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Acute Opioid Tolerance

Intraoperative Remifentanil Increases Postoperative Pain and Morphine Requirement

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Background: **Rapid development of acute opioid tolerance is well established in animals and is more likely to occur with large doses of short-acting drugs. The authors therefore tested the hypothesis that intraoperative remifentanil administration results in acute opioid tolerance that is manifested by increased postoperative pain and opioid requirement.**

Methods: **Fifty adult patients undergoing major abdominal surgery were randomly assigned to two anesthetic regimens: (1) desflurane was kept constant at 0.5 minimum alveolar concentrations and a remifentanil infusion was titrated to autonomic responses (remifentanil group); or (2) remifentanil at 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and desflurane titrated to autonomic responses (desflurane group). All patients were given a bolus of 0.15 mg/kg morphine 40 min before the end of surgery. Morphine was initially titrated to need by postanesthesia care nurses blinded to group assignment. Subsequently, patients—who were also blinded to group assignment—controlled their own morphine administration. Pain scores and morphine consumption were recorded for 24 postoperative h.**

Results: **The mean remifentanil infusion rate was 0.3 ± 0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in the remifentanil group, which was significantly greater than in the desflurane group. Intraoperative hemodynamic responses were similar in each group. Postoperative pain scores were significantly greater in the remifentanil group. These patients required morphine significantly earlier than those in the desflurane group and needed nearly twice as much morphine in the first 24 postoperative h: 59 mg (25–75% interquartile range, 43–71) *versus* 32 mg (25–75% interquartile range, 19–59; $P < 0.01$).**

Conclusion: **Relatively large-dose intraoperative remifentanil increased postoperative pain and morphine consumption. These data suggest that remifentanil causes acute opioid tolerance and hyperalgesia. (Key words: Analgesia; anesthesia.)**

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REMIFENTANIL is a short-acting opioid with a predictable and rapid recovery that is relatively independent of the dose. It can thus be given in high doses until skin closure with little risk of delayed postoperative recovery or respiratory depression.[1] A corollary of short action is that patients may experience considerable surgical pain in the immediate postoperative period.[2] Supplemental opioids are thus often given prophylactically to patients who are likely to experience postoperative pain.[1] Despite this precaution, postoperative analgesic requirement in patients given intraoperative remifentanil is often surprisingly great.[3,4] This observation suggests that remifentanil may be associated with acute opioid tolerance.

Rapid development of acute opioid tolerance is well established in animals.[5–10] The amount of tolerance that results from various opioids appears similar; however, tolerance develops considerably faster in response to short-active narcotics such as alfentanil.[7,9] Furthermore,

profound tolerance has been demonstrated after only 60–90 min of remifentanil in volunteers.[11] However, the clinical consequences of acute tolerance to remifentanil have yet to be evaluated. We therefore tested the hypothesis that intraoperative remifentanil administration results in acute opioid tolerance that is manifested by increased postoperative pain and opioid requirement.

Materials and Methods

With approval of the Ethics Committee of the Hôpital Ambroise Paré, we studied adult patients who were scheduled for open colorectal surgery lasting at least 2 h. All patients were American Society of Anesthesiologists physical status I–III.

Patients were excluded from the study when: (1) immediate extubation was not planned after surgery; (2) they had chronic inflammatory disease, including inflammatory bowel disease; (3) they regularly took analgesics or had used opioids within 12 h of surgery; (4) they had a history of drug or alcohol abuse, psychiatric disorder, or obesity (> 130% of ideal body weight); or (5) there were contraindications to the self-administration of opioids (*i.e.*, unable to understand the patient-controlled analgesia [PCA] device).

Postoperative morphine consumption was used to calculate the statistical power. Reported postoperative morphine consumption varies widely. Mean patient-controlled morphine consumption during the initial 24 h after laparotomy varies between 38 and 76 mg, with SDs ranging from 7 to 45 mg.[12–15] Our experience indicated that morphine use over the initial 24 postoperative h after major abdominal surgery is 40 ± 20 mg. A sample size estimate indicated that 24 patients per group would give a power of 80% at an α level of 0.05 for detecting a difference in morphine consumption of at least 40%. The study size was thus prospectively set to 50 patients.

