minutes. Patients randomly received either open label remifentanil or fentanyl (2:1 randomization). Patients in the remifentanil arm received 2 $mg \cdot kg^{-1}$ thiopental *iv* bolus followed by 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil infusion, whereas patients in the fentanyl arm received 4 $\mu g \cdot kg^{-1}$ fentanyl *iv* bolus followed by 2 $mg \cdot kg^{-1}$ thiopental *iv* bolus. Patients in both arms were treated with additional thiopental doses as needed until loss of consciousness (LOC).

After LOC, all patients received 0.15 $mg \cdot kg^{-1}$ cisatracurium to facilitate tracheal intubation. Following intubation, the remifentanil infusion rate was decreased to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$. In both arms, isoflurane was started to achieve an end-tidal concentration of 0.25%, and nitrous oxide 67%/oxygen 33% was initiated. Sustained responses to intubation were treated with a 1 $\mu g \cdot kg^{-1}$ remifentanil bolus administered over 30 sec in the remifentanil arm and a 1 $\mu g \cdot kg^{-1}$ fentanyl bolus

in the fentanyl arm also administered over 30 sec. If the anticipated time between intubation and skin incision was >15 min and stimulation was not present, the remifentanil infusion rate could be decreased to 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The rate was increased to 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ at the time of skin incision.

During maintenance, patients in the remifentanil arm continued to receive 0.5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ remifentanil, while patients in the fentanyl arm received a 1 $\mu g \cdot kg^{-1}$ maintenance bolus of fentanyl every hour. Signs of light anesthesia (i.e., hypertension, somatic or autonomic responses) in the remifentanil arm were treated with infusion rate increases (0.125-0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ increments) and/or 30 sec infusions of 1 $\mu g \cdot kg^{-1}$ remifentanil at two-five minute intervals. If signs of light anesthesia remained after two boluses or infusion rate increases, the end-tidal concentration of isoflurane was increased (0.2% increments) up to 1.2%. After the response was controlled for five minutes, the end-tidal isoflurane concentration was decreased to 0.25%. Signs of light anesthesia in patients in the fentanyl arm were treated with increases in end-tidal isoflurane (0.2%) increments up to 1.2%. After the response was controlled for five minutes, the end-tidal isoflurane was decreased to 0.5%. If signs persisted, patients in the fentanyl arm also received 1 $\mu g \cdot kg^{-1}$ fentanyl bolus, unless signs of light anesthesia were present within 20 min before the anticipated end of surgery.

In both arms, hypotension was initially treated with *iv* fluid administration and decreasing isoflurane (0.2% decrements). The remifentanil infusion rate could also be reduced in the remifentanil arm. If hemodynamic instability persisted in either arm, additional pharmacologic agents could be administered at the investigator's discretion.

ANALGESIA PHASE. Thirty minutes before the end of surgery, patients in the remifentanil arm randomly received either a double-blind bolus of 0.15 $mg \cdot kg^{-1}$ morphine or 0.20 $mg \cdot kg^{-1}$ morphine (1:1 randomization). Twenty minutes before the end of surgery, end-tidal isoflurane concentration was reduced to 0.25% and fentanyl boluses were discontinued. Ten minutes before the end of surgery isoflurane administration was discontinued, and glycopyrrolate and neostigmine were administered if neuromuscular blockade reversal was required. At the end of surgery, the remifentanil infusion and nitrous oxide were discontinued.

All patients received PCA morphine for postoperative analgesia. Prior to morphine PCA initiation, all patients were asked to assess their pain level according to a four-point rating scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). If the patient had moderate or severe pain before PCA initiation, 2 mg morphine *iv*, was administered and repeated as needed. Subsequent pain was managed with PCA morphine.

Efficacy assessment

ANALGESIA. The primary efficacy endpoint was the mean total amount of morphine sulphate used in the 24 hr postoperative period. The mean total amount of morphine included PCA morphine and any additional morphine used after extubation and before PCA morphine initiation. Measures of secondary efficacy included the mean total amount of morphine used in the PACU and the mean total morphine used in the 48 hr postoperative period.

