

# A New Model of Electrically Evoked Pain and Hyperalgesia in Human Skin

## The Effects of Intravenous Alfentanil, S(+)-ketamine, and Lidocaine

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**Background:** The authors used the analgesics alfentanil, S(+)-ketamine, and systemic lidocaine to examine a new human model of experimental pain and hyperalgesia.

**Methods:** Transcutaneous electrical stimulation at a high current density (5 Hz,  $67.5 \pm 6.6$  mA) was used to provoke acute pain (numeric rating scale, 5 of 10), stable areas of secondary mechanical hyperalgesia to pin prick ( $43.6 \pm 32.1$  cm<sup>2</sup>), and light touch ( $27.5 \pm 16.2$  cm<sup>2</sup>) for 2 h. Alfentanil, S(+)-ketamine, and lidocaine were applied for 20 min in a double-blind, placebo-controlled, crossover design in 12 subjects using target controlled infusions.

**Results:** In the placebo session, pain ratings and areas of hyperalgesia were stable during the stimulation period, which facilitated the assessment of analgesic effects. Alfentanil effectively inhibited electrically evoked pain and reduced pin prick hyperalgesia and allodynia during its infusion. S(+)-ketamine-induced inhibition of secondary hyperalgesia was more pronounced and lasted for the whole experimental protocol. Therapeutic levels of systemic lidocaine showed only marginal analgesic effects, but lasting antihyperalgesic effects.

**Conclusions:** A new model of electrically induced pain and hyperalgesia was established, which enabled assessment of the time course of analgesic and antihyperalgesic effects with high temporal resolution and minimum tissue damage and which was further validated by use of common intravenous anesthetics.

FOR the evaluation of analgesics in humans, experimental models of pain and hyperalgesia have been used, such as capsaicin injection,<sup>1,2</sup> application of mustard oil,<sup>3</sup> or burn injury.<sup>4,5</sup> In addition to acute pain and hyperalgesia to heating at the site of injury, these models also produce mechanical hyperalgesia to pin prick (punctate hyperalgesia) and light touch (allodynia) in the noninjured surrounding sites (secondary hyperalgesia).<sup>6</sup> Similar patterns of secondary hyperalgesia are observed in neuropathic pain but also constitute part of the clinical features of postoperative pain, suggesting common underlying mechanisms for its induction and maintenance.

Recently, Petersen and Rowbotham<sup>7</sup> developed a model in which capsaicin-induced sensitization to heat was used to rekindle pain and hyperalgesia at regular

intervals and thereby produce stable areas of secondary hyperalgesia. Thus, analgesic and antihyperalgesic effects of anesthetics can be tested more easily and without overt tissue damage.<sup>8,9</sup> This approach allows a direct comparison of heat pain and hyperalgesic areas before and after application of the drug and thereby reduce the variability inhering these psychophysical measures.<sup>10</sup>

A new class of primary afferent nociceptive neurons, the mechanically insensitive “sleeping” nociceptors, has been suggested to play a pivotal role for the induction of capsaicin-induced pain and hyperalgesia in human skin.<sup>11</sup> The mechano-insensitive class of C-nociceptors is characterized by an unusually high transcutaneous electrical activation threshold.<sup>12</sup> Consequently, application of strong transcutaneous electrical stimuli (50 mA, 0.5 ms) induced large areas of secondary mechanical hyperalgesia (allodynia and punctate hyperalgesia) and axon reflex flare in addition to the expected pain sensation.<sup>13</sup>

In the current study, we induced pain, secondary mechanical hyperalgesia, and axon reflex flare by transcutaneous electrical stimulation at a frequency of 5 Hz and investigated their stability on ongoing electrical stimulation for 2 h. Intravenous application of the opioid alfentanil, the N-methyl-D-aspartate (NMDA) receptor antagonist S(+)-ketamine, and the sodium-channel blocker lidocaine were used to further validate the new model.

## Materials and Methods

Twelve healthy, right-handed subjects participated in this randomized, crossover, double-blind, placebo-controlled study. Their average age ( $\pm$  SD) was  $31 \pm 8$  yr (range, 20–52 yr). All subjects were familiar with the described stimulation procedures. None had previously suffered from a hypersensitivity to drugs or was taking medication that may have interfered with itch or pain sensations and flare response (*i.e.*, analgesics, antihistamines, calcium or sodium channel blockers). Each subject gave informed consent to take part in the study; the experiments were performed in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of the Medical Faculty of the University of Erlangen-Nuremberg.

### Experimental Protocol

**Medication and Study Design.** On four separate treatment trials, at least 1 week apart, subjects received

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**Table 1. Pharmacokinetic Model Parameters**

	Alfentanil <sup>22</sup>	S(+)-ketamine <sup>23</sup>	Lidocaine <sup>24</sup>
Compartments	3	3	2
$k_{12}$ (l/min)	0.104	0.107	0.041
$k_{21}$ (l/min)	0.067	0.057	0.029
$k_{13}$ (l/min)	0.017	0.047	
$k_{31}$ (l/min)	0.013	0.008	
$V_c$ (ml/kg)	110	343	480
Cl (ml · min <sup>-1</sup> · kg <sup>-1</sup> )	5.1	27.1	9.9

$k_{ij}$  = rate constant for drug transfer from compartment *i* to compartment *j*;  $V_c$  = central volume of distribution; Cl = total clearance.

