Analgesic and Antihyperalgesic Properties of Propofol in a Human Pain Model

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ABSTRACT

Background: Propofol (Disoprivan®, AstraZeneca AG, Zug, Switzerland) has long been considered to be nonanalgesic. However, accumulating evidence shows that propofol possesses modulatory action on pain processing and perception. In this study, the authors investigated the modulatory effects of propofol and a formulation similar to the solvent of propofol (10% Intralipid®; Fresenius Kabi, Stans, Switzerland) on pain perception and central sensitization in healthy volunteers.

Methods: Fourteen healthy volunteers were included in this randomized, double-blind, placebo-controlled, crossover study. Intracutaneous electrical stimulation (48.8 ± 25.8 mA) induced spontaneous acute pain (Numeric Rating Scale, 6 of 10) and stable areas of hyperalgesia and allodynia. Pain intensities and areas of hyperalgesia were assessed regularly before, during, and after a 45-min target-controlled infusion (2 µg/ml) of propofol, the solvent 10% Intralipid®, and saline.

Results: During administration, propofol significantly decreased pain scores and areas of hyperalgesia and allodynia compared with both 10% Intralipid® and saline (placebo-corrected mean Numerical Rating Scale score reduction by propofol: 38 ± 28%). This difference disappeared shortly after cessation of the infusion. Thereafter, no significant group differences were observed in the Numerical Rating Scale score and the areas of hyperalgesia or allodynia. However, there was a trend to reduced hyperalgesia and allodynia after propofol treatment. Pharmacodynamic modeling regarding the analgesic effect of propofol showed an EC50 (half-maximum effect site concentration) of 3.19 ± 0.37 µg/ml. Ten percent Intralipid® was free of pain-modulatory effects in the authors’ experiments.

Conclusions: Propofol showed short-lasting analgesic properties during its administration, whereas the solvent-like formulation 10% Intralipid® had no effect on pain perception.

- Whether propofol or its solvent has analgesic or antihyperalgesic effects is unclear, given conflicting reports in experimental and clinical pain.

- In 14 healthy volunteers with pain and areas of hypersensitivity from controlled electrical stimulation, propofol, but not its solvent, reduced pain by 40% and nearly abolished hypersensitivity.

- The EC50 for the analgesic effect of propofol was 3.2 µg/ml.

PROPOFOL (Disoprivan®, AstraZeneca AG, Zug, Switzerland) has long been considered to be nonanalgesic. However, several clinical studies observed reduced postoperative pain and reduced opioid use in patients after propofol anesthesia when compared with isoflurane anesthesia. Anker-Møller et al. noted the analgesic effects of propofol in their 1991 experimental study, and propofol has been shown subsequently to interact with N-methyl-D-aspartic acid receptors. In contrast, other clinical and experimental data have demonstrated pain-enhancing effects associated with propofol use.

In a recent study by Singler et al., propofol attenuated opioid-induced postinfusion antianalgesia, but it led to enlarged areas of secondary hyperalgesia. In a further study, the solvent of propofol (10% Intralipid®; Fresenius Kabi, Stans, Switzerland) in combination with isoflurane anesthesia was associated with slightly higher postoperative pain scores of recovery room patients when compared with anesthesia using isoflurane alone or propofol (unpublished data: Oliver Bandschapp, M.D., Geneva, Switzerland).
land, clinical trial, 2006). Administration of Intralipid® was shown to enhance the level of prostanoids (consisting of the three main groups, the prostaglandins, prostacyclins, and thromboxanes). Prostaglandins are known to sensitize nociception at the level of peripheral nociceptors and centrally at the level of the spinal cord.

We hypothesized that Intralipid® could be involved in the contradictory effects of propofol on pain sensitivity and hyperalgesia. Therefore, we compared the time course of analgesic and the antihyperalgesic effects of propofol, the solvent-like formulation 10% Intralipid®, and saline in a human model of electrically evoked pain and secondary hyperalgesia.

Materials and Methods

Subjects

The study protocol was approved by the local ethics committee (Ethikkommision beider Basel, EKBB, Basel, Basel-Stadt, Switzerland). The study was conducted at the Department of Anesthesia and Intensive Care Medicine at the University Hospital Basel, Switzerland, after receiving written informed consent from each volunteer.

