Comparison of the Potency of Different Propofol Formulations

A Randomized, Double-blind Trial Using Closed-loop Administration

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ABSTRACT

Background: Several commercial formulations of propofol are available. The primary outcome of this study was the required dose of propofol alone or combined with lidocaine to achieve induction of general anesthesia.

Methods: This multicenter, double-blinded trial randomized patients (American Society of Anesthesiologists physical status I–III) just before elective surgery with the use of a computer-generated list. Three different propofol 1% formulations—Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany)—were compared with either placebo (saline solution) or lidocaine 1% mixed to the propofol solution. Depth of anesthesia was automatically guided by bispectral index and by a computerized closed-loop system for induction, thus avoiding dosing bias. The authors recorded the total dose of propofol and duration of induction and the patient's discomfort through a behavioral scale (facial expression, verbal response, and arm withdrawal) ranging from 0 to 6. The authors further evaluated postoperative recall of pain using a Visual Analog Scale.

Results: Of the 227 patients enrolled, 217 were available for analysis. Demographic characteristics were similar in each group. Propofol® required a higher dose for induction (2.2 ± 0.1 mg/kg) than Diprivan® (1.8 ± 0.1 mg/kg) or Lipuro® (1.7 ± 0.1 mg/kg; $P = 0.02$). However, induction doses were similar when propofol formulations were mixed with lidocaine. Patient discomfort during injection was significantly reduced with lidocaine for every formulation: Diprivan® (0.5 ± 0.3 *vs.* 2.3 ± 0.3), Propofol® (0.4 ± 0.3 *vs.* 2.4 ± 0.3), and Lipuro® (1.1 ± 0.3 *vs.* 1.4 ± 0.3), all differences significant, with $P < 0.0001$. No adverse effect was reported.

Conclusion: Plain propofol formulations are not equipotent, but comparable doses were required when lidocaine was concomitantly administered. **(Anesthesiology 2014; 120:355-64)**

THERE are several commercial formulations of propofol available. The original formulation, Diprivan® 1% (Astra-Zeneca, Cheshire, United Kingdom), is a fat emulsion consisting of 10% soybean oil containing long-chain triglycerides (LCTs). Propoven® 1% (Fresenius-Kabi AG, Bad Homburg, Germany), a generic version of the original formulation without an antimicrobial retardant approved in European countries, was imported into the United States when the Food and Drug Administration exercised its regulatory enforcement discretion to fill a gap in supply when two companies decided to recall or stop production of propofol for different reasons.[1]

What We Already Know about This Topic

- Available commercial propofol formulations are not identical
- Their hypnotic potency and the pain they cause on injection may differ

What This Article Tells Us That Is New

- The dose of Propofol required for induction of anesthesia was larger than that of either Diprivan or Lipuro when administered as a closed-loop infusion guided by bispectral index
- Addition of lidocaine to the propofol formulations eliminated differences in pain severity at induction of anesthesia and in total dose required to reach a predefined depth of sedation

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Lipuro® 1% (B-Braun, Melshungen AG, Germany) contains a mixture of long- and medium-chain triglycerides (MCTs) and is reported to reduce injection pain.[2,3]

Despite the rigorous standards imposed by the Food and Drug Administration for generic drug approval, the therapeutic equivalence of certain generic products has been questioned. This is especially the case of drugs with a narrow therapeutic index including warfarin,[4] some antiepileptics[5] and antibiotics,[6] levothyroxine,[7] some immunosuppressants,[8] and bupropion, an antidepressant.[9]

Because propofol formulations are not identical, their pharmacologic potency may differ. Collier[10] reported 12 yr ago that two generic formulations of propofol (Abbott Australasia Pty Ltd., Botany and David Bull Laboratories, Sydney, Australia) induce less pain upon injection than Diprivan® although they differed mainly on one constituent: disodium edetate present in Diprivan® to inhibit the rate of growth of microorganisms.[10] However, Fassoulaki *et al.*[11] reported that Diprivan® and a propofol marketed by Abbott Laboratories with identical constituents are equipotent regarding bispectral index (BIS) and hemodynamic effects.

Numerous comparisons of the hypnotic effect of various formulations of propofol have been performed but often with methodological flaws including administration of a fixed dose and ignoring high interindividual variability of the dose–effect relationship.[12,13] Furthermore, although most studies monitored depth of anesthesia, far fewer used hypnotic depth to guide propofol administration.[12–15]

Everyday practice makes it difficult to ignore pain on injection as a confounding factor when assessing hypnotic potency. Jalota *et al.*[16] in their analysis of 177 randomized trials containing total of 25,260 adults did not study this interaction but recommended lidocaine or ketamine pretreatment with the use of propofol emulsion containing MCT/LCT (*i.e.*, Lipuro®) when a hand vein is used. We hypothesized that a painful propofol infusion for the induction of anesthesia may delay the induction and consequently increase the total dose required to reach a predefined depth of sedation. Conversely, we also hypothesized that addition of lidocaine would mask such differences in pain severity.