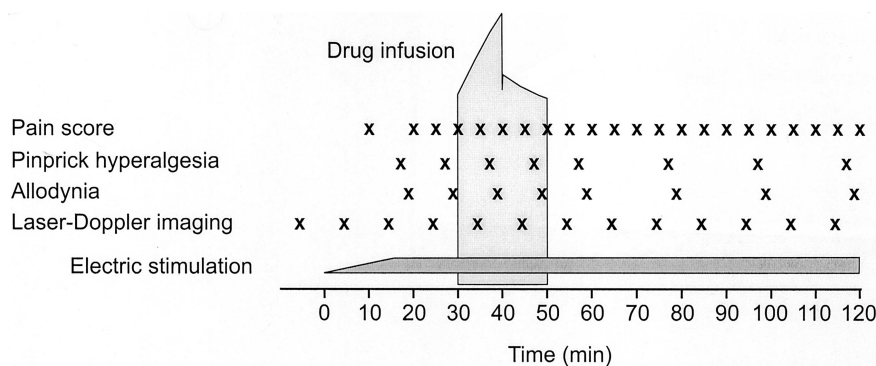
alfentanil (Rapifen®; Janssen, Neuss, Germany), S(+)-ketamine (S-Ketanest®; Parke-Davis, Freiburg, Germany), lidocaine (Xylocain®; Astra, Wedel, Germany), or placebo (0.9% NaCl) intravenously. The drugs were delivered as target-controlled infusions by using a microprocessor controlled system (Braun Perfusor fm, Braun, Melsungen, Germany; IVA Feed for Windows, version 4.5, Erlangen, Germany). Linearly increasing plasma concentrations with anticipated slopes (10 ng · ml<sup>-1</sup> · min<sup>-1</sup> alfentanil, 30 ng · ml<sup>-1</sup> · min<sup>-1</sup> S(+)-ketamine, 350 ng · ml<sup>-1</sup> · min<sup>-1</sup> lidocaine) were generated for 10 min and were followed by plateau phases for another 10 min. Pharmacokinetic model parameters used in this study are shown in table 1. During the infusion, an examiner asked the subjects about side effects such as pruritus, perioral numbness, hypoacusis or hyperacusis, dizziness, nausea, sedation, or dissociative effects. Pulse oximetry (oxygen saturation), electrocardiogram, and noninvasive arterial pressure were monitored continuously during the time of the study.

**Electrical Stimulation.** A stainless-steel needle (Nicolet-EME, Kleinostheim, Germany) was inserted intracutaneously at a length of 1 cm in the central volar forearm of the subjects 30 min before drug infusion. A surface electrode (1.2 × 0.5 cm) attached on the skin directly above the needle served as anode. After a baseline period of 5 min, electric stimuli were applied *via* a constant current stimulator (Viking IV, Nicolet-EME, Kleinostheim, Germany) at 5 Hz (0.5 ms). The current was gradually increased during the first 15 min of the stimulation, targeting a pain rating 5

(of 10) and then kept constant for the remaining 100 min of the experiment (fig. 1).

**Sensory Testing.** During the time of the experiment, a second examiner asked the subjects to rate pain sensations induced by the electric stimuli on a numeric rating scales every 5 min. The end points of the scale were defined as “no pain” (numeric rating scale = 0) and “maximum pain” (numeric rating scale = 10). In addition, the areas of secondary hyperalgesia were measured. The area of pin-prick hyperalgesia was determined with a 450 mN von Frey filament (Stoelting, Chicago, IL), and the area of touch-evoked allodynia was determined with a cotton-wool tip gently stroked on the skin. The borders of the hyperalgesic areas were delineated by stimulating along four linear paths parallel and vertical to the axis of the forearm from distant starting points toward the injection site, until the volunteer reported increased pain sensations evoked by the von Frey filament (pin-prick hyperalgesia) or unpleasant sensations by stroking the skin with the cotton-wool tip (allodynia). These sites were marked on the skin and traced on an acetate sheet at the end of the experiment. For further analysis, both diameters were used to estimate the areas of secondary hyperalgesia ( $D/2 \times d/2 \times \pi$ ). Pin-prick hyperalgesia and allodynia were determined two times before drug infusion, two times during infusion, and four times after the infusion (fig. 1).

