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

A Double-blind, Randomized, Crossover Trial

Eckhard Mauermann, M.D., Joerg Filitz, M.D., Patrick Dolder, M.Sc., Katharina M. Rentsch, Ph.D., Oliver Bandschapp, M.D., Wilhelm Ruppen, M.D.

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,[1–3] a body of evidence shows that opioid administration may induce hyperalgesia,[4–9] a phenomenon termed opioid-induced hyperalgesia (OIH). Surprisingly, with the exception of remifentanil,[6,10–26] 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,[27] greater morphine consumption,[28,29] or both[30] in the high-dose fentanyl groups. Chia *et al.*[30] examined the application of intravenous fentanyl, whereas the other three studies examined intrathecal fentanyl as an adjunct to neuraxial anesthesia in parturients during Caesarian 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.[31–35] The extent to which specifically intravenous

What We Already Know about This Topic

- The intravenous administration of remifentanil is associated with enhanced hyperalgesia
- Relatively little information is available concerning the ability of fentanyl to enhance hyperalgesia after intravenous administration

What This Article Tells Us That Is New

- High-dose (10 µg/kg) fentanyl infusion can increase cold pressor test pain threshold and tolerance 4.5 to 6.5 h after infusion
- Simultaneously, high-dose fentanyl infusion can increase the area of hyperalgesia caused by electrical burn

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.

<zdoi;10.1097/ALN.0000000000000976>

These measures were assessed by using two established human models: (1) an intradermal electrical stimulation model evoking acute pain, hyperalgesia, and allodynia[36] and (2) a cold pressor pain (CPP) model examining acute pain.[37] 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 pain 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 (Sp$_{O_2}$), 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 continually induce pain and secondary hyperalgesia, as described previously[36] and as utilized in a number of pain experiments.[22,36,38–41] 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
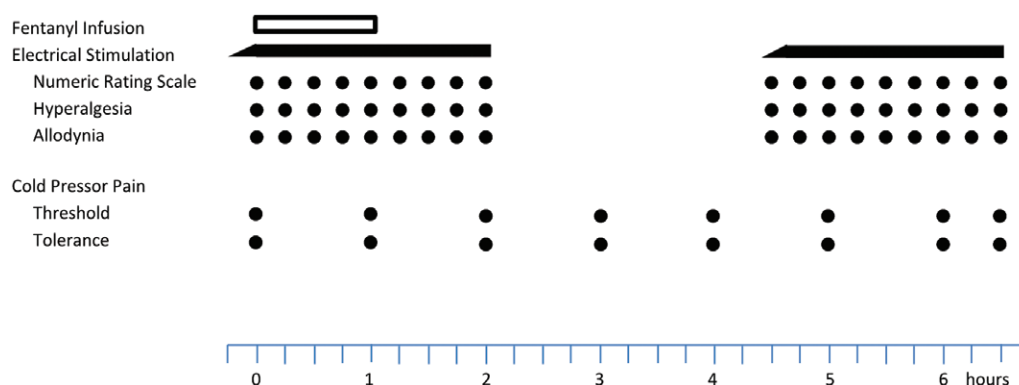
Fig. 1. Schematic illustration of important protocol steps.

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 milliampere, 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 milliampere 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 mechanoinsenstive C-nociceptors[42] (a class of nociceptors shown to be activated electrically, preferentially at high current densities, as used in this model).[43,44]

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. Measurements were conducted from a more distant to a more central site along four orthogonal lines (distal, proximal, lateral, and medial) drawn onto the skin with tick marks indicating each centimeter (fig. 2).

Distal and proximal measurements were begun 12 cm from the site of electrical stimulation, whereas the lateral and medial measurements were begun 6 cm from this site. In both cases, the filament was moved toward the site of stimulation in 0.5-cm increments until the subject reported either increased pain sensations from the von Frey filament (hyperalgesia) or an unpleasant, "rougher" sensation from the 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 $\frac{1}{4}\pi D \cdot d$.