The aim of the current study was to compare the anesthetic potency and the severity of pain on injection of Diprivan® 1%, Propofol® 1%, and Lipuro® 1% as plain solutions or with lidocaine using a closed-loop method of propofol delivery guided by BIS to limit human intervention.[17] To examine this relationship, the primary outcome was the required dose of propofol with or without lidocaine to achieve induction of general anesthesia.

Materials and Methods

This controlled, randomized, double-blinded, multicenter study was approved by a relevant ethics committee (Comité de Protection des Personnes Île-de-France VIII), and the French drug agency (Agence Française de Sécurité Sanitaire des Produits de Santé). All patients received detailed oral and written information during the preanesthetic consultation and gave their written informed consent during the preanesthetic visit the day before surgery. The study was registered under Clinical Trial number: NCT01041872 and was conducted between January 2010 and February 2011 in two French Departments of Anesthesiology (University hospital and Private hospital) with a common multidisciplinary operating theater. It complies with Good Clinical Practices guidelines and is in agreement with European and French laws and regulations. Pharmaceutical companies were not involved at any stage and did not provide financial support.

We enrolled nonpregnant adults with American Society of Anesthesiologists physical status I–III who presented for elective surgery requiring general anesthesia for at least 30 min. Patients were not eligible if they had to undergo cardiac surgery or cranial neurosurgery, used psychotropic drugs, had supraspinal neurologic disorders, or used a pacemaker.

Protocol

Randomization was based on computer-generated codes in blocks of 18 that were maintained in sequentially numbered sealed envelopes until immediately before use. Patients were randomly allocated to one of six parallel groups with a 1:1 ratio. Three different propofol 1% formulations—Diprivan®, Propofol®, or Lipuro®—were compared during induction of anesthesia mixed with either placebo (saline solution) or lidocaine 1%. The propofol formulations were prepared by a pharmacist or an anesthetist not involved in the patient's induction. In each case, 45 ml of the designated propofol was mixed with 5 ml of saline or lidocaine 1%. The syringe was then gently shaken.

Patients were not premedicated, and no opioid was given before propofol induction. Upon admission to the operating room, routine monitoring was set up. An intravenous cannula (20 gauge) was inserted in a dorsal vein of the nondominant hand. In case of failure or high risk of failure, a vein in the forearm was used. A Bispectral electrode (BIS™, Zipprep; Covidien, Dublin, Ireland) was positioned on the patient's forehead and connected to an A-2000 XP (version 3.11; Covidien) BIS monitor. Patients received one of the six formulations of propofol using the same closed-loop controller allowing an entirely automated induction. The controller uses Infusion Toolbox 95® version 4.11 software,[18] which served as a platform: (1) to calculate the effect-site concentrations with the use of the pharmacokinetic model by Schnider *et al.*[19]; (2) to display the calculated effect-site concentration in real time; (3) to provide a user interface allowing to key in patient's demographic data (sex, age, weight, and height); (4) to control the propofol infusion pump (Alaris Medical, Hampshire, United Kingdom); and (5) to continuously record BIS, calculated effect-site concentrations, and hemodynamic data (heart rate and blood pressure) every 5-s interval. In all groups, the initially prescribed propofol effect-site

target was 5 μg/ml, and automated induction was performed while patients spontaneously breathed 100% oxygen *via* a facemask without any stimulation. The controller has a cascade structure, based on a proportional-derivative algorithm, and a target-controlled infusion system for intravenous propofol administration during induction. The controller measures and calculates the error or the difference between the BIS set point (50) and the measured BIS. If the BIS error is different from 0, the controller determines a new propofol concentration in proportion to the error. The minimal interval between the two consecutive propofol controls is set equal to the time to peak effect given by the model.[19] A detailed description and performances of the controller have been provided previously.[17,20,21]

Induction was defined as the end of the first period of 30 s during which BIS was always less than 60. After induction, anesthesia was continued according to the anesthesiologist's routine practice.

Measurements

In all cases, pH of injected solutions was measured with a dipstick colorimetric method on the residue of the propofol formulation. The precision of this method is approximately 0.2 units for pH ranging from 5.0 to 8.

Data from the monitors (mean arterial pressure, heart rate, and Spo_2) were stored before propofol injection and at time of induction while calculated effect-site propofol concentrations were stored at 5-s intervals. Hypotension was defined as a decrease in systolic blood pressure of more than 20% below baseline (blood pressure measurement preceding the start of induction). Changes in heart rate were taken into account when deviation from baseline values exceeded 20%.