**Flare Analysis.** Superficial blood flow of the stimulated arm was measured repetitively by laser Doppler imager (LDI, Moor Instruments Ltd., Devon, United Kingdom). For this purpose, an area of 16 × 8 cm around the injection sites was scanned with a resolution of 22,400 pixels, with each pixel representing a separate Doppler flux measurement. They were stored on hard disk and processed offline with dedicated software (MoorLDI Version 3.0, Moor Instruments Ltd.). The flare area was calculated from all pixels around the stimulation site in which flux values exceeded the 99% percentile of the baseline distribution. Laser Doppler images were recorded before insertion of the needle (baseline image), before stimulation, and 11 times during stimulation (fig. 1).



**Fig. 1.** Schematic illustration of the experimental protocol. Twenty-five minutes after start of electrical stimulation, drugs were infused for 20 min (10-min linear increase followed by a 10-min steady state period). Sensory effects (pain, pin-prick hyperalgesia, and allodynia) and vascular reactions (*via* laser Doppler imager) were determined.

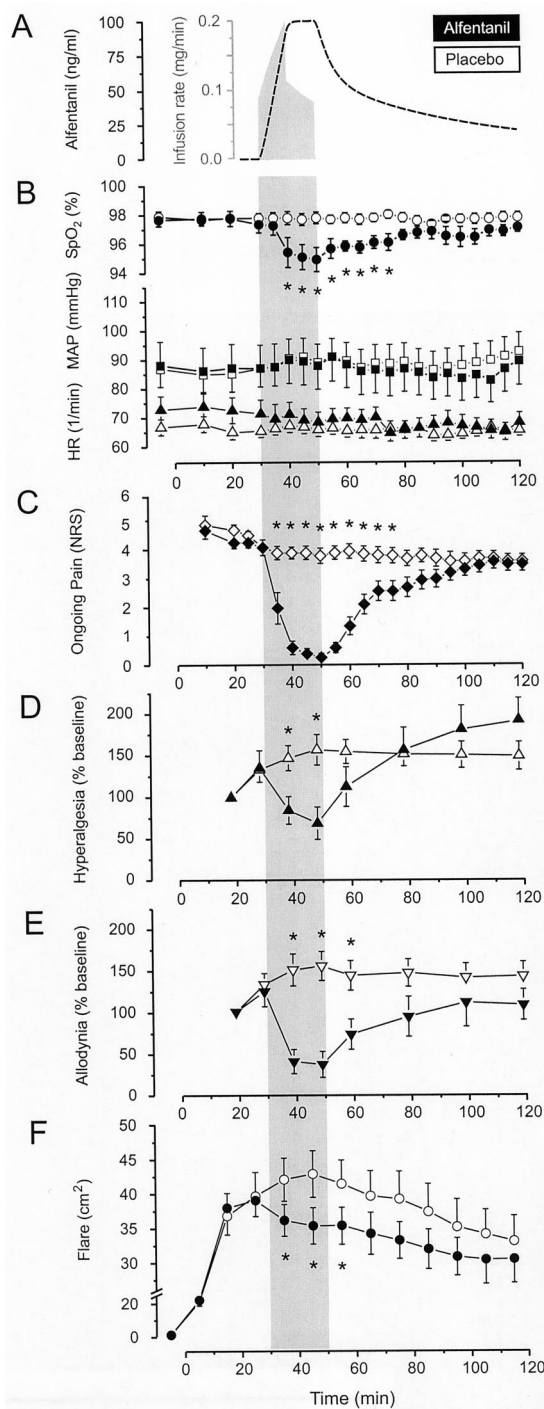


Fig. 2. Time course of calculated alfentanil plasma concentrations (broken line) caused by infusion rates shown as area under the curve (male subject; age, 30 yr; weight, 75 kg) (A). Infusion of alfentanil resulted in a significant decrease in oxygen saturation ( $\text{SpO}_2$ ;  $P < 0.01$ , analysis of variance), whereas mean arterial pressure (MAP) and heart rate (HR) remained unchanged (nonsignificant, analysis of variance) (B). Pain ratings (C) as well as areas of pin-prick hyperalgesia (D) and touch-evoked allodynia (E) were significantly reduced by alfentanil ( $P < 0.01$ , analysis of variance). The flare reaction, determined via laser Doppler imaging, was slightly diminished by the medication ( $P < 0.05$ , analysis of variance) (F). Data are expressed as mean  $\pm$  SEM ( $n = 12$ ); \* $P < 0.05$ , planned comparisons corrected with the Bonferroni procedure. NRS = numeric rating scale.

### Statistical Analysis

Before entering statistical analyses, data regarding areas of secondary hyperalgesia were normalized to achieve the same point of reference in subjects from all of the 4 days. All results were expressed as mean  $\pm$  SD, except for figures, in which data are presented as mean  $\pm$  SEM. Data were statistically evaluated using analysis of variance (ANOVA) in a two-way within-subjects (repeated-measures) model. Scheffé tests and planned comparisons, corrected with the Bonferroni procedure, were performed as *post hoc* tests. Significance levels throughout the study were  $P < 0.05$ . The Statistica software package (Statsoft, Tulsa, OK) was used for statistical analysis.