CPP is another frequently used model examining opioid-induced analgesia and tolerance.[13,45–47] The arm not used in intradermal electrical stimulation was immersed in a 15-l ice water cooler filled with one-third water and two-third crushed ice and maintained at 0° to 1°C as described elsewhere.[13] Subjects were instructed to place the palm of their hand on the bottom of the cooler, thereby submersing their arm approximately 15 cm upto 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.[13] This model reliably activates peripheral nociceptors and has been used in a number of studies.[13,37,48] 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[49] (iTIVA 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.[50]

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

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

No.	Age (yr)	Weight (kg)	Height (m)	BMI (kg/m²)	First Dose (Low/High)	Baseline Current at Low Dose (mA)	Baseline Current at High Dose (mA)	Baseline CPP at Low-dose Threshold/ Tolerance (s)	Baseline CPP at High-dose Threshold/ Tolerance (s)
1	28	85	1.85	24.8	Low	15.80	28.90	15/35	22/47
2	24	76	1.79	23.7	Low	11.90	16.90	11/23	17/42
3	32	58	1.69	20.3	High	36.00	19.00	21/41	14/25
4	23	73	1.79	22.8	Low	14.10	31.50	17/49	15/50
5	22	86	1.87	24.6	High	78.40	32.10	31/300	30/240
6	25	64	1.70	22.1	High	15.10	10.50	27/53	45/67
7	20	74	1.81	22.6	Low	37.00	90.00	100/300	98/300
8	38	69	1.87	19.7	High	30.70	37.30	15/22	10/14
9	26	78	1.80	24.1	Low	19.50	15.40	20/35	25/36
10	24	79	1.95	20.8	High	40.20	13.90	12/124	15/300
11	27	64	1.69	22.4	High	46.50	27.80	45/80	25/38
12	23	77	1.82	23.2	Low	18.70	17.90	27/45	44/59
13	34	90	1.85	26.3	High	39.30	26.60	12/34	18/57
14	25	78	1.79	24.3	Low	43.90	57.00	80/164	135/300
15	34	73	1.73	24.4	Low	57.00	90.00	180/300	300/300
16	26	85	1.89	23.8	High	37.80	33.90	190/256	300/300
17	39	77	1.77	24.6	High	49.30	52.50	300/300	41/300
18	21	63	1.73	21.0	Low	17.60	21.90	12/38	10/32
19	24	86	1.87	24.6	Low	31.90	47.00	14/38	15/38
20	22	63	1.69	22.1	High	42.70	63.20	118/230	45/156
21	23	82	1.82	24.8	Low	37.50	31.20	54/73	67/114
Mean ± SD, median (IQR), or counts (%)	27±6	75±9	1.80±0.07	23.0±1.7	Low =11 (52%); high =10 (48%)	37.0 (19.0–43.0)	31.2 (19.0–47.0)	27 (15–80)/ 53 (38–230)	25 (15–45)/ 59 (38–300)

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

456

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 $AUC_{NRShigh}$ = 176 units × min [interquartile range {IQR}, 128 to 304 units × min) *vs.* median AUC_{NRSlow} = 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 $AUC_{Hyperalgesiahigh}$ = 1,737 cm² × min [IQR, 1,163 to 2,352 cm² × min] *vs.* median $AUC_{Hyperalgesialow}$ = 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 $AUC_{Allodyniahigh}$ = 751 cm² × min [IQR, 348 to 1,113 cm² × min] *vs.* median $AUC_{Allodynialow}$ = 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 NRS, hyperalgesia, and allodynia from 4.5 to 6.5 h after the begin of fentanyl administration is shown in Supplemental Digital Content 2, http://links.lww.com/ALN/B234,

which is a table summarizing the mixed-effects model. For acute pain (NRS), the low dose revealed an NRS 0.83 units higher (95% CI, 0.63 to 1.02; *P* < 0.001) than the high-dose group. This was a time-dependent effect with a decrease of 0.02 units/min (95% CI, –0.023 to –0.018; *P* < 0.001). The other outcomes were log transformed for normality. Unlike the pain score, the area of hyperalgesia was increased by 30.5% (95% CI, 16.6 to 44.4%; *P* < 0.001) by the high dose, which was independent of time (–0.001 [95% CI, –0.003 to 0.001]; *P* = 0.432). The area of allodynia was not significantly different between groups, with the high-dose group exhibiting 4.0% more allodynia (95% CI, –15.4 to 23.5%; *P* = 0. 682) from 4.5 to 6.5 h. The area of allodynia significantly decreased over time (*P* = 0. 010). The second session had significantly less pain (*P* < 0.001), hyperalgesia (*P* < 0.001), and allodynia (*P* = 0.002). However, the order of treatment allocation was not a statistically significant factor for any of the three outcomes.

