Does Fentanyl Lead to Opioid-induced Hyperalgesia in Healthy Volunteers?

A Double-blind, Randomized, Crossover Trial

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ABSTRACT

Background: Although opioids in general and remifentanil in particular have been shown to induce hyperalgesia, data regarding fentanyl are scarce. Thus, the authors investigated the effect of fentanyl dosing on pain perception and central sensitization in healthy volunteers using established pain models.

Methods: Twenty-one healthy, male volunteers were included in this randomized, double-blind, crossover study and received either intravenous low-dose (1 μg/kg) or high-dose (10 μg/kg) fentanyl. Pain intensities and hyperalgesia were assessed by intracutaneous electrical stimulation, and cold pressor pain was used as an additional measure of acute pain. The primary outcome was hyperalgesia from 4.5 to 6.5 h after fentanyl administration.

Results: A higher dose of fentanyl led to significantly decreased pain scores as measured by the numeric rating scale (0.83 units lower [95% CI, 0.63 to 1.02]; P < 0.001) but increased areas of hyperalgesia (+30.5% [95% CI, 16.6 to 44.4%]; P < 0.001) from 4.5 to 6.5 h after fentanyl administration. Allodynia did not differ between groups (+4.0% [95% CI, −15.4 to 23.5%]; P = 0.682). The high dose also led to both increased cold pressor pain threshold (+43.0% [95% CI, 29.7 to 56.3%]; P < 0.001) and tolerance (+32.5% [95% CI, 21.7 to 43.4%]; P < 0.001) at 4.5 to 6.5 h. In the high-dose group, 19 volunteers (90%) required reminders to breathe, 8 (38%) required supplemental oxygen, and 12 (57%) experienced nausea.

Conclusions: A higher dose of fentanyl increased hyperalgesia from 4.5 to 6.5 h in healthy volunteers while simultaneously decreasing pain scores. (Anesthesiology 2016; 124:453-63)

Although opioids are a mainstay of perioperative and postoperative analgesia, a body of evidence shows that opioid administration may induce hyperalgesia, a phenomenon termed opioid-induced hyperalgesia (OIH). Surprisingly, with the exception of remifentanil, there is a paucity of data regarding the postoperative setting.

The few clinical trials examining fentanyl and postoperative OIH in opioid-naïve patients have shown higher pain scores, greater morphine consumption, or both in the high-dose fentanyl groups. Chia et al. examined the application of intravenous fentanyl, whereas the other three studies examined intrathecal fentanyl as an adjunct to neuraxial anesthesia in parturients during Caesarean section. However, these clinical studies assessed acute postoperative pain and not hyperalgesia per se, thereby not allowing for a differentiation between acute opioid tolerance and OIH. In animal studies, however, fentanyl has been shown to reliably induce hyperalgesia. The extent to which specifically intravenous fentanyl may induce hyperalgesia in humans is largely unexamined but is of great clinical relevance in daily practice.

The aim of this study was to examine the effect of fentanyl dosing regimens on measures of acute pain as well as hyperalgesia and allodynia, which are both measures of central sensitization resulting from ongoing nociceptive stimulation.
These measures were assessed by using two established human models: (1) an intradermal electrical stimulation model evoking acute pain, hyperalgesia, and allodynia and (2) a cold pressor pain (CPP) model examining acute pain. We hypothesized that the area of hyperalgesia as measured by intradermal electrical stimulation from 4.5 to 6.5 h after fentanyl administration would be greater in healthy volunteers receiving a high dose than a low dose of fentanyl.

Materials and Methods

Subjects

Approval was granted by the local ethics committee and national board (EKNZ, ID 2014–054, Basel, Switzerland; Swissmedic 2014DR1106, Bern, Switzerland). The study was conducted at the University Hospital of Basel (Basel, Switzerland) after obtaining written informed consent form each volunteer. The trial was performed in accordance with the Declaration of Helsinki and registered with clinicaltrials.gov (NCT02252458; PI: W. Ruppen; September 8, 2014) before recruitment.

