

# Review of the efficacy and safety of remifentanyl for the prevention and treatment of pain during and after procedures and surgery

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**Abstract:** Remifentanyl is an ultrashort-acting synthetic opioid. It is metabolized by nonspecific tissue and plasma esterases. Remifentanyl's metabolism is responsible for its unique pharmacokinetic profile and flat, context-sensitive half-time. Since its introduction into clinical practice, remifentanyl has been used for a variety of anesthetic and analgesic applications; however, concerns regarding a potential for rapid induction of tolerance and/or induced hyperalgesia, coupled with an ultrarapid offset of effect, make the drug less than optimal for use in the pharmacologic management of pain.

**Keywords:** regional anesthesia, intravenous anesthesia, tolerance, hyperalgesia, rapid offset

## Discussion

### Pharmacologic principles

Remifentanyl is a synthetic opioid receptor agonist. It is a 4-anilidopiperidine with ester side chain, by which it is metabolized by nonspecific blood and tissue esterases to the renally excreted, inactive metabolite, carboxylic acid (GR90291).<sup>1</sup> In healthy adult volunteers, remifentanyl has a short elimination half-life of 9.5 ( $\pm$  4 minutes) minutes<sup>1</sup> and its clearance is three to four times greater than liver blood flow.<sup>2</sup> Like other opioids, remifentanyl's volume of distribution has an inverse relationship with age. However, unlike other opioids that depend on end organ elimination for drug clearance and have the lowest clearance values in the neonatal period, remifentanyl clearance is highest in the neonatal period. Because of the age-related changes in volume of distribution and the inverse relationship of age with clearance, there are no age-related changes in remifentanyl's half-life.<sup>3</sup> Perhaps the most interesting characteristic of remifentanyl is its context-sensitive half-time, which remains constant or flat regardless of the duration of infusion.<sup>4,5</sup> The context-sensitive half-time in healthy adults was determined to be 3.2 minutes and pharmacodynamic offset was 5.4 minutes.<sup>5</sup>

Organ failure changes the metabolism of many drugs; however, end stage hepatic or renal failure does not affect remifentanyl clearance. In a study performed in 12 adult patients undergoing liver transplantation, Navapurkur demonstrated that clearance during the anhepatic stage of liver transplant was similar to clearance in healthy adults.<sup>6</sup> In patients with end organ renal disease, Hoke and others noted that remifentanyl's clearance was not affected by renal failure, but there was a marked reduction in elimination of GR90291, the metabolite of remifentanyl, which does not appear to have clinical significance.<sup>7</sup> Although tissue and plasma esterases metabolize remifentanyl, pseudocholinesterase deficiency does not alter the drug's metabolism either *in vivo* or *in vitro*. *In vitro* studies reported by Davis and colleagues, using blood

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and plasma from butyrylcholinesterase deficient patients, showed a similar half-life to that of volunteers with normal butyrylcholinesterase levels.<sup>8</sup> In addition, a published case report by Manullang and others noted a normal duration of remifentanyl effect in a patient with known pseudocholinesterase deficiency.<sup>9</sup>

Remifentanyl can be used to reduce the minimum alveolar concentration (MAC) of volatile anesthetic agents. In healthy adults having elective surgery under general anesthesia, Lang reported that the MAC of isoflurane was reduced by one-third with 1 ng/mL blood concentration of remifentanyl.<sup>10</sup> At plasma concentrations of 4–8 ng/mL of remifentanyl, isoflurane MAC could be further reduced by 65%–70%. There was, however, a ceiling effect of remifentanyl on MAC reduction. The maximum reduction of isoflurane's MAC by remifentanyl was 92%. Thus, remifentanyl is not suitable as a sole anesthetic agent and is used in conjunction with other anesthetic and/or hypnotic drugs.