Analysis of Cold Pressor Pain

CPP threshold and tolerance levels were significantly lower in the low-dose group for the duration of the trial (fig. 4). Both the high-dose and the low-dose showed increases in CPP duration from baseline to the peak fentanyl concentration at 60 min and then a decrease at 120 min.

The results for the time period from 4.5 to 6.5 h after 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 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

Side Effects	High Dose	Low Dose	*P* Value
Systolic blood pressure < 70 mmHg	0/21 (0)	0/21 (0)	N/A
Heart rate < 40 bpm	0/21 (0)	0/21 (0)	N/A
SpO_2 < 90%, requiring reminders to breathe	19/21 (90)	0/21 (0)	< 0.001
SpO_2 < 90%, requiring supplemental oxygen	8/21 (38)	0/21 (0)	0.006
SpO_2 < 90%, requiring naloxone/stopping	0/21 (0)	0/21 (0)	N/A
Nausea during trial	10/21 (48)	0/21 (0)	0.001
Vomiting during trial	7/21 (33)	0/21 (0)	0.013
Nausea at home	12/21 (57)	1/21 (5)	< 0.001
Vomiting at home	7/21 (33)	0/21 (0)	0.013
Intolerable pain	0/21 (0)	0/21 (0)	N/A

Data are represented as n (%).
Bpm = beats per minute; N/A = not applicable; SpO_2 = pulse oximetry oxygen saturation.
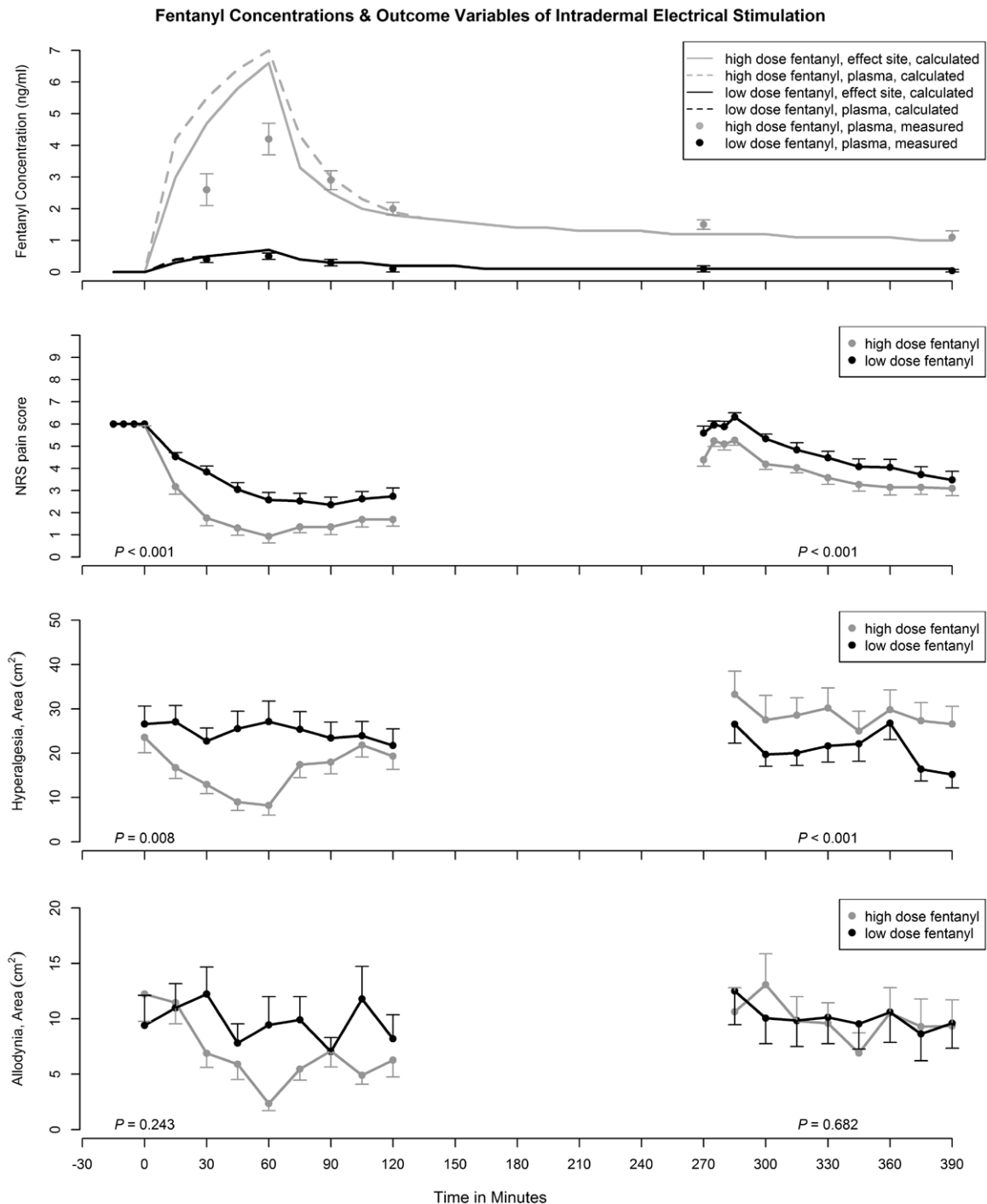
Fig. 3. Fentanyl concentrations and outcome variable of intradermal electrical stimulation. All values are represented as mean ± SE. Fentanyl concentrations were calculated by the iTIVA app (Shafer Model); *P* values from 4.5 to 6.5 h are based on the mixed-effects model; *P* values for 0 to 2 h are based on the area under the curve and a paired Wilcoxon Mann–Whitney *U* test. NRS = numeric rating scale.