Fourteen healthy male volunteers (20- to 35-yr old) were screened for participation in the study. Thirteen volunteers were whites, and one was of African heritage (no. 13, table 1). All volunteers were familiarized with the stimulation procedure before participating in the study. Exclusion criteria were known drug allergies and medication that might interfere with pain sensation (analgesics, antihistamines, and calcium or sodium channel blockers). The experiments were performed in accordance with the Declaration of Helsinki.

Experimental Pain Model

Intradermal electrical stimulation was used to induce ongoing pain and secondary mechanical hyperalgesia as described previously. Two microdialysis fibers equipped with inter-

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Mean ± SD 24 ± 4 79 ± 10 183 ± 7 24 ± 3 48.8 ± 25.8

Mean electrical current used in the three sessions is shown (mean ± SD). BMI = body mass index.
volunteers were unaware of the current treatment assignment. Pulse oximetry (SpO2), electrocardiography, and non-invasive blood pressure were monitored continuously during the study.

**Sensory Testing**

The examiner asked the volunteer every 5 min to rate the intensity of ongoing pain induced by the electrical stimulation according to the NRS. The area of pinprick hyperalgesia was determined with a 256-mN von Frey filament; the area of allodynia was determined using a dry cotton swab. The borders of the hyperalgesic and allodynic areas were determined by moving along four linear paths parallel and perpendicular to the axis of the forearm, beginning at a distant point and moving radially toward the stimulation site (step size 0.5 cm), until the volunteer reported either the increased pain sensations evoked by the von Frey filament (pinprick hyperalgesia) or an unpleasant sensation evoked by touch with the cotton swab (allodynia). For further analysis, the diameter of both regions was used to estimate the areas of secondary hyperalgesia (according to the calculation of the area of an ellipse: \( A = \frac{1}{4} \pi \times D \times d \)). Areas of pinprick hyperalgesia and allodynic areas were tested repeatedly in 20-min intervals during the 180-min observation period.

**Data and Statistical Analysis**

All results are expressed as mean ± SD, unless stated otherwise. NRS was considered as ordinal data, and hyperalgesic and allodynic areas were considered as continuous data. Treatment effects over time regarding NRS were evaluated using Friedman test. Two-way ANOVA with repeated measures followed by the Bonferroni posttest was used for the evaluation of the allodynic and hyperalgesic areas and the oxygen saturation, mean arterial blood pressure, and heart rate. Significance levels throughout this study were \( P \leq 0.05 \).

All statistical analyses were performed using a Prism software package (GraphPad version 5.01 for Windows; GraphPad Software, La Jolla, CA). Whenever possible, we used two-tailed tests for the significance testing.

The postinfusion baselines of the hyperalgesic and allodynic areas were further analyzed as follows: we calculated the ratio between the recovery value (t = 180 min) and the baseline value (t = 15 min). This ratio was then tested for each group (control, propofol, and Intralipid®) against the null hypothesis of 100% (recovery = baseline) with one sample \( t \) test. Furthermore, we compared the ratios of the three groups (control, propofol, and Intralipid®) with one-way ANOVA for repeated measurements.

**Pharmacodynamic Modeling**

For each volunteer and for each treatment, the relative change of the pain rating compared with the baseline value was calculated for each measurement. Subsequently, the obtained individual percentage values of the propofol treatment were corrected for time-related effects (e.g., tolerance or sensitization) by subtracting the corresponding values of the placebo treatment. A sigmoid model was fitted to these normalized data:

\[
E = E_{\text{max}} \frac{C_E}{C_E + EC_{50}},
\]

where the effect \( E \) is the percentage change of the pain rating, \( E_{\text{max}} \) is the maximum effect, \( C_E \) is the effect site concentration of propofol, \( EC_{50} \) is the half-maximum effect site concentration, and \( \gamma \) is a coefficient describing the steepness of the concentration–effect curve. \( E_{\text{max}} \) was set to 100%, assuming that propofol is able to suppress pain completely. For the effect site concentration, we tested two models: in model 1, the effect site concentration \( C_E \) was equal to the plasma concentration \( C_{Pi} \); in model 2, the effect site concentration

