British Journal of Anaesthesia 1997; **78**: 502–506

Effect of lignocaine and pH on propofol-induced pain

M. ERIKSSON, S. ENGLESSON, F. NIKLASSON AND P. HARTVIG

Summary

Propofol has the disadvantage of pain on injection. A higher partition of propofol in the aqueous phase of the preparation causes a higher incidence of pain on injection while addition of 1% lignocaine to propofol reduces pain. The low concentration of this local anaesthetic and the rapid pain relief observed indicates that mechanisms other than local anaesthesia are involved, that is change in pH. We performed a clinical study to investigate the influence of lignocaine and pH on pain during injection of 1% Diprivan. Ten parts of 1% Diprivan were mixed with one part of saline, 1% lignocaine or hydrochloric acid to achieve the same pH as that after addition of lignocaine. Diprivan 1% mixed with 1% lignocaine and with hydrochloric acid gave mean pain ratings (1–10) of 0.32 (SD 0.75) ($n=25$) and 0.88 (1.30) ($n=24$), respectively. These ratings were significantly lower than ratings after injection of a saline–Diprivan mixture (2.18 (2.06), $n=22$). The pH of the 1% Diprivan formulation decreased after mixing with 1% lignocaine. The concentration of propofol in the aqueous phase was lower when 1% Diprivan was mixed with 1% lignocaine (0.376 g litre^{-1}) or HCl (0.392 g litre^{-1}) compared with 1% Diprivan and saline (0.476 g litre^{-1}) mixed in the same proportion. Thus pH changes may modify propofol-induced pain on injection by a mechanism different from the effect of the local anaesthetic on the vascular endothelium. Our findings may explain why lignocaine mixed with propofol causes less pain than injection of lignocaine followed by propofol. (*Br. J. Anaesth.* 1997; **78**: 502–506).

Key words
Formulations, propofol. Formulations, pH. Pain, injection. Anaesthetics i.v., propofol. Anaesthetics local, lignocaine.

Propofol (Diprivan; 2,6-diisopropyl phenol) causes pain on i.v. administration.[1] Initially it was formulated in Cremophor EL which may increase the risk of anaphylactic reactions and as a consequence propofol was formulated as an aqueous emulsion in soybean oil.[2,3] Dissolving diazepam and etomidate in soybean oil (Intralipid) almost abolished the pain associated with their injection[4,5] but the same is not true for propofol although pain is known to be related to the aqueous concentration of propofol in the emulsion.[6,7] Pain after injection of propofol is thought to be caused by direct stimulation of venous nociceptive receptors or free nerve endings, the nerve impulse being transmitted by thinly myelinated A delta fibres.[8] If a local anaesthetic affects these nerve cells it must penetrate the cell membrane in its uncharged form and is then converted to its ionized form which anaesthetizes intracellular receptors.

Pain on injection induced by propofol has been found to be reduced by a preceding injection of lignocaine.[2] A direct effect of local anaesthetics on vascular smooth muscle has been suggested.[9] Comparisons between the efficacy of lignocaine injected before propofol and of mixtures of lignocaine and propofol injected simultaneously have shown that the latter causes less pain on injection.[3,10] Knowledge of the mechanism by which a small amount of lignocaine counteracts pain caused by subsequent injection of propofol is valuable. Small quantities of local anaesthetic can reduce such pain at the injection site, but also the pain observed at more proximal sites. This suggests an effect of lignocaine on propofol-induced pain on injection separate from its local anaesthetic action.