Ce50 corresponds to the calculated value of propofol effect-site concentration in real time at induction for 50% of the patients.[22]

Intensity of pain during injection was evaluated by an investigator who was blinded to propofol formulation, using a behavioral three-point scale for facial expression (0: none, 1: frowning, or 2: grimacing), verbal response (0: none, 1: groan, or 2: clear verbal pain expression), and attempt to withdraw the infused arm (0: none, 1: moderate, or 2: strong). The discomfort scale was the sum of these three clinical parameters (range, 0–6). Side effects were monitored throughout the study including extravasation of propofol, vasoconstrictor requirement, and bronchospasm.[23] If apnea occurred during propofol induction, a gentle manual assistance was applied if Spo_2 decreased below 92%.

For the measurement of serum propofol, venous blood sample was collected at the time of induction in one of five randomly selected patients in each group. Plasma propofol and lidocaine concentrations were then determined with a validated gas chromatography–mass spectrometry method. Plasma samples (500 μl) were spiked with 25 μl internal standard solution (thymol and ropivacaine, 0.1 and 0.01 g/l in methanol, respectively) and were shaken for 15 min and centrifuged at 3,500 rpm for 10 min. The supernatant that contained the free ratio of anesthetics in its upper organic layer was decanted into another tube and evaporated to dryness under a nitrogen stream. Samples were reconstituted with 25 μl of ethyl acetate and transferred into injection vials for analysis. One microliter was injected into the chromatographic system, composed of an AS3000 autosampler (ThermoFisher, Les Ulis, France), a Focus GC oven (ThermoFisher), and a DSQII mass spectrometer (ThermoFisher).

Analytical conditions were as follows: injection mode: surge splitless, capillary DBS-5MS column (30 m long, 0.25 mm internal diameter), carrier gas 1.20 ml/min helium, initial temperature 90°C for 1 min, then a ramp of 30°C/min to reach 210°C with a hold time of 4.0 min, and a second ramp of 50°C/min to reach 300°C with a hold time of 5.0 min. Source temperature was 260°C, and ionization was performed with electronic impact. The limit of quantification was 0.5 mg/l for propofol and 0.05 mg/l for lidocaine, and the method was linear up to 20 and 2 mg/l for propofol and lidocaine, respectively. For the low, medium, and high levels of quality controls and for both propofol and lidocaine, intra- and interassay accuracy was between 89.9 and 106.6%, and intra- and interassay precision was between 0.8 and 14.6%.

Upon recovery, patients were asked to rate pain they might have experienced during injection using a 100-mm Visual Analog Scale (where 0 is no pain and 100 the worst possible pain) and to make any comments they might have about their induction of anesthesia. The occurrence of any serious adverse event within 24 h of surgery was to be notified to an independent safety officer.

Data Analysis

The primary study outcome was the dose of propofol given alone or associated with lidocaine until the moment of induction.

Secondary outcomes included the duration of induction, calculated and measured propofol and lidocaine plasma concentrations, pain on injection as reflected by the verbal and nonverbal expression, arm withdrawal, and hemodynamic variation, and postoperative recollection of pain at the intravenous catheter site during induction.

An *a priori* estimate of sample size was determined for a factorial ANOVA with interaction between lidocaine and propofol using a two-tailed significance level of 0.05. We expected a difference of 0.5 mg/kg with an SD of 1 mg/kg for the groups given propofol alone compared with propofol combined with lidocaine. This difference was based on a previous publication on the difference between manual and automated administration of propofol guided by the BIS: 1.8 ± 0.6 mg/kg *versus* 1.4 ± 0.5 mg/kg ($P < 0.0001$).[17] This 30% reduction in propofol need during induction can be considered clinically relevant. A sample size of 27 patients per group was needed to provide a power of 0.89 for propofol, 0.98 for lidocaine, and 0.81 for interaction. Anticipating 20% attrition, a total of 35 patients per group were scheduled.

Ordinal data were considered continuous. For such data, means and SEM are used as summaries. Categorical data are expressed as percentages with 95% CIs.

Continuous variables were analyzed using a factorial ANOVA with a brand factor (three levels), a lidocaine factor (two levels present/absent), and an interaction term. The brand factor (*i.e.*, pooled values for brands with or without lidocaine), if significant, led to pairwise comparisons of brands using Bonferroni–Simes correction to adhere to the experiment-wise nominal *P* value (0.05) despite multiple comparisons. The lidocaine factor, if significant, indicates whether lidocaine administration has some effect when results from all brands are pooled. Finally, brand × lidocaine multiple cell comparisons (with Bonferroni–Simes correction) indicate whether lidocaine effects vary among brands. The Bonferroni–Simes correction that was used precludes provision of exact *P* values for comparisons, and they are only expressed as significant ($P < 0.05$) or not significant.

A log-linear model was fitted over categorical data, which includes predictors for brand, lidocaine, and brand × lidocaine, indicating if brands, effect of lidocaine, and the differential effect of lidocaine on various brands are significant. If such significant differences existed, a series of 2 × 2 Fisher exact test (with Bonferroni–Simes correction) was used for pairwise comparisons of proportions in relevant cells.

Statistical tests were performed using NCSS 7 and 8 (NCSS LLC, Kaysville, UT) and R 2.12 (R Statistical Foundation, Vienna, Austria).