Protocol

The evening before surgery, patients were instructed on the use of a 10-cm-long visual analog scale, with 0 cm identifying no pain and 10 cm being defined as the worst imaginable pain. They were also instructed in the use of a four-point verbal rating scale (0 = no pain; 1 = slight pain; 2 = moderate pain; 3 = intense or severe pain), and we explained the use of the PCA system (Graseby 3300 PCAS; Graseby Medical, Watford, United Kingdom). Patients were premedicated with lorazepam 1 mg orally the night before surgery.

Anesthesia was induced with thiopental 6 mg/kg followed by atracurium 0.5 mg/kg to facilitate orotracheal intubation. One minute after thiopental injection, a 1-μg/kg loading dose of remifentanil was given over 60 s. After tracheal intubation, the patients were ventilated to normocapnia with desflurane in 50% oxygen and without nitrous oxide. An atracurium infusion was titrated to maintain one twitch in response to a supramaximal train-of-four stimulus at the orbicularis oculi; atracurium was then discontinued 15 min before the end of surgery.

Randomization was based on computer-generated codes maintained in sequentially numbered, opaque envelopes. The envelopes were opened after induction of general anesthesia. In one group (remifentanil), end-tidal desflurane concentration was maintained at 0.5 minimum alveolar concentration, adjusted to age.[16,17] A remifentanil infusion was started in these patients at a rate of 0.25 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and subsequently increased stepwise by 0.05-$\mu g \cdot kg^{-1} \cdot min^{-1}$ increments if insufficient anesthesia was suspected. In the other group (desflurane), a remifentanil infusion was maintained at a rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ and maintained at that dose throughout anesthesia. In contrast, the inspired desflurane concentration was increased stepwise by 1% if insufficient anesthesia was suspected.

Our criteria for possibly insufficient anesthesia was a heart rate that exceeded preinduction values by 15% and/or a systolic arterial blood pressure that exceeded baseline values by 20% for at least 1 min. Patient movement, coughing, tearing, or sweating were also considered signs of inadequate anesthesia. Hypotension, defined by a systolic arterial pressure less than 80 mmHg or a mean arterial pressure less than 60 mmHg, was treated by stepwise reductions in the designated study drugs. Additional intravenous fluids were also given as deemed appropriate by the responsible anesthesiologist. Similarly, atropine or intermittent bolus doses of ephedrine were given as necessary for bradycardia or persistent hypotension. The anesthesiologist was not blinded to group assignment.

Thirty minutes before the end of surgery, a 0.15-mg/kg bolus dose of morphine was administered intravenously. At skin closure, desflurane and remifentanil were discontinued, and residual neuromuscular blockade was antagonized with 40–60 μg/kg intravenous neostigmine and 15–20 μg/kg intravenous atropine. The trachea was extubated when patients responded to the verbal command, the spontaneous respiratory rate exceeded 12 breaths/min and end-tidal carbon dioxide was less than 45 mmHg.

Patients were transferred to the postanesthetic care unit within 5 min of tracheal extubation. They remained in the unit for at least 4 h and were given oxygen *via* facemask at a rate of 3 l/min throughout this period. Postoperative pain was initially treated with morphine chlorhydrate that was titrated to need by nurses who were unaware of patients' group assignments or intraoperative remifentanil dose. During this period, morphine was given intravenously a rate of 3 mg at 5-min intervals until the behavioral pain score (defined later) was < 1 or the verbal response score (defined later) was < 2. However, morphine administration was discontinued in patients having a sedation score > 3 or a respiratory rate < 12 breaths/min. Subsequently, in a delay that did not exceed 3 h after tracheal extubation, patients were connected to a PCA device set to deliver morphine, 1 mg as an intravenous bolus, with a lock-out interval of 5 min and no background infusion or limits. This regimen of PCA was continued until 24 h after tracheal extubation.