Volunteer recruitment occurred by advertisement on the University's homepage, and inclusion occurred on a “first-come, first-served” basis. Inclusion criteria were healthy (American Society of Anesthesiologists I to II), male volunteers with a body mass index between 18 and 25 kg/m². Exclusion criteria were recreational drug abuse, opioid consumption during the last month, regularly taking medication potentially interfering with pain sensitization (analgesics, antihistamines, and calcium or potassium channel blockers), a history of motion sickness, neuropathy, chronic pain, neuromuscular or psychiatric disease, known or suspected kidney or liver disease, known drug allergies or intolerance to opioids, and sleep apnea syndrome. Urine samples for toxicology screening were obtained (Accu-Tell, Newark, DE). All volunteers were familiarized with the pain scale, intradermal electrical stimulation, and the cold pressor model before participating in the study. As a full training session would have been rather invasive, patients were shown material during the detailed explanation of the sessions. No performance criteria were used for patient selection.

Study Design

This study was a prospective, randomized, double-blinded, crossover study examining two different concentrations of fentanyl in a superiority design, with a type I error of 0.05 using two-tailed hypothesis testing. A schematic representation is shown in figure 1. A washout period of 3 weeks between study arms was instituted to prevent contamination. The subjects were randomized to receive either the high dose or the low dose of fentanyl first, using a one-time, virtual coin toss (www.random.org) by a study nurse exclusively involved in randomization and fentanyl administration. The nurse then set the delivery rate on a completely covered syringe pump (Injectomat Agilia, Fresenius Kabi, Bad Homburg, Germany) to intravenously apply either 1 or 10 μg·kg⁻¹·h⁻¹ according to a weight/rate table. After precisely 1 h, the syringe pump was stopped, and the study nurse removed the perfusion syringe and connection and recovered the syringe pump. During the second session, the same study nurse administered the dose not received during the first trial day. This information was kept in a sealed, opaque envelop in the study nurse’s office. Both the investigator and the subjects were unaware of the treatment assignment at all times. The investigator carried out the measurements of acute pain, hyperalgesia, allodynia, CPP threshold, and CPP tolerance. Subjects were continuously monitored by pulse oximetry (SpO₂), electrocardiography, and noninvasive blood pressure (IntelliVue X2, Philips, Best, Netherlands).

Experimental Pain Models and Sensory Testing

Two separate models were used: (1) intradermal electrical stimulation for acute pain hyperalgesia and allodynia and (2) CPP for acute pain.

Intradermal electrical stimulation was used to continuously induce pain and secondary hyperalgesia, as described previously and as utilized in a number of pain experiments. Two microdialysis catheters with internal stainless steel wires were inserted in parallel into the intradermal, volar surface of the forearm for a length of approximately 10 mm and separated by 5 mm from each other. The catheters were filled with 0.9% saline and a continuous flow...
of 0.2 μl/min ensured by a syringe pump (CMA 402, Cma Microdialysis AB, Kista, Sweden) to facilitate conduction. The stainless steel wires were attached to a constant current stimulator (Digitimer S7; Digitimer Ltd, Hertfordshire, United Kingdom) and monophasic, rectangular electrical pulses of 0.5-ms duration were applied with alternating polarity at 2 Hz. The current was increased to target a pain rating of 6 of 10 on a numeric rating scale (NRS) (0 = no pain and 10 = maximum tolerable pain). Three further increases in current were made every 5 min for the next 15 min to compensate for habituation. This final current was kept constant for the next 2 h. After a 2.5-h break, the intradermal electrical stimulation was restarted for another 2 h with the current being increased in the same way (i.e., same milliamperes, same time) as in the first 2-h block. Once the current was restarted, patients were asked to report pain (NRS). After the crossover in the second session, current was once again titrated to a NRS of 6, independent of and blinded to the milliamperes values of the first session. This particular pain model has been shown to provoke stable areas of secondary hyperalgesia to pinprick and touch caused by an activation of mechanoinsensitive C-nociceptors (a class of nociceptors shown to be activated electrically, preferentially at high current densities, as used in this model).

The investigator asked each subject to rate the intensity of pain as measured by the NRS every 15 min during electrical stimulation. Immediately afterward, the area of pinprick hyperalgesia was determined using a 256-mN von Frey filament, and subsequently the area of allodynia was determined using a dry cotton swab (allodynia). To create an area from these linear measurements, the assumption was made that this field had the shape of an ellipse. The area was calculated using the formula \( \pi \cdot d \cdot d \).