## Remifentanyl as an adjunct anesthetic agent

Given the unique pharmacokinetic properties of remifentanyl, it has been used extensively for a wide variety of surgical procedures and in a wide age range of patients, from neonates to geriatric patients.<sup>10</sup> Table 1 demonstrates that infusions of remifentanyl are rapidly titratable and predictable with respect to its onset and offset of effect. Thus remifentanyl, as part of an outpatient surgical procedure, may provide fast emergence from anesthesia and early patient discharge from the facility. Studies have been done to compare desflurane and remifentanyl anesthetics to desflurane alone, and found that recovery time was faster with remifentanyl, with no difference in postoperative nausea and vomiting (PONV), or need for

analgesic medications.<sup>11</sup> In a study of women undergoing outpatient gynecologic surgery, Beers and colleagues compared fentanyl with remifentanyl anesthetic. Although no difference was observed in recovery times, postanesthesia care unit (PACU) pain scores, or fentanyl consumption postoperatively, the authors did note that patients in the remifentanyl group had greater incidences of both PONV and rescue antiemetic treatment.<sup>12</sup> In a study of women undergoing breast surgery, Hong and others compared sevoflurane and nitrous oxide to infusions of propofol and remifentanyl.<sup>13</sup> Patients receiving the propofol-remifentanyl combination had faster induction and emergence times, but no significant difference was noted in facility discharge times. Emergence from a remifentanyl-propofol anesthetic and return of cognitive function was demonstrated to be faster than that of nitrous oxide combined with either sevoflurane or desflurane.<sup>14</sup> The difference was only measurable in the first 90 minutes after the anesthetics after which the cognitive function appeared to be the same in all groups.

Remifentanyl use has been reported in pediatric patients. In a study of children undergoing tonsillectomy and adenoidectomy, Davis and others compared the following anesthetic regimens: 1) halothane and fentanyl bolus; 2) halothane and remifentanyl infusion; 3) sevoflurane and fentanyl bolus; and 4) sevoflurane and remifentanyl infusion.<sup>15</sup> Children in the groups receiving remifentanyl had faster emergence and extubation times, but higher pain scores in the recovery room. There was no difference among the groups in time to discharge from the facility. In a study of children aged 2–12 years undergoing strabismus surgery, Eltschig and colleagues compared fentanyl and remifentanyl anesthetics.<sup>16</sup> Postoperatively, the fentanyl group experienced a higher frequency of postoperative nausea and vomiting, but significantly lower

**Table 1** Studies of remifentanyl use during general anesthesia

Study	Surgery	Control group	Study group	N	Recovery time	PONV	Discharge time	Postoperative pain
Song et al <sup>11</sup>	Gyn	Des titration and N <sub>2</sub> O	Remi titration, with Des 2%, N <sub>2</sub> O	46	>control group	No difference	NR	No difference
Beers et al <sup>12</sup>	Gyn	Fentanyl	Remi	34	No difference	>study group	NR	No difference
Hong et al <sup>13</sup>	Breast	Sevo/N <sub>2</sub> O/ Fentanyl	Remi/propofol	42	>control group	>control group	Similar	>study group
Larsen et al <sup>14</sup>	Orthopedic	Sevo/N <sub>2</sub> O or Des/N <sub>2</sub> O	Remi/propofol	60	>control groups	No difference	NR	No difference
Davis et al <sup>15</sup>	Pediatric tonsil/adenoid	Sevo/fentanyl or Hal/fentanyl	Sevo/remi or Hal/remi	206	>control groups	No difference	No difference	>study group
Eltzschig et al <sup>16</sup>	Pediatric strabismus	Fentanyl	Remi	81	NR	>control group	NR	>study group early

pain scores in the early postoperative period. Another study of pediatric strabismus surgery compared remifentanyl, alfentanil, isoflurane, and propofol, and found that the group receiving remifentanyl reported higher pain scores in the recovery room.<sup>17</sup> Remifentanyl, combined with propofol, has also been studied to provide procedural sedation for children undergoing lumbar puncture.<sup>18</sup>

Remifentanyl has been demonstrated to be effective for sedation combined with regional anesthesia. Table 2 shows the results of the study done by Lauwers and colleagues, which studied 160 patients undergoing either spinal or brachial plexus nerve block in trial, and comparing different doses of remifentanyl infusion with placebo.<sup>19</sup> Remifentanyl infusion was effective at providing sedation, reducing the necessary dose of midazolam, and promoting a quick return to alertness (10–12 min). However, remifentanyl also increased nausea, pruritus, sweating, and respiratory side effects. In a smaller study by Lauwers of 28 patients, remifentanyl and propofol were compared after spinal or axillary anesthesia.<sup>20</sup> While similar levels of sedation were achieved with both regimens, the group receiving propofol had a 20% decrease in mean arterial blood pressure and heart rate. The remifentanyl group demonstrated greater hemodynamic stability but with a higher incidence of nausea and respiratory depression. Two different groups have also reported studies comparing propofol with remifentanyl infusions for sedation during surgery performed under regional block.<sup>21,22</sup> During both

