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Effect of electrokinetic stabilizers on the physicochemical properties of propofol emulsions

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ABSTRACT

The aims of the present study were to elucidate the potential mechanism of propofol emulsion destabilization following the addition of lidocaine, and to evaluate the effects of various electrokinetic stabilizers on the physicochemical properties of lidocaine–propofol emulsions. The assessments included pH observations and determination of the maximum globule diameter (MGD) and zeta potential (ZP). The MGD of propofol emulsions increased up to several tens μm following the addition of 50 mg of lidocaine to 200 mg of propofol, and the proposed destabilization mechanism involves localization of protonated lidocaine molecules between lecithin molecules in propofol emulsions, which consequently leads to increased ZP. The ZP of propofol emulsions containing acidic amino acid or neutral amino acid increased following the addition of lidocaine, and a charge reversal occurred. Therefore, the MGD of emulsions increased to several tens (m. However, the MGD of emulsions that contained basic amino acids or basic compounds remained below 5 (m, despite the addition of large amounts lidocaine (50 mg), and the ZP did not pass through the point of zero charge. In conclusion, our results provide not only further insight into the physical stability of propofol emulsions containing lidocaine, but also a better understanding of the administration of propofol in existing applications.

1. Introduction

Propofol (2,6-diisopropylphenol) is a parenteral anesthetic that has hypnotic properties and can be used to induce and maintain general anesthesia and sedation. Its onset time for reaction and recovery from anesthesia is fast, since it can pass through the blood brain barrier easily and acts quickly on the central nervous system due to its high lipophilicity. Propofol is poorly water-soluble, and is therefore generally formulated as a lipid emulsion (Cockshott et al., 1992, 1990; Gepts et al., 1985). The commercial propofol emulsion consists of 10 mg/mL propofol, 100 mg/mL soybean oil, 22.5 mg/mL glycerin, 12.0 mg/mL egg lecithin, water and sodium hydroxide to adjust the pH 6.0–8.5 (Lilley et al., 1996). Its mean globule diameter is 100–300 nm, and its zeta potential is −40 mV to −50 mV at pH 8 (Han et al., 2001). It has been reported that more than 70% of patients experienced pain with the injection of propofol emulsion in clinical trials (Klement and Arndt, 1991; Picard and Tramer, 2000). Propofol causes injection pain because free propofol released from emulsion system irritates free nerve endings in vascular endothelium. Propofol-induced pain was not mediated by plasma bradykinin (Sim et al., 2009). The usual method to prevent propofol-induced pain is to inject lidocaine 20–40 mg intravenously, immediately prior to the administration of propofol. The main effect of lidocine on the injection pain caused by propofol may be attributed to local analgesia (Fujii and Nakayama, 2004; King et al., 1992). In the field of anesthesiology, pre-mixing of lidocaine with propofol emulsion before the induction of anesthesia is seldom used. Further, continuous infusion of propofol–lidocaine mixture is also rarely used in clinical settings. However, it has been reported that the addition of lidocaine or other drugs to the propofol emulsion for alleviating pain on propofol injection (Bano et al., 2007; Doenicke et al., 1996; Gajraj and Nathanson, 1996; Kwak et al., 2007a, 2008; Picard and Tramer, 2000; Tan and Onsiong, 1998). Especially, after the addition of lidocaine, a significant amount of propofol is dissociated into a colorless, immiscible surface layer on emulsions (Lilley et al., 1996; Masaki et al., 2000) and the globule diameters of the emulsions increases to >5 μm (Masaki et al., 2000, 2003; Park et al., 2003). Moreover, the addition of even very small amounts of lidocaine decreases the absolute value of the zeta potential, which is an electrostatic repulsive force required to maintain emulsion stability (Lilley et al., 1996). Therefore the addition of 20–40 mg of lidocaine to 200 mg of propofol results in coalescence of oil droplets, which

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finally become a separate visible layer, indicating physicochemical incompatibility of the lidocaine–propofol mixture (Masaki et al., 2003). However, the overall process of destabilization is not clear, and there are few published articles concerning the mechanism of lidocaine–propofol destabilization. Large oil globules (over 5 (m in the emulsion) can cause pulmonary embolism, which can have fatal results (Driscoll et al., 1995; Koster et al., 1996). The United States Pharmacopeia (USP) has proposed specific globule size limits to ensure the physical stability of lipid injectable emulsions. In the globule size standards identified in USP Chapter <729> entitled "Globule Size Distribution in Lipid Injectable Emulsions," there are two separate droplet/globule size populations wherein limits are proposed. The intensity-weighted mean droplet diameter for lipid injectable emulsions must be less than 500 nm or 0.5 μm, and the volume-weighted, large-diameter fat globule limits of the dispersed phase, expressed as the percentage of fat residing in globules larger than 5 μm for a given lipid injectable emulsion, must be less than 0.05% (USP, 2009).

In our previous study (Park et al., 2003), 100% of volume-based diameter (maximum globule diameter) of the propofol emulsion increased to several tens μm after the addition of a large amount of lidocaine to the emulsion. However, there are few reports on elimination of the unfavorable effects of lidocaine on the physicochemical stability of propofol emulsions. Thus, the aims of this work were to elucidate the potential destabilization mechanism of propofol emulsions containing lidocaine and to evaluate the effects of various electrokinetic stabilizers on the physicochemical properties of lidocaine–propofol emulsions.

2. Materials and methods

2.1. Materials

Propofol emulsion (DIPRIVAN® 1%) and lidocaine injection (LITAINE 4%) were purchased from Zeneca (Macclesfield, Cheshire, UK) and Dai Han Pharm. Co. Ltd. (Ansan, Korea), respectively. L-Lysine, diethanolamine, sodium carbonate and sodium citrate were purchased from Sigma (St. Louis, MO, USA). L-Arginine, L-histidine, L-aspartic acid, L-glutamic acid, and L-isoleucine were supplied by Ajinomoto Co., Inc. (Tokyo, Japan). Other chemicals were reagent grade and were used as supplied.