Results

Only 10 of 227 enrolled patients were excluded from analysis (mostly for technical reasons), leaving 217 patients who completed the study as scheduled (fig. 1). The mean ± SD age was 55 ± 15 yr, with a comparable men/women ratio. Patients had low rates of comorbidity, with American Society of Anesthesiologists physical status scores of I in 40% of the patients, II in 49% of the patients, and III in 11% of the patients. Neither demographic and baseline characteristics nor types of surgery did differ among the groups (table 1).

Figure 2 represents individual curves of BIS values during induction according to the specific group. After 6 min of induction, 11 (5%) patients were still awake: one patient with Diprivan® 1%, four with Diprivan® 1% + lidocaine, three with Propofol®, one with Propofol® + lidocaine, one with Lipuro®, and one with Lipuro® + lidocaine.

The propofol dose required for induction was significantly greater using the Propofol® with saline (2.2 ± 0.1 mg/kg) than with Diprivan® with saline (1.8 ± 0.1 mg/kg) or Lipuro® with saline (1.7 ± 0.1 mg/kg, $P = 0.02$ for the global analysis and $P < 0.05$ for Propofol® *vs.* Diprivan® or for Propofol® *vs.* Lipuro®). Lidocaine use had no statistically significant impact on doses of propofol ($P = 0.67$). The time required for induction was not significantly different among the formulations ($P = 0.07$), and lidocaine use again had no significant effect ($P = 0.49$; table 2).

Calculated effect-site concentrations at induction were similar among all plain formulations ($P = 0.17$) and with lidocaine ($P = 0.90$). Nonetheless, the Ce50 at induction was significantly greater for Propofol® (7.3 ± 0.3 μg/ml) than Diprivan® with saline (6.3 ± 0.2 μg/ml) or Lipuro® (6.4 ± 0.3 μg/ml; $P = 0.02$). Addition of lidocaine had no significant effect on estimated effect-site concentrations at the time of induction (table 2). In the subset of patients who participated in the pharmacokinetic study, measured plasma concentrations of propofol at induction were similar among all formulations ($P = 0.08$) with no effect of lidocaine ($P = 0.15$; table 3).

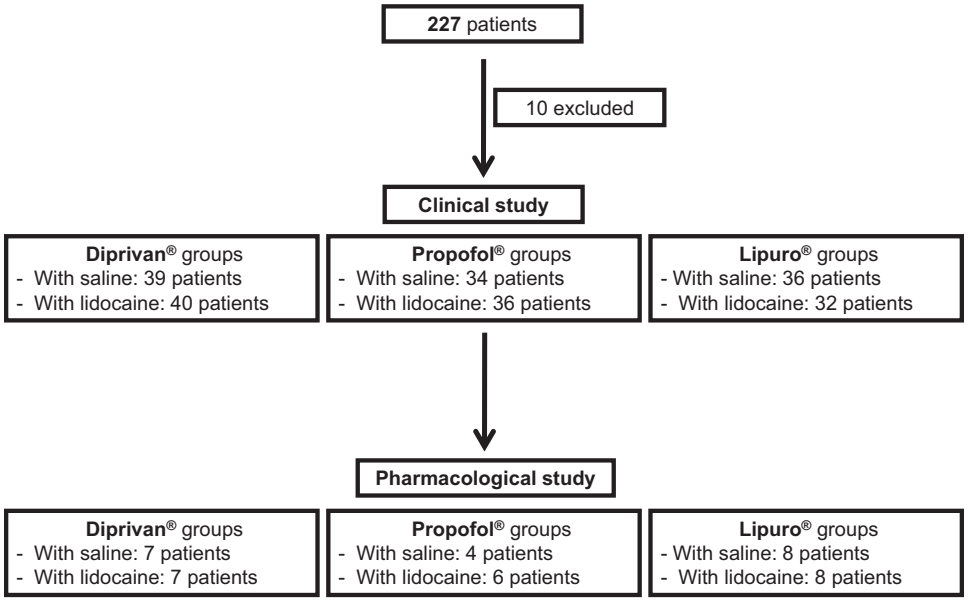

Fig. 1. Trial profile. Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany).

Pain during induction was similar among all formulations whatever the recorded variable (facial expression, verbal response, and arm withdrawal) or using the global discomfort score. Addition of lidocaine reduced the value of all these variables, equalizing all formulations for this adverse event (all $P < 0.001$). Lidocaine admixture led to significant effect for LCT formulations where a larger gain was expected ($P < 0.05$ for Propofol® and Diprivan®). Similarly, postoperative recollection of pain was significantly reduced with addition of lidocaine ($P < 0.0001$; table 4).

Hemodynamic profiles were similar among all groups. Blood pressure typically decreased during induction, with 76% (95% CI, 60–92) of the patients experiencing decreases of more than 20% of the systolic arterial pressure, but without significant differences among formulations. Heart rates were similar before and after induction ($P = 0.66$).