studies, remifentanyl was more effective at preventing pain, but was associated with an increased incidence of nausea and respiratory depression. Krenn and colleagues studied patients sedated with remifentanyl or propofol who were scheduled to undergo carotid endarterectomy under cervical plexus block.<sup>23</sup> Although both remifentanyl and propofol provided adequate sedation, patients receiving remifentanyl experienced a greater incidence of respiratory depression and increase in arterial carbon dioxide tensions (PaCO<sub>2</sub>). Savoia and colleagues studied 328 vascular surgery patients anesthetized with a regional block, including deep and superficial cervical block, lumbar epidural or plexus block, combined with various hypnotic agents, propofol or midazolam with either sufentanil or remifentanyl.<sup>24</sup> Their group reported successful sedation using either propofol <3 mg/kg/h or midazolam 0.5–3 mg with sufentanil 5–10 µg/hr or remifentanyl 0.05 µg/kg/min. Further combinations and techniques of sedation, including remifentanyl, combined with regional anesthesia were reviewed by Höhener and colleagues.<sup>25</sup> This paper reported use of remifentanyl infusions from 0.03–0.5 µg/kg/min or bolus 0.5–1 µg/kg combined with plexus, spinal, or retrobulbar block. Given the ultrashort action of remifentanyl, bolus administration was used to facilitate block placement during ophthalmologic surgery, and then propofol infusion for sedation.

Use of remifentanyl combined with propofol has been studied in patients undergoing procedural sedation. Mandel

**Table 2** Studies of remifentanyl use with regional anesthesia

Study	Surgery	Type of regional	Control group	Study group	N	Measured outcome	Adverse effects
Lauwers et al <sup>19</sup>	Orthopedic	Spinal or brachial plexus	Placebo with midazolam	Remifentanyl infusion with midazolam	160	>sedation and <midazolam required in study group	Respiratory depression, PONV, pruritis
Lauwers et al <sup>20</sup>	Orthopedic	Spinal or axillary	Propofol infusion	Remifentanyl infusion	28	Sedation and comfort equal	>respiratory depression and nausea in study group
Mingus et al <sup>21</sup>	Orthopedic or urologic	Spinal, axillary or ankle	Propofol infusion	Remifentanyl infusion	107	>pain relief in study group	>respiratory depression and nausea in study group
Krenn et al <sup>23</sup>	Carotid endarterectomy	Cervical plexus	Propofol infusion	Remifentanyl	60	No difference in sedation or hemodynamic variables	>respiratory depression and PaCO <sub>2</sub> in study group
Servin et al <sup>22</sup>	Orthopedic, urologic, gynecologic, vascular	Neuraxial or peripheral block	Propofol	Remifentanyl	125	>pain relief in study group	>respiratory depression and nausea in study group

and colleagues compared propofol and remifentanyl with midazolam and fentanyl in adults undergoing colonoscopy.<sup>26</sup> Both groups were treated with patient-controlled infusions of study medications. The infusions each had an initial bolus dose, demand doses, and lockout times. The patients in the remifentanyl/propofol group were sedated faster ( $3.4 \pm 1.3$  minutes vs  $7.6 \pm 3.6$  minutes), able to ambulate earlier ( $9.2 \pm 4$  minutes vs  $36.4 \pm 5.3$  minutes), and spent significantly less time in the recovery room ( $4.9 \pm 4.3$  minutes vs  $32 \pm 25$  minutes). Procedure time was not significantly different between groups; however, two patients in the remifentanyl/propofol group required intervention for hypoxia ( $\text{SaO}_2 < 85\%$ ). In another study evaluating the effectiveness of remifentanyl in adult patients undergoing colonoscopy in spontaneously ventilating patients, Moerman's group examined propofol and remifentanyl infusions where remifentanyl was administered manually, either as a bolus followed by a continuous infusion, or as a target-controlled infusion to a preset concentration of 1 ng/ml.<sup>27</sup> In addition, a third group (control group) received a propofol infusion alone. In all three groups, propofol was administered using target-controlled infusions with the initial target concentration set to 4  $\mu\text{g}/\text{mL}$ . The propofol target levels were then adjusted based on clinical indications (patient movement, ventilation, and responsiveness to verbal commands). Although patients in the placebo group moved, coughed, and hiccupped more than either of the remifentanyl groups (and so interfering with the colonoscopy), the remifentanyl groups had more respiratory side effects requiring intervention. The target-controlled remifentanyl infusion group received less total remifentanyl and experienced fewer respiratory complications than the group that received remifentanyl manually. Recovery appeared to be fastest in the target-controlled remifentanyl group; however recovery in this study was defined only as the times at which the patient opened their eyes, followed

commands, and correctly stated their date of birth, not actual discharge time.