CPP is another frequently used model examining opioid-induced analgesia and tolerance. The arm not used in intradermal electrical stimulation was immersed in a 15-l ice water cooler filled with one-third water and two-thirds crushed ice and maintained at 0° to 1°C as described elsewhere. Subjects were instructed to place the palm of their hand on the bottom of the cooler, thereby submerging their arm approximately 15 cm up to the forearm. Temperature was continually measured, and the ice bath was stirred before and after immersion of the arm. The CPP threshold was defined as the time in seconds until the ice water became painful, and the CPP tolerance was defined as the time in seconds until the subject was forced to withdraw the hand due to pain or until 300 s had passed, a time after which numbness sets in. This model reliably activates peripheral nociceptors and has been used in a number of studies. Measurements were made on an hourly basis and on completion of the trial with the use of a stop watch.

Fentanyl concentrations were assumed to be those generated by the Shafer model (ITTVA app, version 3.1, David Eduardo Ramirez, Colombia), with control measurements made at 30, 60, 90, 120, 270, and 390 min by the Central Laboratory of Basel University Hospital in 8 of 21 volunteers. Blood was drawn from a peripheral catheter placed in the cubital vein of the arm not used for electrical stimulation and without the use of a tourniquet. Samples were immediately centrifuged at 4°C, placed on dry ice, refrigerated at -20°C, and then analyzed by a method based on the chromatographic separation, as described elsewhere.

Endpoints

The primary focus of this study was the intradermal electrical stimulation model, with hyperalgesia from 4.5 to 6.5 h after commencement of fentanyl administration as the sole primary endpoint. Secondary endpoints from 4.5 to 6.5 h were pain as measured by the NRS, allodynia, and the CPP threshold and tolerance. In addition, we examined the area under

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**Fig. 2.** Picture of intradermal electrical stimulation model with grid (**A**), for hyperalgesia assessment with a von Frey filament (**B**), and allodynia assessment with a cotton swab (**C**).
the curve (AUC) for NRS, hyperalgesia, and allodynia from 0 to 2 h after fentanyl administration. When endpoints or events occurred at the same time, intradermal electrical stimulation measures were made before CPP, and electrical stimulation was ceased only after measurements were completed.

**Statistical Analysis**

The sample size of 22 participants per study arm of a crossover design was calculated on the assumption of a 25% effect size in a mixed-effects model at 4 h with a type I error of 0.05 and power of 0.80. A resampling procedure was used, and a difference was declared when a paired Wilcoxon rank sum test showed a significant result. This more conservative approach was used because there was an insufficient basis for assumptions required for linear mixed effects.

Pain scores (NRS) were considered to be ordinal, whereas hyperalgesia and allodynia areas as well as cold pressor threshold and tolerance were considered to be continuous. For all endpoints during the time of interest from 4.5 to 6.5 h, a mixed-effects model was used. Fixed independent variables were dose, time, session, and treatment allocation order; the subject was the random independent variable allowing for individual y-intercepts, but not individual slopes. Normality was examined by Q-Q-plots and if necessary was log transformed. P values were assessed by ANOVA using a likelihood ratio test with and without the parameter for which a P value was to be determined. NRS, hyperalgesia, and allodynia from 0 to 2 h were analyzed by AUC due to nonlinearity for time and analyzed by paired Wilcoxon Mann Whitney U test. Baseline milliampere to elicit an NRS of 6 as well as time to CPP threshold and CPP tolerance were considered to be continuous data and were analyzed using a paired Wilcoxon Mann Whitney U test. Measured fentanyl concentrations were compared with calculated values using a Wilcoxon Mann Whitney U test. The incidence of side effects was count data with percentages and was examined via Pearson’s chi square test. All statistical analysis was performed using R version 3.1.3 (R Foundation for Statistical Computing, Austria) including the “lme4” package.