2.2. Methods

2.2.1. Preparation of propofol emulsions containing electrokinetic stabilizers

Propofol emulsions containing electrokinetic stabilizers were prepared by the addition of electrokinetic stabilizer to commercial propofol emulsions. The electrokinetic stabilizers were: L-aspartic acid and L-glutamic acid (acidic amino acids); L-isoleucine (neutral amino acids); L-lysine, L-arginine, and L-histidine (basic amino acids); diethanolamine, sodium carbonate, and sodium citrate (basic compounds). An appropriate amount of electrokinetic stabilizer was added to a propofol emulsion and then dissolved thoroughly. The emulsion was aseptically subdivided into glass vials and sealed under a nitrogen atmosphere. The concentrations of electrokinetic stabilizer used in this study were 0.01, 0.05, 0.1 and 0.2% (w/v) for L-lysine and 0.2% (w/v) for other stabilizers. The prepared formulations were stored at room temperature and protected from light until used for experiments.

2.2.2. Characterization of the physicochemical properties of propofol emulsions containing electrokinetic stabilizers

After the addition of 0, 10, 20, 30, 40, and 50 mg lidocaine to 200 mg of propofol (equivalent to 20 mL of propofol emulsion), changes in the physicochemical properties of the propofol emulsions were assessed. The pH of the propofol emulsions was determined using a pH meter (420A, Thermo Orion, USA) combined with a Sure-Flow electrode (91–72, Thermo Orion, USA). The zeta potentials of the propofol emulsions were measured according to the method of Lilley et al. (1996) using AcoustoSizer IIs (Colloidal Dynamic Inc., Eveleigh, Australia). The maximum globule diameter of each propofol emulsion was measured with Mastersizer X (Malvern Instruments, UK). The prepared samples were added to the dispersant in the system at suitable concentration, which generated 10–30% obscuration. The maximum globule diameter was calculated in polydisperse analysis mode. All measurements were performed in triplicate at room temperature.

3. Results

Changes in pH and zeta potential of the emulsion after the addition of 0–50 mg of lidocaine to propofol emulsions containing different L-lysine concentrations (0%, 0.01%, 0.05%, 0.1%, and

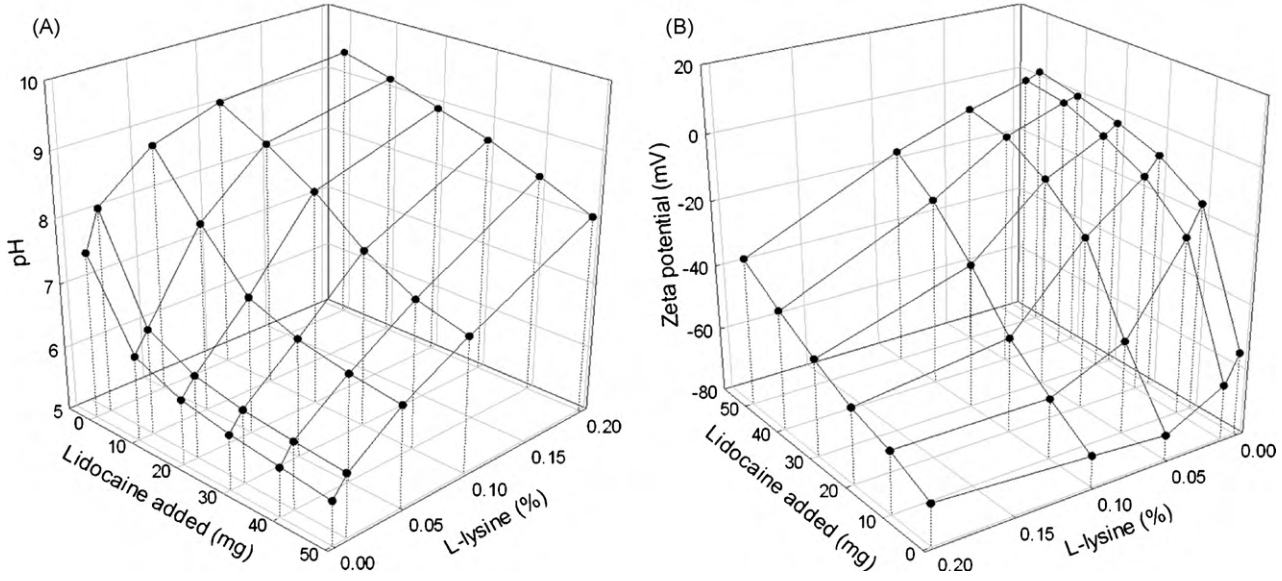

Fig. 1. Effect of L-lysine concentration on pH (A) and the zeta potential (B) of propofol emulsion (1% propofol) after the addition of lidocaine.

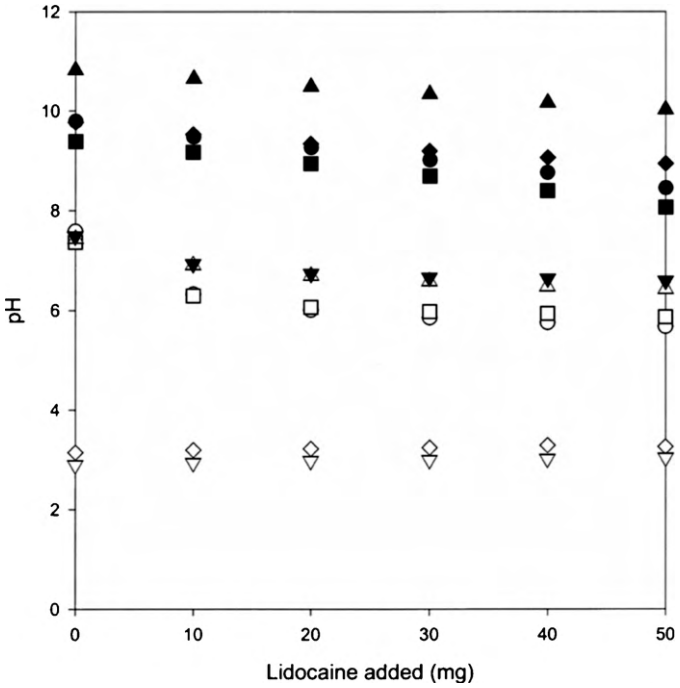

Fig. 2. Changes in pH of propofol emulsions (1% propofol) with 0.2% (w/v) electrokinetic stabilizers after the addition of lidocaine: ■, L-lysine; ●, L-arginine; ▼, L-histidine; □, L-isoleucine; ◊, L-glutamic acid; ▽, L-aspartic acid; ▲, sodium carbonate; ♦, diethanolamine; △, sodium citrate; ○, no addition.

