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Emulsion of flurbiprofen axetil reduces propofol injection pain due to a decrease in free propofol concentration

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Abstract

Purpose. Flurbiprofen axetil emulsion (FA), a prodrug of nonsteroidal anti-inflammatory drugs (NSAIDs) that is widely used for perioperative pain relief in Japan, has been effective for reducing propofol injection pain, but the mechanism is unclear. The purpose of this study was to test the hypothesis that the reduction of propofol injection pain by FA may be attributed to a decrease in free propofol concentration.

Methods. Diprivan (propofol emulsion; Dipri; AstraZeneca, Cheshire, UK) and Propofol-Lipuro (Lipuro; B. Braun, Melsungen, Germany) were used. A randomized double-blind study was performed to compare pain on injection with six kinds of propofol solution: plain Dipri, a 3:1 (v/v) mixture of Dipri and saline (Dipri-S), a 3:1 mixture of Dipri and FA (Dipri-FA), plain Lipuro, a 3:1 mixture of Lipuro and saline (Lipuro-S), and a 3:1 mixture of Lipuro and FA (Lipuro-FA). Three hundred patients (American Society of Anesthesiologists [ASA] physical status [PS] I–II) scheduled for elective surgery received one of these six propofol emulsions ($n = 50$, each group). Injection pain was evaluated every 10 s after the start of a 1-min infusion of up to 2 mg·kg^{-1} propofol. We also measured the in vitro free propofol concentrations of the propofol preparations that we tested ($n = 5$, each).

Results. The mixture of FA with propofol decreased the incidence of injection pain, compared with plain propofol, for Lipuro ($P < 0.01$) but not for Dipri. The free propofol concentration in each emulsion in vitro was also decreased by mixing the propofol with saline or FA. The incidence of pain was reduced in a free-propofol concentration-dependent manner ($R^2 = 0.926$).

Conclusion. The findings suggest that the reduction of propofol injection pain by FA may be explained, at least in part, by a reduction in the free propofol concentration.

Key words Anesthetics i.v. · Flurbiprofen axetil emulsion · Free fraction · Injection pain · Propofol

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Introduction

Although propofol is commonly used for the induction of anesthesia, pain on its injection is an annoying side effect. On receiving an injection with propofol, 32% to 67% of patients experience moderate to severe pain [1–3]. A variety of methods to alleviate the injection pain have been reported, but the mechanism of the injection pain is still unclear [3–6]. The most likely mechanism for propofol injection pain lies in the free propofol concentration (i.e., in the aqueous phase) [7,8]. In comparison with Diprivan (Propofol emulsion; Dipri; AstraZeneca, Cheshire, UK), Propofol-Lipuro (Lipuro; B. Braun, Melsungen, Germany) shows reduced injection pain in Lipuro, the addition of medium-chain fatty acids to the emulsion decreases the free propofol concentration, supporting the above hypothesis [9–11]. In addition, a mixture of long-chain and medium-chain triglycerides in the carrier emulsion has been reported to decrease the incidence of pain on bolus injection in volunteers [12]. These findings suggest that modulation of the free propofol concentration plays a key role in reducing the incidence of injection pain, but we could not find any studies confirming this notion, based on clinical findings and laboratory data.

Flurbiprofen axetil emulsion (FA) (Ropion; Kaken Pharmaceutical, Tokyo, Japan), a prodrug of nonsteroidal anti-inflammatory drugs (NSAIDs), is widely used for perioperative pain relief in Japan [13,14]. Previous studies [15,16] showed that FA reduced propofol injection pain, but different administration methods of propofol and FA, in terms of timing and sample preparation, may complicate elucidation of the mechanism. Because FA contains 10% soybean oil, a mixture of FA with propofol may decrease the free propofol concentration, probably due to the dispersion of propofol into the lipid phase of FA, thereby reducing the injection pain, as found for long-chain and medium-chain triglycerides. In

the current study, this hypothesis was tested by comparing the incidence of propofol injection pain when propofol was administered with or without FA. In addition, we measured the in vitro free propofol concentrations of the propofol preparations with or without FA and we examined the relationship between injection pain and the free propofol concentration