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**Fig. 1.** Schematic illustration of the experimental protocol. Three separate treatment trials were performed. The volunteers received propofol (at a target concentration of 2.0 \( \mu \)g/ml), 10% Intralipid® (Fresenius Kabi, Stans, Switzerland) (corresponding to a target-controlled infusion of propofol with a concentration level of 2.0 \( \mu \)g/ml), or saline as a control. The drugs were delivered during 45 min, starting 30 min after the onset of electrical stimulation. Continuous pain and areas of punctate hyperalgesia and allodynia were determined repeatedly.
was calculated from the plasma concentration by convolution with the effect site disposition function: 
\[ C_{eq}(t) = k_e \cdot P_{TV} \cdot e^{0} \cdot C_{p}(t) \cdot dt, \]
where the transfer rate constant \( k_e \) characterizes the equilibration between plasma and effect site concentration. The plasma concentration of propofol was estimated using the pharmacokinetic model of Marsh et al.\textsuperscript{22}

The pharmacodynamic parameters were estimated by population analysis (NONMEM\textsuperscript{®} version VI, level 2.0; GloboMax LLC, Hanover, MD). The interindividual variability of the parameters between the subjects was assumed to be log-normally distributed: 
\[ P_{i} = P_{TV} \times e^{0} \]
where \( P_{i} \) is the parameter value in the \( i \)th subject, \( P_{TV} \) is the typical value of the parameter in the population, and \( \eta \) is a random variable with a mean of 0 and a variance of \( \sigma^2 \). The residual intrindividual error within the subjects was described by an additive error model: 
\[ E_{ij} = E_{Pij} + \epsilon_{ij}, \]
where \( E_{ij} \) is the \( j \)th measured effect value in the \( i \)th subject, \( E_{Pij} \) is the corresponding effect value as predicted by the model, and \( \epsilon_{ij} \) is a random variable with a mean of 0 and a variance of \( \sigma^2 \). Initially, the first-order estimation method was used to obtain the parameter estimates. After the best model was selected, the parameters of the model were reestimated using the first-order conditional estimation method with \( e-\eta \) interaction. The two investigated different models were compared using the likelihood ratio test of the NONMEM objective function value. The model with effect compartment was accepted as significantly better than that without an effect compartment if the difference in the objective function was \( \geq 6.6 \) (corresponding to \( P < 0.01 \)). Concentration–effect curves were constructed from the typical values of the parameters \( EC_{50} \) and \( \gamma \) in the population and also from the individual Bayesian post hoc estimates of these parameters.

**Results**

**Side Effects**

All 14 volunteers completed the study, and none withdrew. The average age was 24 ± 4 yr (range, 21–35 yr; table 1). All subjects developed subjective sedative side effects during propofol infusion. Thirteen volunteers promptly responded to the questions asked by the investigator during propofol infusion. One of the subjects (no. 13, table 1) was not arousable on questioning during propofol infusion. Therefore, in this subject, the propofol infusion rate was reduced to a target control infusion level of 1.5 \( \mu \)g/ml for the last 15 min of infusion. All subjects denied any sedative effect within 10–15 min after termination of the infusions. Apart from sedation, there were no severe side effects noticed by the investigator or reported by the volunteer. There were no significant differences in heart rate (\( P = 0.42 \)) among the three treatment groups during the experiments. However, mean blood pressure was significantly lower in the propofol group when compared with the solvent and control groups (\( P < 0.0004 \)). In the propofol group, the oxygen saturation decreased slightly during the infusion period compared with the control and Intralipid\textsuperscript{®} groups, but it was not statistically significant (\( P = 0.23 \)).

**Electrical Stimulation**

To provoke a pain rating of NRS 6, the average current was increased to 48.8 ± 25.7 mA (range, 18.6–94.7 mA; table 1) during the first 15 min of electrical stimulation. The current established in the first session to provoke a pain rating of NRS 6 was repeated for the following two sessions individually in each volunteer.