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 allodynia. 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.*[30] examined 60 female American Society of Anesthesiologists I to II patients undergoing total abdominal
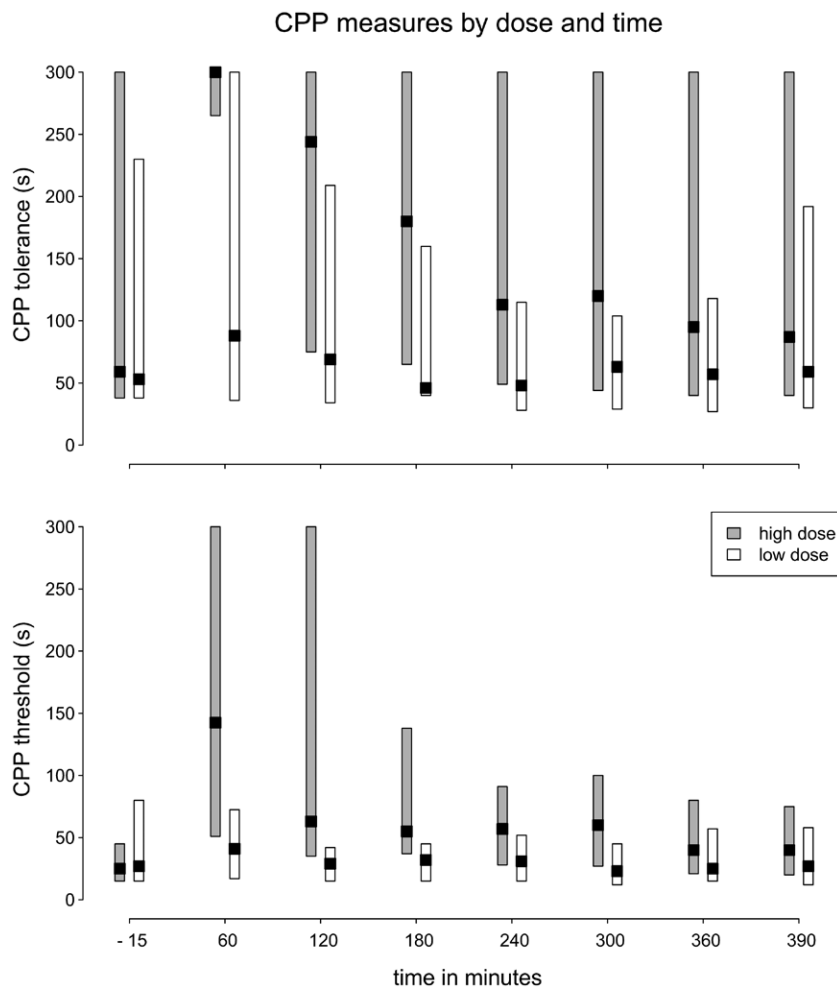
Fig. 4. *Box plots* of cold pressor pain (CPP) tolerance (*top*) and threshold (*bottom*) in seconds for high and low doses during the course of the trial. *Black squares* indicate medians, and *boxes* indicate the interquartile range.