It is not clear how such low concentrations of lignocaine mixed with propofol (e.g. 1:10) and thereby diluted to a 0.1% solution almost instantaneously prevents propofol-induced pain on injection. Alternative explanations for the efficacy of lignocaine on injection pain caused by propofol include: lignocaine hydrochloride is a weak free base–cation solution which, when exposed to lipids, liberates protons as the free base dissolves in the lipids, thereby decreasing the pH of the mixture; the lower pH produced after mixing lignocaine with Diprivan reduces the concentration of propofol anions as propofol is a weak acid with a pK_a of 11. The net effect would be an increased amount of propofol which migrates into the lipid phase. Such an effect would result in reduced pain on injection.[7,11]

In order to determine if the change in pH achieved by adding lignocaine to the Diprivan solution or the local anaesthetic effect of lignocaine is the main mechanism for reduction of pain on injection, we observed the responses of solutions in which the pH

M. ERIKSSON, MD, PHD, S. ENGLESSON, MD, PHD (Department of Anaesthesia and Intensive Care); F. NIKLASSON, MD, PHD (Department of Clinical Chemistry); P. HARTVIG, PHD (Hospital Pharmacy); University Hospital, S-751 85, Uppsala, Sweden.
Accepted for publication: January 20, 1997
Correspondence to M. E.

change was created by lignocaine or by addition of hydrochloric acid. Diprivan 1% mixed with lignocaine, hydrochloric acid or saline, all three with the same degree of dilution, were prepared and tested in patients. Chemical analysis was also performed whereby pH titrations were made with 1% Diprivan mixed with increasing amounts of lignocaine or hydrochloric acid. These titrations were also made with 10% and 20% Intralipid solutions, the former corresponding to the emulsion used in 1% Diprivan.

Patients and methods

PAIN DETERMINATION

After obtaining approval from the local Ethics Committee of the University of Uppsala and the Swedish Medical Products Agency, we studied 44 patients (18 males), ASA I or II, undergoing elective ENT surgery. All patients gave informed consent to participate in this study. Mean age was 43 (range 18–72) yr. Patients were requested to name which of two propofol injections, one in each hand, at its maximum caused most discomfort and in addition to grade the pain, where "0" = no pain, "1" = hardly recognizable and "10" = extreme pain. Premedication was with ketobemidon (Ketogan Novum; an analogue to morphine) 2.5–5 mg and atropine 0.5 mg or glycopyrronium (Robinul) 0.2 mg injected i.m. 30 min before induction of anaesthesia. A 20-gauge i.v. cannula was inserted in a dorsal vein of each hand. Coded ampoules containing 2 ml of either sterile 1% lignocaine, sterile hydrochloric acid 0.064 mol litre^{-1} or saline were prepared in advance. No efforts were made to stratify the material. Diprivan 1% (10 ml) at room temperature was mixed with 1 ml of the contents of a randomly chosen ampoule. All mixtures were prepared immediately before injection and all injections were made in a double-blind manner. Two millitres of the mixtures were injected simultaneously in each cannula over a period of 25–30 s.

DRUGS AND EQUIPMENT

We used propofol (1% Diprivan; Zeneca AB, Sweden), lignocaine (1% Xylocain; Astra AB, Sweden) and a soybean oil emulsion (Intralipid; Kabi Pharmacia AB, Sweden), similar to the solvent in which propofol is emulsified. pH values of each compound and the mixtures were determined with a pH meter (PHM 92, Radiometer, Copenhagen, Denmark) calibrated at pH values of 4.00 and 7.00. All experimental procedures were performed at least in duplicate.

Analysis of propofol and lignocaine concentrations was performed by liquid chromatography of the aqueous phases obtained by ultracentrifuging the Diprivan preparations. These analyses were performed by Dr Björn Norlander, Department of Clinical Pharmacology, University of Linköping.

Diprivan 1% was mixed randomly (10 + 1) with 1% lignocaine, hydrochloric acid 0.0064 mol litre^{-1} or saline and administered into surgical patients in a double-blind, randomized manner.

The following chemical experiments and titrations were performed with Diprivan and Intralipid mixed with either lignocaine, hydrochloric acid or saline: pH was measured in 1% Diprivan and in the commercially available 1% and 4% solutions of lignocaine. pH was also measured in the mixture (10:1) of 1% Diprivan and 1% lignocaine. A titration was also made with increasing amounts of lignocaine (10:2, 10:4) and the pH of each mixture measured. A new titration with 4% lignocaine was also made (10:0.25, 10:0.5, 10:1, 10:2, 10:4) which added the same amount of lignocaine to 1% Diprivan.