## Remifentanyl as an analgesic agent

Remifentanyl can be used for postoperative pain control if it is administered by a constant infusion or by patient-controlled analgesia (PCA). Table 3 shows the results of 56 women Choi studied who underwent abdominal hysterectomy and compared postoperative remifentanyl vs fentanyl infusions with respect to postoperative pain control. There was no clear difference in pain scores, the use of other analgesics, or side effects in either group. However, three episodes (10.7%) of serious respiratory depression requiring intervention occurred in the remifentanyl group.<sup>28</sup> The researchers reported these cases of respiratory depression in a letter to the editor of *Anesthesia and Analgesia*.<sup>29</sup> All three cases were thought to have been a result of small boluses of remifentanyl being administered inadvertently, either during replacement of an infusion bag or with the administration of another drug in the same IV tubing. These cases highlight the need for careful monitoring of patients receiving narcotic infusions, and perhaps makes a case for not utilizing remifentanyl infusions on busy nursing floors where monitoring is more difficult. Kucukemre and colleagues reported that after major abdominal surgery, patients could be managed with either remifentanyl or morphine PCA with good outcomes.<sup>30</sup> In this randomized study of 60 patients, there were no statistical differences with respect to hemodynamic, respiratory, sedation or visual analogue scores between the remifentanyl and morphine groups; however, there were more bolus doses demanded and delivered in the remifentanyl group.

Remifentanyl PCA treatment has been reported by Gurbet and colleagues for use in patients after cardiac surgery.<sup>31</sup> This randomized, double-blinded study compared remifentanyl, morphine, and fentanyl PCA utilizing continuous and

**Table 3** Studies of remifentanyl as an analgesic

Study	Surgery	Control group	Study group	N	Pain scores	PONV	Adverse events
Choi et al <sup>28</sup>	Abdominal hysterectomy	Fentanyl infusion	Remifentanyl infusion	56	No difference	No difference	Respiratory depression in study group
Kucukemre et al <sup>30</sup>	Abdominal surgery	Morphine PCA	Remifentanyl PCA	60	No difference	No difference	Apnea after loading dose of remifentanyl in one patient
Gurbet et al <sup>31</sup>	Cardiac Surgery	Morphine or Fentanyl PCA	Remifentanyl PCA	75	No difference	>morphine group	Pruritis in fentanyl group
Baltali et al <sup>32</sup>	Cardiac surgery	Morphine PCA	Remifentanyl PCA	60	<pain with cough and movement in study group	No difference	No difference
Volmanen et al <sup>35</sup>	Labor analgesia	Epidural bupivacaine	Remifentanyl PCA	52	< pain in control group	>study group	Maternal desaturation, sedation in study group

bolus doses in 75 off-pump, coronary artery bypass surgery patients, beginning immediately after completion of the surgery. Pain scores, sedation, and extubation times were all similar. Demand and delivered doses were higher in the remifentanyl group, but nausea and vomiting and pruritus were all lower in the remifentanyl group. Baltai's group also examined coronary artery bypass surgery patients and compared remifentanyl to morphine.<sup>32</sup> This group found that pain scores with both cough and movement were lower in the group receiving remifentanyl. At the conclusion of PCA usage, the need for supplemental pain medications was similar for both groups.

The use of remifentanyl has been reported in obstetrical patients where IV narcotics are used cautiously for fear of causing fetal depression.<sup>33</sup> Volmanen has reported on the use of remifentanyl PCA in parturients who did not receive neuraxial pain control. Although remifentanyl rapidly crosses the placenta, these authors noted low umbilical vein to artery ratio (0.29) and suggested that remifentanyl undergoes rapid metabolism and redistribution in the fetus. The dose range for effective labor PCA was examined in a study of 20 women with results ranging from 0.2  $\mu\text{g}/\text{kg}$  to 0.8  $\mu\text{g}/\text{kg}$  with lockout times of one minute.<sup>34</sup> All women received remifentanyl PCA with bolus doses alone during the first stage of labor for 60 minutes, and were followed for an additional 20 minutes after the infusion was discontinued. Three women were removed from the study because they entered the second stage of labor prior to completion of 60 minutes of remifentanyl infusion. Pain scores decreased by an average of 4 points on a 0–10 VAS (visual analog scale). Side effects, including maternal oxygen desaturation, sedation, and decreased beat-to-beat variability in fetal heart rate were observed during this study. All but one infant, including the infants of the three women prematurely discontinued from the study, were delivered with Apgar scores  $>8$ ; the exception was born 6 hours after last remifentanyl dose with Apgars of 6 and 7 at 1 and 5 minutes respectively. This baby's mother was treated for suspected chorioamnionitis.