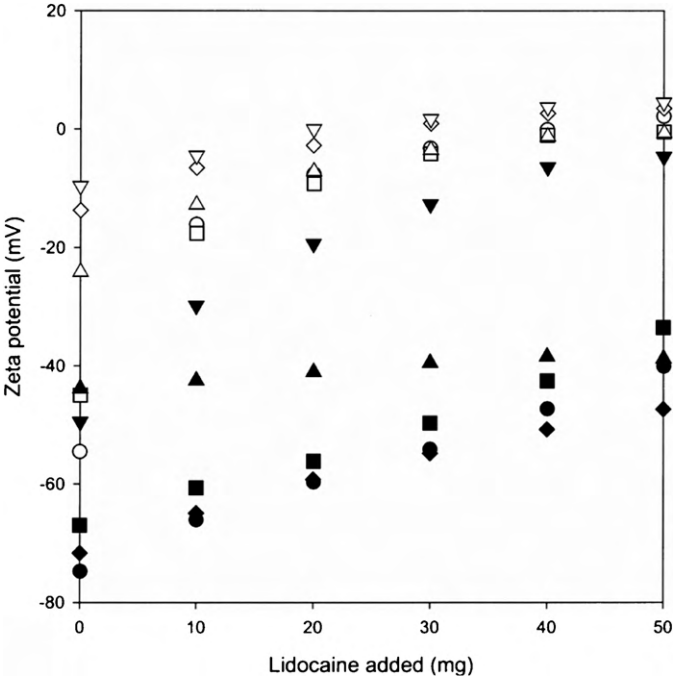

Fig. 3. Effect of 0.2% (w/v) electrokinetic stabilizer on the zeta potential of propofol emulsions (1% propofol) after the addition of lidocaine: ■, L-lysine; ●, L-arginine; ▼, L-histidine; □, L-isoleucine; ◊, L-glutamic acid; ▽, L-aspartic acid; ▲, sodium carbonate; ♦, diethanolamine; △, sodium citrate; ○, no addition.

0.2%) are shown in Fig. 1A and B, respectively. Both the pH and the absolute value of zeta potential of the emulsions gradually decreased when lidocaine was mixed with propofol emulsion containing L-lysine. However, the zeta potential of emulsions did not pass through the point of zero charge (PZC), except with 0.01% (w/v) L-lysine (Fig. 1B).

Changes in the pH of the propofol emulsions containing various electrokinetic stabilizers after the addition of lidocaine are shown in Fig. 2. The pH decreased from 9.8 to 8.5 in the emulsion containing 0.2% (w/v) L-arginine. Similar changes occurred in other formulations, except in the emulsion containing acidic amino acids. There was little change in the pH of the emulsion containing acidic amino acid, even though the concentration of lidocaine was increased.

The influence of the amount of lidocaine on the zeta potential of emulsions containing various electrokinetic stabilizers is shown in Fig. 3. The zeta potentials of the emulsions containing 0.2% (w/v) L-aspartic acid and L-glutamic acid were −9.7 mV and -13.7 mV, respectively. These emulsions had higher zeta potentials than commercial propofol emulsion, which had a value of −40.0 to −50 mV (Han et al., 2001). After adding 20–30 mg of lidocaine to propofol emulsion containing acidic amino acids, the zeta potential values passed through PZC, and reversal of the charge occurred. The zeta potential of emulsion containing 0.2% (w/v) neutral amino acid was very similar to that of commercial propofol emulsion without electrokinetic stabilizer. The absolute value of the zeta potential of the emulsion containing 0.2% (w/v) basic compounds also decreased with increasing concentration of lidocaine. After the addition of 0–50 mg of lidocaine to propofol emulsions containing basic compounds, the zeta potential of the emulsion increased from −71.7 mV to −47.4 mV (diethanolamine), from −43.7 mV to −38.7 mV (sodium carbonate), and from −24.0 mV to −0.6 mV (sodium citrate).

The effects of lidocaine concentration on the maximum globule diameters of emulsions containing various electrokinetic stabilizers are shown in Fig. 4. Immediately after addition of lidocaine to emulsions, the maximum globule diameters of emulsion admixtures were slightly increased; however, the maximum globule diameters were no larger than 5.0 μm at all lidocaine concentrations (Fig. 4A, C, and E). At 6 h after addition of lidocaine to emulsion containing basic amino acids/basic compounds (except sodium citrate), the maximum globule diameters had slightly increased, but the MGDs were less than 3.0 μm at all lidocaine concentrations (Fig. 4B and F). The maximum globule diameter of emulsions containing sodium citrate drastically increased up to the maximal detection limit (79.98 μm) at 6 h after addition of lidocaine. For acidic amino acids, the changes in the maximum globule diameters of the emulsion were very different from those of emulsions containing basic amino acids. At 6 h after addition of lidocaine, the maximum globule diameters of emulsions containing acidic amino acids increased to above 50 μm with 20–40 mg of lidocaine, while with 50 mg of lidocaine, the maximum globule diameters decreased to below 50 μm. Changes in maximum globule diameters of emulsions containing neutral amino acids were similar to those of emulsion that had no electrokinetic stabilizer. The maximum globule diameter of the emulsion increased to the maximal detection limit (79.78 μm) at 6 h after addition of 50 mg of lidocaine (Fig. 4D).

Thus, the physicochemical properties of the propofol emulsions were retained with basic amino acids, such as L-lysine, L-histidine, or L-arginine, and basic compounds, such as diethanolamine and sodium carbonate, even when a large amount of lidocaine (50 mg) was added.