After keeping the current constant, the pain ratings decreased significantly; at 30 min, the NRS was 4.2 ± 1.1 for the control group, 4.1 ± 1.3 for Intralipid\textsuperscript{®}, and 4.4 ± 1.0 for propofol (\( P = 0.001 \) for the control group, \( P < 0.001 \) for Intralipid\textsuperscript{®}, and \( P = 0.002 \) for propofol; fig. 2A). Until this time point, no significant differences in NRS among the treatment groups were observed (\( P = 0.52 \), fig. 2A). At 25 min of electrical stimulation, mean areas of pinprick hyperalgesia were 62.54 (59.00 [36.82, 78.64]) cm\(^2\) in the propofol group, 64.75 (57.14 [36.37, 88.31]) cm\(^2\) in the Intralipid\textsuperscript{®} group, and 64.94 (61.26 [32.84, 94.98]) cm\(^2\) in the control group (median [25%, 75% percentiles]) (fig. 2B). The mean areas of allodynia at this time point were 55.12 (45.36 [29.26, 69.95]) cm\(^2\) in the propofol group, 56.75 (46.14 [30.93, 84.63]) cm\(^2\) in the Intralipid\textsuperscript{®} group, and 50.53 (52.72 [23.12, 69.85]) cm\(^2\) in the control group (median [25%, 75% percentiles]) (fig. 2C).

**Ongoing Pain**

Infusion of propofol at a target control infusion level of 2.0 \( \mu \)g/ml led to significantly decreased pain ratings (\( P = 0.02 \), compared with the control or Intralipid\textsuperscript{®} group; fig. 2A). In the placebo-corrected mean model, NRS score reduction by propofol was 38 ± 28% (fig. 3). However, shortly after cessation of the infusion, the pain ratings increased and were similar to those in the control and Intralipid\textsuperscript{®} groups. There was no difference in the pain ratings between the Intralipid\textsuperscript{®} group and the control group for the duration of the experimental period (\( P > 0.05 \); fig. 2A).

**Pinprick Hyperalgesia and Allodynia**

Propofol significantly reduced the areas of punctate hyperalgesia after 30 min of infusion of propofol to 24.09 (25.13 [8.688, 35.44]) cm\(^2\) compared with the control (\( P < 0.05 \)) or Intralipid\textsuperscript{®} (\( P < 0.05 \)) group (68.74 [64.11 [41.87, 80.11]] and 63.34 [51.35 [39.56, 84.92]], respectively; fig. 2B) and the areas of allodynia to 18.54 (17.08 [5.449, 28.72]) cm\(^2\) compared with the control (\( P < 0.01 \)) or Intralipid\textsuperscript{®} (\( P < 0.001 \)) group (56.16 [57.33 [28.86, 80.85]] and 60.36 [54.59 [41.09, 84.48]], respectively; fig. 2C). These effects were evident only during the administration of propofol. As soon as the infusion of propofol was halted, neither the hyperalgesic nor the allodynic areas differed significantly from control values. In the setting of 10% Intralipid\textsuperscript{®}, the areas of hyperalgesia and allodynia were not different from the control (\( P > 0.05 \) for hyperalgesia and allodynia; figs. 2B and C). The recovery ratios of the hyper-
algesic areas from all of the study groups were not significantly different from 100% ($P = 0.30$). The recovery ratios of the allodynic areas were less than 100% in the Intralipid® group (74 ± 45%) and propofol group (77 ± 41%), whereas this was not the case in the control group (120 ± 88%). Because of a large variation of the values in the control group, this difference was only a trend and did not reach statistical significance in our analysis ($P = 0.09$, 10% Intralipid® vs. control and $P = 0.12$, propofol vs. control).

Pharmacodynamic Modeling

The time course of the analgesic effect could be described by a sigmoid $E_{\text{max}}$ model (fig. 3). Compared with a model without an effect compartment (i.e., $C_E = C_P$), the model with an effect compartment did not yield a significantly better fit; and the estimate of $k_0$ was rather high (0.97 ± 0.18 min$^{-1}$), indicating that there was no clear hysteresis between the propofol plasma concentration and the analgesic effect. Table 2 shows the results of the population analysis for the sigmoid $E_{\text{max}}$ model with $C_E = C_P$. The EC$_{50}$ was characterized by a large interindividual variability, which is also obvious from the individual concentration–effect curves (fig. 4).