In a follow-up study of another group of parturient patients studied during early labor (defined as cervical dilation of 4–7 cm), Volmanen compared PCA remifentanyl with bolus epidural bupivacaine and fentanyl.<sup>35</sup> The authors noted that pain scores reported on a 0–10 scale were higher (7.3) in the remifentanyl group compared with the epidural group (5.2), but average pain relief scores, which were reported on a 0–4 scale with 0 = no relief to 4 = complete relief, were not different between the two groups (median scores of 2.8 for the epidural group and 2.5 for the remifentanyl group). Sedation

and hypoxia were more common in the remifentanyl group. In a feasibility study of 21 parturients allowed to administer PCA remifentanyl (0.25–0.5  $\mu\text{g}/\text{kg}$ ) beginning at 3 cm cervical dilation and continuing up until the time of delivery, Blair noted no significant reductions in fetal heart rate defined as  $<110$ ; median 1 and 5 minute Apgar scores were 8 and 9 respectively; and mean infant cord pH was 7.34 in the women who continued remifentanyl until delivery. Thirteen continued to use remifentanyl until the time of delivery, four decided to change to a regional technique during the first stage of labor, one changed to a regional technique during second stage (which required forceps delivery), and three required a regional technique for Caesarean section.<sup>36</sup>

Based on the current evidence, remifentanyl PCA is a reasonable solution for parturients who desire pain medication during labor but are not candidates for, or not accepting of, neuraxial anesthesia. There is a paucity of studies comparing neuraxial analgesia to remifentanyl analgesia to recommend replacement of neuraxial analgesia at this time.

## Opioid hyperalgesia

Opioid induced hyperalgesia, or the increased perception of pain following administration of opioids, is a topic that has been studied since the 1970s. Even short (30–90 minute) remifentanyl infusions have been reported to result in hyperalgesia.<sup>37</sup> The exact mechanism of opioid induced hyperalgesia is unknown, but there are many different theories as to where within the pain pathways this may occur. The proposed mechanisms include: sensitization of peripheral nerve endings, enhanced descending nociceptive signal transmission, enhanced production, release and decreased reuptake of nociceptive neurotransmitters, and sensitization of second-order neurons to nociceptive neurotransmitters.<sup>37</sup>

Varying doses of remifentanyl infusions have been studied to determine if an association exists between remifentanyl dose and the development of hyperalgesia. In 2007 Schmidt's group studied 42 adult patients undergoing eye surgery with isoflurane and remifentanyl anesthesia.<sup>38</sup> Patients were randomized to receive either high (0.4  $\mu\text{g}/\text{kg}/\text{min}$ ) or low (0.1  $\mu\text{g}/\text{kg}/\text{min}$ ) dose remifentanyl. Hyperalgesia was assessed by enhanced sensitivity to pressure stimulation postoperatively. Patients were assessed postoperatively for surgical site pain, and if VAS  $>3$  they were treated with analgesics and eliminated from the rest of the study. This resulted in five patients from each group (high and low remifentanyl doses) being eliminated. In the remaining 32 patients, the use of high dose, but not low dose, remifentanyl was associated with development of hyperalgesia to painful



pressure. No patient in this study developed a positive response to cold stimuli as tested in the patient's hands and forearms. The reason for the difference in response to different types of stimuli is unknown, but the authors of this paper suggested that perhaps this could be explained by different neurons carrying signals for different types of pain. Mechanical pain (pressure in this model) is thought to be carried by A $\beta$  fibers, with A $\delta$  fibers being responsible for cold detection. Perhaps opioid induced hyperalgesia affects different neuronal fibers differently. Rodent models have also been used to examine the influence of dose and duration of remifentanyl infusion on hyperalgesia. In these animal models, the extent and duration of thermal and mechanical hyperalgesia was related to the administered dose of remifentanyl; however, the duration of the infusion did not influence the development of hyperalgesia.<sup>39</sup>