4. Discussion

In this study, the propofol emulsion alone had a pH of 7.6 and zeta potential of −54.5 mV, but the pH and zeta potential of propofol emulsion (200 mg propofol) following the addition of 50 mg of lidocaine were 5.7 mV and 2.5 mV, respectively. The change in pH after addition of lidocaine was in agreement with the study by Eriksson et al. (1997), who documented a similar pH change after mixing 1% propofol emulsion with 1% lidocaine solution at a ratio of 10:1.

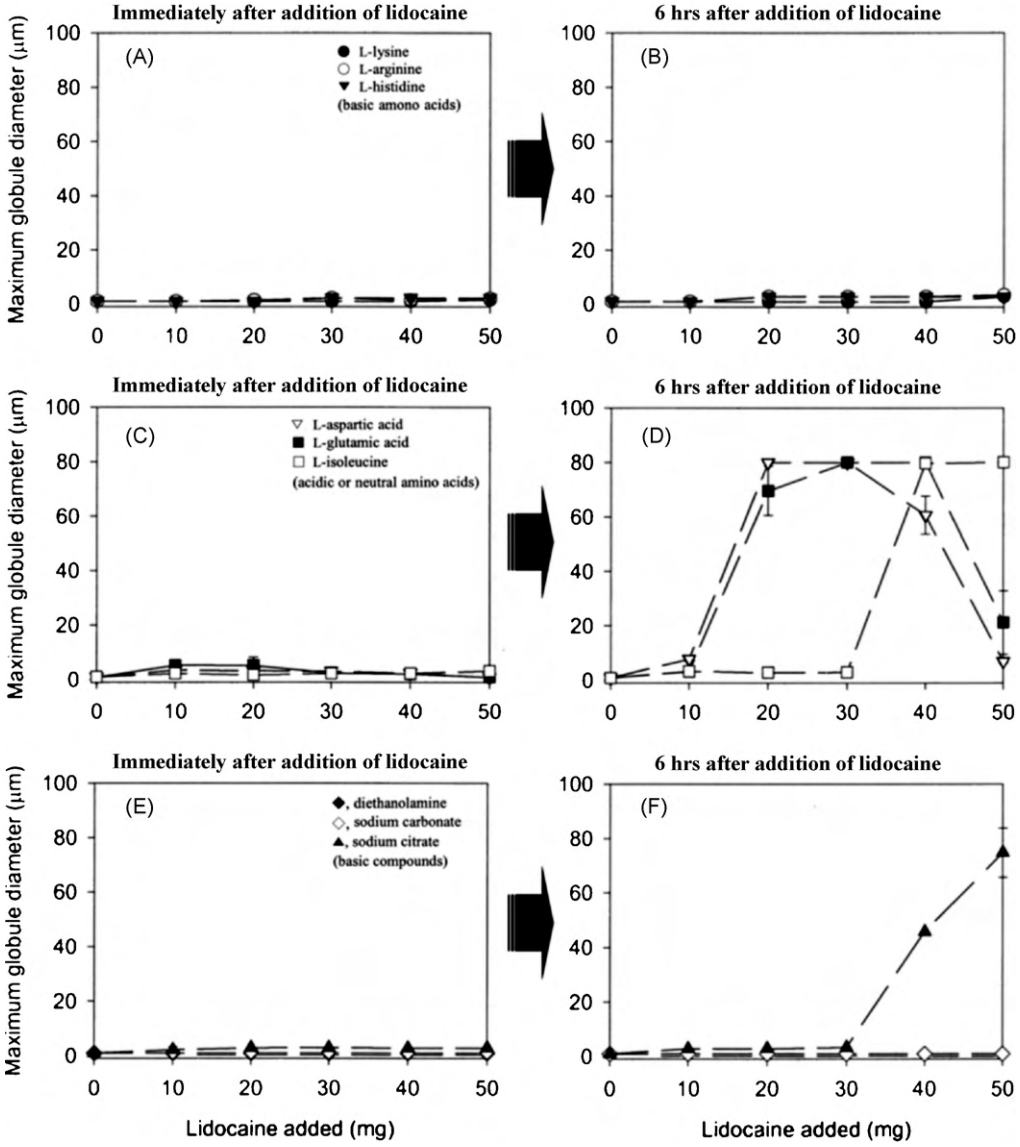

Fig. 4. Effect of 0.2% (w/v) electrokinetic stabilizer on the maximum globule diameter of propofol emulsions (1% propofol) after the addition of lidocaine: (A), (C), (E) at 0 h after admixture; (B), (D), (F) at 6 h after admixture.

The pH of the 1% propofol emulsion varied between 7.97 and 8.02, while the pH values of 1% lidocaine and lidocaine–propofol mixture were 6.75 and 6.32, respectively. Lidocaine solution is a weak free base-cation solution that, when exposed to lipids, liberates protons as the free base dissolves in the lipids, thereby decreasing the pH of the mixture (Eriksson et al., 1997).

Generally the most important factor that affects zeta potential is pH, but pH is not the main origin of instability in the lidocaine–propofol mixture. Addition of acids can cause a build-up of positive charge in the emulsion system. Therefore the zeta potential of emulsion will be higher at low pH and lower at high pH. However, as shown in Figs. 2 and 3, even though the pHs of propofol emulsions containing 0.2% aspartic acid (pH 2.9) and 0.2% glutamic acid (pH 3.1) were lower than that of propofol emulsion containing 50 mg of lidocaine (pH 5.7), the zeta potential of propofol emulsion containing 50 mg of lidocaine (2.5 mV) was higher than that of propofol emulsions containing 0.2% acidic amino acids without lidocaine (−13.7 mV to −9.7 mV). This indicates that lidocaine concentration, as well as hydrogen ion concentration, in the emulsion can strongly influence the zeta potential. In aqueous solution, lidocaine molecules (pK_a = 7.92) exist as a mixture of uncharged and positively charged (protonated) species depending on the pH of the solution (Matsuki et al., 2005). At pH 6.8, more than 90% of lidocaine molecules exist in the protonated form (MarvinSketch version 5.2, ChemAxon Ltd., Budapest, Hungary). Therefore, after mixing the propofol emulsion with lidocaine (pH < 6.8), protonated lidocaine is a major species (>90%).