Discussion

In this study, we investigated the effects of propofol and 10% Intralipid® (as a substitute for the solvent of commercially available propofol) on analgesia and hyperalgesia in a human model of electrically evoked pain and secondary hyperalgesia. Administration of propofol at a target concentration of 2 µg/ml was associated with significantly decreased pain scores and smaller areas of hyperalgesia and allodynia when compared with the control or Intralipid® group. However, our results provide no evidence for a modulatory role of the solvent of propofol (10% Intralipid®) in the analgesic and (anti-)
hyperalgesic properties of propofol. The solvent 10% Intralipid\textsuperscript{30} was neutral and void of any clear effect in our experiments.

A number of studies have observed reduced postoperative pain in patients after propofol anesthesia when compared with anesthesia with volatile anesthetic agents.\textsuperscript{24–28} However, postoperative pain was not their primary outcome, and therefore, this finding remains debatable. Nevertheless, in a recent study,\textsuperscript{3} specifically designed to evaluate postoperative pain, general anesthesia with propofol was associated with less postoperative pain and morphine consumption compared with general anesthesia with isoflurane. Volatile anesthetics are known to have hyperalgesic effects at low concentrations.\textsuperscript{29,30} These characteristics of volatile agents could, therefore, be an explanation. Conversely, in our own experiments, propofol infusion itself was associated with decreased pain ratings and significantly smaller areas of hyperalgesia and allodynia. As soon as the propofol concentration decreased, however, this analgesic effect disappeared. As subhypnotic doses of propofol lead to an antinicotinic effect in the first few hours postoperatively\textsuperscript{31,32} and to the relief of cholestatic pruritus or pruritus induced by spinal opiates,\textsuperscript{33,34} one could argue that these same subhypnotic doses may lead to a detectable effect concerning pain perception in the recovery room. Interestingly, in the study by Cheng \textit{et al.}\textsuperscript{3} the greatest difference of analgesia between propofol and isoflurane was present during the first few minutes after anesthesia. A postoperative hangover of propofol and, thereby, a certain subhypnotic dose of propofol could explain this immediate postoperative pain relief. Hand \textit{et al.}\textsuperscript{35} observed the analgesic properties of propofol when administered at subhypnotic concentrations. In our own study, the low target concentrations of propofol may have resulted in a more rapid washout of propofol, and as a consequence, postinfusion analgesia was minimal. Important to note is that in the study by Cheng \textit{et al.}\textsuperscript{3} the analgesic effect in the propofol-treated group was maintained up to 24 h. Accordingly, in our study, we observed a similar persistent antihyperalgesic and antiallodynic tendency in the propofol-treated group during the study follow-up of 180 min (this effect, however, was not statistically significant). This persistent trend to reduced hyperalgesic and allodynic areas after propofol treatment is not well explained by a residual propofol concentration alone. It may rather have been the result of reduced central sensitization during propofol treatment. O’Connor \textit{et al.}\textsuperscript{36} observed such significant suppression of spinal sensitization by propofol in an animal pain model. More specifically, the known direct\textsuperscript{37} and indirect\textsuperscript{37} interaction of propofol with N-methyl-D-aspartate acid receptors may have led to diminished hyperalgesia and spinal wind-up.

In further animal experiments, propofol depressed the nociceptive transmission in the neurons\textsuperscript{38} and led to a reduction of continuing nociceptive barrage.\textsuperscript{39} Interestingly, in our own study, the first sign at which the “blinded” examiner recognized that propofol was administered was shortly after starting the infusion, when the electrically evoked pain decreased dramatically. At this point, central sedative effects had not yet manifested. This clinical observation was mirrored in our pharmacodynamic analysis of the analgesic effects of propofol. The transfer constant $k_{10}$ for the analgesic effects was high at 0.97 ± 0.18 min$^{-1}$. In comparison, the transfer rate constant $k_{10}$ of propofol for the sedative effects is approximately 0.3–0.5 min$^{-1}$ and for the hemodynamic effects is 0.1 min$^{-1}$ (i.e., the maximal hemodynamic effects follow the maximal sedative effects). One explanation for this observed high transfer rate constant of propofol with regard to its analgesic effects could be an additional mechanism, distinct from central sedation, through which propofol provides analgesia. For example, propofol is a well-known γ-aminobutyric acid A receptor agonist.\textsuperscript{40} Potentiation of inhibitory transmission within a pain pathway could, therefore, account for the analgesic effect.\textsuperscript{41} Otherwise, there is potentially an even more peripheral site of action, at the level of nociceptors or axons. In daily anesthesia practice, addition of propofol infusion (at sedative doses) to an incomplete regional anesthesia often proves fairly beneficial. Subhypnotic doses of propofol may provide mild analgesia through mechanisms linked to both central hypnotic effects and direct peripheral analgesic action. Obviously, our study was not designed to distinguish clearly between the hypnosis and the analgesic effects of propofol.