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.*[29] 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.[28] Similarly, Carvalho *et al.*[27] 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.*[30]) or than parturients (Cooper *et al.*[28,29] and Carvalho *et al.*[27]). Differences in opioid analgesia between men and women[51–53] and across age,[54–56] race/ethnicity,[57,58] and genetic factors[59,60] have been shown. A second difference is the mode of application. Cooper *et al.*[28,29] and Carvalho *et al.*[27] administered fentanyl intrathecally. Although Chia *et al.*[30] 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

(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 deserves 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[46] and has been used in examining OIH in opioid-dependent individuals,[13,47] 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 hyperalgesia[20,62,77] 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 boli application. Although one can speculate whether this may influence OIH, boli 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.

Acknowledgments

References

1. Collard V, Mistraletti G, Taqi A, Asenjo JF, Feldman LS, Fried GM, Carli F: Intraoperative esmolol infusion in the absence of opioids spares postoperative fentanyl in patients undergoing ambulatory laparoscopic cholecystectomy. Anesth Analg 2007; 105:1255–62

2. White PF, Wang B, Tang J, Wender RH, Naruse R, Sloninsky A: The effect of intraoperative use of esmolol and nicardipine on recovery after ambulatory surgery. Anesth Analg 2003; 97:1633–8

3. Zöllner C: [Do opioids induce hyperalgesia?]. Anaesthesist 2010; 59:983–6, 988–93

4. Angst MS, Clark JD: Opioid-induced hyperalgesia: A qualitative systematic review. ANESTHESIOLOGY 2006; 104:570–87

5. Bekhit MH: Opioid-induced hyperalgesia and tolerance. Am J Ther 2010; 17:498–510

6. Angst MS, Koppert W, Pahl I, Clark DJ, Schmelz M: Short-term infusion of the mu-opioid agonist remifentanil in humans causes hyperalgesia during withdrawal. Pain 2003; 106:49–57

7. Arnér S, Rawal N, Gustafsson LL: Clinical experience of long-term treatment with epidural and intrathecal opioids—A nationwide survey. Acta Anaesthesiol Scand 1988; 32:253–9

8. Laulin JP, Célèrier E, Larcher A, Le Moal M, Simonnet G: Opiate tolerance to daily heroin administration: An apparent phenomenon associated with enhanced pain sensitivity. Neuroscience 1999; 89:631–6

9. Singla A, Stojanovic MP, Chen L, Mao J: A differential diagnosis of hyperalgesia, toxicity, and withdrawal from intrathecal morphine infusion. Anesth Analg 2007; 105:1816–9

10. Fletcher D, Martinez V: Opioid-induced hyperalgesia in patients after surgery: A systematic review and a meta-analysis. Br J Anaesth 2014; 112:991–1004

11. Fishbain DA, Cole B, Lewis JE, Gao J, Rosomoff RS: Do opioids induce hyperalgesia in humans? An evidence-based structured review. Pain Med 2009; 10:829–39

12. Angst MS, Chu LF, Tingle MS, Shafer SL, Clark JD, Drover DR: No evidence for the development of acute tolerance to analgesic, respiratory depressant and sedative opioid effects in humans. Pain 2009; 142:17–26

13. Compton P, Athanasos P, Elashoff D: Withdrawal hyperalgesia after acute opioid physical dependence in nonaddicted humans: A preliminary study. J Pain 2003; 4:511–9

14. Compton P, Miotto K, Elashoff D: Precipitated opioid withdrawal across acute physical dependence induction methods. Pharmacol Biochem Behav 2004; 77:263–8

15. Cortínez LI, Brandes V, Muñoz HR, Guerrero ME, Mur M: No clinical evidence of acute opioid tolerance after remifentanil-based anaesthesia. Br J Anaesth 2001; 87:866–9

16. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, Fletcher D, Chauvin M: Acute opioid tolerance: Intraoperative remifentanil increases postoperative pain and morphine requirement. ANESTHESIOLOGY 2000; 93:409–17

17. Gustorff B, Nahlik G, Hoerauf KH, Kress HG: The absence of acute tolerance during remifentanil infusion in volunteers. Anesth Analg 2002; 94:1223–8