## Results

### Electrical Stimulation

To achieve a pain rating of 5 (numeric rating scale from 0 to 10), the current was increased to  $67.5 \pm 6.6$  mA (range, 55–80 mA) during the first 15 min of electrical stimulation and kept constant for the remaining protocol. Sensory testings as well as laser Doppler images were performed twice in the following 10 min before drug infusion. In this period, pain ratings decreased significantly from 5.0 to  $4.2 \pm 0.4$  ( $P < 0.01$  by ANOVA and planned comparison), pin-prick hyperalgesia increased from  $36.5 \pm 26.2$  to  $43.6 \pm 32.1$   $\text{cm}^2$  ( $P < 0.05$  by ANOVA and planned comparison), and allodynia increased from  $25.4 \pm 15.9$  to  $27.5 \pm 16.2$   $\text{cm}^2$  (nonsignificant, by ANOVA and planned comparison). The flare area increased slightly from  $36.8 \pm 9.4$  to  $39.7 \pm 12.9$   $\text{cm}^2$  (nonsignificant, by ANOVA and planned comparison).

### Intraindividual and Interindividual Variability of the Model

Transcutaneous electrical stimulation of 15 min induced an area of pin-prick hyperalgesia in all the subjects with a mean area of  $43.6 \pm 32.1$   $\text{cm}^2$  (range, 28–525  $\text{cm}^2$ ). The area did not differ significantly between subjects ( $P = 0.14$ , ANOVA). The mean intraindividual variation expressed as mean coefficient of variation was 62%. Similarly, the electrical stimulation evoked an area of allodynia in all the subjects that measured  $27.5 \pm 16.2$   $\text{cm}^2$  (range, 20–301  $\text{cm}^2$ ). The area of allodynia varied between subjects; however, the difference just failed to be significant ( $P = 0.06$ , ANOVA). The mean intraindividual variation expressed as mean coefficient of variation was 42%. In the placebo session, the areas of pin-prick hyperalgesia and allodynia did not change significantly during the ensuing stimulation period of 100 min (nonsignificant, ANOVA for repeated measures; figs. 2D and E).

Table 2. Demographic Data and Medication

Number	Sex	Age (yr)	Weight (kg)	Alfentanil (mg)	S(+)-ketamine (mg)	Lidocaine (mg)
1	F	29	58	2.0	24	180
2	F	31	65	2.2	26	205
3	F	27	64	2.2	27	197
4	M	25	76	2.5	30	239
5	M	28	92	3.0	36	295
6	M	29	82	2.6	34	254
7	F	20	63	2.1	25	210
8	M	24	75	2.5	28	240
9	M	36	92	3.0	35	286
10	M	36	64	2.2	26	200
11	M	30	80	2.8	32	252
12	M	52	95	3.2	37	298
Mean $\pm$ SD		30.6 $\pm$ 8.1	75.5 $\pm$ 12.9	2.5 $\pm$ 0.4	30.0 $\pm$ 4.6	237.8 $\pm$ 40.2

The table presents sex, age, and weight of subjects and total amount of drugs administered.

The flare area after 15 min of transcutaneous stimulation measured  $39.7 \pm 12.9 \text{ cm}^2$  (range, 25–56  $\text{cm}^2$ ). There was an obvious interindividual variation with a significant difference between the subjects ( $P < 0.01$ , ANOVA). The mean intraindividual variation expressed as mean coefficient of variation was 14%. During the last 100 min of electrical stimulation, flare area decreased significantly from  $42.1 \pm 3.8$  to  $35.5 \pm 4.9 \text{ cm}^2$  ( $P < 0.01$ , ANOVA for repeated measures; fig. 2F).

#### Medication and Side Effects

The target controlled infusion led to weight- and age- (clearance) adjusted doses (table 2). Subjects received  $0.034 \pm 0.001 \text{ mg/kg}$  alfentanil,  $0.399 \pm 0.014 \text{ mg/kg}$  S(+)-ketamine, or  $3.7 \pm 0.06 \text{ mg/kg}$  lidocaine during 20 min. Infusion rates and estimated plasma concentrations, based on the pharmacokinetic model parameters, are exemplified for a male, 30-yr-old subject (figs. 2–4A).

Almost all subjects developed subjective side effects during the drug infusions (table 3). The side effects generally appeared during the plateau phase of the infusion. Especially after alfentanil and S(+)-ketamine infusion, subjects showed moderate sedation (8 and 11 of 12 subjects, respectively). Sedation produced by S(+)-ketamine was accompanied by dissociative effects in 8 of 11 subjects (table 3). In contrast, infusion of lidocaine produced only weak sedation in 4 of 12 subjects but regularly elicited sensory and acoustical changes (table 3). However, all subjects answered promptly to the questions of the investigators; the pain ratings and estimations of hyperalgesic areas were accurate and reproducible. At no time did subjects complain of bothersome side effects or anxiety.

