

Opioid Tolerance Blunts the Reduction in the Sevoflurane Minimum Alveolar Concentration Produced by Remifentanil in the Rat

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Background: **Acute opioid tolerance is a known entity leading to reduced analgesic efficacy of these drugs in the postoperative period. However, the development of acute opioid tolerance in the very short term, *i.e.*, during the intraoperative period when opioids are being administered, has not been reported. Therefore, the aim of this study was to determine if acute opioid tolerance could develop and limit the opioid-induced reduction in the minimum alveolar concentration (MAC) for inhalant anesthetics.**

Methods: **Male Wistar rats were randomly allocated to receive two doses of remifentanil (120 and 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$) under sevoflurane anesthesia, and the sevoflurane MAC was determined before and at two time intervals afterwards. In a second experiment, the low dose of remifentanil was increased once an acute opioid tolerance effect was observed. The sevoflurane MAC was determined from alveolar gas samples at the time of tail clamp.**

Results: **A remifentanil constant rate of infusion dose-dependently reduced the sevoflurane MAC from 2.4 to 1.8 ± 0.2 vol% and from 2.3 ± 0.3 vol% to 1.5 ± 0.3 vol%, at the low and high doses, respectively. However, 90 min later, when the sevoflurane MAC was redetermined, the observed reduction was blunted to nearly 50% of the previous sevoflurane MAC values. When this acute opioid tolerance effect was observed with the low dose, the sevoflurane MAC reduction originally achieved could be reattained by doubling the dose; *i.e.*, giving the high dose.**

Conclusions: **Remifentanil efficacy in reducing the sevoflurane MAC diminishes within a short term, suggesting that increased opioid doses may be required to maintain intraoperative analgesia during sevoflurane anesthesia.**

REMIFENTANIL is a potent short-acting opioid characterized by a rapid recovery despite the dose or time of infusion and, therefore, additional opioids are commonly given before discontinuing a remifentanil infusion to prevent pain in the postoperative period. However, there is evidence indicating that the dose required to prevent pain postoperatively is higher than expected, and this has been associated with acute opioid tolerance and opioid-induced hyperalgesia.[1]

Opioid tolerance after the administration of drugs such as morphine has been known for many years.[2] After the introduction of remifentanil in perioperative use, several reports have emphasized the potential for acute opioid tolerance and opioid-induced hyperalgesia in the postoperative period, characterized by increased postoperative pain and morphine consumption.[3] Acute opioid tolerance has been widely documented in animals for almost 40 yr[4,5] and has also recently been associated with the administration of short-acting and relatively high opioid doses to rats.[6–9]

Studies performed in human volunteers showed the development of acute opioid tolerance to the analgesic action of remifentanil only a few hours after the initiation of its administration *via* continuous infusion, suggesting a need to recalculate the dose administered postoperatively.[10–13] However, a lack of a tolerance effect to remifentanil has been reported, mostly in surgical patients in the postoperative period.[14–17]

Surprisingly, there are no studies that actually determine if acute opioid-induced tolerance or opioid induced hyperalgesia do occur over the very short term during the intraoperative period, limiting the intraoperative analgesic efficacy of opioids. Since studies in volunteers have observed the appearance of acute opioid tolerance within only 60 to 90 min after initiating a remifentanil infusion,[13] it has been suggested that intraoperative analgesia levels may decrease afterwards, and this reduction could become clinically relevant in longer surgeries.

An indirect, although clinically valuable method to determine the analgesic potency of opioids in the intraoperative period is the determination of the minimum alveolar concentration (MAC) of an inhalant anesthetic. We hypothesized that the decrease in the effectiveness of remifentanil-induced reduction in the sevoflurane MAC could occur within a relatively short time; *i.e.*, the onset of acute tolerance to remifentanil might occur before surgery is finished.

Materials and Methods

After obtaining Institutional Animal Care Committee approval (Madrid, Spain), the reduction in the sevoflurane MAC in response to remifentanil given in continuous infusion was evaluated in rats. Sevoflurane was obtained from Abbott (Sevorane; Abbott Laboratories, Madrid, Spain), and remifentanil from Glaxo-Wellcome (Ultiva; Glaxo-Wellcome Laboratories, Madrid, Spain).