The propofol emulsion contains egg lecithin (Lilley et al., 1996) as a surfactant, and egg lecithin consists mainly of phosphatidylcholine (PC) with a relatively small amount of phosphatidylethanolamine (Ikeda and Foegeding, 1999). The interactions of lidocaine with the structure of egg phosphatidylcholine (EPC) vesicles, which are used as model lipid membranes, have been studied extensively to better understand the molecular pharmacological mechanism of lidocaine (Boulanger et al., 1980; Darke et al., 1972; de Paula et al., 2008; Depaula and Schreier, 1995; Fraceto et al., 2002, 2005; Gargiulo et al., 1973; Giotta et al., 1974; Kelusky and Smith, 1984; Lee et al., 1972; Oda et al., 1991; Ondrias et al., 1987; Westman et al., 1982). In addition, Hogberg et al. (2007) have examined the behavior of charged and uncharged lidocaine in lipid dimyristoylphosphatidylcholine (DMPC) bilayers, which contain the same head group structures as EPC. Although the

charged lidocaine molecules cannot pass through the lipid bilayer (Hogberg et al., 2007), protonated lidocaine can be partitioned into PC unilamellar vesicles from the aqueous phase (logarithm of membrane-water partition coefficient, log P = 1.22) (Avdeef et al., 1998). Another study demonstrated that the positively charged nitrogen of lidocaine can interact with polar part of the egg lecithin vesicles (Oda et al., 1991). Hogberg et al. (2007) investigated the orientation of lidocaine molecules in the bilayer and concluded that the charged lidocaine adopts an orientation parallel to the bilayer; the aromatic ring is always oriented to the alkyl interior of the bilayer and the protonated nitrogen is positioned in the head group region. Based on these studies, we propose that protonated lidocaine molecules (1) are inserted and oriented between EPC molecules in propofol emulsions, (2) neutralize the net charge of emulsion globules and (3) increase the zeta potential of emulsion. Therefore, even though the pH of emulsion containing lidocaine is higher than that of emulsion containing acidic amino acids, the zeta potential of emulsion containing lidocaine is higher than that of emulsion containing acidic amino acids without lidocaine. On the other hand, the direct influence of the protonated nitrogen of acidic amino acids on the egg lecithin in emulsions seems to be negligible compared with that of lidocaine. Calculated partition coefficients of acidic amino acids (MarvinSketch version 5.2, ChemAxon Ltd., Budapest, Hungary) gave negative log P values (−3.64 for L-aspartic acid and −3.38 for L-glutamic acid). Hence acidic amino acids may have less chance to partition into egg lecithin vehicles due to their extreme hydrophilic properties.

To evaluate the effects of electrokinetic stabilizers on the physicochemical properties of lidocaine–propofol mixture, amino acids and basic compounds were used as electrokinetic stabilizers. As shown in Fig. 1, pH and zeta potential of propofol emulsion can be affected not only by the concentration of electrokinetic stabilizer in emulsions but also by the amount of lidocaine added to the emulsion. The maximum globule diameter of propofol emulsions without electrokinetic stabilizer increased to 50 μm at 6 h after addition of 50 mg of lidocaine to 200 mg of propofol (Park et al., 2003). However, the addition of basic amino acids or basic compounds (except sodium citrate) kept the maximum globule diameter of the propofol emulsions below 5.0 μm at 6 h even with 50 mg lidocaine. In contrast, the addition of acidic or non-ionic (neutral) amino acids did not keep the maximum globule diameter of propofol emulsions within the clinically acceptable range (<5 (m). 0.2% (w/v) sodium citrate in propofol emulsion did not increase the electrostatic repulsive forces of the oil globule surface because its concentration in the emulsion was too low; this was proven by the zeta potential measurements in propofol emulsions (Fig. 3). When basic amino acids or basic compounds are present in propofol emulsions, the emulsion globules will tend to acquire a more negative charge due to the hydroxide ion and the uncharged lidocaine ratio will increase. Fig. 5 shows the relationship between