RECOVERY. The level of postoperative pain was assessed by patient questioning utilizing a four-point scale (0 = none; 1 = mild; 2 = moderate; 3 = severe). Pain was assessed upon PACU arrival, then every 15 min during the initial two hours following PACU entry, then every 30 min for the next two hours, then every four hours until 24 hr after PACU entry, then every four hours until discontinuation of PCA morphine or 48 hr after PACU entry (whichever occurred first). Additional endpoints were time to first postoperative morphine bolus (if given) and time to first administration of PCA morphine. Postoperative Aldrete scores,[4] were assessed at 5, 10, 15, 30, 45, and 60 min after PACU entry, then every 30 min until PACU discharge.

The times from the end of surgery to the following recovery parameters were evaluated for each patient: adequate respiration, tracheal extubation, operating room discharge, and response to verbal command. The times to qualification for PACU discharge (first two consecutive Aldrete score 9 and pain and nausea/emesis controlled), actual PACU discharge, and hospital discharge were also recorded. In addition, an Anesthesiologist's Satisfaction Assessment form, which assessed the predictability of patient response and overall quality of the study drug, was completed.

INTRAOPERATIVE RESPONSES. An assessment of intraoperative responses during the maintenance phase, including responses to light anesthesia, hypotensive and bradycardic responses, and responses to intraoperative stimuli (i.e., intubation, skin incision, skin closure and extubation) was conducted. Intraoperative responses were defined as one or more of the following occurring within five minutes of an event: hypertension (SBP >15 mmHg above preoperative baseline one minute), tachycardia (HR >90 bpm for one minute), somatic (movement, swallowing, grimacing, eye opening), or autonomic (tearing, sweating, mydriasis) response.

Safety assessment

Safety was assessed by monitoring adverse events, vital signs (SBP and DBP, HR, RR), electrocardiography, respiratory parameters (S_pO_2 and $P_{ET}CO_2$), and response to surgical stimuli. All observed adverse events were categorized by treatment group and within treatment groups by drug-related status.

Statistical analysis

This study was 90% powered to detect a 10 mg difference in total amount of PCA morphine sulphate used in the 24 hr postoperative period, between two treatment groups at the 5% statistical significance level. The total amount of morphine used 24 hr postoperatively was compared between groups using analysis of variance (ANOVA), adjusting for investigator and age (=65 yr and >65 yr). The total amount of morphine used 48 hr postoperatively and in the PACU was compared between groups using analysis of variance, adjusting for investigator.

Morphine use was summarized in two ways. In the analysis above, mean total amount included all doses, regardless of when the patients were discharged. Another summary statistic, mean cumulative amount, included only doses for patients who had completed a given time period.

Analysis of postoperative pain was based on calculating an average pain score for each patient, weighted by the number of minutes that pain (0-4) was endured. This average pain score, called an area under the curve (AUC), was calculated for each patient for time intervals of 2, 4, 12, 24, 36 and 48 hr. Patients discharged before reaching a given time interval were not included in the calculation for that mean AUC. Mean AUCs were compared among groups using analysis of variance, adjusting for investigator.

The time from the end of surgery to first morphine bolus (2 mg) and the time from the end of surgery to the first administration of PCA morphine were compared using the Cox proportional hazards model; stratified by investigator. The Cox proportional hazards model, stratified by investigator, was also used to assess treatment differences in the time to the first of two consecutive 9Aldrete scores, and times to recovery endpoints between two treatment groups. Finally, a logistic regression model was used to assess treatment differences in the proportion of patients with responses to surgical stimuli between the two groups.