Methods

After obtaining approval from our local Institutional Review Boards, and informed consent from the patients, 300 patients, American Society of Anesthesiologists (ASA) physical status I or II, scheduled for elective surgery were included in the study. We excluded patients whose weight was more than 75 kg. The dilution of propofol with saline was also tested to investigate the contribution of the dilution of propofol to injection pain. In a randomized double-blind study, we prepared six kinds of propofol solution, diluted with saline or FA, based on 1% Diprivan (Dipri) or 1% Propofol Lipuro (Lipuro): (1) plain 1% Dipri; (2) a 3:1 (v/v) mixture of Dipri and saline (Dipri-S); (3) a 3:1 (v/v) mixture of Dipri and FA (Dipri-FA); (4) plain 1% Lipuro; (5) a 3:1 (v/v) mixture of Lipuro and saline (Lipuro-S); and (6) a 3:1 (v/v) mixture of Lipuro and FA (Lipuro-FA).

None of the patients were premedicated. After the patient entered the operating room, a small vein on the dorsum of the patient's hand was cannulated with a 20-gauge IV catheter (Angiocath; BD Biosciences, Franklin Lakes, NJ, USA). The anesthesiologist in charge prepared the test emulsion in a 20-ml syringe about 10 min before use and set a 1-min infusion speed for 2 mg·kg^{-1} propofol in the syringe pump (Graseby 3500; Graseby Medical, Watford, UK). Two members of staff other than the anesthesiologist in charge were involved in the study. One instructed the anesthesiologist in charge on the type of test emulsion and the other judged the injection pain. Immediately after Ringer's acetate solution was infused as fast as possible by fully opening the line, the anesthesiologist in charge started the pump, which was blinded to one examiner. As shown in Table 1, the pain score was defined as 0, none; 1, mild; 2, moderate; and 3, severe, according to previous studies [17,18]. After the start of the drug infusion, the patient was asked about injection pain every 10 s, and pain incidence was defined as a pain score of 1 or more. Time to loss of eyelash reflex, and blood pressure and heart rate were also recorded.

The in vitro free propofol concentrations in the aqueous phase of the test solutions were measured by high-performance liquid chromatography (HPLC) [19]. Aliquots of 9 ml of test solutions were placed outside the container (dialysis cups MWCO 3500; BioTech International, Needville, TX, USA) and 0.25 ml of a glycerol solution at the same concentration as each test solution was placed in the dialysis cup. The samples were left for 24 h at room temperature to separate free propofol molecules from the propofol solutions. Then, we measured the free propofol concentration in the contents of the dialysis cups by HPLC (LC-10AD; Shimadzu, Kyoto, Japan). The pH of each test solution was also measured.

Values are expressed as means ± SD. Subject variables among groups receiving plain propofol and a mixture with saline or FA were analyzed with the χ^2 test or one-way analysis of variance (ANOVA). The free propofol concentration in the emulsions was compared among the six groups by one-way ANOVA. The number needed to treat (NNT) was calculated on the basis of pain incidence with plain Dipri. The relationship between injection pain incidence and the free propofol concentration was analyzed by logistic regression, using GraphPad Prism (GraphPad Software, San Diego, CA, USA). $P < 0.05$ was considered statistically significant.

Results

None of the patients were excluded from the study. The six test solution groups were comparable with respect to age, weight, height, and sex. There were no significant differences between groups regarding time to loss of eyelash reflex or blood pressure and heart rate.

Figure 1 shows the pain incidence and pain intensity for each propofol solution. Although the admixture

Table 1. Assessment of pain during injection of propofol

Pain score	Degree of pain	Response
0	None	Negative response to questioning
1	Mild	Pain reported in response to questioning only, without any behavioral sign
2	Moderate	Pain reported in response to questioning, accompanied by behavioral sign; or pain reported spontaneously without questioning
3	Severe	Strong vocal response; or response accompanied by facial grimacing, arm withdrawal, or tears

of saline and FA appeared to decrease pain incidence for both Dipri and Lipuro, a significant difference was found only between plain Lipuro and Lipuro-FA ($P = 0.0048$). In each group, mild pain accounted for more than 50% of all pain incidence and severe pain was found in no more than three patients.