No adverse effect was recorded. pH was similar with each propofol formulation, with or without lidocaine (table 2).

Discussion

We compared three propofol 1% suspensions available in Europe: Astra-Zeneca's original form Diprivan®, Fresenius' generic Propofol®, and B-Braun's Lipuro® using a computer-controlled infusion system. Our study found that the greatest difference between formulations is between plain Propofol® and plain Lipuro®. This −23% difference in dose required for induction (sparing effect) cannot be considered as anecdotal, but only studies powered to find a difference in adverse effects, especially hypotension, could provide a precise answer to the question of relevance of such a difference. Conversely, addition of lidocaine 1% to the propofol formulations erased any difference in dose and pain.

Our results demonstrated differences in potency between propofol formulations which may be explained by physicochemical features. Propofol is a highly lipophilic and almost water-insoluble drug which has to be mixed with solubilizing additives or prepared as an emulsion for administration to humans. The formulations used in the current study are all lipid emulsions consisting in either LCT alone for Diprivan® and Propofol® or mixed with MCT for Lipuro®. The composition of lipid emulsion was previously shown to affect the onset in anesthesia, the potency, as well as the duration of anesthesia.[24] However, differences between Diprivan® and Propofol®, which both contain LCT but not MCT, cannot thus be fully explained by qualitative differences in emulsion composition. Other determining parameters for efficacy include emulsion droplet size that conditions the diffusion rate of propofol toward its action site and ζ potential that indicates emulsion stability. However, Lipuro® formulation was shown to contain less free propofol in the aqueous phase than other formulations,[25] which may decrease the direct contact between the active free propofol and free nerve endings outside the endothelial layer of the injection site vessel. This may explain the observed sparing effect to reach the same depth of sedation with Lipuro® although induction duration was similar to others.[25–28] In a complete physicochemical characterization of the different marketed propofol formulations (including the three formulations of the current study), it was demonstrated that Diprivan® and Lipuro® were very similar in pH, particle size, and particle dispersion.[29]

Table 1. Demographics and Patient Characteristics

		Diprivan® 1%	Propofol® 1%	Lipuro® 1%
Number of cases	With saline	39 (18.0)	34 (15.7)	36 (16.6)
	Plus lidocaine	40 (18.4)	36 (16.6)	32 (14.7)
Age (yr)	With saline	56 ± 14	54 ± 16	56 ± 18
	Plus lidocaine	53 ± 11	55 ± 14	58 ± 12
Sex (M/F)	With saline	18/21	16/18	22/14
	Plus lidocaine	22/18	15/21	18/14
Weight (kg)	With saline	69 ± 14	68 ± 12	77 ± 12
	Plus lidocaine	72 ± 14	71 ± 12	72 ± 13
Height (cm)	With saline	167 ± 7	168 ± 8	170 ± 8
	Plus lidocaine	171 ± 9	168 ± 8	168 ± 8
BMI (kg/m^2)	With saline	25 ± 4	25 ± 4	25 ± 4
	Plus lidocaine	25 ± 4	25 ± 4	26 ± 4
ASA I/II/III	With saline	17/19/3	12/17/5	17/18/1
	Plus lidocaine	19/19/2	12/17/7	9/17/6
Site of injection				
Dorsum of hand	With saline	27 (15.1)	23 (12.8)	25 (14.0)
	Plus lidocaine	25 (14.0)	20 (11.2)	16 (8.9)
Antecubital	With saline	7 (3.9)	7 (3.9)	5 (2.8)
	Plus lidocaine	5 (2.8)	10 (5.6)	9 (5.0)

Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany). Data are expressed as number of patients (%) or mean ± SD.

ASA = American Society of Anesthesiologists; BMI = body mass index; M/F = male/female.