Another area of interest regarding opioid induced hyperalgesia has focused on the N-methyl-D-aspartate (NMDA) receptor. This receptor is found throughout the brain and spinal cord and utilizes glutamate to transmit pain signals. In a study by Zhao and others involving rat dorsal horn neurons cultured and treated with remifentanyl, these investigators noted that remifentanyl induced an acute increase in the NMDA response, as evidenced by an increase in peak current amplitudes.<sup>40</sup> This may suggest that enhancement of NMDA responses by remifentanyl is responsible for opioid induced hyperalgesia or tolerance. In another set of experiments reported in the same paper, the investigators noted that the observed enhancement of NMDA receptors (increase in peak current amplitudes) could be attenuated by either  $\mu$  or  $\delta$  antagonists such as naloxone and naltrindole. Selective  $\delta$ -opioid agonists, enkephalin and deltorphin II, were able to attenuate the response seen at NMDA receptors. Thus, administering a  $\delta$ -opioid antagonist along with remifentanyl may diminish opioid induced hyperalgesia while preserving opioid function at  $\mu$  pain receptors.

Ketamine, a NMDA receptor antagonist, has been studied as a possible treatment for opioid induced hyperalgesia. In adult patients undergoing abdominal surgery, Fu and others studied the effect of low dose, subanalgesic ketamine administered prior to incision and then continued as an infusion. In this study, the investigators noted that ketamine administration decreased total morphine consumption.<sup>41</sup> However, no intraoperative narcotics were administered, so while ketamine may have an opioid sparing effect, the study design precluded comments regarding hyperalgesia. Guillou and others also studied the effects of low dose ketamine in adult patients undergoing abdominal surgery. In this study, sufentanil was

administered intraoperatively for maintenance of anesthesia and ketamine was administered postoperatively.<sup>42</sup> The study also demonstrated that the administration of ketamine reduced total morphine consumption in the postoperative period. However, since no ketamine was administered during the procedure, the question of whether ketamine has an effect on narcotic hyperalgesia remains unanswered. Neither of these studies examined the role of ketamine with respect to remifentanyl administration, but do show a narcotic sparing effect of NMDA receptor antagonists.

Human volunteers have been studied to determine the interaction of remifentanyl and ketamine on the perception of pain. Koppert and colleagues used a transdermal electrical stimulation module of forearm pain and compared remifentanyl, ketamine, and clonidine to test analgesic or hyperalgesic properties of each alone or in combination.<sup>43</sup> This group determined that the combination of remifentanyl and ketamine prevented the development of opioid-induced hyperalgesia, but not secondary hyperalgesia, which was prevented by administration of clonidine. The hyperalgesic effect of remifentanyl and ketamine was further studied by Angst and others in 10 normal adult male human volunteers.<sup>44</sup> The investigators induced a hyperalgesic state in the skin of volunteers by intradermal electrical stimulation, and compared the men's perception of pain in both normal skin and in skin that was rendered hyperalgesic. The normal skin was exposed to thermal pain, which was induced by heating a circular thermode in contact with skin on the right forearm. The hyperalgesic skin was created on the left forearm and then exposed to mechanical pain, which consisted of applying a steel wire tip perpendicular to the skin. Hyperalgesia was believed to be present when men complained of the mechanical force causing pain in the area exposed to electrical stimulation, but not painful when the same force was applied to the opposite arm. The men were each tested four different times with either remifentanyl or ketamine infusions alone, the two drugs combined, or placebo. Each patient was randomly selected for the order of each test and both the patient and observer were blinded to the specific drug combination on each test day. When comparing remifentanyl and ketamine infusions alone, remifentanyl was found to increase the area of hyperalgesic skin generated by the same electrical stimulation, but did not change perception of heat-related pain in the normal skin area. When a combination of remifentanyl and ketamine were administered, there was no increase in area of hyperalgesic skin, providing further evidence for a possible role of NMDA antagonists in preventing opioid induced hyperalgesia.