TABLE I Patient demographic data

	R/M15 Group n=71	*R/M20 Group n=68*	*F/I Group n=71*
Sex – n			
Female / Male 53 / 18	56 / 12	55 / 16	
Mean age – yr ±SD	47.6 ±12.3	45.2 ±14.0	43.9 ±13.4
Mean weight – kg ±SD	75.5 ±16.2	75.2 ±18.3	74.5 ±18.0
Median duration of anesthesia – min (range)	132 (43-412)	135 (53-351)	124 (56-300)

TABLE II Mean total morphine sulphate during first 24 hr, during PACU, and during 48 hr postoperative period

Efficacy Endpoint	*Treatment Group*		
	R/M15	*R/M20*	*F/I*
During PACU			
Mean – mg ±S.E.	15.52 ±1.19	16.48 ±1.46	13.30 ±0.98
95% C.I.	13.19-17.86	13.61-19.35	11.38-15.22
24 hr Post-Op			
Mean – mg ±SEM.	58.07 ±3.67	56.93 ±4.45	53.58 ±2.95
95% C.I.	50.88-65.26	48.19-65.67	47.80-59.37
Mean (≤ 65 yr) – mg	60.97	59.61	53.83
Mean (>65 yr) – mg	31.57	43.54	50.90
48 hr Post-Op			
Mean – mg ±S.E.	69.76 ±5.25	64.70 ±5.09	62.12 ±4.20
95% C.I.	59.46-80.05	54.72-74.69	53.88-70.37

Note: All statistical comparisons resulted in $P >$ NS

Results

Patient demographics

All 210 patients who received study drug (164 women, 46 men) were included in the efficacy analyses. Groups were similar with regard to demographics and baseline parameters (Table I). The median durations of anesthesia were 132, 135 and 124 min in the R/M15, R/M20 and F/I groups, respectively. The majority of patients were ASA II (67%), female (78%) and Caucasian (80%). Urogenital procedures accounted for the majority of the procedures performed.

Efficacy evaluations

ANALGESIA. Analysis of primary efficacy data showed that the mean total amounts of morphine used in the 24 hr postoperative period were 58.1 mg, 56.9 mg and 53.6 mg in the R/M15, R/M20 and F/I groups, respectively (Table II, Figure 1). Statistical comparisons between treatment groups showed no differences with respect to mean total amount of morphine (R/M15 *vs* F/I, P=0.391; R/M20 *vs* F/I, P=0.427). Patients >65 yr required less morphine than patients 65 yr.

Secondary efficacy analyses indicated that the differences among the remifentanil groups and the fentanyl group in 48 hr mean total morphine requirements were not statistically significant. Likewise, the mean total amount of PACU morphine was similar between remifentanil and fentanyl groups (Table II).

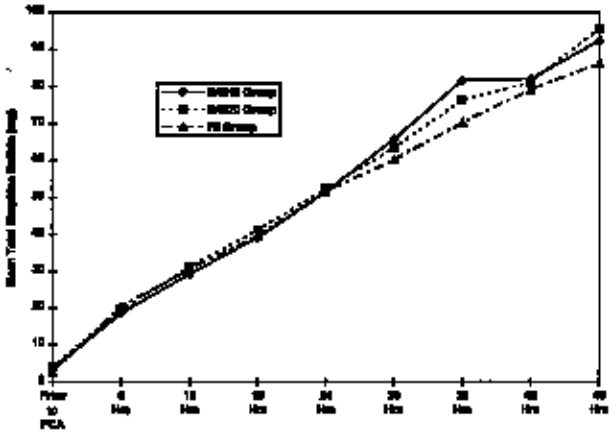

FIGURE 1 Mean cumulative amount of morphine sulphate (included patients that completed time period)

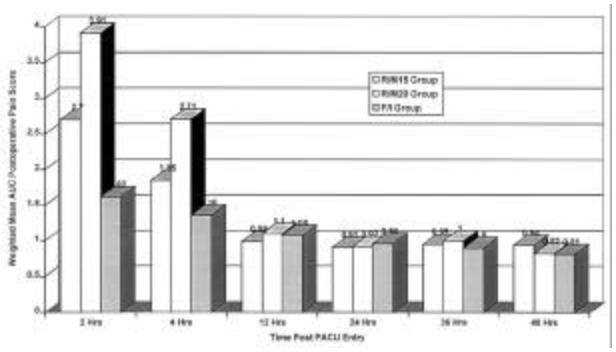

FIGURE 2 Weighted mean postoperative pain scores

RECOVERY. Comparisons between postoperative AUC of pain scores of remifentanil groups and the fentanyl group were not different at 2, 4, 12, 24, 36, or 48 hr following PACU entry (Figure 2). Treatment groups were similar with respect to pain severity ratings at all postoperative time points.