Infusion of alfentanil resulted in a significant decrease in oxygen saturation (fig. 2B), and infusion of S(+)-ketamine caused a longer-lasting increase in oxygen saturation as well as heart rate and blood pressure (fig. 3B). Intravenous lidocaine produced a moderate increase only in heart rate (fig. 4B).

#### Pain Rating

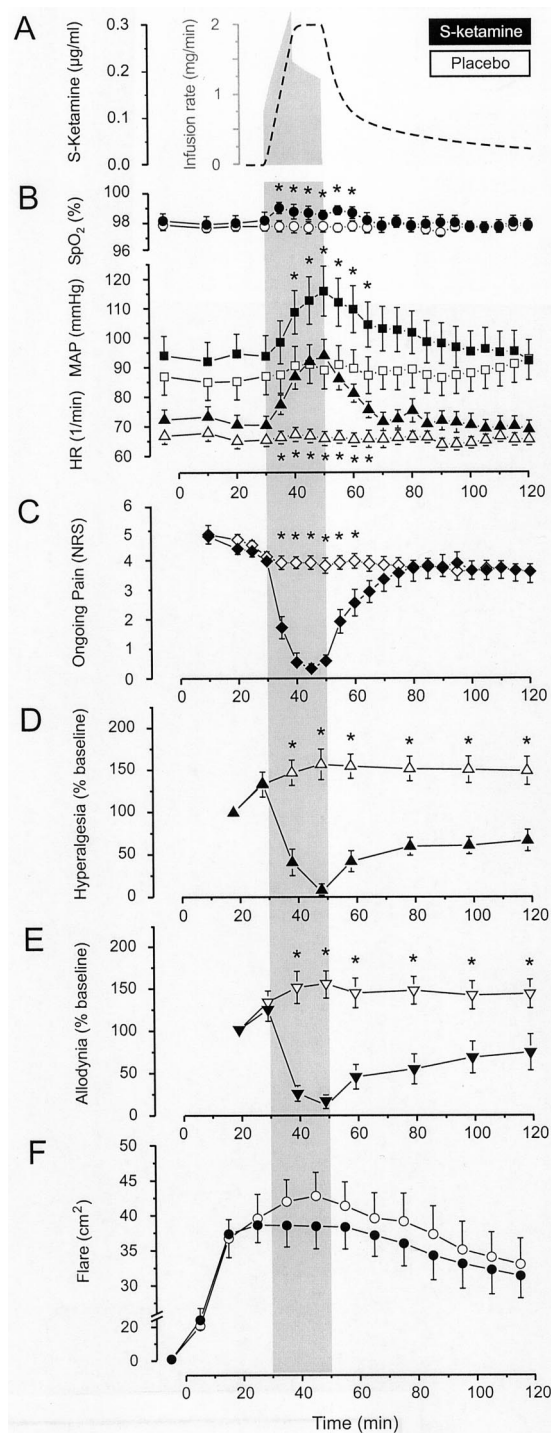
Pain ratings were significantly reduced by alfentanil, S(+)-ketamine, and lidocaine infusion compared with placebo treatment (figs. 2, 3, and 4C). During infusion, alfentanil and S(+)-ketamine nearly abolished pain sensations. After termination of the infusion, analgesia produced by alfentanil lasted for another 30 min, whereas S(+)-ketamine had shorter-lasting analgesic effects. The analgesic effect of lidocaine was restricted to the time of infusion and was significantly weaker as compared with alfentanil or S(+)-ketamine infusion ( $P < 0.01$ , by ANOVA and planned comparisons, respectively).

#### Pin-prick Hyperalgesia

All subjects developed hyperalgesia to pin prick and light touch. Infusion of all three anesthetics significantly reduced the areas of pin-prick hyperalgesia as compared with placebo ( $P < 0.01$ , ANOVA and Scheffé *post hoc* tests for each anesthetic). Moreover, the antihyperalgesic effect of S(+)-ketamine was more pronounced as compared with alfentanil and lidocaine ( $P < 0.01$  and  $P < 0.05$ , Scheffé *post hoc* test). S(+)-ketamine caused significantly reduced areas of pin-prick hyperalgesia during the whole observation period, with a minimum at the plateau phase shortly before termination of the infusion ( $6.2 \pm 13.9\%$  of placebo treatment; fig. 3D). Lidocaine reduced areas of pinprick hyperalgesia to a lesser extent (minimum,  $42.1 \pm 57.7\%$  of placebo treatment; fig. 4D). Alfentanil showed significant antihyperalgesic effects to pin prick only during the infusion (minimum,  $55.1 \pm 56.9\%$  of placebo treatment; fig. 4B). Moreover, the opioid tended to expand the area of pin-prick hyperalgesia in the end of the experiment ( $P < 0.10$ , planned comparison).