**Results**

**Descriptive Analysis**

A total of 22 Caucasian male volunteers were recruited from September 2014 to January 2015. Aside from one “no show” for the first session, all volunteers who began the trial completed both arms of the study. Data from all 21 volunteers were complete (table 1). Eleven volunteers (52%) received the low-dose treatment first, and 10 volunteers (48%) received the high-dose treatment first. Baseline scores were similar in both groups with no evidence of variation between the low- and high-dose baseline current (37.0 mA [19.0 to 43.0 mA] and 31.2 mA [19.0 to 47.0 mA]; P = 0.772) or in CPP threshold

Table 1. Demographic Data and Baseline Characteristics of Volunteers

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (yr)</th>
<th>Weight (kg)</th>
<th>Height (m)</th>
<th>BMI (kg/m²)</th>
<th>First Dose (Low/High)</th>
<th>Baseline Current at Low Dose (mA)</th>
<th>Baseline Current at High Dose (mA)</th>
<th>Baseline CPP at Low-dose Threshold (s)</th>
<th>Baseline CPP at High-dose Threshold (s)</th>
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<tbody>
<tr>
<td>1</td>
<td>28</td>
<td>85</td>
<td>1.85</td>
<td>24.8</td>
<td>Low</td>
<td>15.80</td>
<td>28.90</td>
<td>15/35</td>
<td>22/47</td>
</tr>
<tr>
<td>2</td>
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<td>76</td>
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<td>23.7</td>
<td>Low</td>
<td>11.90</td>
<td>16.90</td>
<td>11/23</td>
<td>17/42</td>
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<td>19.00</td>
<td>21/41</td>
<td>14/25</td>
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<td>4</td>
<td>23</td>
<td>73</td>
<td>1.79</td>
<td>22.8</td>
<td>Low</td>
<td>14.10</td>
<td>31.50</td>
<td>17/49</td>
<td>15/50</td>
</tr>
<tr>
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<td>32.10</td>
<td>31/300</td>
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<td>6</td>
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<td>64</td>
<td>1.90</td>
<td>22.1</td>
<td>Low</td>
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<td>10.50</td>
<td>27/53</td>
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<td>90.00</td>
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<td>30.70</td>
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<td>1.80</td>
<td>24.1</td>
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<td>20/35</td>
<td>25/36</td>
</tr>
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<td>25/38</td>
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<td>77</td>
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<td>23.2</td>
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<td>18.70</td>
<td>17.90</td>
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<td>44/59</td>
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<td>26.60</td>
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<td>18/57</td>
</tr>
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<td>25</td>
<td>78</td>
<td>1.79</td>
<td>24.3</td>
<td>High</td>
<td>43.90</td>
<td>57.00</td>
<td>80/164</td>
<td>135/300</td>
</tr>
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<td>34</td>
<td>73</td>
<td>1.73</td>
<td>24.4</td>
<td>Low</td>
<td>57.00</td>
<td>90.00</td>
<td>180/300</td>
<td>300/300</td>
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<td>85</td>
<td>1.89</td>
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<td>33.90</td>
<td>190/256</td>
<td>300/300</td>
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<td>1.77</td>
<td>24.6</td>
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<td>49.30</td>
<td>52.50</td>
<td>300/300</td>
<td>41/300</td>
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<td>21.0</td>
<td>Low</td>
<td>17.60</td>
<td>21.90</td>
<td>12/38</td>
<td>10/32</td>
</tr>
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<td>19</td>
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<td>88</td>
<td>1.87</td>
<td>24.6</td>
<td>Low</td>
<td>31.90</td>
<td>47.00</td>
<td>14/38</td>
<td>15/38</td>
</tr>
<tr>
<td>20</td>
<td>22</td>
<td>63</td>
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<td>22.1</td>
<td>High</td>
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<td>45/156</td>
</tr>
<tr>
<td>21</td>
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<td>24.8</td>
<td>Low</td>
<td>37.50</td>
<td>31.20</td>
<td>54/73</td>
<td>67/114</td>
</tr>
</tbody>
</table>

Mean ± SD, median (IQR), or counts (%)

BMI = body mass index; CPP = cold pressor pain; IQR = interquartile range.

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and tolerance (27 s [15 to 80 s] vs 25 s [15 to 45 s]; P = 0.960; and 53 s [38 to 230 s] vs 59 s [38 to 300 s]; P = 0.667, respectively). As the measures of hyperalgesia and allodynia were first measured with concurrent fentanyl administration due to some time being required for the fields to become stable, these values were not incorporated into baseline measures (table 1). Measured fentanyl concentrations were similar to calculated values from 4.5 to 6.5 h in both the high- and the low-dose groups (high dose at 4.5 and 6.5 h: P = 0.106 and P = 0.742, respectively; low dose at 4.5 and 6.5 h: P = 0.720 and P = 0.152, respectively; see Supplemental Digital Content 1, http://links.lww.com/ALN/B233, which is a table of measured and calculated fentanyl concentrations).