There were 43, 40 and 38 patients in the R/M15, R/M20 and F/I groups, respectively, who required at least one morphine bolus prior to PCA initiation. The median time from the end of surgery to the first morphine bolus was similar in each group (20, 20 and 19 min in the R/M15, R/M20 and F/I groups, respectively) (Table III). Likewise, the median time from the end of surgery to first PCA morphine use was similar among remifentanil and fentanyl groups (42, 49 *vs* 40 min in the R/M15, R/M20 and F/I groups, respectively).

Longer median times were observed between both the R/M15 and the R/M20 *vs* the F/I group for the following recovery endpoints: adequate respiration, extubation, response to verbal command, and actual PACU discharge (Table III). There was a difference between the R/M20 and F/I groups with respect to median time to discharge from the operating room and median time to qualification for PACU discharge. However, the difference between the R/M15 and F/I groups was not significant for these parameters.

The median time to the first of two consecutive 9 Aldrete scores was similar between remifentanil and fentanyl groups (20, 20 and 17 min in the R/M15, R/M20 and F/I groups, respectively). Additionally, the time to hospital discharge was not different between the R/M15 and F/I groups or the R/M20 and F/I groups.

The results of the Anesthesiologist's Satisfaction Assessment indicated that anesthesiologists rated the predictability of response as either very good or excellent in 80%, 86% and 78% of the R/M15, R/M20 and F/I patients, respectively. Overall study opioid performance was rated as good, very good or excellent in 97%, 99% and 87% of the R/M15, R/M20 and F/I patients, respectively.

INTRAOPERATIVE RESPONSES. There were differences between both remifentanil groups and the fentanyl group when responses to intubation, skin incision and skin closure were analyzed. Patients receiving remifentanil regimens experienced fewer responses to these intraoperative stimuli (Table IV). Response to extubation was not different between treatment groups. A review of intraoperative hemodynamic data indicated that the most common responses to all intraoperative stimuli were hypertension and tachycardia.

Safety evaluations

All 210 patients who received study drug were included in the safety analyses. The overall incidence of patients experiencing at least one adverse event was 87% in the R/M20 group and 85% in the R/M15 and F/I groups. Of these adverse events, 48% in the R/M15 group, 47% in the R/M20 group and 37% in the F/I group were drug-related (Table V). Nausea was the most prevalent adverse event with an occurrence rate of 65%, 60% and 62% in the R/M15, R/M20 and F/I groups, respectively. The incidence decreased to 31%, 26% and 27%, respectively, for nausea considered to be drug-related. All reports of nausea occurred during the postoperative period.

The overall incidence of emesis was 11%, 21% and 17% in the R/M15, R/M20 and F/I groups, respectively, whereas the incidence of drug-related emesis

TABLE III Recovery endpoints

Efficacy Endpoint *Time to:*		*Treatment Group* *R/M15*	*R/M20*	*F/I*
Adequate Respiration	Median – min (range)	7 (-3-19)*	6 (-2-26)*	3 (-17-47)
Response to Verbal Commands	Median – min (range)	7 (0-27)*	6 (1-28)*	5 (0-46)
Extubation	Median – min (range)	9 (1-23)*	8 (2-28)*	5 (0-49)
Discharge from Operating Room	Median – min (range)	12 (6-26)	14 (4-30)*	11 (4-51)
First Morphine Bolus Dose	Median – min (range)	20 (7-41)	20 (6-49)	19 (8-48)
First PCA Morphine Dose	Median – min (range)	42 (9-232)	49 (12-145)	40 (9-385)
First of Two Consecutive Aldrete Scores (≥ 9)	Median – min (range)	20 (7-140)	20 (9-108)	17 (6-108)
Qualification for PACU Discharge	Median – min (range)	74 (14-315)	72 (19-625)	70 (11-165)
Actual Discharge from PACU	Median – min (range)	112 (74-536)*	125 (66-1705)*	101 (62-492)
Hospital Discharge	Median – hrs (range)	70 (24-215)	54 (2-266)	74 (19-433)