STATISTICAL ANALYSIS

Analysis of variance was used to test the hypothesis of no difference between treatment groups. If this hypothesis was rejected at the 5% level using the *F* test, least-square means were calculated and compared between each pair of treatment groups. The magnitude of the differences was explored by use of 95% confidence limits. Results are expressed as mean (SD).

Results

IN VIVO EXPERIMENTS

Pain rating after administration of 10 parts of 1% propofol mixed with one part of either 1% lignocaine, hydrochloric acid 0.0064 mol litre^{-1} or saline, respectively, was determined verbally. The highest pain rating was observed in the group of patients that received 1% propofol mixed with saline (table 1).

The discomfort caused by injection of 1% propofol mixed with saline was significantly higher than

Table 1 Pain on injection caused by propofol 10 mg ml^{-1} mixed with saline, hydrochloric acid 0.0064 mol litre^{-1} or 1% lignocaine in a ratio of 10 + 1

	Propofol + saline	Propofol + HCl	Propofol + lignocaine
n	22	24	25
Mean	2.18	0.88	0.32
SD	2.06	1.30	0.75
LS mean	2.18	0.88	0.32

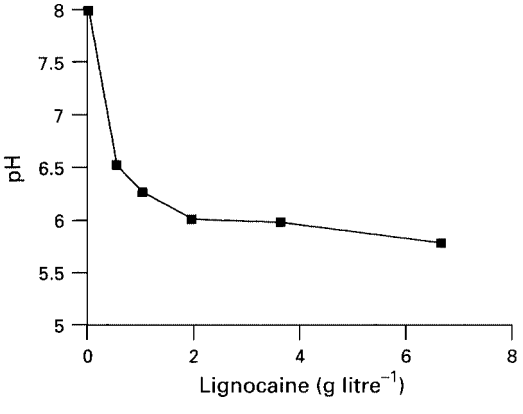

Figure 1 Effect on pH of increasing amounts of lignocaine added to 1% Diprivan.

Table 2 Differences between groups of patients given propofol 10 mg ml^{-1} mixed with saline, hydrochloric (HCl) acid 0.0064 mol litre^{-1} or 1% lignocaine in a ratio of 10 + 1

	Difference	95% Confidence interval	*P*
Propofol + HCl *vs* propofol + lignocaine	0.5550	−0.4322, 1.5422	0.1824
Propofol + saline *vs* propofol + HCl	1.3068	0.2872, 2.3264	0.0031
Propofol + saline *vs* propofol + lignocaine	1.8616	0.8520, 2.8716	<0.0001

Table 3 Effect on pH in a commercial propofol emulsion (Diprivan) by increasing volumes and concentrations of lignocaine

Preparation	pH
1% Lignocaine	6.75
1% Propofol in Diprivan	7.97–8.02
1% Diprivan 2 ml + 1% lignocaine 0.1 ml	6.57
1% Diprivan 2 ml + 1% lignocaine 0.2 ml	6.32
1% Diprivan 2 ml + 1% lignocaine 0.4 ml	6.14
4% Lignocaine	6.59
1% Diprivan 2 ml + 4% lignocaine 0.025 ml	6.52
1% Diprivan 2 ml + 4% lignocaine 0.05 ml	6.27
1% Diprivan 2 ml + 4% lignocaine 0.1 ml	6.09–6.01
1% Diprivan 2 ml + 4% lignocaine 0.2 ml	5.89
1% Diprivan 2 ml + 4% lignocaine 0.4 ml	5.78

Table 4 Effect on pH of increasing volumes and concentrations of lignocaine on a commercial 10% and 20% soybean emulsion (Intralipid)