No major adverse effects occurred. Minor side effects (table 2) included nausea and vomiting (both during the trial and at home), oxygen desaturations requiring reminders to breathe, and/or supplemental oxygen and were significantly more common in the high-dose regimen.

**Analysis of NRS, Hyperalgesia, and Allodynia**

The time course for NRS values, hyperalgesia, and allodynia as well as fentanyl concentrations are shown in figure 3. On beginning the fentanyl infusion, pain scores dropped in both the high- and low-dose groups (median AUC_{NRS_{high}} = 176 units × min [interquartile range [IQR], 128 to 304 units × min] vs median AUC_{NRS_{low}} = 375 units × min [IQR, 270 to 446 units × min]; P < 0.001). Similarly, the area of hyperalgesia was lower in the high-dose group from 0 to 2 h (median AUC_{hyperalgesia_{high}} = 1,737 cm² × min [IQR, 1,163 to 2,352 cm² × min] vs median AUC_{hyperalgesia_{low}} = 2,708 cm² × min [IQR, 1,566 to 3,842 cm² × min], P = 0.008). The areas of allodynia were not significantly different between doses (median AUC_{allodynia_{high}} = 751 cm² × min [IQR, 348 to 1,113 cm² × min] vs median AUC_{allodynia_{low}} = 977 cm² × min [IQR, 531 to 1,240 cm² × min], P = 0.243).

The results of the mixed effects model examining the effect of fentanyl dose, time, session, and order of treatment allocation on CPP, hyperalgesia, and allodynia from 4.5 to 6.5 h after the begin of fentanyl administration are also shown in Supplemental Digital Content 2, http://links.lww.com/ALN/B234. The high dose led to a 43.0% (95% CI, 29.7 to 56.3%, P < 0.001) higher CPP threshold and a 32.5% (95% CI, 21.7 to 43.4%, P < 0.001) higher CPP tolerance. Time was not a statistically significant factor. Volunteers had a significantly higher threshold (P < 0.001) and tolerance (P = 0.004) in the second session, whereas the order or treatment allocation was not again not statistically significant.

**Discussion**

In this trial, we compared the effect of two clinical dosages of fentanyl on analgesia and hyperalgesia in human volunteers using different pain models. In the intracutaneous electrical stimulation model, a fentanyl administration of

### Table 2. Side Effects by Dose

<table>
<thead>
<tr>
<th>Side Effects</th>
<th>High Dose</th>
<th>Low Dose</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure &lt; 70 mmHg</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Heart rate &lt; 40 bpm</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>SpO₂ &lt; 90%, requiring reminders to breathe</td>
<td>19/21 (90)</td>
<td>0/21 (0)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SpO₂ &lt; 90%, requiring supplemental oxygen</td>
<td>8/21 (38)</td>
<td>0/21 (0)</td>
<td>0.006</td>
</tr>
<tr>
<td>SpO₂ &lt; 90%, requiring naloxone/stopping</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>N/A</td>
</tr>
<tr>
<td>Nausea during trial</td>
<td>10/21 (48)</td>
<td>0/21 (0)</td>
<td>0.001</td>
</tr>
<tr>
<td>Vomiting during trial</td>
<td>7/21 (33)</td>
<td>0/21 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Nausea at home</td>
<td>12/21 (57)</td>
<td>1/21 (6)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Vomiting at home</td>
<td>7/21 (33)</td>
<td>0/21 (0)</td>
<td>0.013</td>
</tr>
<tr>
<td>Intolerable pain</td>
<td>0/21 (0)</td>
<td>0/21 (0)</td>
<td>N/A</td>
</tr>
</tbody>
</table>

Data are represented as n (%).

Bpm = beats per minute; N/A = not applicable; SpO₂ = pulse oximetry oxygen saturation.