* $P < 0.05$ for comparison with F/I

TABLE IV Percentage of patients with one or more responses to intraoperative stimuli

Intraoperative Stimuli		*Treatment Group* *R/M15*	*R/M20*	*F/I*
Intubation	Patients with ≥ 1 response – %	37*	29*	69
Skin Incision	Patients with ≥ 1 response – %	6*	4*	21
Skin Closure	Patients with ≥ 1 response – %	35*	46*	77
Extubation	Patients with ≥ 1 response – %	82	90	84

* $P < 0.05$ for comparisons with F/I

TABLE V Percent of patients experiencing drug–related adverse events

	Treatment Group *R/M 15*	*R/M 20*	*F/I*
Percentage of patients with any event	48%	47%	37%
Gastrointestinal	34%	31%	28%
Nausea	31%	26%	27%
Emesis	4%	7%	8%
Cardiovascular	21%	26%	6%
Hypotension	21%	19%	4%
Bradycardia	3%	7%	3%
Musculoskeletal	0	1%	3%
Muscle rigidity	0	1%	3%
Infusion site reactions	0	1%	0
Erythema at study *iv* site	0	1%	0
Pruritis at study *iv* site	0	1%	0
Respiratory	0	0	1%
Respiratory depression	0	0	1%

was 4%, 7%, and 8%, respectively. The second most prevalent adverse event was hypotension with an occurrence rate of 23% (R/M15), 21% (R/M20) and 7% (F/I). The incidence of drug-related hypotension was 21% (R/M15), 19% (R/M20) and 4% (F/I). However, 27% of R/M15 patients, 15% of R/M20 patients and 48% of F/I patients did not experience any hypotensive or bradycardic responses. There were no differences in mean RR, S_pO_2, or $P_{ET}CO_2$ at any time point among the groups.

Discussion

Remifentanil hydrochloride is a potent ultrashort-acting μ-opioid agonist that may be useful in clinical situations where rapid recovery is desirable. The disadvantage of the short-acting nature of remifentanil is the need for a transition analgesic regimen before discontinuation of the infusion in surgery with moderate to severe postoperative pain. Without such a transition analgesic, patients may experience greater than average pain in the PACU and require increased doses of morphine to be comfortable postoperatively. The present study found that the mean total amount of morphine used in the PACU, and the 24 and 48 hr postoperative periods in both remifentanil groups and the fentanyl group were not different; indicating that the transition analgesic was effective.

The mean individual postoperative morphine requirements in this study are within the ranges reported by White[5] and Tamsen.[6] This study also confirmed previous studies indicating that elderly patients require less analgesic medication.[7] The mean total morphine requirement in the 24 hr postoperative period was almost halved in patients older than 65 yr compared with patients 65 yr of age or less.

Other measurements that support the effectiveness of the transition analgesic include similar times from the end of surgery to the first morphine bolus and first PCA morphine administration between treatment groups. In addition, the differences between the weighted mean postoperative pain scores of the

remifentanil groups and the fentanyl group were not significantly different at any time points following PACU entry.

Generally, patients in the fentanyl arm experienced faster times to various recovery endpoints than patients receiving remifentanil and morphine as a transition analgesic. The longer times to recovery endpoints in the remifentanil groups observed in this study are probably due to morphine, which achieves peak effect approximately 5 - 20 min following *iv* administration.[9] The timing of anesthetic agent discontinuation may also have contributed to longer times to recovery endpoints experienced by remifentanil patients. The remifentanil infusion was discontinued at the end of surgery, whereas the median time of last bolus dose of fentanyl in the fentanyl arm was 44 min (range, -4 to 118) prior to the end of surgery. Although the usual duration of action of the analgesic effect of fentanyl is 30 to 60 min after a single *iv* dose of up to 100 µg,[10] the timing of the administration of fentanyl meant that patients in the fentanyl arm had an opportunity to emerge from anesthesia sooner than remifentanil patients.