Fifty-two male Wistar rats (Charles River Laboratories. Barcelona, Spain) with an average weight of 391 g (SD,

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67 g), were housed in groups of 4 to 6 with a 12-h light, 12-h dark cycle; a relative humidity of 50 to 70%; and 20 ± 2°C ambient temperature. Food (B&K Universal, Grimston, England) and water were provided *ad libitum*. The animals were allowed to acclimatize for at least 1 week. All the studies were performed during the morning (starting at 9:00 AM).

The rats were placed in an induction chamber into which 8% sevoflurane in a continuous oxygen flow of 3 l/min was directed (Sevoflurane Vaporizer, Sevorane Dräger Vapor 2000, Lübeck, Germany). After 2 to 3 min, the inhaled sevoflurane concentration was reduced to 3 to 5%. Tracheal intubation was performed using a 14-gauge polyethylene catheter (Terumo Surflo IV Catheter, Terumo Europe NV, Leuven, Belgium) with the animal positioned in sternal recumbency. A flexible, blunt-tip wire guide was inserted into the trachea with an otoscope and used to direct the endotracheal catheter. After positioning of the catheter was ascertained, it was connected to a small T piece breathing system with minimum dead space. Fresh gas flow to the T piece was adjusted to 1l/min oxygen, and sevoflurane concentration was adjusted as necessary. Remifentanil was administered with an infusion pump (Syringe pump, model Sep11S, Ascor S.A. Medical Equipment, Warsaw, Poland) by means of a 22-gauge polyethylene catheter inserted in a tail vein.

Monitoring

Heart and respiratory rates were continuously monitored. Arterial blood pressure, pulseoxymetry, and heart and respiratory rates were recorded immediately before each MAC step, and after 30 min of drug administration. The carotid artery was catheterized (Venocath-18, Venisystems, Abbott, Sligo, Ireland) *via* surgical cutdown. This access allowed arterial blood sampling and blood pressure measurement *via* a calibrated pressure transducer (Transpac IV; Abbott Laboratories, Abbott Park, IL). Systolic, diastolic, and mean arterial blood pressures were recorded continuously (RGB Medical Devices, Madrid, Spain). Arterial blood (1 ml) was collected for blood gas analysis (Rapidlab 860; Bayer AG, Leverkusen, Germany) at the end of the study to ensure that the values (at that time point) were within normal limits of pH (7.34–7.44), and oxygen (P_{AO_2}; > 90 mmHg), and carbon dioxide arterial partial pressures below 55 mmHg (P_{ACO_2}; 35–55 mmHg). Rectal temperature was also monitored and maintained between 37.0°C and 38.5°C by means of a water-circulating warming blanket (Heat Therapy Pump, Model TP-220; Gaymar, Orchard Park, NY). A heating light was also used when necessary to maintain body temperature above 37.0°C.

Determination of the MAC

Intratracheal gas sampling was used to measure anesthetic gas concentration and determine the MAC. This method has been described in detail previously.[18] In brief, a fine catheter with an 0.9-mm external diameter was inserted through the endotracheal catheter, with the fine catheter tip located at the level of the carina. The proximal end of the catheter was connected to a 10-ml gas-tight glass syringe (Hamilton Syringe, 1000 Series Gastight, model 26211-U; Sigma-Aldrich, St. Louis, MO). Samples were obtained by withdrawing 10 ml of gas over 5 min using an infusion pump (Mod. 55-2226; Harvard Apparatus, Millis, MA). Gas sampling actually mixed both alveolar and inspired gases, which were obtained consecutively in duplicate to ensure a constant alveolar concentration, and the final value was the mean, at every sevoflurane concentration step. The fine catheter was withdrawn between samples. After every step change in anesthetic concentration delivered by the anesthetic circuit, at least 10 min were allowed for equilibration before tail clamping. The samples were assayed using a side-stream infrared analyzer (Capnomac Ultima; Datex-Ohmeda, Hertfordshire, England).

The MAC of sevoflurane (MAC_{SEV}) and the MAC of sevoflurane plus remifentanil at a constant rate of infusion were established according to the method described elsewhere.[19] A painful noxious stimulus was applied with a long hemostat (8-inch Rochester Dean Hemostatic Forceps, Martin, Tuttlingen, Germany) clamped to the first ratchet lock onto the tail for 60 s immediately after the gas sample was obtained from the trachea. The tail was always stimulated proximal to a previous test site when the previous response was negative or distal if response was positive, starting 6 cm distal to the tail base. A positive response was considered to be a gross purposeful movement of the head, extremities, or body. A negative response was considered to be the lack of movement or grimacing, swallowing, chewing, or tail flick. Where a negative response was seen, the sevoflurane concentration was then reduced in decrements of 0.2% until the negative response became positive. Similarly, where a positive response was seen, the sevoflurane concentration was then increased until the positive response became negative. The MAC was considered to be the concentration midway between the highest concentration that permitted movement in response to the stimulus and the lowest concentration that prevented such movement. Determination of the MAC was performed in a laboratory 600 m above sea level.