Preparation	pH
10% Soybean emulsion	7.56
10% Soybean emulsion 2 ml + 4% lignocaine 0.1 ml	6.15
10% Soybean emulsion 2 ml + 4% lignocaine 0.2 ml	6.05
10% Soybean emulsion 2 ml + 4% lignocaine 0.4 ml	6.03
20% Soybean emulsion	7.54
20% Soybean emulsion 2 ml + 4% lignocaine 0.1 ml	5.93
20% Soybean emulsion 2 ml + 4% lignocaine 0.2 ml	5.77
20% Soybean emulsion 2 ml + 4% lignocaine 0.4 ml	5.77

that caused by injection of 1% propofol mixed with either 1% lignocaine or hydrochloric acid 0.0064 mol litre^{-1} in the same ratio. The difference in pain rating between 1% propofol mixed with 1% lignocaine and 1% propofol mixed with hydrochloric acid 0.0064 mol litre^{-1} was not significant (table 2).

There was a difference in pain rating between the patients' two hands even when identical mixtures were injected. The mean difference was 1.13 (SD 1.06) ($n = 15$). This "subject reporting error" may be considered as a methodological error of the pain rating.

IN VITRO EXPERIMENTS

The pH of the 1% Diprivan formulation varied between 7.97 and 8.02, while the pH of 1% lignocaine was 6.75. The resulting pH after mixing 1% Diprivan with 1% lignocaine in a ratio 10 to 1 was 6.32. An even lower pH was measured after increasing the volume of 1% lignocaine or increasing the lignocaine concentration (table 3). It is noticeable that the pH of this mixture was lower than that of 1% Diprivan or 1% lignocaine. A similar pH was obtained by mixing Diprivan with hydrochloric acid 0.0064 mol litre^{-1} in the same ratio.

A typical pH curve is shown in figure 1.

Table 5 Concentration (g litre^{-1}) and deviation (%) of propofol in the aqueous phase of a commercial preparation (1% Diprivan) *per se* and after addition of saline, 1% lignocaine or hydrochloric acid (HCl) 0.0064 mol litre^{-1} in a ratio of 10 + 1

Mixture	Concentration	Deviation
1% Diprivan	0.495	
1% Diprivan + saline	0.476	−
	vs	*vs*
1% Diprivan + 1% lignocaine	0.376	−21%
1% Diprivan + HCl 0.0064 mol litre^{-1}	0.392	−18%

The soybean oil concentration of 1% Diprivan is 10%. Increasing volumes of 4% lignocaine added to both 10% and 20% soybean oil mixtures resulted in further lowering of the pH (table 4).

Diprivan 10 mg ml^{-1} mixed with 1% lignocaine (10 + 1) separated into two immiscible layers within a few days, whereas 1% Diprivan mixed with saline or hydrochloric acid 0.0064 mol litre^{-1}, respectively, appeared stable on prolonged storage at room temperature. No macroscopic changes in these solutions were seen when stored in the dark for several months.

The concentration of propofol in the aqueous phase of 1% Diprivan was 0.495 g litre^{-1}. The aqueous concentration of propofol decreased in proportion when 1% Diprivan was mixed, and thus diluted, with saline. Diprivan 1% mixed with 1% lignocaine or hydrochloric acid 0.0064 mol litre^{-1} (10 + 1) was also analysed regarding the concentration of propofol in the aqueous phase of these mixtures. The concentrations of propofol in the aqueous phase decreased markedly when either 1% lignocaine or hydrochloric acid 0.0064 mol litre^{-1} was added (table 5).

The concentration of lignocaine in this phase was 1.015 g litre^{-1}. This concentration did not differ from that expected.