Measurements

Baseline heart rate and systolic arterial pressure were defined as the mean of the two lowest measurements recorded during a 3- to 5-min interval just before induction of anesthesia. Values from all routine anesthetic monitors were recorded at 5-min intervals during surgery.

The total dose of remifentanil given in the operating room was recorded, as was the age-adjusted number of minimum alveolar concentration--hours. Complications, including laryngospasm, bronchospasm, respiratory depression, muscular rigidity, agitation, or shivering, were recorded. Pain was evaluated for the first 15 min after extubation with a behavioral score defined as follows: 0 = calm patient with no verbal or behavioral manifestation of pain; 1 = behavioral or verbal expression of pain; 2 = intense behavioral or verbal manifestation (crying, extreme agitation). This behavioral pain scale was performed 5, 10, and 15 min after tracheal extubation.

Both in the postanesthetic care unit and surgical ward, patients were observed by nurses who were blinded to treatment group and intraoperative management. Pain intensity was assessed by patients with both a visual analog scale and a verbal response score at 15-min intervals during the first hour and then hourly for 3 h. Subsequently, pain was evaluated only with a visual analog scale at 4-h intervals for an additional 20 h. The time interval from discontinuation of intraoperative remifentanil until the first request of morphine was recorded, as was the amount of morphine used during the first 24 h after tracheal extubation.

Anesthetic-related complications were recorded, including nausea, vomiting, pruritus, dysphoria, hallucinations, or diplopia. Nausea and vomiting were treated by intravenous bolus doses of droperidol 0.5 mg. Sedation was monitored using the following four-point rating scale: 0 = patient fully awake; 1 = patient somnolent and responsive to verbal commands; 2 = patient somnolent and responsive to tactile stimulation; and 3 = patient asleep and responsive to painful stimulation. Respiratory depression was defined in the postanesthetic care unit by a persistent respiratory rate < 10 breaths/min or hypoxemia as defined by a pulse oximeter saturation $< 90\%$. In the surgical wards, respiratory depression was defined by the combination of a sedation score > 1 and a respiratory rate < 10 breaths/min.

Statistical Analysis

Age, weight, height, time intervals, remifentanil consumption, average desflurane concentration, temperature at end of study, and cumulative postoperative morphine consumption at 24 h were compared with unpaired Student *t* test. The relative frequencies of gender, American Society of Anesthesiologists status, and nausea and vomiting were compared with Fisher exact tests.

Hemodynamic parameters, end-tidal desflurane concentration, and visual analog scale scores over 24 h were analyzed with one-way analysis of variance. Sedation, behavioral and verbal response scores for pain, as well as ephedrine, droperidol, and intravenous morphine doses were compared with Mann–Whitney U tests. Fisher posteriori least-significant difference tests were used for between-group, *post hoc* comparisons.

The fraction of patients not requiring supplemental postoperative morphine were evaluated with survival curves and were compared with the Kaplan-Meier log-rank test. Cumulative consumption of morphine during the initial 24 postoperative h were analyzed with an unpaired Student *t* test. Results are presented as mean ± SD or median and 25–75% interquartile ranges; $P < 0.05$ was considered statistically significant.

Results

One patient among the 50 was excluded from the remifentanil group because of prolonged surgery (> 12 h) and hypothermia that required postoperative mechanical ventilation. Morphometric and demographic charac-

Table 1. Morphometric and Demographic Data, Surgical Procedures, and Duration of Surgery and Anesthesia

	Desflurane (n = 25)	Remifentanil (n = 24)
Age (yr)	62 ± 9	60 ± 13
Weight (kg)	69 ± 12	64 ± 9
Height (cm)	167 ± 9	165 ± 7
Sex (men/women)	13/12	13/11
ASA I/II/III	5/17/3	3/19/2
Procedure		
Right colectomy	5	7
Colectomy with colorectal anastomosis	10	8
Colectomy with coloanal anastomosis	10	7
Total colectomy	0	2
Duration of Anesthesia (h)	4.8 (3.9–5.3)	4.9 (4.2–5.8)
Duration of Surgery (h)	3.9 (3.0–4.6)	4.3 (3.5–4.9)

Values are mean ± SD, median (25–75% interquartile range), or number of patients. There were no statistically significant differences between the groups.