#### Allodynia

Alfentanil, S(+)-ketamine, and lidocaine significantly reduced allodynic areas ( $P < 0.001$ , by ANOVA, respectively; figs. 2, 3, and 4E). Maximal antiallodynic effects



**Fig. 3.** Time course of calculated *S(+)*-ketamine plasma concentrations (broken line) caused by infusion rates shown as area under the curve (male subject; age, 30 yr; weight, 75 kg) (A). Infusion of *S(+)*-ketamine resulted in a significant increase in oxygen saturation (SpO<sub>2</sub>), mean arterial pressure (MAP), and heart rate (HR) ( $P < 0.05$ , analysis of variance) (B). Pain ratings (C) as well as areas of pin-prick hyperalgesia (D) and touch-evoked allodynia (E) were significantly reduced by *S(+)*-ketamine ( $P < 0.001$ , analysis of variance). The flare reaction, determined via laser Doppler imaging, was not affected by the medication (nonsignificant, analysis of variance) (F). Data are expressed as mean  $\pm$  SEM ( $n = 12$ ); \* $P < 0.05$ , planned comparisons corrected with the Bonferroni procedure. NRS = numeric rating scale.

were observed shortly before termination of the infusion; no significant differences were observed between the treatments (alfentanil,  $36.6 \pm 59.8\%$ ; *S(+)*-ketamine,  $5.5 \pm 10.3\%$ ; lidocaine,  $22.3 \pm 22.4\%$  of placebo treatment; nonsignificant, Scheffé test).

#### Flare Analysis

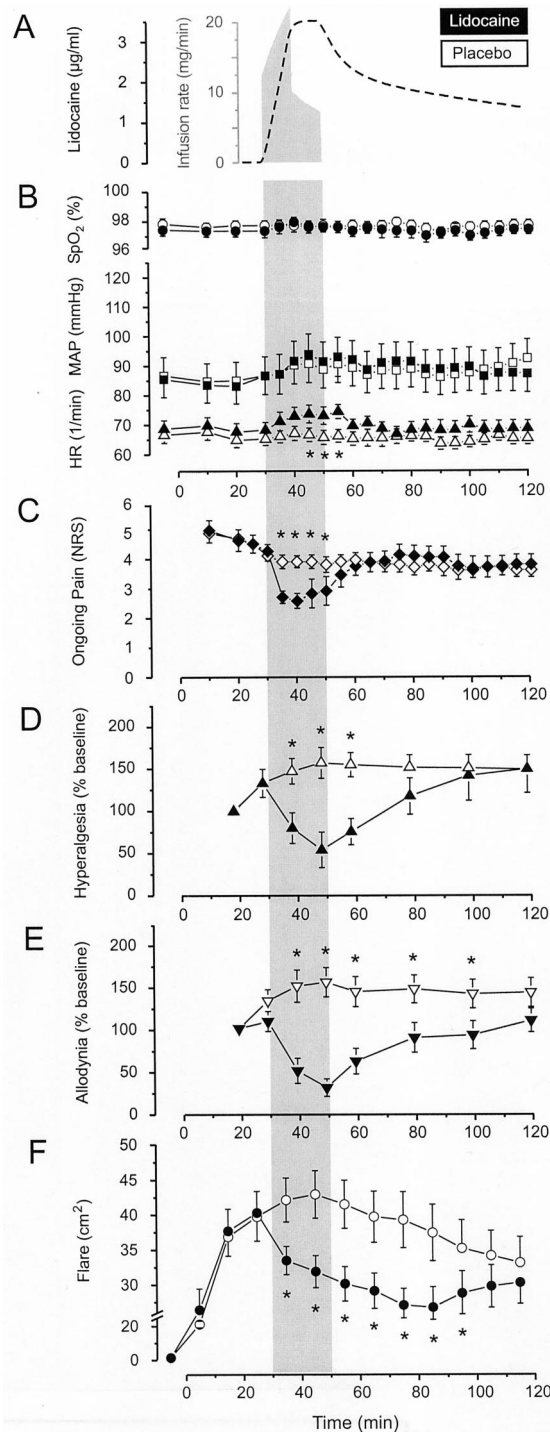
The flare area assessed with the laser Doppler imager was significantly reduced during alfentanil infusion ( $P < 0.05$ , by ANOVA and planned comparisons; fig. 2F). However, 20 min after termination of the infusion, significant effects on superficial blood flow were no longer observed (nonsignificant, by ANOVA and planned comparisons). *S(+)*-ketamine did not affect the extent of the flare area (nonsignificant, by ANOVA and planned comparisons). In contrast, lidocaine produced a significant reduction in flare size lasting nearly for the whole observation period ( $P < 0.01$ , by ANOVA and planned comparisons).

#### Discussion

In our study, a new model of electrically induced pain and hyperalgesia was evaluated and further validated by the analgesic and antihyperalgesic effects of alfentanil, *S(+)*-ketamine, and systemic lidocaine.