Experimental Design

The MAC_{SEV} was determined four times in every animal. Once the animals were anesthetized and instrumented, a baseline MAC_{SEV} was determined, and each animal acted as its own control. Remifentanil (RMF) was given intravenously by continuous infusion in the tail vein with no loading dose and the MAC was determined then (RMF-1), and again approximately 90 min later (RMF-2). Finally, the remifentanil infusion was stopped

and the MAC redetermined (PostRMF). Thirty minutes were allowed between MAC determinations, and 1 h was usually necessary to determine the MAC value. Overall, every experiment lasted between 6 and 7 h. No attempt was made to determine the existence of an opioid-induced hyperalgesia effect when baseline MAC_{SEV} was regained. In a further experiment, the dose of remifentanil was increased once an acute opioid tolerance effect was observed (RMF-3), and in these rats the MAC_{SEV} was determined five times.

Drug Groups

Baseline MAC_{SEV} was determined in all animals before starting the opioid infusion. The animals were randomly given 1 of 2 doses of remifentanil at a constant rate of infusion, 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 14) and 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (n = 14). The animals were euthanized with potassium chloride given intravenously while still deeply anesthetized. In a further group (n = 19), the rats were given 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and, once the MAC values determination indicated an acute opioid tolerance effect, the remifentanil dose was increased to 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the MAC value reassessed (RMF-3).

A pilot study (n = 5) was performed to ensure that the MAC value was not modified over time. Therefore, the MAC_{SEV} was determined at the four different studied times of the first experiment, but while administering saline instead of remifentanil.

Statistical Analysis

Sample size calculation (N Query Advisor 2.0; Statistical Solutions; Saugus, MA) indicated an n value of 14 to determine differences as a result of an opioid tolerance effect with both remifentanil constant infusion rate doses. However, a larger n value (n = 19) was necessary to establish these differences in the second experiment.

A two-way ANOVA (dose × time) for repeated measures was performed, with the intrasubject factor being time and the intersubject factor being dose. Since an interaction between dose and time was found (P = 0.004, Greenhouse-Geisser correction) a one-way ANOVA for repeated measures (intrasubject factor being time) was performed for dose = 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and for dose = 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Student's t test was employed using dose (120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$) as factor to determine differences between the two doses at each study time. A P value of < 0.05 was set to indicate statistical significance. All analyses were performed using the SPSS statistical package (v. 15 for Windows; SPSS Inc., Chicago, IL). Results are presented as mean ± SD.

Results

The MAC_{SEV} ranged from 1.7 to 2.8%, with an average value of 2.3% ± 0.3%.

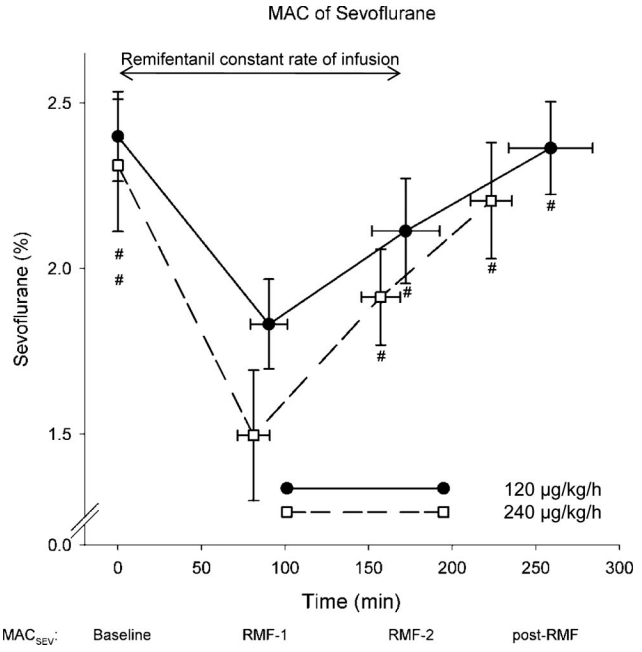

Fig. 1. Sevoflurane minimum alveolar concentration (MAC) in rats given a remifentanil constant rate of infusion. Baseline sevoflurane MAC was determined before and approximately 1.5 h Remifentanil (RMF-1) and 3 h (RMF-2) after starting a continuous remifentanil infusion rate at either 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ or 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Once the infusion was stopped, the sevoflurane MAC was redetermined (PostRMF). Data are expressed as mean ± SD. # Significant differences with RMF-1. (Analysis of variance [ANOVA] repeated measures, $P < 0.05$).