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Fentanyl: Opioid-induced Hyperalgesia in Volunteers

10 μg·kg\(^{-1}\)·h\(^{-1}\) over 60 min was found to be associated with significantly lower levels of acute pain from 4.5 to 6.5 h after the start of the fentanyl infusion compared with a 1 μg·kg\(^{-1}\)·h\(^{-1}\) dose regimen, while at the same time showing a greater area of secondary hyperalgesia. No difference was found in allostynia. In the cold pressure pain model, high-dose fentanyl was associated with significantly higher threshold and tolerance levels throughout the trial.

Only a few clinical studies have examined OIH and fentanyl in opioid-naïve subjects undergoing a surgical procedure. Chia et al. examined 60 female American Society of Anesthesiologists I to II patients undergoing total abdominal

Fig. 3. Fentanyl concentrations and outcome variable of intradermal electrical stimulation. All values are represented as mean ± SE. Fentanyl concentrations were calculated by the iTIVA app (Shafer Model); P values from 4.5 to 6.5 h are based on the mixed-effects model; P values for 0 to 2 h are based on the area under the curve and a paired Wilcoxon Mann–Whitney U test. NRS = numeric rating scale.
hysterectomy, randomized to receive either 1 μg/kg or 15 μg·kg⁻¹·h⁻¹ fentanyl as a slow 20-min continuous infusion before the induction of anesthesia. Although the visual analog scale was significantly higher in the high-dose group at 4 and 8 h after fentanyl administration, there was no statistically significant difference thereafter. Another study by Cooper et al. examined the effect of intrathecal fentanyl (25 μg vs. saline) for Caesarean section in 60 parturients. Although postoperative morphine requirements were higher at 6 h in the fentanyl group, pain scores did not differ statistically. A follow-up study with a similar design showed higher pain at rest—but not when coughing—for intrathecal fentanyl. Similarly, Carvalho et al. examined four different doses of intrathecal fentanyl in patients undergoing Caesarean section and found dose-dependent differences in postoperative pain measured in the first 24 h, with higher doses of fentanyl associated with more pain.

Several factors make it difficult to directly compare our data with these aforementioned clinical studies. A first obvious difference is that healthy, young, Caucasian males represent a different collective than older, Asian women undergoing hysterectomy (Chia et al.) or than parturients (Cooper et al. and Carvalho et al.). Differences in opioid analgesia between men and women and across age, race/ethnicity, and genetic factors have been shown. A second difference is the mode of application. Cooper et al. and Carvalho et al. administered fentanyl intrathecally. Although Chia et al. administered fentanyl intravenously, they used a higher dose during a shorter time period than in our trial, leading to different initial pharmacokinetic profiles. However, during the time of interest beginning at 4.5 h, the calculated concentrations of the high dose and low dose were nearly identical (see Supplemental Digital Content 1, http://links.lww.com/ALN/B233). Third, it is possible that the acute pain elicited by a model of electrical stimulation is significantly different from clinical pain following surgery. Of note and probably the most important difference between our trial and the clinical trials mentioned at the beginning of this paragraph is that the aforementioned trials examined acute pain and/or postoperative opioid requirements and not hyperalgesia per se. However, the distinction between an analgesic effect, acute opioid tolerance

Fig. 4. Box plots of cold pressor pain (CPP) tolerance (top) and threshold (bottom) in seconds for high and low doses during the course of the trial. Black squares indicate medians, and boxes indicate the interquartile range.
(a desensitization to opioid effect requiring more opioid to reach the same effect), and OIH (an increase in pain sensitivity induced or aggravated by opioids) is important.61

The results within our trial with the high-dose group exhibiting lower levels of acute pain but with increased hyperalgesia deserve greater attention, as hyperalgesia is a different entity with different clinical implications. Hyperalgesia and pain have been shown to correlate poorly.20,62-64 Unfortunately, however, many clinical trials examining OIH often equate postoperative pain levels with OIH.10,61 This lacking differentiation may be of lesser importance when examining the ultrashort-acting μ-agonist remifentanil as its rapid analgesic offset largely precludes relevant concentrations of opioids at the time of acute pain assessment.61 In our trial, however, there was still a potentially relevant opioid concentration at the time of measurement, potentially explaining continued analgesia with concurrent hyperalgesia. Reexamining the effect of time in our model shows that although acute pain decreased by 0.02 units/min (95% CI, −0.023 to −0.018; P < 0.001) or about 1 unit/h, fentanyl had caused a time-independent (P = 0.457) increase in the area of pinprick hyperalgesia. Receptive field expansion to pinprick testing is typical for central sensitization, which represents an uncoupling of the clear stimulus response relationship that defines nociceptive pain.65 Although acute noxious stimulation causes local pain, secondary, mechanical hypersensitivity typically arises in the uninjured surroundings. Our results highlight the differences between acute nociceptive pain and hyperalgesia as a form of central sensitization.