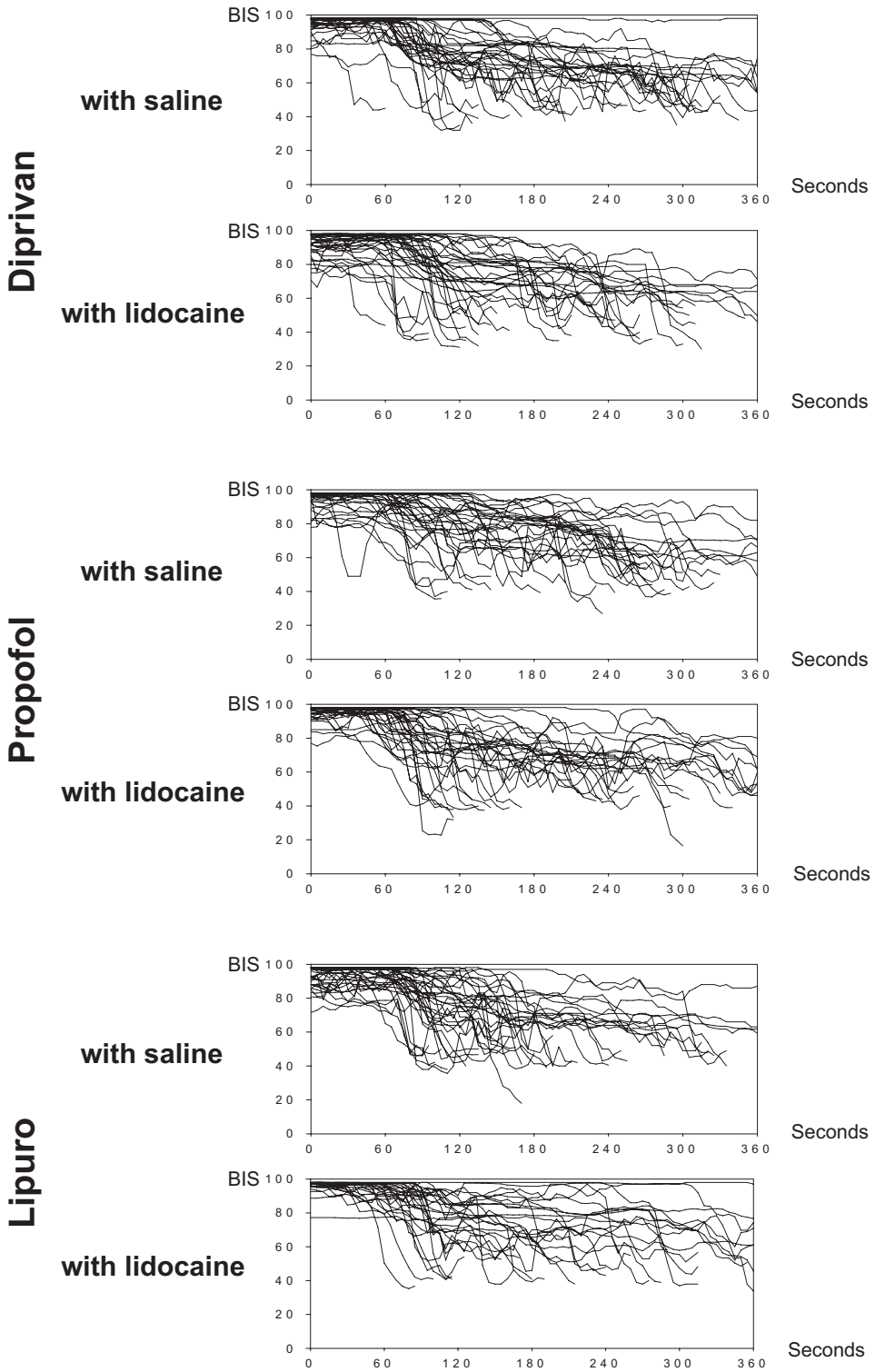

Fig. 2. Individual curves of bispectral index (BIS) values during induction according to the specific group: Diprivan® (AstraZeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany).

When compared with Propofol®, the pH of Diprivan® and Lipuro® was found to be closer to the physiological value, and the particle size was the smallest with the greatest homogeneity and subsequent better potency. These characteristics may partially explain differences during induction. To summarize, MCT content and free propofol fraction as reported in Lipuro® appear as the main explanatory factors of the observed differences between propofol brands. Other factors

Table 2. Characteristics of Induction

		Diprivan®	Propofol®	Lipuro®			
	With Saline	39	34	35	Test for Brand Factor *P* Value	Test for Lidocaine Factor *P* Value	Significant Differences between the Six Formulations. *P* Value for Interaction Term *P* Value
Number of Cases	Plus Lidocaine	40	36	32			
Total dose (mg/kg)	With saline	1.8 (0.1)	2.2 (0.1)	1.7 (0.1)	0.02	0.67	0.09
	Plus lidocaine	2.0 (0.1)	2.0 (0.1)	1.8 (0.1)	*Post hoc* analysis: $P_{pooled} > D_{pooled}$*, $P_{pooled} > L_{pooled}$*		*Post hoc* analysis: P > D*, P > L*
BIS values at induction	With saline	46 (1.3)	44 (1.3)	44 (1.3)	0.54	0.13	0.74
	Plus lidocaine	44 (1.2)	44 (1.3)	43 (1.4)			
Time to induction (s)	With saline	261 (20.5)	309 (22.0)	246 (21.7)	0.07	0.49	0.80
	Plus lidocaine	251 (20.3)	281 (21.4)	247 (22.6)			
Calculated effect-site concentration at induction (μg/ml)	With saline	7.3 (0.3)	8.1 (0.4)	7.5 (0.4)	0.17	0.90	0.93
	Plus lidocaine	7.4 (0.4)	8.0 (0.4)	7.6 (0.4)			
Ce50 at induction (μg/ml)	With saline	6.2 (0.3)	7.5 (0.4)	6.4 (0.4)	0.02	0.95	0.56
	Plus lidocaine	6.5 (0.4)	7.1 (0.4)	6.4 (0.4)	*Post hoc* analysis: $P_{pooled} > D_{pooled}$*, $P_{pooled} > L_{pooled}$*		
pH	With saline	6.4 (0.1)	6.4 (0.1)	6.3 (0.1)	0.22	0.84	0.49
	Plus lidocaine	6.3 (0.1)	6.5 (0.1)	6.4 (0.1)			

Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany). Induction was defined as the end of the first period of 30 s during which BIS was always less than 60. Ce50 at induction (μg/ml): propofol effect-site concentration required at induction in half of cases, expressed as μg/ml. Data are expressed as mean (SEM).