ASA = American Society of Anesthesiologists.

teristics of the remaining patients and the type (or length) of the surgical procedures were similar in each group (table 1).

Remifentanil consumption was threefold greater and desflurane use was reduced by a third in the remifentanil group ($P < 0.01$). Figure 1 summarizes end-tidal desflurane concentrations recorded at specific times. Despite greater intraoperative end-tidal desflurane concentrations in the desflurane group, residual concentrations during awakening, extubation, and recovery were similar in the two groups (table 2). The morphine bolus, 0.15 mg/kg, was given 42 ± 11 min before completion of the skin closure in the desflurane group and 41 ± 12 min in the remifentanil group.

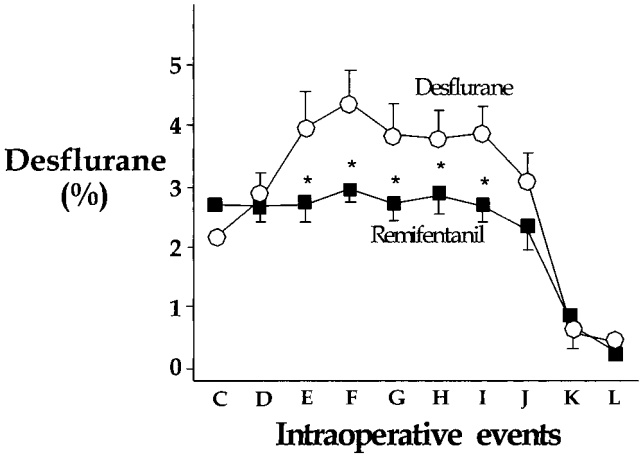

Fig. 1. Intraoperative end-tidal desflurane concentration (mean ± 95% confidence interval) during and after surgery. Open circles = desflurane group; filled squares = remifentanil group. Times are as follows: C = 10 min after tracheal intubation, D = 10 min after incision, E = retractors, F = dissection, G = end of colectomy, H = beginning of closure, I = morphine 0.15 mg/kg, J = end of surgery, K = awake, and L = extubation. Asterisks indicate statistically significant differences between the groups ($P < 0.001$).

Heart rate, systolic and diastolic blood pressures, and ephedrine use were generally similar in each group. However, systolic blood pressure was significantly ($P < 0.05$) lower 10 min after tracheal intubation, and heart rate and systolic blood pressure at tracheal extubation were significantly ($P < 0.05$) higher in the remifentanil group (data not shown).

More patients in the desflurane group were calm with no verbal or behavioral manifestation of pain 5, 10, and 15 min after extubation ($P < 0.05$; fig. 2). Verbal response scores for pain were also significantly ($P < 0.05$) greater in the remifentanil group 15, 30, and 45 min after tracheal extubation (fig. 3). Similarly, visual analog pain scores were greater after 30 min in the remifentanil

Table 2. Anesthetic Characteristics, Postoperative Morphine Use, and Nausea and Vomiting

	Desflurane (n = 25)	Remifentanil (n = 24)
Time-weighted mean remifentanil dose ($\mu g \cdot kg^{-1} \cdot min^{-1}$)	0.1 ± 0.0	0.3 ± 0.2*
Desflurane (MAC/h)	0.7 ± 0.2	0.5 ± 0.1*
Ephedrine (no. of doses/no. of patients)	16/9	25/10
Final intraoperative temperature (°C)	36.9 ± 0.4	36.7 ± 0.5
Awakening time (min)	12 ± 6	12 ± 9
Extubation time (min)	14 ± 7	16 ± 9
Time to first PCA use (h)	3.5 (2.8–5.7)	2.5 (1.7–4.0)
Morphine given by intravenous titration in PACU (mg)	10.5 (6–15)	17 (11–21.5)
Cumulative 24-h postoperative morphine consumption (mg)	32 (19–59)	59 (43–71)*
Postoperative nausea and vomiting (no. of patients)	7	3
Droperidol (no. of doses/no. of patients)	7/7	3/3

Times (awakening, extubation, and first PCA use) were defined from desflurane and remifentanil discontinuations. The cumulative postoperative morphine consumption at 24 h excluded the dose of 0.15 mg/kg given 40 min before the end of surgery. Values are mean ± SD, median (25–75% interquartile range), or number of patients.