To study the interaction of remifentanyl and ketamine in patients, Guignard and colleagues studied 50 patients undergoing colorectal surgery whose maintenance anesthetic consisted of desflurane and remifentanyl, and were randomized to receive either placebo bolus saline followed by an infusion of saline, or a bolus of ketamine 0.15 mg/kg followed by a low dose ketamine infusion 2 µg/kg/min.<sup>45</sup> Patients in the ketamine group required less remifentanyl intraoperatively to control autonomic responses. Postoperatively the ketamine group required morphine later and consumed significantly less morphine than the control group for the first 24 hours. In a study of patients undergoing abdominal surgery, Joly and colleagues reported the hyperalgesic effects of remifentanyl and ketamine. In the patients who received intraoperative high dose remifentanyl, larger areas of hyperalgesia surrounding the wound were noted, and these patients also required higher doses of postoperative morphine for pain control. Interestingly patients who received either low dose remifentanyl alone, or large dose remifentanyl and ketamine, showed similar areas of hyperalgesia and required similar doses of postoperative morphine.<sup>46</sup>

Other potential mediators of remifentanyl induced hyperalgesia which have been studied include cyclooxygenase-2 inhibitor parecoxib and propofol.<sup>47,48</sup> Administering parecoxib prior to the start of remifentanyl infusion in healthy volunteers reduced the hyperalgesic response.<sup>48</sup> There was no response if parecoxib was given simultaneously with remifentanyl. Another study of healthy volunteers examined the effect of propofol infusion given simultaneously with remifentanyl infusion.<sup>47</sup> This study determined that a subhypnotic dose propofol infusion decreased, but did not completely eliminate, the hyperalgesia response seen after remifentanyl infusion alone.

Morphine and ketamine have been studied to determine their role in hyperalgesia in pediatric patients receiving remifentanyl as part of anesthetic management during scoliosis surgery. Crawford and others studied 30 pediatric scoliosis surgery patients randomly assigned to either continuous intraoperative infusion of remifentanyl or bolus morphine doses.<sup>49</sup> In the postoperative period, the patients were started on a morphine PCA, and after 24 hours the consumption of morphine was compared between the two groups. The group that had received remifentanyl intraoperatively used 30% more morphine, suggesting that the intraoperative infusion was associated with the development of acute opioid tolerance. In an attempt to modify this tolerance, Engelhardt's group

studied the role of low dose ketamine in pediatric scoliosis patients.<sup>50</sup> During surgery remifentanyl and propofol infusions were utilized for maintenance anesthesia for all patients. Patients were then randomized to receive either bolus ketamine (0.5 mg/kg) followed by low dose infusion (4 µg/kg/min) or saline placebo. Patients were studied for the next 72 hours with respect to pain scores, morphine consumption, and sedation scores. There was no distinguishable difference in postoperative pain scores or morphine consumption between the two groups, suggesting that low dose ketamine does not effect the development of acute opioid tolerance in these patients. McDonnell's group also examined pediatric scoliosis patients utilizing remifentanyl intraoperatively.<sup>51</sup> This group randomized 40 patients to receive either 150 µg/kg of morphine or placebo prior to remifentanyl infusion. The investigators noted no difference in 24-hour morphine consumption, pain scores, sedation levels, or incidence of nausea or vomiting. Thus, pre-treatment with morphine does not appear to modify remifentanyl-induced hyperalgesia.

## Summary

Remifentanyl's unique pharmacokinetic profile confers the drug with rapid onset and offset of action. The drug's flat context-sensitive half-time makes it clinically predictable with respect to pharmacodynamic properties. An ultrashort half-life makes remifentanyl a drug that can be used for patients with a wide variety of clinical disorders and in a wide age range of patients. Use of remifentanyl during general anesthesia can result in rapid recovery times, but this has not resulted in faster facility discharge times and may in fact result in increased postoperative pain. Combination of remifentanyl with regional anesthesia results in excellent sedation but increased hypoxia, respiratory depression, and nausea. Pain relief after surgery can be well controlled with remifentanyl PCA, but respiratory depression is a serious side effect that mandates close observation. Labor analgesia may also be effectively provided by remifentanyl PCA, however, there are limited studies comparing PCA with neuraxial analgesia. Because remifentanyl is so short acting, concerns regarding its ability to induce tolerance and hyperalgesia in patients have been raised, but not definitively answered. NMDA antagonist, ketamine, cyclooxygenase-2 inhibitor parecoxib, and propofol have been studied to determine the effect on remifentanyl induced hyperalgesia. The results are inconclusive and study populations small, highlighting the need for additional study to combat this phenomena.

## Disclosure

The authors declare no conflicts of interest.

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