* $P < 0.05$.

BIS = bispectral index; D = plain Diprivan®; D_{pooled} = Diprivan® with and without lidocaine; L = plain Lipuro®; L_{pooled} = Lipuro® with and without lidocaine; P = plain Propofol®; P_{pooled} = Propofol® with and without lidocaine.

such as plasma-free fraction, formulation pH, and free-fatty acid concentration should be of more limited influence.[30,31]

Our study was also powered to study the effect of lidocaine coadministration during propofol infusion. Almost two thirds of patients experienced pain during propofol injection, with one third reporting severe or excruciating pain. A recent meta-analysis on pain prevention proposed a simple strategy to significantly reduce pain: (1) choose an antecubital vein; (2) give an opioid and lidocaine (35 mg) as pretreatment under venous tourniquet 30–90 s before propofol administration; or (3) give lidocaine as pretreatment with a propofol emulsion containing MCT/LCT.[16] A lower dose of lidocaine appears to be sufficient in elderly patients (20 mg instead of 40 mg in young patients) and may therefore reduce the risk of adverse cardiac or neurological consequences.[32] Coadministration of lidocaine at 1% with propofol, as in our study, has been shown to be effective at preventing propofol-induced pain and has been shown to be safe.[33] The median measured plasma concentration of lidocaine in our patients was only 0.42 μg/ml (0.36-0.55), a dose highly unlikely to cause toxicity.

Propofol-induced pain involves stimulation of nociceptors and free nerve endings.[34] A key role for the plasma kallikrein–kinin system, and a proinflammatory cascade has also been evoked.[35,36] Several hypotheses could explain an interaction between lidocaine and propofol. The involvement of hypnotic properties of lidocaine, which was observed only during surgical stimulation,[37,38] is unlikely because of the low plasma concentrations and the absence of stimulation in the current study. Regardless of the local venous mechanisms, it seems clear that there is a negative relationship between pain on injection and quality of induction of anesthesia, and therefore, reduced local pain facilitates a smoother and quieter induction. Adding lidocaine to propofol emulsion increases binding of propofol to LCT and/or MCT up to 21%,[39] which reduces the fraction of free propofol, which is involved in pain at the injection site by direct contact with free nerve endings outside the endothelial layer of the vessel.[26] Moreover, pain on injection is associated with facial movement and arm withdrawal which are reduced when lidocaine is mixed with propofol. It is well known that high electromyographic activity can significantly influence BIS monitoring because electromyographic frequencies could simulate the 30–47 Hz component of the BetaRatio, an additional parameter of the BIS algorithm.[40] Then electromyographic activity would be misinterpreted by the BIS algorithm as electrocortical activity with a "falsely increased BIS level" and consequently an increase in propofol delivery according to the algorithm of the closed loop. Finally, lidocaine-related alterations of the physicochemical properties of propofol emulsions may also partially explain the observed effects. Because propofol is administered as an emulsion, the availability of free drug is

Table 3. Estimated and Measured Serum Concentrations of Propofol and Lidocaine at Bispectral Index of 50 for the Subset of Patients Who Participated in the Pharmacokinetic Study

		Diprivan®	Propofol®	Lipuro®	Test for Brand Factor *P* Value	Test for Lidocaine Factor *P* Value	Significant Differences between the Six Formulations
	With Saline	7	4	8			
Number of Cases	Plus Lidocaine	7	6	8			
Propofol							
Calculated effect-site concentration (μg/ml)	With saline	6.4 (0.7)	7.5 (1.1)	5.6 (0.7)	0.80	0.35	ns
	Plus lidocaine	6.3 (0.7)	7.2 (0.8)	7.2 (0.7)			ns
Measured serum concentration (μg/ml)	With saline	5.6 (1.4)	7.1 (1.8)	5.5 (1.3)	0.08	0.15	ns
	Plus lidocaine	3.2 (1.4)	3.9 (1.5)	4.9 (1.3)			ns
Lidocaine							
Measured serum concentration (μg/ml)	With saline	0 (0)	0 (0)	0 (0)	0.02	0.90	ns
	Plus lidocaine	0.3 (0.1)	0.4 (0.1)	0.5 (0.1)			ns

Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany). Data are expressed as means (SEM).

ns = nonsignificant.

slowed because propofol should diffuse across the droplet interface to the bloodstream. The total interfacial surface area is a highly important factor in the rate of drug release,[24] and lidocaine increases droplet size for amounts above 10 mg, a dose used in most of our patients.[39,41,42] As a consequence, propofol distribution may be directly affected.[24] These investigations were performed with Diprivan, and interaction between lidocaine and the other propofol formulations has, to our knowledge, never been reported. We could thus hypothesize that adding lidocaine affects emulsion droplet size of all formulations in a similar manner which could explain why total propofol doses are equivalent between the three formulations when lidocaine is added (table 2).