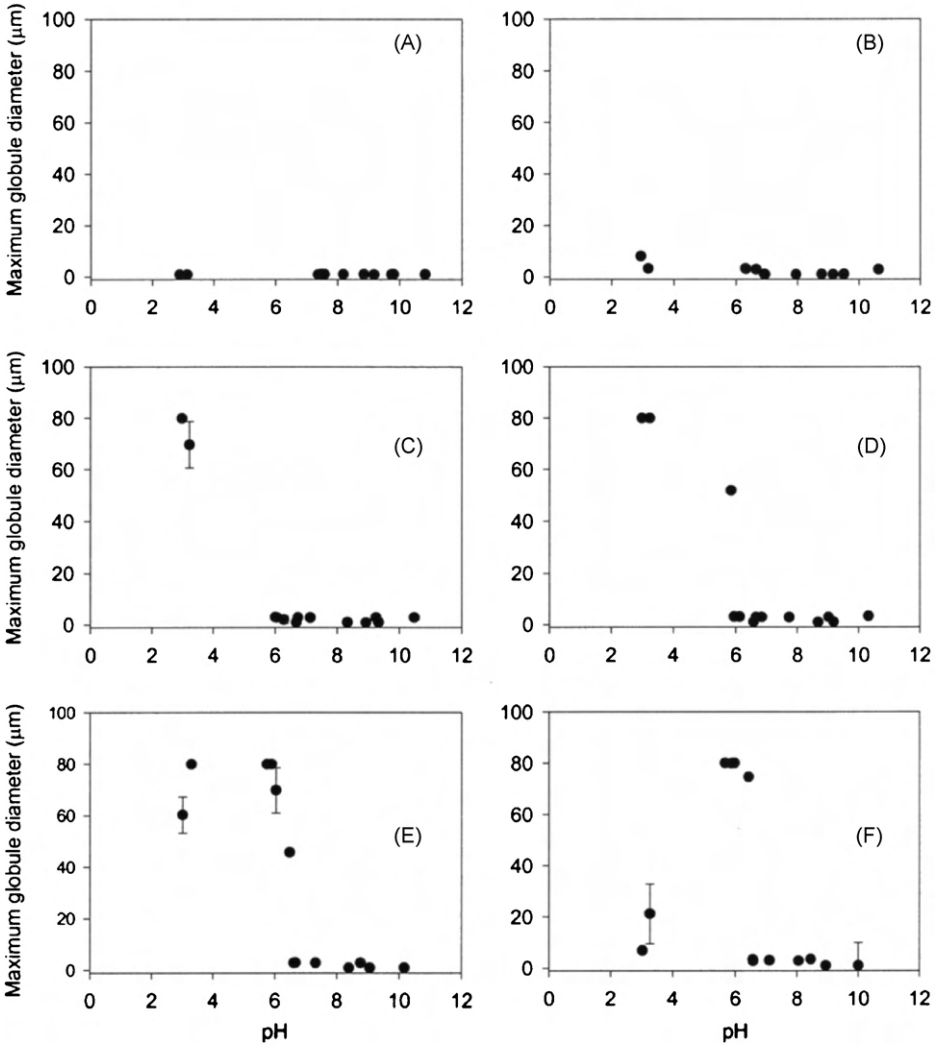

Fig. 5. The relationship between the maximum globule diameter of propofol emulsions and pH at 6 h after the addition of lidocaine to 200 mg of propofol: (A) 0 mg; (B) 10 mg; (C) 20 mg; (D) 30 mg; (E) 40 mg; (F) 50 mg.

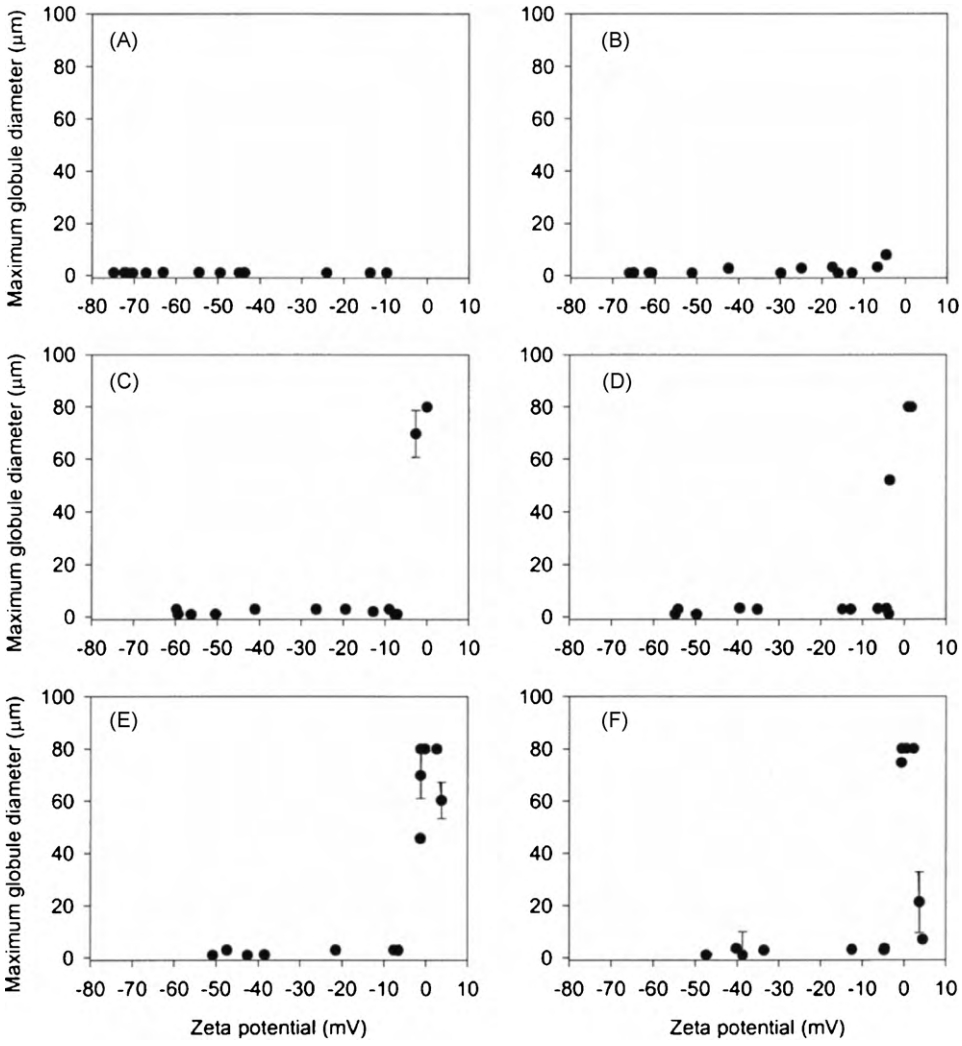

Fig. 6. The relationship between the maximum globule diameter of propofol emulsions and zeta potential at 6 h after the addition of lidocaine to 200 mg of propofol: (A) 0 mg; (B) 10 mg; (C) 20 mg; (D) 30 mg; (E) 40 mg; (F) 50 mg.

the maximum globule diameter of propofol emulsions and pH with 0–50 mg of lidocaine added. As shown in Fig. 5A, the maximum globule diameter of propofol emulsions changed little without lidocaine despite a low pH. Thus, low pH is not the main reason for destabilization of propofol emulsion. This result is consistent with a previous report by Eriksson et al. (1997) that a decrease in pH does not cause the emulsion to stratify, as the mixture between 1% propofol and HCl 0.0064 mol/L, which has the same pH as a mixture of 1% propofol emulsion and 1% lidocaine solution in a ratio 10:1, is macroscopically stable for several months. At 10 mg of lidocaine, the maximum globule diameter of propofol emulsions was slightly altered at low pH, but the change was not dramatic (Fig. 5B). After addition of 20–50 mg of lidocaine (Fig. 5C–F), the maximum globule diameter of propofol emulsions increased to several tens (m when below pH 6.0 (neutral, acidic amino acids and without electrokinetic stabilizer). The relationship between maximum globule diameter of propofol emulsions and zeta potential according to the concentration of lidocaine is shown in Fig. 6. The zeta potential in propofol emulsions shifted gradually to a higher range, with increasing the concentration of lidocaine from 0 mg to 50 mg. As the zeta potential was around −5 mV, the maximum globule diameter of propofol emulsions began to increase and reached the maximum detection limit when the zeta potential of propofol emulsions passed through PZC. The maximum globule diameter subsequently decreased to about 7.0 (m at a zeta potential of +4.5 mV. These results indicate that the zeta potential of −5.0 mV and pH of 6.0 are critical points to retain the propofol emulsion globule size below 5.0 (m following the addition of 50 mg of lidocaine.