#### Experimental Models of Pain and Hyperalgesia

Application of capsaicin has been often used to elicit acute pain and hyperalgesia.<sup>1,2</sup> However, a single application of capsaicin produces only relatively short-lasting pain and brush-evoked allodynia. Repetitive application of capsaicin, on the other hand, is characterized by tachyphylaxis of vanilloid receptor 1 on a molecular level<sup>14</sup> and psychophysically leads to desensitization<sup>15</sup> and degeneration of capsaicin-sensitive afferent nerve fibers.<sup>16</sup> If applied epicutaneously for short periods at intervals of approximately 15–30 min, repetitive epicutaneous application of capsaicin initially provokes increasing sensory effects that convert to desensitization after approximately three to four repetitions.<sup>17,18</sup> Instead of repeating application of capsaicin, Petersen and Rowbotham<sup>7</sup> repetitively applied heating stimuli to capsaicin-treated skin. Capsaicin induces a primary hyperalgesia to heat that is long-lasting and allows rekindling of the capsaicin pain and secondary mechanical hyperalgesia using a nonnoxious temperature of 40°C.<sup>7</sup> In our study, strong electrical transcutaneous stimuli were used to directly activate a subpopulation of mechano-insensitive C-nociceptors (silent nociceptors) that is characterized by an unusual high electrical threshold ( $> 30$  mA).<sup>12</sup> This class of nociceptors is critically involved in the induction of axon-reflex flare<sup>19</sup> and secondary mechanical hyperalgesia.<sup>11</sup> In our study, continuous transcutaneous electrical stimulation at 5 Hz provoked stable areas of secondary



**Fig. 4.** Time course of calculated lidocaine plasma concentrations (broken line) caused by infusion rates shown as area under the curve (male subject; age, 30 yr; weight, 75 kg) (A). Infusion of lidocaine resulted in a short-lasting, significant increase in heart rate (HR) ( $P < 0.05$ , analysis of variance); oxygen saturation ( $SpO_2$ ) and mean arterial pressure (MAP) remained constant (nonsignificant, analysis of variance) (B). Pain ratings (C) as well as areas of pin-prick hyperalgesia (D) and touch-evoked allodynia (E) were significantly reduced by lidocaine ( $P < 0.01$ , analysis of variance). The flare reaction, determined *via* laser Doppler imaging, was diminished by the drug ( $P < 0.01$ , analysis of variance) (F). Data are expressed as mean  $\pm$  SEM ( $n = 12$ ); \* $P < 0.05$ , planned comparisons corrected with the Bonferroni procedure. NRS = numeric rating scale.

**Table 3. Side Effects of Drug Infusions**

	Alfentanil	S(+)-Ketamine	Lidocaine	Placebo
Pruritus	3			
Perioral numbness	1	4	8	
Hypacusis/Hyperacusis		10	7	
Dizziness	4	3	4	1
Nausea	3		1	
Sedation	8	11	4	2
Unconsciousness				
Dissociative effects		8		

Values are number of subjects who reported side effects ( $n = 12$ ).

mechanical hyperalgesia for the 2-h observation period, whereas pain ratings and flare size gradually declined. In our model, ongoing electrical stimulation is required to maintain pain and secondary hyperalgesia. When the stimulation is discontinued, allodynia subsides after few minutes and punctuate hyperalgesia also gradually declines.<sup>13</sup>

Similar to the capsaicin-heat sensitization model, stable areas of hyperalgesia are a prerequisite for the test of anesthetics. Using ongoing electrical stimulation also, the area of allodynia is maintained at a constant level without the need of rekindling. Thus, temporal resolution of pain and hyperalgesia tests in the electrical model is higher. Activation of the nociceptors by electrical stimulation will surpass the nerve terminals, and this constitutes another important difference between the two models: direct activation of the axon yields a well-controlled firing frequency of the nociceptors independent of possible sensitization or desensitization of its endings. However, this method will not detect effects of an anesthetic that impair the response of the peripheral nerve terminals.

The assessment of the axon-reflex flare is a valuable tool to test inhibition of neuropeptide release in the periphery. Although this inhibition does not predict analgesic potency, it is an elegant tool to validate effective drug concentrations in the periphery, as seen for alfentanil and lidocaine in the current study. Moreover, release of substance P and calcitonin gene-related peptide have been implicated in the generation of sensitization of dorsal horn neurons. Thus, if the same inhibition of neuropeptide release is present in the dorsal horn, it might add to central antihyperalgesic effects.