We have reported that measured plasma concentrations of propofol at induction were similar among all formulations. However, they appear smaller when lidocaine was added. These results should be guardedly analyzed for several reasons: assays were done on a limited number of patients, blood samples were never taken during a steady-state period because induction is *per se* an unstable period and because closed-loop propofol administration consisted in several consecutive boluses at short intervals, arteriovenous difference is probably higher during such a period than during a maintenance period, and venous concentrations reflect the effect-site concentration of propofol less well than arterial ones.[43]

Our study has some limitations. Perhaps, the major strength of our study was the use of a computer-controlled infusion system that was based on a completely objective criterion (BIS). The mean dose infused in our study was approximately 2 mg/kg which is a typical dose needed to reach induction when given in successive small boluses.[17] Although arguably there is a short delay between BIS value and real electrocortical activity, this is a systematic error that applies equally to every tested drug formulation. Moreover, use of a closed loop does not avoid overshoot, that is, a decrease in BIS under the lower limit of 40, as published previously.[17] As shown in figure 2, overshoot occurred with all formulations but was infrequent and has only a marginal effect on the dose of propofol required for induction.

Table 4. Characteristics of Pain and Postoperative Recollection

		Diprivan®	Propofol®	Lipuro®	Test for Brand Factor *P* Value	Test for Lidocaine Factor *P* Value	Significant Differences between the Six Formulations
	Plain	34	29	30			
Number of Cases	Plus Lidocaine	30	27	27			
Discomfort score	Plain	2.3 (0.29)	2.4 (0.32)	1.4 (0.31)	0.9	<0.0001	Interaction term: $P = 0.02$
	Plus lidocaine	0.5 (0.31)	0.4 (0.33)	1.1 (0.33)			*Post hoc* analysis: D > DL*, P > PL*
Postoperative recollection (VAS in mm)	Plain	4.0 (0.5)	3.9 (0.5)	1.8 (0.5)	0.07	0.00003	Interaction term: $P = 0.05$
	Plus lidocaine	1.7 (0.5)	1.1 (0.5)	1.5 (0.5)			*Post hoc* analysis: L<P*, L<D*, D > DL*, P > PL*

Diprivan® (Astra-Zeneca, Cheshire, United Kingdom), Propofol® (Fresenius-Kabi AG, Bad Homburg, Germany), and Lipuro® (B-Braun, Melshungen AG, Germany). Discomfort score is the sum of three scores: one for facial expression, one for verbal response, and one for arm withdrawal. Face expression was graded as 0: none, 1: frowning, or 2: grimacing. Verbal response was graded as 0: none, 1: groan, or 2: clear verbal pain expression. Arm withdrawal was graded as 0: none, 1: moderate, or 2: strong. Data are expressed as mean (SEM).

* $P < 0.05$

D = plain Diprivan®; DL = Diprivan® + lidocaine; L = plain Lipuro®; P = plain Propofol®; PL = Propofol® + lidocaine; VAS = Visual Analog Scale.

Other endpoints were possible, including loss of consciousness. However, assessing consciousness requires interacting with patients which would not be an entirely objective process. We therefore relied on our computer-controlled system to deliver propofol.

Direct comparisons with other studies are difficult. Indeed, propofol infusion rates vary from one study to another, as well as, primary outcomes such as loss of eyelash reflex,[44,45] loss of consciousness,[46] level of BIS,[47,48] or infusion rates.[35,49,50]

Although the proportion of puncture sites was not different between groups, a limitation of this study regarding effects on pain at injection site resides in the fact that location of the intravenous catheter was not the same for all patients. This was a consequence of standardizing the choice of the puncture site: dorsal vein of the hand as the first choice and forearm vein in case of failure or of high risk of failure. Jalota *et al.*[16] recommend the use of a forearm vein to limit pain during propofol administration, but we chose to follow our routine use of a dorsal hand vein as first choice to limit investigator bias.

In conclusion, propofol is a key anesthetic drug. Recent shortages have resulted in unfamiliar (and normally unapproved) formulations being available in the United States. Using a closed-loop system, our study demonstrates that more Propofol® than Lipuro® or Diprivan® is required for induction of anesthesia. Addition of lidocaine not only substantially reduces injection pain, but also obliterates differences in dose requirement.

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Competing Interests

The authors declare no competing interests.

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