The Magnitude of Sevoflurane MAC Reduction Produced by Remifentanil Diminishes in the Short Term

Baseline sevoflurane MAC in rats was similar in both dose groups of remifentanil ($P > 0.05$, effect size = 0.297); *i.e.*, 2.4 ± 0.2 vol% (n = 14, mean ± SD; 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$), and 2.3 ± 0.3 vol% (n = 14, 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$). When a constant rate of infusion for remifentanil was used, it reduced the MAC values (RMF-1) in a dose-dependent fashion to 1.8 ± 0.2 vol% and 1.5 ± 0.3 vol%, at the low and high doses, respectively (ANOVA, $P <$ 0.05; effect size = 1.004); *i.e.*, a percentage of reduction in the MAC_{SEV} by 24 ± 6 vol% and 36 ± 7 vol%, respectively. These results were obtained approximately 1.5 h after the baseline MAC_{SEV} determination; *i.e.*, at 90 min and 81 min (low and high doses of remifentanil, respectively) after starting the remifentanil constant rate of infusion (fig. 1).

Approximately 1 h and 30 min later, the MAC values were redetermined (RMF-2) and found to be higher than those previously observed (RMF-1), even though the same remifentanil constant rate of infusion had been maintained; *i.e.*, 2.1 ± 0.3 vol% and 1.9 ± 0.3 vol% at the low and high dose of remifentanil, respectively (ANOVA, $P > 0.05$; effect size = 0.721). These values actually only reduced the baseline MAC_{SEV} by 12 ± 7% and 17 ± 9%, at the low and high dose of remifentanil, respectively, with an increase over the earlier measurements, also

with the remifentanil infusion (RMF-1), of 12 ± 5% and 9 ± 12%. These results were obtained 89 min and 76 min after the previous MAC determination (RMF-1), or 179 min and 157 min after the start of the remifentanil infusion, at the low and high doses, respectively.

After the second sevoflurane MAC determination with remifentanil (RMF-2), the remifentanil infusion was stopped. Then the sevoflurane MAC values for both infusion rate groups were determined again (PostRMF) and found to be higher than the previous MAC determination (RMF-2); *i.e.*, 2.4 ± 0.2 vol% for the low dose and 2.2 ± 0.3 vol% for the high dose (ANOVA, $P > 0.05$; effect size = 0.562). These results were obtained 4 to 5 h after starting the remifentanil infusions. No significant differences were found between the first and fourth MAC determinations; *i.e.*, MAC_{SEV} without remifentanil infusion.

All study times were significantly different when compared with the previous or following study time ($P < 0.001$, Greenhouse-Geisser correction) at both doses, 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$. These differences were found at every time interval: Baseline-RMF-1, $P < 0.001$ for both doses; RMF-1-RMF-2, $P < 0.001$ for both doses; RMF-2-postRMF $P < 0.002$ with dose = 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and $P < 0.001$ with dose = 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$. A dose-dependent effect of remifentanil was found at RMF-1 (Student's *t* test, $P = 0.006$), but not at RMF-2 ($P = 0.055$). No differences between doses were found at baseline and postRMF ($P = 0.442$ and $P = 0.140$, respectively).

Results from the pilot experiment showed no differences over time, and variation was within the normal range for the MAC determination method (10–15%): 2.2 ± 0.1 vol%, 2.3 ± 0.2 vol%, 2.2 ± 0.1 vol%, and 2.2 ± 0.2 vol% at baseline, RMF-1, RMF-2, and postRMF times, respectively.