* Statistically significant differences between the groups ($P < 0.01$).

MAC = minimum alveolar concentration; PACU = postanesthesia care unit; PCA = patient-controlled analgesia.

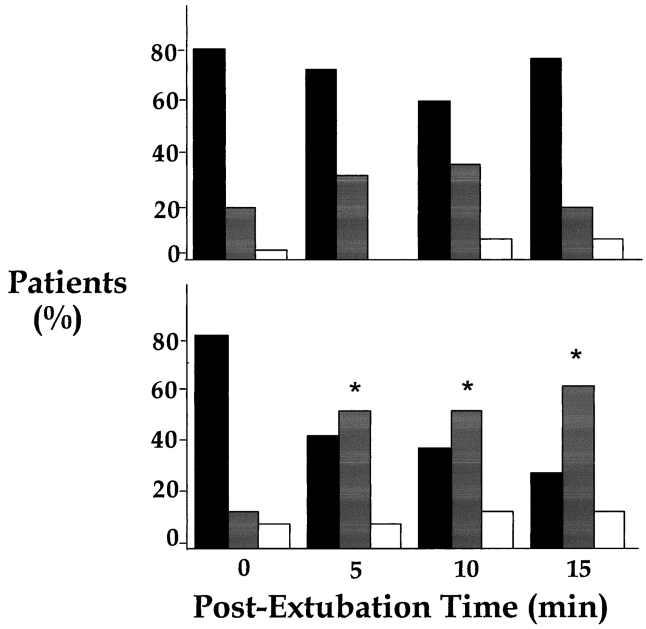

Fig. 2. Time course of the distribution of the behavioral pain scores during the first 15 min after tracheal extubation in the desflurane group (*top*) and in the remifentanil group (*bottom*). Solid bars = calm, gray bars = behavioral or verbal expression of pain, open bars = intense behavioral or verbal manifestation of pain. Asterisks indicate statistically significant differences between the groups ($P < 0.05$).

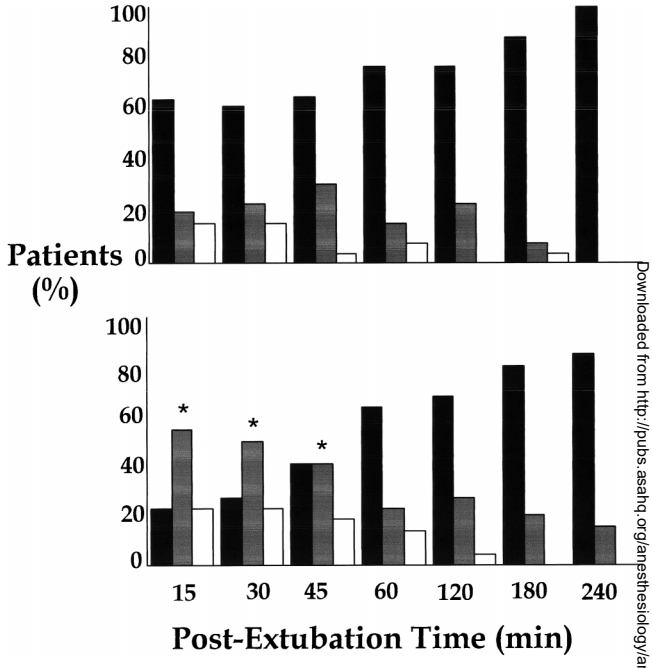

Fig. 3. Time course of the distribution of the verbal rating scale pain scores from 15 to 240 min after tracheal extubation in the desflurane group (*top*) and in the remifentanil group (*bottom*). Solid bars = 0 or 1 verbal response score, gray bars = verbal response score of 2, open bars = verbal response score of 3. Asterisks indicate statistically significant differences between the groups ($P < 0.05$).

group, with a significant difference at 3 and 4 h after tracheal extubation (fig. 4).