The time to CPP threshold and tolerance increased in both groups with a greater increase in both values in the high-dose group for the duration of the trial. This is congruent with the pain measurement from intradermal electrical stimulation. Although this pain model has been used to show acute opioid physical dependence in opioid naïve patients and has been used in examining OIH in opioid-dependent individuals,13,46 we were unable to find compelling evidence that this model can also measure central sensitization per se in opioid-naïve individuals.

The clinical relevance of this trial is difficult to definitely ascertain. However, a few preliminary conclusions can be drawn. First, this trial seriously challenges the common clinical belief that remifentanil is unique in its ability to induce hyperalgesia. As hyperalgesia is a frequent postsurgical form of central sensitization,65,66 caution may be warranted with high doses of fentanyl, especially given the high incidence of nausea shown in this trial. Second, hyperalgesia is relevant for postoperative pain management, as acute opioid tolerance may be treated with opioids, whereas OIH may aggravate pain.61 This is illustrated by the focus on drugs affecting central sensitization postoperatively, such as ketamine,67-69 pregabalin,70,71 and gabapentin.68,72 Knowing that fentanyl-induced hyperalgesia and not acute opioid tolerance may be the problem should change postoperative pain management. Third, wound hyperalgesia may be an important factor in persistent postoperative pain.73-76 Remifentanil has been shown to increase postoperative wound hyperalgesia20,62,77 and also to be associated with a higher incidence of persistent postoperative pain.63,78 It may be possible that higher doses of fentanyl inducing hyperalgesia may also be associated with persistent postoperative pain.

This study has a number of limitations. First, a study in healthy, young, all-Caucasian, male volunteers inherently lacks direct transferability to diverse patients in the clinical setting. However, given the skew in the patients in the few clinical trials available, examining such defined populations in a standardized setting may prove valuable. Second, in our study, the pain stimulus was not constantly present after opioid administration. However, we judged a continuous 6.5-h electrical stimulation without break as neither feasible nor appropriate for such a trial. Third, the second testing phase from 4.5 to 6.5 h after commencing the fentanyl infusion may have been too short or too early as relevant fentanyl concentrations and analgesia were still present. Generally, a washout period of 5 half-lives is propagated. However, this window was selected because (1) it includes the time period in which Chia et al. found clinically increased pain levels in the high-dose group,30 and (2) it was the longest time based on the previous experience that we felt was feasible for volunteers to receive induced pain and maintain a starved status without abandoning the study.38,39 Furthermore, even after 12 h, our calculated fentanyl concentration was 0.6 ng/ml, well above the concentration after 5 half-lives (0.2 ng/ml) and similar to Chia et al’s calculated concentration of 0.7 ng/ml. Fourth, we applied fentanyl using a syringe pump, rather than the clinically prevalent form of bolus application. Although one can speculate whether this may influence OIH, bolus were not an option in volunteers (apnea). Fifth, although a double-blinded study, the side-effect profile largely revealed the volunteers’ allocation to treatment for the anesthesiologist present. Finally, no placebo group was included. Our primary focus was on comparing two clinically sensible fentanyl regimens and opioid-free anesthesia still remains the clinical exception, even for low-pain surgery.

In summary, this study is the first to show fentanyl-induced hyperalgesia in healthy volunteers. Interestingly, hyperalgesia was significantly higher in the high-dose group, whereas pain scores were lower, highlighting the importance of distinguishing between acute pain and central sensitization. Given that central sensitization is an important postoperative factor in pain perception and processing and given the great differences in side effects in our trial, selecting a lower rather than a higher opioid dose may be in the patient’s best interest.

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Competing Interests
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