The free propofol concentration was significantly lower in Lipuro than in Dipri (11.6 ± 0.4 vs 15.5 ± 0.3 μg·ml^{-1}) implying that the free fraction was only 0.12% and 0.16% of each of these plain propofol formulations (Table 2). Dilution with saline and FA significantly reduced the free propofol concentrations in both plain propofol emulsions, but the magnitudes of reduction were larger for FA than for saline. Namely, the free propofol concentration was decreased to two-thirds that in both the plain propofol emulsions by the addition of FA, whereas only a 10% decrease was found for saline. The pH of Dipri was 7.0 and that of Lipuro was 7.2. Dilution with saline and FA significantly reduced the pH in both propofol solutions, by 0.4–0.5 and 0.9–1.1, respectively (Table 2).

The NNT, standardized by plain Dipri, as 12.5 for Dipri-S, 6.3 for Dipri-FA, 8.3 for Lipuro, 3.6 for Lipuro-S, and 2.5 for Lipuro-FA.

The relationship between the free propofol concentration and the incidence of injection pain was described by a sigmoid concentration-response curve, as shown in Fig. 2 ($R^2 = 0.926$). The drug concentration at which 50% of patients did not have injection pain (EC_{50}) was calculated to be 10.7 μg·ml^{-1}.

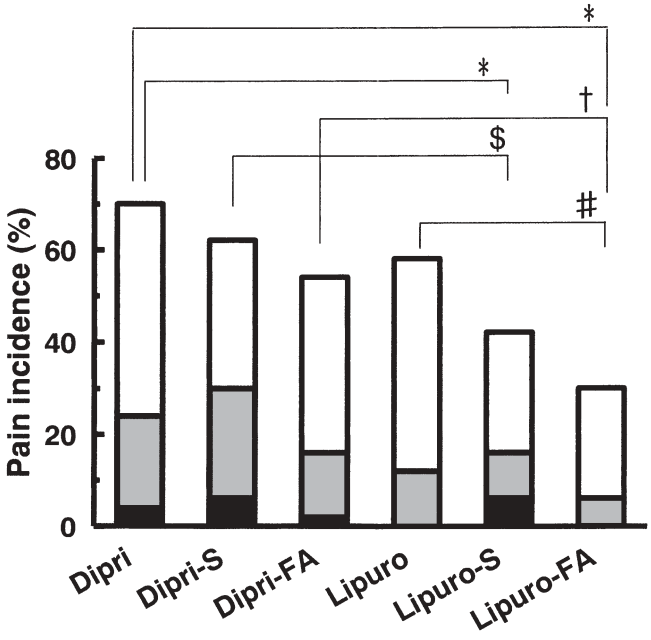

Fig. 1. Pain incidence (pain score ≥ 1) and pain intensity (*white bars*, mild; *gray bars*, moderate; *black bars*, severe) with each propofol emulsion. *Dipri*, Diprivan (Astra-Zeneca), *Lipuro*, Propofol-Lipuro (B. Braun); *S*, saline; *FA*, flurbiprofen axetil emulsion. # ($P < 0.01$) vs Lipuro; * ($P < 0.01$) vs Dipri; $ ($P < 0.05$) vs Dipri-S; † ($P < 0.05$) vs Dipri-FA