Despite the generally longer times to recovery endpoints, no difference was detected between remifentanil groups and the fentanyl group when Aldrete scores, the major eligibility criteria for PACU discharge, were compared. Furthermore, as evidenced by the Anesthesiologist's Satisfaction Assessment, clinicians did not feel the difference in the recovery profile impacted patient response or quality of study opioid performance.

Opioids may decrease arterial blood pressure and heart rate.[11] Remifentanil produces hemodynamic effects typical of potent opioids with a rapid onset of action and short time to peak effect. Opioid-based anesthesia may also prevent episodic tachycardia and hypertension which may occur intraoperatively in response to varying levels of surgical stimulation. Remifentanil is potent in this regard because higher doses may be given intraoperatively without fear of prolonging recovery. Patients in this study who received remifentanil-based regimens experienced fewer responses to intraoperative stimuli and had a more stable anesthetic course.

Generally, remifentanil was well tolerated with similar adverse events profiles observed between remifentanil- based and traditional fentanyl-based anesthetic regimens. Nausea was the most prevalent drug-related adverse event experienced by patients during the postoperative period. Nausea and vomiting are common side effects of emergence from general anesthesia.

In conclusion, this study demonstrated that morphine sulphate regimens of 0.15 or 0.20 $mg \cdot kg^{-1}$ administered 30 min prior to discontinuation of a remifentanil infusion are equally effective transition analgesic regimens for inpatient procedures lasting one hour or more. Postoperative analgesic requirements of morphine sulphate in the PACU and 24 and 48 hr postoperatively were similar between all regimens studied.

Acknowledgments

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References

1 *Glass PSA.* Remifentanil: a new opioid. J Clin Anesth 1995; 7: 558–63.

2 *Bürkle H, Dunbar S, Van Aken H.* Remifentanil: a novel, short-acting µ-opioid. Anesth Analg 1996; 83: 646–51.

3 *Hogue CW Jr, Bowdle TA, O'Leary C, et al.* A multicenter evaluation of total intravenous anesthesia with remifentanil and propofol for elective inpatient surgery. Anesth Analg 1996; 83: 279–85.

4 *Aldrete JA, Kroulik D.* A postanesthetic recovery score. Anesth Analg 1970; 49: 924–33.

5 *White PF.* Patient-controlled analgesia: a new approach to the management of postoperative pain. Seminars in Anesthesia 1985; 4: 255–66.

6 *Tamsen A, Hartvig P, Fagerlund C, Dahlström B, Bondesson U.* Patient-controlled analgesic therapy: clinical experience. Acta Anaesthesiol Scand 1982; 74: 157–60.

7 *Burns JW, Hodsman NBA, McLintock TTC, Gillies GWA, Kenny GNC, McArdle CS.* The influence of patient characteristics of the requirements for postoperative analgesia. Anaesthesia 1989; 44: 2–6.

8 *Ginsberg B.* Patient controlled analgesia: application and monitoring guidelines. *In*: Sinatra R, Hord A, Ginsberg B, Prebbles L (Eds.). Acute Pain Mechanisms and Management. PA: Mosby Year Book, 1992: 165.

9 *Omoigui S.* The Anesthesia Drugs Handbook, 2nd ed. Mosby, 1995.

10 Sublimaze® Injection (Akorn): Physicians' Desk Reference, 51st ed. NJ: Medical Economics Data Production, 1997.

11 *Nauta J, Stanley TH, de Lange S, Koopman D, Spierdijk J, van Kleef J.* Anaesthetic induction with alfentanil: comparison with thiopental, midazolam, and etomidate. Can Anaesth Soc J 1983; 30: 53–60.