Survival curve analysis of the first morphine administration revealed that patients in the remifentanil group required morphine significantly earlier ($P < 0.05$; fig. 5). The cumulative dose of morphine given intravenously by nurses in the postanesthesia care unit was significantly ($P < 0.01$; table 2) greater in the remifentanil group. The time until the first patient-controlled request for morphine was similar in the two groups. However, the mean morphine consumption was significantly increased throughout the 24 h ($P < 0.05$; fig. 6), and median cumulative morphine dose used in the first 24 postoperative h, including morphine titrated in the postanesthetic care unit, was almost doubled in the remifentanil group ($P < 0.01$; table 2).

There were no significant differences in nausea or vomiting or droperidol consumption. The percentage of sedated patients (scores 0 or 1) were comparable except for the fourth postoperative hour, when the fraction of sedation scores > 1 were significantly greater in the desflurane group. Dysphoria or other subjective effects such as dizziness or drowsiness were not reported. No respiratory depression was detected.

Discussion

We confirmed our hypothesis that major abdominal surgery with relatively large-dose remifentanil is followed by greater postoperative pain scores. Consequently, patients in the remifentanil group required morphine earlier and required greater doses to achieve satisfactory analgesia. Interestingly, this increased morphine demand extended for many postoperative hours. As a result, the difference in cumulative morphine use was among our clearest outcomes.

The most likely explanation for the greater morphine requirement in the remifentanil than desflurane group is development of acute opioid tolerance. A similar effect may explain the unusually large postoperative morphine requirements observed in previous studies of intraoperative remifentanil.[3,4] However, acute tolerance does not entirely fit with our results. Indeed, despite higher morphine requirement, higher pain scores were observed in the remifentanil group. This indicates that the development of sustained hyperalgesia from exposure to high-dose opioid occurred in our patients. Recently, Célèrier *et al.*[18] observed a long-lasting and dose-dependent hy-

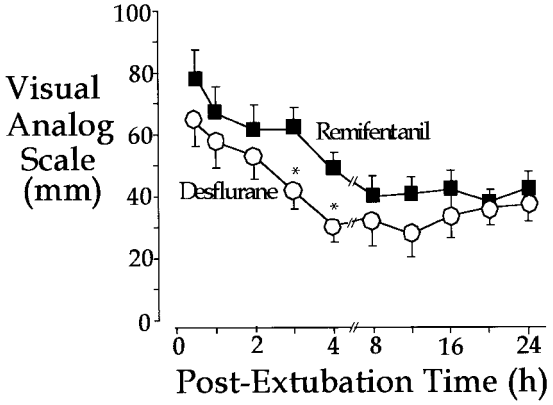

Fig. 4. Visual analog scale pain scores (0–100 mm) in the two groups during the 24 h after tracheal extubation. Open circles = desflurane group, filled squares = remifentanil group. Values are median ± 95% confidence intervals. Asterisks indicate statistically significant differences between the groups ($P < 0.05$).

peralgesia. The same group reported an opiate tolerance to daily heroin administration that was associated with enhanced pain sensitivity.[19] These findings support the hypothesis that a mixture of these two phenomena (tolerance and delayed hyperalgesia) may be produced by the acute exposure to large doses of opioids.[20] Further studies may be performed in the future to distinguish between these two mechanisms to demonstrate whether one is prevalent on the other. Such a hyperalgesia underlies a central sensitization that clinically might produce reduction in threshold expansion of receptive fields and increase in response to noxious stimuli.[21]