18. Hansen EG, Duedahl TH, Rømsing J, Hilsted KL, Dahl JB: Intra-operative remifentanil might influence pain levels in the immediate post-operative period after major abdominal surgery. Acta Anaesthesiol Scand 2005; 49:1464–70

19. Hood DD, Curry R, Eisenach JC: Intravenous remifentanil produces withdrawal hyperalgesia in volunteers with capsaicin-induced hyperalgesia. Anesth Analg 2003; 97:810–5

20. Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M: Remifentanil-induced postoperative hyperalgesia and its prevention with small-dose ketamine. ANESTHESIOLOGY 2005; 103:147–55

21. Kim SH, Lee MH, Seo H, Lee IG, Hong JY, Hwang JH: Intraoperative infusion of 0.6–0.9 µg·kg(-1)·min(-1) remifentanil induces acute tolerance in young children after laparoscopic ureteroneocystostomy. ANESTHESIOLOGY 2013; 118:337–43

22. Koppert W, Angst M, Alsheimer M, Sittl R, Albrecht S, Schüttler J, Schmelz M: Naloxone provokes similar pain facilitation as observed after short-term infusion of remifentanil in humans. Pain 2003; 106:91–9

23. Lee LH, Irwin MG, Lui SK: Intraoperative remifentanil infusion does not increase postoperative opioid consumption compared with 70% nitrous oxide. ANESTHESIOLOGY 2005; 102:398–402

24. Luginbühl M, Gerber A, Schnider TW, Petersen-Felix S, Arendt-Nielsen L, Curatolo M: Modulation of remifentanil-induced analgesia, hyperalgesia, and tolerance by small-dose ketamine in humans. Anesth Analg 2003; 96:726–32

25. Petersen KL, Jones B, Segredo V, Dahl JB, Rowbotham MC: Effect of remifentanil on pain and secondary hyperalgesia associated with the heat—Capsaicin sensitization model in healthy volunteers. ANESTHESIOLOGY 2001; 94:15–20

26. Tröster A, Sittl R, Singler B, Schmelz M, Schüttler J, Koppert W: Modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by parecoxib in humans. ANESTHESIOLOGY 2006; 105:1016–23

27. Carvalho B, Drover DR, Ginosar Y, Cohen SE, Riley ET: Intrathecal fentanyl added to bupivacaine and morphine for cesarean delivery may induce a subtle acute opioid tolerance. Int J Obstet Anesth 2012; 21:29–34

28. Cooper DW, Garcia E, Mowbray P, Millar MA: Patient-controlled epidural fentanyl following spinal fentanyl at Caesarean section. Anaesthesia 2002; 57:266–70

29. Cooper DW, Lindsay SL, Ryall DM, Kokri MS, Eldabe SS, Lear GA: Does intrathecal fentanyl produce acute cross-tolerance to i.v. morphine? Br J Anaesth 1997; 78:311–3

30. Chia YY, Liu K, Wang JJ, Kuo MC, Ho ST: Intraoperative high dose fentanyl induces postoperative fentanyl tolerance. Can J Anaesth 1999; 46:872–7

31. Célérier E, González JR, Maldonado R, Cabañero D, Puig MM: Opioid-induced hyperalgesia in a murine model of postoperative pain: Role of nitric oxide generated from the inducible nitric oxide synthase. ANESTHESIOLOGY 2006; 104:546–55

32. Li X, Angst MS, Clark JD: A murine model of opioid-induced hyperalgesia. Brain Res Mol Brain Res 2001; 86:56–62

33. Richebé P, Rivalan B, Rivat C, Laulin JP, Janvier G, Maurette P, Simonnet G: Effects of sevoflurane on carrageenan- and fentanyl-induced pain hypersensitivity in Sprague-Dawley rats. Can J Anaesth 2009; 56:126–35

34. Van Elstraete AC, Sitbon P, Benhamou D, Mazoit JX: The median effective dose of ketamine and gabapentin in opioid-induced hyperalgesia in rats: An isobolographic analysis of their interaction. Anesth Analg 2011; 113:634–40

35. Van Elstraete AC, Sitbon P, Mazoit JX, Benhamou D: Gabapentin prevents delayed and long-lasting hyperalgesia induced by fentanyl in rats. ANESTHESIOLOGY 2008; 108:484–94