5. Conclusions

There have been many reports to reduce propofol injection pain, and combination therapy using various drugs, such as ketamine (Bano et al., 2007; Saadawy et al., 2007), metoprolol (Asik et al., 2003), metoclopramide (Fujii and Nakayama, 2005), bupivacaine (Senturk et al., 2002), dexamethasone (Kwak et al., 2008), remifentanil (Kwak et al., 2007a,b; Roehm et al., 2003), ropivacaine (Xiang and Li, 2007), alfentanil (Fang and Keyes, 2006), dexmedetomidine (Turan et al., 2005) and flurbiprofen (Fujii and Nakayama, 2004) have been suggested for the prevention of propofol pain. Consequently, our results can provide further insight into the physicochemical stability of propofol emulsions containing other drugs, and these data can also help clinical researchers gain a better understanding of propofol's administration in existing applications.

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References

Asik, I., Yorukoglu, D., Gulay, I., Tulunay, M., 2003. Pain on injection of propofol: comparison of metoprolol with lidocaine. Eur. J. Anaesthesiol. 20, 487–489.

Avdeef, A., Box, K.J., Comer, J.E., Hibbert, C., Tam, K.Y., 1998. pH-metric log *P* 10. Determination of liposomal membrane–water partition coefficients of ionizable drugs. Pharm. Res. 15, 209–215.

Bano, F., Zafar, S., Sabbar, S., Aftab, S., Haider, S., Sultan, S.T., 2007. Intravenous ketamine attenuates injection pain and arterial pressure changes during the induction of anesthesia with propofol: a comparison with lidocaine. J. Coll. Physicians Surg. Pak. 17, 390–393.

Boulanger, Y., Schreier, S., Leitch, L.C., Smith, I.C., 1980. Multiple binding sites for local anesthetics in membranes: characterization of the sites and their equilibria by deuterium NMR of specifically deuterated procaine and tetracaine. Can. J. Biochem. 58, 986–995.

Cockshott, I.D., Douglas, E.J., Plummer, G.F., Simons, P.J., 1992. The pharmacokinetics of propofol in laboratory animals. Xenobiotica 22, 369–375.

Cockshott, I.D., Douglas, E.J., Prysroberts, C., Turtle, M., Coates, D.P., 1990. The Pharmacokinetics of Propofol during and after intravenous–infusion in man. Eur. J. Anaesthesiol. 7, 265–275.

Darke, A., Finer, E.G., Flook, A.G., Phillips, M.C., 1972. Nuclear magnetic resonance study of lecithin–cholesterol interactions. J. Mol. Biol. 63, 265–279.

de Paula, E., Schreier, S., Jarrell, H.C., Fraceto, L.F., 2008. Preferential location of lidocaine and etidocaine in lecithin bilayers as determined by EPR, fluorescence and H-2 NMR. Biophys. Chem. 132, 47–54.

Depaula, E., Schreier, S., 1995. Use of a novel method for determination of partition-coefficients to compare the effect of local-anesthetics on membrane-structure. Biochim. Biophys. Acta – Biomemb. 1240, 25–33.

Doenicke, A.W., Roizen, M.F., Rau, J., Kellermann, W., Babl, J., 1996. Reducing pain during propofol injection: the role of the solvent. Anesth. Analg. 82, 472–474.

Driscoll, D., Bhargava, H., Li, L., Zaim, R., Babayan, V., Bistrian, B., 1995. Physicochemical stability of total nutrient admixtures. Am. J. Health Syst. Pharm. 52, 623–634.

Eriksson, M., Englesson, S., Niklasson, F., Hartvig, P., 1997. Effect of lignocaine and pH on propofol-induced pain. Br. J. Anaesth. 78, 502–506.

Fang, Z.T., Keyes, M.A., 2006. A novel mixture of propofol, alfentanil, and lidocaine for regional block with monitored anesthesia care in ophthalmic surgery. J. Clin. Anesth. 18, 114–117.

Fraceto, L.F., Pinto, L.D.A., Franzoni, L., Braga, A.A.C., Spisni, A., Schreier, S., de Paula, E., 2002. Spectroscopic evidence for a preferential location of lidocaine inside phospholipid bilayers. Biophys. Chem. 99, 229–243.

Fraceto, L.F., Spisni, A., Schreier, S., de Paula, E., 2005. Differential effects of uncharged aminoamide local anesthetics on phospholipid bilayers, as monitored by H-1-NMR measurements. Biophys. Chem. 115, 11–18.

Fujii, Y., Nakayama, M., 2004. Reduction of propofol-induced pain through pretreatment with lidocaine and/or flurbiprofen. Clin. Drug Invest. 24, 749–753.

Fujii, Y., Nakayama, M., 2005. A lidocaine/metoclopramide combination decreases pain on injection of propofol. Can. J. Anaesth. 52, 474–477.

Gajraj, N.M., Nathanson, M.H., 1996. Preventing pain during injection of propofol: the optimal dose of lidocaine. J. Clin. Anesth. 8, 575–577.

Gargiulo, R.J., Giotta, G.J., Wang, H.H., 1973. Spin-labeled analogs of local anesthetics. J. Med. Chem. 16, 707–708.

Gepts, E., Claeys, A.M., Camu, F., 1985. Pharmacokinetics of propofol (diprivan) administered by continuous intravenous–infusion in man – a preliminary-report. Postgrad. Med. J. 61, 51–52.

Giotta, G.J., Chan, D.S., Wang, H.H., 1974. Binding of spin-labeled local anesthetics to phosphatidylcholine and phosphatidylserine liposomes. Arch. Biochem. Biophys. 163, 453–458.