In animal experiments, acute tolerance is easily demonstrated with various opioids, including morphine, sufentanil, and alfentanil.[5–9,22,23] The magnitude of tolerance seems unrelated to the potency of the opioid used.[7] However, the speed at which tolerance develops depends greatly on the pharmacokinetic characteristics of the drugs.[7,9] Specifically, shorter duration of action is associated with faster development of tolerance. It is therefore likely that tolerance develops more rapidly with a rapid offset drug like remifentanil than with longer-acting opioids. Concerning this point, remifentanil is unique as a fentanyl derivate with an ester linkage that leads to a very rapid breakdown.[1] Moreover, the mean remifentanil infusion rate of 0.3 $\mu g \cdot kg^{-1} \cdot min^{-1}$ used in the remifentanil group is a high dose that was demonstrated to decrease approximately by 80% isoflurane minimal alveolar concentration in humans.[24] Such a dose likely produced intense opioid receptor activation that led to a persistent increase in pain sensitivity. This is in line with reports of hyperalgesia induced by naloxone in morphine- or fentanyl-treated rats.[25]

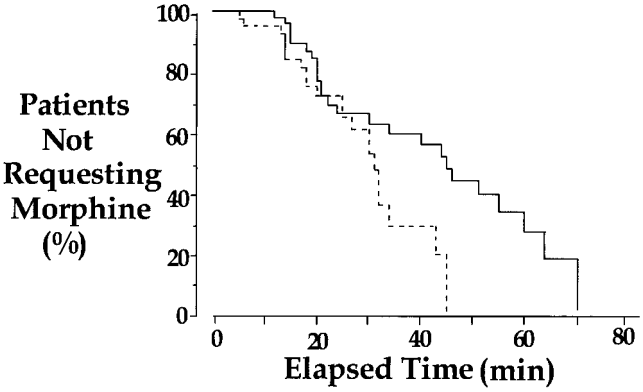

Fig. 5. Cumulative survival curves for patients who did not request an additional morphine injection after remifentanil was discontinued. Dashed line = remifentanil group, solid line = desflurane group. The two groups differed significantly ($P < 0.05$, log-rank test).

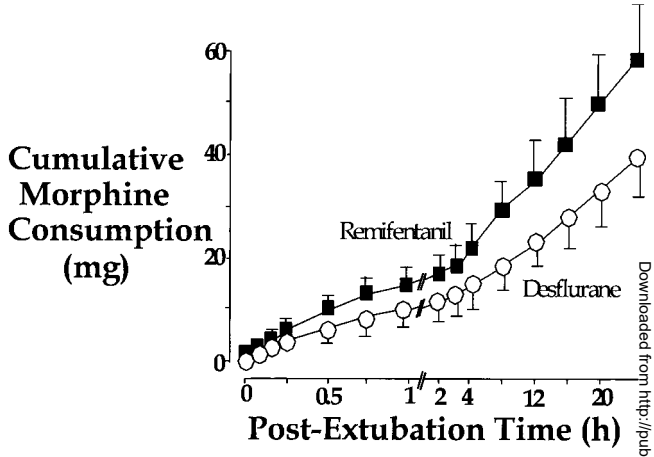

Fig. 6. Cumulative postoperative morphine consumption in the two groups during 24 h after tracheal intubation. Values are mean ± 95% confidence interval. Open circles = desflurane group, filled squares = remifentanil group. Area under the curve differed significantly in the two groups ($P < 0.05$).

Tolerance to opioids is pharmacodynamic[8]; it is therefore hardly surprising that tolerance is dose-dependent.[26] Animal studies demonstrate that intrathecal morphine infusion induces tolerance to somatic and visceral antinociception, and that this tolerance is dose-dependent.[27] Results are similar in patients: increased morphine administration during the initial postoperative period is associated with greater opioid requirement in subsequent hours.[28] Moreover, animal studies[9,29] suggest that opioid tolerance develops more rapidly when larger doses are given. Although both our treatment groups were given remifentanil, one group was given

more than three times as much—explaining the observed postoperative differences.

Vinik and Kissin[11] measured pain tolerance to thermal and mechanical noxious stimulation in volunteers given intravenous remifentanil at a constant rate of 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 4 h. They observed that, after reaching maximum analgesia in 60–90 min, the analgesic effect of remifentanil began to decline. After 3 h of infusion, only one fourth of the maximum analgesic effect remained. These experimental observations support our clinical results and are consistent with our hypothesis.