36. Koppert W, Dern SK, Sittl R, Albrecht S, Schüttler J, Schmelz M: A new model of electrically evoked pain and hyperalgesia in human skin: The effects of intravenous alfentanil, S(+)-ketamine, and lidocaine. ANESTHESIOLOGY 2001; 95:395–402

37. Chéry-Croze S: Relationship between noxious cold stimuli and the magnitude of pain sensation in man. Pain 1983; 15:265–9

38. Bandschapp O, Filitz J, Ihmsen H, Berset A, Urwyler A, Koppert W, Ruppen W: Analgesic and antihyperalgesic properties of propofol in a human pain model. ANESTHESIOLOGY 2010; 113:421–8

39. Bandschapp O, Filitz J, Urwyler A, Koppert W, Ruppen W: Tropisetron blocks analgesic action of acetaminophen: A human pain model study. Pain 2011; 152:1304–10

40. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schüttler J: Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. ANESTHESIOLOGY 2003; 99:152–9

41. Tröster A, Ihmsen H, Singler B, Filitz J, Koppert W: Interaction of fentanyl and buprenorphine in an experimental model of pain and central sensitization in human volunteers. Clin J Pain 2012; 28:705–11

42. Ørstavik K, Weidner C, Schmidt R, Schmelz M, Hilliges M, Jørum E, Handwerker H, Torebjörk E: Pathological C-fibres in patients with a chronic painful condition. Brain 2003; 126(pt 3):567–78

43. Schmelz M, Schmidt R, Ringkamp M, Handwerker HO, Torebjörk HE: Sensitization of insensitive branches of C nociceptors in human skin. J Physiol 1994; 480(pt 2):389–94

44. Weidner C, Schmelz M, Schmidt R, Hansson B, Handwerker HO, Torebjörk HE: Functional attributes discriminating mechano-insensitive and mechano-responsive C nociceptors in human skin. J Neurosci 1999; 19:10184–90

45. Angst MS, Phillips NG, Drover DR, Tingle M, Ray A, Swan GE, Lazzeroni LC, Clark JD: Pain sensitivity and opioid analgesia: A pharmacogenomic twin study. Pain 2012; 153:1397–409

46. Compton P, Miotto K, Elashoff D: Precipitated opioid withdrawal across acute physical dependence induction methods. Pharmacol Biochem Behav 2004; 77:263–8

47. Compton P, Canamar CP, Hillhouse M, Ling W: Hyperalgesia in heroin dependent patients and the effects of opioid substitution therapy. J Pain 2012; 13:401–9

48. Garcia de Jalon PD, Harrison FJ, Johnson KI, Kozma C, Schnelle K: A modified cold stimulation technique for the evaluation of analgesic activity in human volunteers. Pain 1985;22:183–9

49. Shafer SL, Varvel JR, Aziz N, Scott JC: Pharmacokinetics of fentanyl administered by computer-controlled infusion pump. ANESTHESIOLOGY 1990; 73:1091–102

50. Dolder PC, Liechti ME, Rentsch KM: Development and validation of a rapid turboflow LC-MS/MS method for the quantification of LSD and 2-oxo-3-hydroxy LSD in serum and urine samples of emergency toxicological cases. Anal Bioanal Chem 2015; 407:1577–84

51. Bartley EJ, Fillingim RB: Sex differences in pain: A brief review of clinical and experimental findings. Br J Anaesth 2013; 111:52–8

52. Paller CJ, Campbell CM, Edwards RR, Dobs AS: Sex-based differences in pain perception and treatment. Pain Med 2009; 10:289–99

53. Bodnar RJ, Kest B: Sex differences in opioid analgesia, hyperalgesia, tolerance and withdrawal: Central mechanisms of action and roles of gonadal hormones. Horm Behav 2010; 58:72–81

54. Farrell MJ: Age-related changes in the structure and function of brain regions involved in pain processing. Pain Med 2012; 13(suppl 2):S37–43

55. Gagliese L: Pain and aging: The emergence of a new subfield of pain research. J Pain 2009; 10:343–53

56. Wilder-Smith OH: Opioid use in the elderly. Eur J Pain 2005; 9:137–40

57. Cintron A, Morrison RS: Pain and ethnicity in the United States: A systematic review. J Palliat Med 2006; 9:1454–73

58. Lee A, Gin T, Oh TE: Opioid requirements and responses in Asians. Anaesth Intensive Care 1997; 25:665–70

59. Hwang IC, Park JY, Myung SK, Ahn HY, Fukuda K, Liao Q: OPRM1 A118G gene variant and postoperative opioid requirement: A systematic review and meta-analysis. ANESTHESIOLOGY 2014; 121:825–34