An Acute Opioid Tolerance Effect Is Determined Although Opioid-induced Hyperalgesia Cannot Be Ruled Out

While the degree of reduction in the MAC_{SEV} (2.3 ± 0.3 vol%) produced by remifentanil (RMF-2, 1.8 ± 0.3 vol%) decreased over time (RMF-2, 2.1 ± 0.3 vol%), the initial reduction (RMF-1) could be reattained by increasing the remifentanil dose from 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$ (RMF-3, 1.5 ± 0.3 vol%). This observation demonstrates an acute opioid tolerance effect since, if the MAC_{SEV} had risen, it would have been a consequence of opioid-induced hyperalgesia. The remifentanil dose was not doubled from 240 to 480 $\mu g \cdot kg^{-1} \cdot h^{-1}$ to counteract the induced remifentanil tolerance, because the latter dose produced severe respiratory depression in the rats. These results were obtained 5 to 6 h after starting the remifentanil infusion (fig. 2).

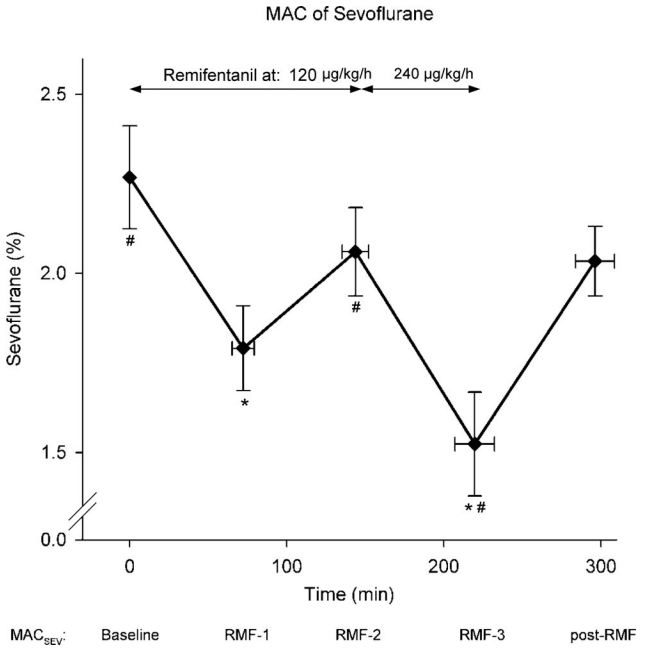

Fig. 2. Sevoflurane minimum alveolar concentration (MAC) in rats given a remifentanil constant rate of infusion. Baseline sevoflurane MAC was determined before and approximately 1.5 h Remifentanil (RMF-1) and 3 h (RMF-2) after starting a continuous remifentanil infusion rate of 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$. Once a tolerance effect was observed (RMF-2), the remifentanil dose was increased to 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$ and the sevoflurane MAC redetermined (RMF-3). Once the infusion was stopped, the sevoflurane MAC was again determined (postRMF). Data are expressed as mean ± SD. * Significant differences with baseline MAC_{SEV}. # Significant differences with RMF-1. (Analysis of variance [ANOVA] repeated measures, $P < 0.05$).

Discussion

Like other potent opioids, remifentanil reduces the sevoflurane MAC in the rat in a dose-dependent fashion.[20] However, this reduction is not constant and is rapidly blunted in the short term, since a significant reduction is observed some 1.5 h after beginning the remifentanil infusion. This finding is consistent with previous reports reflecting the rapid development of acute opioid tolerance to remifentanil in people in the immediate postoperative period,[3,21] although the opposite, *i.e.*, a lack of an acute opioid tolerance effect, has also been reported, mostly in postsurgical patients.[14–17] Similarly, an acute opioid tolerance effect[13] and opioid-induced hyperalgesia[10] have been observed in healthy volunteers receiving remifentanil, possibly reflecting the importance of the surgical stimulus in the development of opioid-induced tolerance. Since increasing the remifentanil infusion dose maintained the initial reduction in the MAC_{SEV}, an acute opioid tolerance effect is suggested where increased doses were required to maintain the same level of analgesic effect.

The most commonly used method to determine acute opioid tolerance to remifentanil during the postoperative period in the clinical setting is to measure the dose of opioid administered, as the amount of morphine re-

quired over 24 h postoperatively, usually through patient-controlled administration. This has proven to be a more consistent method since it is a relatively objective measurement, although large interindividual differences may occur, and this may reduce the reliability of the method. However, no attempts have been made as yet to demonstrate acute opioid tolerance in the intraoperative period when a reduction of the MAC under inhalation anesthesia would consistently reflect the analgesic effect of opioids.