Prostaglandins were found to sensitize the spinal nociceptive system directly by depolarizing deep neurons of the dorsal horn.\textsuperscript{42} In addition, prostaglandins were shown to stimulate glutamate release from both astrocytes and neurons of the dorsal horns.\textsuperscript{43,44} Spinal prostaglandin production by cyclooxygenase is thought to play an important role in the development of pathologic and neuropathic pain states.\textsuperscript{44} In a previous study, Singer \textit{et al.}\textsuperscript{13} observed that the coadministration of propofol with remifentanil tended to enlarged postinfusion areas of secondary hyperalgesia. In an additional study (unpublished data: Oliver Bandschapp, M.D., Geneva Switzerland, clinical trial, 2006), patients treated with the combination of isoflurane and 10% Intralipid\textsuperscript{30} experienced slightly more postoperative pain and tended to have higher opioid requirements when compared with patients treated with isoflurane or propofol alone. However,
this was not the primary outcome of that study. We wondered whether an increased availability of long-chain fatty acids (from 10% Intralipid®), as substrates for the cyclooxygenase enzyme system, may lead to an increased generation of prostaglandins and thereby to increased pain sensitivity. Our experiments, however, did not provide any evidence for such pain modulatory effects of 10% Intralipid®. There are several possibilities as to why: first, 10% Intralipid® could be free of modulatory effects on pain perception. Second, in our experimental model, there was presumably no activation and up-regulation of the spinal cyclooxygenase. Third, the concentration of our Intralipid® solution was too low. Fourth, there may have been delayed hyperalgesic responses, but they remained undetected during our short 3-h study period. Finally, we emphasize that our conclusion regarding the pain-modulatory role of the vehicle of propofol cannot be generalized because 10% Intralipid® is the solvent for some but not all preparations of propofol.

Our study has further limitations. First, although the study was double-blinded, the blinding of propofol treatment was difficult. This is an inherent problem when testing anesthetic agents in pain models. However, although all volunteers, except for one participant, replied readily to the questions asked, the sedative action of propofol at a target concentration of 2 μg/ml was substantial. Second, the pain rating by volunteers is not as objective as, for example, an electroencephalogram. It is more a sensation rated by the volunteers, where the sedative and euphoric actions of propofol certainly have their impact. We did not control for psychometric effects in parallel with the pain rating. However, one of the core tasks as anesthetists is to make patients feel comfortable. The best assessment of such state must be the rating by the patients themselves. Therefore, we believe that, irrespective of the subjective nature of our studies, our approach is realistic and does represent daily clinical routine. Third, as sex-dependent differences in pain and analgesia are well established, we included men only. Therefore, our findings may apply to men only. Finally, we did not perform actual blood sample analysis of the plasma levels of propofol in our volunteers, but we relied on previous pharmacokinetic data of propofol to derive our pharmacodynamic model.

In conclusion, propofol administration at sedative levels exerts analgesic and antihyperalgesic effects in our pain model. These analgesic effects disappear as soon as the propofol concentration decreases. However, potentially, there is an antihyperalgesic and antiallodynic effect lasting propofol administration. The solvent of propofol is free of clear pain-modulatory action in our study. Further clinical studies are warranted to verify whether propofol anesthesia is associated with less postoperative pain in the recovery period and to elucidate the potential mechanisms behind this analgesic effect.

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