60. Sadhasivam S, Chidambaran V: Pharmacogenomics of opioids and perioperative pain management. Pharmacogenomics 2012; 13:1719–40

61. Angst MS: Intraoperative use of remifentanil for TIVA: Postoperative pain, acute tolerance, and opioid-induced hyperalgesia. J Cardiothorac Vasc Anesth 2015; 29(suppl 1):S16–22

62. Richebé P, Pouquet O, Jelacic S, Mehta S, Calderon J, Picard W, Rivat C, Cahana A, Janvier G: Target-controlled dosing of remifentanil during cardiac surgery reduces postoperative hyperalgesia. J Cardiothorac Vasc Anesth 2011; 25:917–25

63. Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, Cappello M, Engelman E: Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: Low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth 2010; 24:608–16

64. Suzan E, Eisenberg E, Treister R, Haddad M, Pud D: A negative correlation between hyperalgesia and analgesia in patients with chronic radicular pain: Is hydromorphone therapy a double-edged sword? Pain Physician 2013; 16:65–76

65. Woolf CJ: Central sensitization: Implications for the diagnosis and treatment of pain. Pain 2011; 152(3 suppl):S2–15

66. Latremoliere A, Woolf CJ: Central sensitization: A generator of pain hypersensitivity by central neural plasticity. J Pain 2009; 10:895–926

67. Remérand F, Le Tendre C, Baud A, Couvret C, Pourrat X, Favard L, Laffon M, Fusciardi J: The early and delayed analgesic effects of ketamine after total hip arthroplasty: A prospective, randomized, controlled, double-blind study. Anesth Analg 2009; 109:1963–71

68. Sen H, Sizlan A, Yanarates O, Emirkadi H, Ozkan S, Dagli G, Turan A: A comparison of gabapentin and ketamine in acute and chronic pain after hysterectomy. Anesth Analg 2009; 109:1645–50

69. Stubhaug A, Breivik H, Eide PK, Kreunen M, Foss A: Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scand 1997; 41:1124–32

70. Burke SM, Shorten GD: Perioperative pregabalin improves pain and functional outcomes 3 months after lumbar discectomy. Anesth Analg 2010; 110:1180–5

71. Mathiesen O, Rasmussen ML, Dierking G, Lech K, Hilsted KL, Fomsgaard JS, Lose G, Dahl JB: Pregabalin and dexamethasone

in combination with paracetamol for postoperative pain control after abdominal hysterectomy. A randomized clinical trial. Acta Anaesthesiol Scand 2009; 53:227–35

72. Sen H, Sizlan A, Yanarateş O, Senol MG, Inangil G, Sücüllü I, Ozkan S, Dağli G: The effects of gabapentin on acute and chronic pain after inguinal herniorrhaphy. Eur J Anaesthesiol 2009; 26:772–6

73. De Kock M, Lavand'homme P, Waterloos H: 'Balanced analgesia' in the perioperative period: Is there a place for ketamine? Pain 2001; 92:373–80

74. De Kock M, Lavand'homme P, Waterloos H: The short-lasting analgesia and long-term antihyperalgesic effect of intrathecal clonidine in patients undergoing colonic surgery. Anesth Analg 2005; 101:566–72

75. Lavand'homme P, De Kock M, Waterloos H: Intraoperative epidural analgesia combined with ketamine provides effective preventive analgesia in patients undergoing major digestive surgery. ANESTHESIOLOGY 2005; 103:813–20

76. Eisenach JC: Preventing chronic pain after surgery: Who, how, and when? Reg Anesth Pain Med 2006; 31:1–3

77. Song JW, Lee YW, Yoon KB, Park SJ, Shim YH: Magnesium sulfate prevents remifentanil-induced postoperative hyperalgesia in patients undergoing thyroidectomy. Anesth Analg 2011; 113:390–7

78. van Gulik L, Ahlers SJ, van de Garde EM, Bruins P, van Boven WJ, Tibboel D, van Dongen EP, Knibbe CA: Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth 2012; 109:616–22