When the acute opioid tolerance effect was observed, the reduction in the MAC of remifentanil was roughly only 50% of the previous measurement. A similar or even stronger acute opioid tolerance effect has been described in conscious human volunteers in whom the analgesic effect declined, despite the constant rate of infusion, after 3 h of infusion to only one-fourth of the peak value, which had been observed 1 to 1.5 h after initiating the infusion,[13] and a threefold increase in pain scores was found as a result of acute opioid tolerance. Given the rapid development of acute opioid tolerance to remifentanil, the MAC reduction determined immediately after starting the remifentanil infusion may not reflect the maximum level of reduction potentially achieved, since it usually takes 80 to 90 min to determine MAC in rats. Similarly, tolerance might have been increased by allowing a longer intermeasurement period between MAC determinations during the remifentanil infusion. The magnitude of the MAC change produced by remifentanil is high enough as to be of clinical relevance, since either the dose of remifentanil or the concentration of the inhalant anesthetic should be increased to maintain a similar level of anesthesia. Obviously this may lead to a potential increase in the appearance of side effects derived from higher doses of opioids and inhalant anesthetics. However, since contradictory findings have been reported in clinical trials,[3,10–17,21] caution should be taken when extrapolating these findings to the clinical setting, and further studies in humans are necessary to confirm the results observed in the rat.

Determination of the MAC usually provides more consistent results when a standardized supramaximal noxious stimulus is employed.[22] While surgical incision is usually employed in humans,[23] tail clamping is the most common and consistent noxious stimulus used in the rat.[20] MAC values remain stable for long periods of anesthesia and are typically reduced by opioids such as morphine, buprenorphine, fentanyl, or remifentanil[18,24] in a dose-related fashion. Typical reductions range from 15 to 70%, although the doses employed in the rat are higher than in humans when comparing the mg per kg doses.[25] Accordingly, the reduction in the MAC value should be 20 to 30% when remifentanil is administered at a dose of 120 $\mu g \cdot kg^{-1} \cdot h^{-1}$, and 40 to 60% when the remifentanil dose is doubled to 240 $\mu g \cdot kg^{-1} \cdot h^{-1}$.[20] MAC reductions of up to 90% can be obtained in humans[26,27] when large doses of opioids are administered.

Although there is evidence that different noxious stimuli may reflect a similar acute opioid tolerance response,[13] a differential response has been suggested; *i.e.*, temperature (heat or cold), mechanical or electrical, may affect responses so a modified response cannot be ruled out.[11] The noxious stimulus produced by surgery may actually elicit a different response, so the acute opioid tolerance effect produced by remifentanil should be confirmed in a clinical setting. Thus the conflicting reports on the existence of a tolerance effect might be a consequence of, among other causes, the nociceptive stimulus employed.[28]

In conclusion, short term infusion, *i.e.*, 90 min or less, of remifentanil at doses capable of decreasing the sevoflurane MAC in the rat actually decreases the effectiveness of the analgesic effect of the opioid. The observed effect would probably be a consequence of acute opioid tolerance and, if confirmed in humans, this loss of analgesic efficacy would have clinically significant implications.

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ANESTHESIOLOGY REFLECTIONS

The Edison Etherizer

To electrify North America, Thomas A. Edison (1847–1931) proposed using direct current (D.C.) rather than the alternating current (A.C.) suggested by his rival, George Westinghouse, Jr. (1846–1914). To undermine acceptance of A.C. for household use, Edison terminally "Westinghoused" test animals in 1887 and then advocated similar use of A.C. upon death-row inmates. When the State of New York tried Edison's "Westinghouse [electric] chair" in 1888, the first victim survived a 17-second electrocution before succumbing to a 72-second one. This debacle and D.C.'s economic costs backfired on Edison, and America adopted his rival's A.C. Over a half century after the botched electrocution, Thomas A. Edison, Inc., of New Jersey manufactured an apparatus for passing "multitudinous air streams" through an ether-adsorbing "channeled carbon mass" whose heat-conducting container was surrounded by a "crystallizable liquid." Heats of "adsorption and solidification," designed into this apparatus by 1946, were counteracting the chill of vaporizing ether, the inefficiency of which had plagued earlier bubble-through vaporizers. After inscribing the signature of "Thomas A. Edison" on the front of their "Edison Etherizer" (pictured above from the Wood Library-Museum Gallery), the New Jersey team powered it with A.C. Quite an ironic posthumous salute to one-time D.C.-advocate, Thomas Alva Edison ! – (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

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