Discussion

After addition of 1% lignocaine or hydrochloric acid 0.0064 mol litre^{-1}, 1% Diprivan caused less pain on injection compared with addition of saline. Addition of 1% lignocaine to 1% Diprivan caused propofol to migrate from the aqueous phase of the 1% Diprivan emulsion into its lipid phase. This migration was accompanied by a change in pH. There was an inverse relationship between pH and amount of lignocaine added, not only to 1% Diprivan but also to the soybean emulsion (Intralipid) in which propofol is formulated. An increased proportion of propofol in the lipid phase caused less pain on injection.[6,7] The lesser discomfort caused by injection of a mixture of lignocaine and propofol, compared with for

example saline and propofol, may be explained only partly by the local anaesthetic action of lignocaine. This is suggested by the fact that lignocaine mixed and administered together with propofol is more effective in preventing pain on injection than pretreatment with lignocaine.[3 10] Propofol- induced pain on injection occurs quite slowly[10] giving lignocaine an opportunity to induce local anaesthesia. However, the amount of lignocaine and the injection technique are not the only important factors, but also local factors such as the contact between lignocaine and the vascular endothelium. Prolonging the effect of i.v. lignocaine on the vascular endothelium by proximal venous stasis eliminates the pain caused by subsequent injection of propofol.[12 13]

We observed a decreased incidence of pain on injection caused by 1% Diprivan when mixed with lignocaine. It is known[14] that the pH of the 1% Diprivan solution decreases when lignocaine is added and that this decrease is greater for larger doses of lignocaine. The question we tried to elucidate in this study was whether or not analgesia is obtained by local anaesthesia from lignocaine or indirectly from the decrease in pH. Therefore, a similar change in pH was created by adding hydrochloric acid to the 1% Diprivan. The results showed that the addition of hydrochloric acid to 1% Diprivan produced pain relief and that local anaesthesia by lignocaine was the less important factor for pain relief. There are three reasons for this: (1) pain prevention is instantaneous and the onset of anaesthesia from a local anaesthetic usually takes some time; (2) the concentration of lignocaine was less than 0.1%, too low for rapid onset of anaesthesia; and (3) the pH of the solution was so low that the proportion of lipophilic and diffusible free base of the lignocaine was insignificant in the water phase of the solution from which the local anaesthetic would be expected to come.

Comparisons between groups of patients are difficult to interpret as highly variable pain ratings were reported after injection of the same test solution in the same patient. This might be because of variations in the technique and rate of injection (although these were standardized as far as possible), in the area of vascular endothelium exposed to the solution and intra-individual differences in pain perception of blood vessels. This variation contributed to difficulties in isolating the effect of pH alone. Theoretically, a lower pH gives a higher fraction of propofol in an uncharged form with higher partition to the micelles of the soybean emulsion. Efforts have been made to change the emulsion formulation. Addition of blood to propofol[15] increases the amount of propofol in the emulsion phase. Also, an increased amount of fat decreases the aqueous partition of propofol by nearly 60%.[11] This deviation is more pronounced than that observed for 1% Diprivan and 1% lignocaine, and 1% Diprivan and hydrochloric acid 0.0064 mol litre^{-1} (-21% and -18%, respectively) compared with 1% Diprivan and saline. However, the main difference between our findings and theirs is that we detected a higher concentration of propofol in the aqueous phase. It is reasonable to assume that this difference was caused by different methodological procedures (equilibrium dialysis[11] *vs* ultracentrifugation (this study), respectively). Also, micelles may be soluble in both the aqueous and lipid phases of the emulsion. Because of this difference, the main focus should be on the physicochemical events and changes, not absolute levels.

The pH of the solution resulting from mixing 1% Diprivan with 1% lignocaine was even lower than the pH of the two ingredients by themselves. This finding might be because of changes in the surface area structure of the micelles. The decrease in pH *per se* does not cause the emulsion to stratify, as the mixture between 1% propofol and HCl 0.0064 mol litre^{-1} is macroscopically stable for several months. The same is not true when 1% lignocaine is mixed with 1% propofol.[16]

The mechanism by which propofol induces pain on injection is still not known. The release of kininogens may contribute to its origin[10 17] while vascular prostaglandin receptors do not seem to be important.[18] Local anaesthetics may bind to the vascular endothelium and binding of the local anaesthetic directly to propofol might also reduce its analgesic effects. Such an effect might explain the observed reduction of propofol-induced pain on injection by metoclopramide,[19] a structural analogue of procainamide but almost entirely lacking in local anaesthetic activity. However, a pH-lowering effect of the metoclopramide solution might also now be suggested as the principal mechanism for the reported pain relieving effect.