Han, J., Davis, S.S., Washington, C., 2001. Physical properties and stability of two emulsion formulations of propofol. Int. J. Pharm. 215, 207–220.

Hogberg, C.J., Maliniak, A., Lyubartsev, A.P., 2007. Dynamical and structural properties of charged and uncharged lidocaine in a lipid bilayer. Biophys. Chem. 125, 416–424.

Ikeda, S., Foegeding, E.A., 1999. Effects of lecithin on thermally induced whey protein isolate gels. Food Hydrocolloids 13, 239–244.

Kelusky, E.C., Smith, I.C., 1984. Anesthetic-membrane interaction: a 2H nuclear magnetic resonance study of the binding of specifically deuterated tetracaine and procaine to phosphatidylcholine. Can. J. Biochem. Cell Biol. 62, 178–184.

King, S.Y., Davis, F.M., Wells, J.E., Murchison, D.J., Pryor, P.J., 1992. Lidocaine for the prevention of pain due to injection of propofol. Anesth. Analg. 74, 246–249.

Klement, W., Arndt, J.O., 1991. Pain on injection of propofol: effects of concentration and diluent. Br. J. Anaesth. 67, 281–284.

Koster, V.S., Kuks, P.F.M., Lange, R., Talsma, H., 1996. Particle size in parenteral fat emulsions, what are the true limitations? Int. J. Pharm. 134, 235–238.

Kwak, K., Chung, H., Lim, C., Han, C., Choi, G., Lim, D., Kim, S., Jeon, Y., 2007a. A combination of lidocaine (lignocaine) and remifentanil reduces pain during propofol injection. Clin. Drug Invest. 27, 493–497.

Kwak, K., Kim, J., Park, S., Lim, D., Kim, S., Baek, W., Jeon, Y., 2007b. Reduction of pain on injection of propofol: combination of pretreatment of remifentanil and premixture of lidocaine with propofol. Eur. J. Anaesthesiol. 24, 746–750.

Kwak, K.H., Ha, J., Kim, Y., Jeon, Y., 2008. Efficacy of combination intravenous lidocaine and dexamethasone on propofol injection pain: a randomized, double-blind, prospective study in adult Korean surgical patients. Clin. Ther. 30, 1113–1119.

Lee, A.G., Birdsall, N.J., Levine, Y.K., Metcalfe, J.C., 1972. High resolution proton relaxation studies of lecithins. Biochim. Biophys. Acta 255, 43–56.

Lilley, E.M., Isert, P.R., Carasso, M.L., Kennedy, R.A., 1996. The effect of the addition of lignocaine on propofol emulsion stability. Anaesthesia 51, 815–818.

Masaki, Y., Tanaka, M., Nishikawa, T., 2000. Changes in propofol concentration in a propofol–lidocaine 9:1 volume mixture. Anesth. Analg. 90, 989–992.

Masaki, Y., Tanaka, M., Nishikawa, T., 2003. Physicochemical compatibility of propofol–lidocaine mixture. Anesth. Analg. 97, 1646–1651.

Matsuki, H., Yamanaka, M., Kamaya, H., Kaneshina, S., Ueda, I., 2005. Dissociation equilibrium between uncharged and charged local anesthetic lidocaine in a surface-adsorbed film. Colloid Polym. Sci. 283, 512–520.

Oda, K., Kokubu, M., Shinya, N., Machida, M., 1991. Proton magnetic resonance study on the interaction of lidocaine derivatives with lecithin vesicles. Masui 40, 72–79.

Ondrias, K., Gallova, J., Szocsova, H., Stolc, S., 1987. pH-dependent effects of local anaesthetics in perturbing lipid membranes. Gen. Physiol. Biophys. 6, 271–277.

Park, J.W., Park, E.S., Chi, S.C., Kil, H.Y., Lee, K.H., 2003. The effect of lidocaine on the globule size distribution of propofol emulsions. Anesth. Analg. 97, 769–771.

Picard, P., Tramer, M.R., 2000. Prevention of pain on injection with propofol: a quantitative systematic review. Anesth. Analg. 90, 963–969.

Roehm, K.D., Piper, S.N., Maleck, W.H., Boldt, J., 2003. Prevention of propofol-induced injection pain by remifentanil: a placebo-controlled comparison with lidocaine. Anaesthesia 58, 165–170.

Saadawy, I., Ertok, E., Boker, A., 2007. Painless injection of propofol: pretreatment with ketamine vs thiopental, meperidine, and lidocaine. Middle East J. Anesthesiol. 19, 631–644.

Senturk, M., Pembeci, K., Menda, F., Ozkan, T., Gucyetmez, B., Tugrul, M., Camci, E., Akpir, K., 2002. Effects of intramuscular administration of lidocaine or bupivacaine on induction and maintenance doses of propofol evaluated by bispectral index. Br. J. Anaesth. 89, 849–852.

Sim, J.Y., Lee, S.H., Park, D.Y., Jung, J.A., Ki, K.H., Lee, D.H., Noh, G.J., 2009. Pain on injection with microemulsion propofol. Br. J. Clin. Pharmacol. 67, 316–325.

Tan, C.H., Onsiong, M.K., 1998. Pain on injection of propofol. Anaesthesia 53, 468–476.

Turan, A., Memis, D., Kaya, G., Karamanlioglu, B., 2005. The prevention of pain from injection of propofol by dexmedetomidine and comparison with lidocaine. Can. J. Anaesth. 52, 548–549.

USP 32, 2009. United States Pharmacopeia, chapter <729>, The United States Pharmacopeial Convention, Rockville, MD, pp. 283–285.

Westman, J., Boulanger, Y., Ehrenberg, A., Smith, I.C., 1982. Charge and pH dependent drug binding to model membranes. A 2H-NMR and light absorption study. Biochim. Biophys. Acta 685, 315–328.

Xiang, Y., Li, Y.H., 2007. Comparison of 1.5% lidocaine and 0.5% ropivacaine epidural anesthesia combined with propofol general anesthesia guided by bispectral index. J. Zhejiang Univ. Sci. B 8, 428–434.