An important clinical aspect of opioid tolerance is that it lasts well beyond the period of opioid administration. For example, Célèrier *et al.*[18] reported a delayed and long-lasting enhancement of pain sensitivity after fentanyl injection in rats. The results were similarly prolonged in our patients, who were relatively resistant to opioid in the postoperative period. It remains unclear to what extent tolerance to the analgesic effects of opioids is accompanied by tolerance to the toxic effects of the drugs. However, there is at least some experimental evidence to suggest that analgesic tolerance does not necessarily protect against respiratory toxicity.[22] Although we did not observe respiratory toxicity in our patients, an alternative to large-dose opioid in these patients may be to coadminister drugs that prevent and/or reduce acute tolerance to opioids.

The opioid tolerance mechanism remains poorly understood, and it is likely that multiple mechanisms contribute.[30] Potential mechanisms include decoupling from transduction systems,[31] antianalgesia systems,[32] and alterations of the *N*-methyl-D-aspartate (NMDA) receptor and its intracellular second messenger systems. For example, NMDA receptor antagonists such as magnesium and ketamine have been shown to block morphine tolerance.[33,34] μ Opioid receptor agonists have been shown to elicit activation of the NMDA receptor, likely *via* activation of protein kinase C.[35,36] Moreover, opioid exposure,[37] especially in large doses,[38] seems to increase release of glutamate from presynaptic terminals within the spinal cord. Delayed hyperalgesia from opioid exposure may reflect similar mechanisms.[20] In agreement with this hypothesis, recent studies demonstrated that pretreatment with NMDA receptor antagonists blocked hyperalgesia induced by heroin[19] or fentanyl[18,25] in rats. These data thus suggest that NMDA receptor antagonists may be useful adjuncts to morphine to control postoperative pain after remifentanil-based anesthesia.

In a recent experimental study, volunteers reported dose-related dysphoria, unpleasant bodily sensations, difficulty in concentrating, and a feeling of heaviness or sluggishness lasting approximately 30 min after discontinuation of a remifentanil infusion.[39] Differences in mood and drug-induced dysphoria might also worsen subjective pain perception and generate increased analgesic demand. We failed to note dysphoric effects in our patients; however, we did not perform an exhaustive mood assessment. Further studies using validated subjective measures and psychomotor and cognitive tests will be necessary to determine if mood alterations are a consistent finding after remifentanil-based anesthesia. Dysphoria would suggest development of behavioral dependence unmasked by the abrupt withdrawal of a short-acting opioid.

Increased pain and analgesic requirement in the remifentanil patients might suggest that the intraoperative morphine dose was inadequate. However, we recently demonstrated that morphine supplementation is still required postoperatively, even when large-dose morphine (0.25 mg/kg) is used intraoperatively.[4] This is relevant because surgical pain during morphine infusion attenuates development of morphine tolerance in rats.[21] We have no way of assuring that the effects of surgical manipulations were comparably perceived by the brain during our different anesthetic techniques. However, we titrated intraoperative remifentanil and desflurane to autonomic responses, which were therefore comparable in the two study groups. It thus seems unlikely that hypothalamic-pituitary-adrenal axis activation or release of endorphins by surgical stress would differ much between the groups. This conclusion is supported by the intraoperative hemodynamic patterns, which were similar (per protocol) in the two groups.

Conflicting results have been published concerning the effect of the volatile anesthetics at very low concentrations (*i.e.*, 0.05–0.1 minimum alveolar concentrations) on pain. Some studies have demonstrated an increase in pain threshold.[40,41] For example, Goto *et al.*[42] reported a dose-dependent antagonization in morphine-induced analgesia. However, other studies found no hypoalgesic or hyperalgesic effect of subanesthetic concentrations of inhalation anesthetics.[43–45] Patients in the desflurane group naturally had greater intraoperative end-tidal desflurane concentrations; however, concentrations of the gas were comparable by extubation. It is thus unlikely that residual desflurane confounded our results.

In summary, our study suggests that intraoperative administration of relatively large remifentanil doses increases postoperative pain and morphine consumption. The most likely explanation for this observation is acute opioid tolerance.

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