Acknowledgement

We thank Kjell Pennert, MSc, Clinical Data Care, Lund AB, for statistical calculations

References

1. Johnson RA, Harper NJN, Chadwick S, Vohra A. Pain on injection of propofol. Methods of alleviation. *Anaesthesia* 1990; **45**: 439–442.
2. McCulloch MJ, Lees NW. Assessment and modification of pain on induction with propofol (Diprivan). *Anaesthesia* 1985; **40**: 1117–1120.
3. Brooker J, Hull CJ, Stafford M. Effect of lignocaine on pain caused by propofol injection. *Anaesthesia* 1985; **40**: 91–92.
4. von Dardel O, Mebius C, Mossberg T, Svensson B. Fat emulsion as a vehicle for diazepam. A study in 9492 patients. *British Journal of Anaesthesia* 1983; **55**: 41–47.
5. Gran L, Bleie H, Jeppson R, Maartmann-Moe H. Etomidat mil Intralipid. Eine lösung zur schmerzfreien Injection. *Anaesthetist* 1983; **32**: 475–477.
6. Klement W, Arndt JO. Pain on intravenous injection of some anaesthetic agents is evoked by the unphysiological osmolality or pH of their formulations. *British Journal of Anaesthesia* 1991; **66**: 189–195.
7. Klement W, Arndt JO. Pain on injection of propofol. Effects of concentration and diluent. *British Journal of Anaesthesia* 1991; **67**: 281–284.
8. Arndt JO, Klement W. Pain evoked by polymodal stimulation of hand veins in humans. *Journal of Physiology* (*London*) 1991; **440**: 467–468.
9. Nicol ME, Moriarty J, Edwards J, Robbie DS, A'Hern RP. Modification of pain on injection of propofol—A comparision between lignocaine and procaine. *Anaesthesia* 1991; **46**: 67–69.
10. Scott RPF, Saunders DA, Norman J. Propofol: Clinical strategies for preventing the pain of injection. *Anaesthesia* 1988; **43**: 492–494.

11. Babl J, Doenicke A, Mönck V. New formulation of propofol in an LCT/MCT emulsion. Approach to reduce pain on injection. *European Journal of Hospital Pharmacy* 1995; **1**: 15–22.
12. Ewart MC, Whitman JG. Prevention of pain during injection of propofol. *Lancet* 1990; **335**: 798–799.
13. Mangar D, Holak EJ. Torniquet at 50 mm Hg followed by intravenous lidocaine diminishes hand pain associated with propofol injection. *Anesthesia and Analgesia* 1992; **74**: 250–252.
14. Kirk GA, Koontz FP, Chavez AJ. Lidocaine inhibits growth of *Staphylococcus aureus* in propofol. *Anesthesiology* 1992; **77**: A407.
15. McDonald DS, Jameson P. Injection pain with propofol. Reduction with aspiration of blood. *Anaesthesia* 1996; **51**: 878–880.
16. Lilley EMM, Isert PR, Carasso ML, Kennedy RA. The effect of the addition of lignocaine on propofol emulsion stability. *Anaesthesia* 1996; **51**: 815–818.
17. Derbyshire DR, Smith G. Sympathoadrenal responses to anaesthesia and surgery. *British Journal of Anaesthesia* 1984; **56**: 849–853.
18. Eriksson M. Prilocaine reduces injection pain caused by propofol. *Acta Anaesthesiologica Scandinavica* 1995; **39**: 210–213.
19. Ganta R, Fee JPH. Pain on injection of propofol: Comparison of lignocaine with metoclopramide. *British Journal of Anaesthesia* 1992; **69**: 316–317.