### Medication Effects

We used microprocessor controlled infusions with linearly increasing plasma levels to achieve and maintain stable plasma concentrations. This method was used successfully for pharmacokinetic and pharmacodynamic modeling investigations.<sup>20,21</sup> In our study, the population pharmacokinetic variables of a three-compartment model was used for alfentanil and S(+)-ketamine, and a two-compartment model was assumed for intravenous lidocaine (table 1).<sup>22-24</sup> Although alfentanil compartmental models have been studied extensively,<sup>22,25-29</sup>

less pharmacokinetic data sets were published for *S*(+)-ketamine and lidocaine in adults.<sup>24,30-33</sup>

The study had a crossover, double-blind, placebo-controlled design. However, the blinding was incomplete because nearly all subjects experienced dissociative effects of *S*(+)-ketamine. As *S*(+)-ketamine elicited differential effects on pain and hyperalgesia, the incomplete blinding did not seem to bias the results systematically. The same was true for sedative side effects, which were elicited frequently during alfentanil, *S*(+)-ketamine, and, in some cases, also during lidocaine infusion. Again, differential effects of the analgesics on acute pain and hyperalgesia cannot be explained by simple sedation. In addition, prompt answers and accurate, reproducible estimations of pain and hyperalgesic areas given by the subjects corroborate this view. This was confirmed by a study by Park *et al.*,<sup>34</sup> in which an active control (midazolam) did not affect areas of secondary hyperalgesia after intradermal capsaicin injection.

#### *Alfentanil*

Pain ratings as well as areas of pin-prick hyperalgesia and allodynia were reduced during infusion of alfentanil. After termination of infusion, all subjects reported the reappearance of pain and secondary hyperalgesia. Moreover, although not significant, the areas of pin-prick hyperalgesia exceeded the control values.

It has been suggested that analgesic and antihyperalgesic effects are mediated by central nervous mechanisms of alfentanil, although reduction of flare areas observed during infusion reflects a peripheral action of the opioid. However, the reduction of flare areas is most likely caused by a peripheral inhibition of electrically evoked neuropeptide release.<sup>35,36</sup> Peripheral analgesic effects of opioids have been observed mainly in sensitized peripheral nerve endings, and these endings will be surpassed by our mode of electrical stimulation.

Our results are in line with observation on antihyperalgesic effects of opioids in the capsaicin model. Park *et al.*<sup>34</sup> found a reduction of capsaicin-induced pain and secondary hyperalgesia by alfentanil, suggesting that opioid-sensitive mechanisms are involved in the sensitization of central neurons. Eisenach *et al.*<sup>37</sup> determined a reduction of acute pain as well as pin-prick hyperalgesia and allodynia with increasing plasma concentration of alfentanil; the reduction in pin-prick hyperalgesia and allodynia correlated well with the reduction in acute pain.

#### *S*(+)-ketamine

As observed for alfentanil, intravenous *S*(+)-ketamine led to a significant decrease in pain ratings as well as pin-prick hyperalgesia and allodynia. However, analgesia after *S*(+)-ketamine was rather short-lasting, whereas antihyperalgesic effects to pin prick and touch lasted for the whole observation period.

Antihyperalgesic effects of ketamine to pinprick and touch were determined in different studies using intradermal injection of capsaicin and the first-degree burn injury.<sup>5,34,37,38</sup> In all of these studies, ketamine reduced secondary hyperalgesia even when administered after induction of central sensitization. These observations were confirmed in our study. Furthermore, our results are consistent with findings from Sethna *et al.*,<sup>39</sup> who showed similar effects of alfentanil and ketamine on capsaicin-evoked pain and secondary hyperalgesia during and just after drug infusion.

No peripheral effects of *S*(+)-ketamine were determined at concentrations used in this study. There are some reports about peripheral analgesic properties of NMDA receptor antagonists. Zhou *et al.*<sup>40</sup> and Carlton *et al.*<sup>41</sup> found an attenuation of mechanical hyperalgesia by local injection of glutamate antagonists, and Warncke *et al.*<sup>42</sup> determined an increase in heat pain thresholds after local administration of ketamine. They postulated interactions with peripheral NMDA receptors, although local anesthetic properties by blocking Na<sup>+</sup> and K<sup>+</sup> currents in peripheral nerves could not be completely excluded.<sup>36,40,42</sup> The concentrations necessary, however, were much larger than those reached during systemic administration and could only be achieved by local application.

#### *Lidocaine*

Systemic lidocaine produced only moderate and short-lasting reduction in electrically induced pain. Antihyperalgesic effects, however, extended the time of lidocaine infusion.

The decrease in electrically induced axon-reflex flare with systemic lidocaine is most probably a result of a decreased neuropeptide release in the skin,<sup>43</sup> although a direct vasoconstrictive effect of lidocaine cannot be excluded.<sup>44</sup> However, unchanged blood pressure in combination with increased heart rate speak against a relevant vasoconstriction. Our results are in line with antihyperalgesic effect of perioperative systemic lidocaine observed in the postoperative period.<sup>45-47</sup> Lidocaine treatment after surgery failed to produce analgesic effects,<sup>48</sup> suggesting that the perioperative period is of particular importance for the sensitization process.

In conclusion, electrically evoked pain and secondary hyperalgesia provides a stable experimental model that is suitable to test analgesic and antihyperalgesic effects of anesthetics with a high temporal resolution and minimum tissue damage. Ongoing electrical stimulation might mimic ongoing activity of chemonociceptors in postoperative pain states and in part of neuropathic pain conditions. Thus, the new experimental approach appears to more closely resemble pathophysiologic conditions than do single applications of capsaicin.

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