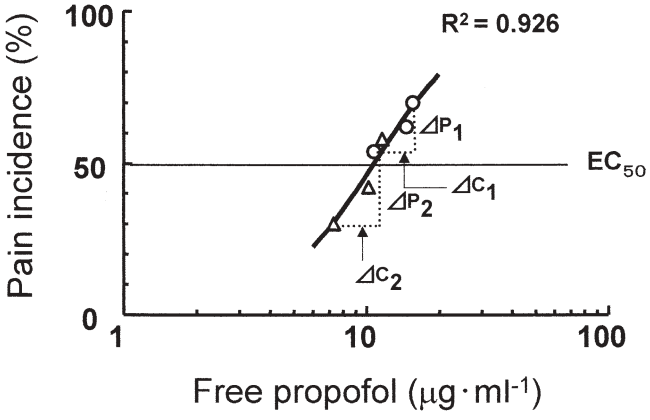

Fig. 2. Relationship between free propofol concentration and incidence of propofol injection pain. *The Thick line* denotes the fitted curve. *Open circles* and *open triangles* denote Diprivan (Dipri) and Propofol-Lipuro (Lipuro), respectively. *The dotted lines* show differences in pain incidence and free propofol concentrations between plain propofol and mixture with flurbiprofen axetil emulsion (FA). ΔP_1, ΔP_2, differences in pain incidence between Dipri and Dipri-FA, and between Lipuro and Lipuro-FA; ΔC_1, ΔC_2, differences in free propofol concentration between Dipri and Dipri-FA, and between Lipuro and Lipuro-FA. EC_{50}, drug concentration at which 50% of the patients did not have injection pain

Table 2. Free propofol concentration and pH of each propofol emulsion

	Diprivan			Propofol-Lipuro		
	Dipri	Dipri-S	Dipri-FA	Lipuro	Lipuro-S	Lipuro-FA
Free propofol (μg·ml^{-1})	15.5 ± 0.3	14.6 ± 0.5[1]*	10.7 ± 0.3[2]*	11.6 ± 0.4	10.2 ± 0.6[3]*	7.3 ± 0.2[4]*
pH	7.0 ± 0.2	6.6 ± 0.4	6.1 ± 0.5	7.2 ± 0.0	6.7 ± 0.3	6.1 ± 0.3

[1]* $P < 0.05$ vs Dipri; [2]* $P < 0.01$ vs Dipri; [3]* $P < 0.05$ vs Lipuro; [4]* $P < 0.01$ vs Lipuro
Values are expressed as means ± SD ($n = 5$)
Dipri, Diprivan (Astra-Zeneca); Lipuro, Propofol-Lipuro (B. Braun); S, saline; FA, flurbiprofen axetil emulsion

Discussion

This study investigated the relationship between propofol injection pain and the free propofol concentration in the presence of flurbiprofen axetil emulsion (FA). A significant difference in propofol pain incidence was found only between Lipuro and Lipuro-FA. The NNT was also lowest for Lipuro-FA. As a possible mechanism of pain reduction by FA, the analgesic effect of FA as an NSAID is unlikely, because FA is a prodrug that must be metabolized, taking several minutes to exert its analgesic effect [20,21]. Protection of the intima of the vein by FA may also be possible [16], but we could not find any evidence or literature supporting this speculation. A previous report [22] showed that a reduction of pH alleviated injection pain. Therefore, the contribution of pH change (caused by the mixtures of saline and FA) to propofol injection pain cannot be ruled out. However, it is unlikely that pH changes alone can sufficiently explain the pain reduction by FA found for Lipuro, because the addition of FA to propofol decreased the pH almost to the same degree for Dipri and Lipuro (0.9 vs 1.1).

The good correlation between pain incidence and the in vitro free concentration of propofol (Fig. 2) suggests that decreasing the free propofol concentration by FA may be the most reasonable explanation for the reduced incidence of propofol injection pain. The decrease in pH induced by the admixture of saline and FA is unlikely to be central to the mechanism of reducing the free propofol concentration, because our preliminary study showed no significant changes in free propofol concentrations when the pH of propofol solutions was changed to 5, 7, or 9. The mixture of saline or FA with the two propofol emulsions in the present study significantly decreased the free propofol concentration, but a significant reduction of injection pain was found only for Lipuro-FA. This discrepancy may be reasonably explained by the nature of the dose-response curve. Namely, Dipri and Dipri-FA showed free propofol concentrations higher than the EC_{50} (Fig. 2, ΔP_1, ΔC_1). In contrast, a mixture-induced change in free propofol concentration will show a significant reduction in pain incidence when the incidence exceeds the pain threshold by a large amount (i.e., EC_{50}) as found for Lipuro-FA (Fig. 2, ΔP_2, ΔC_2). Thus, a reduction in pain incidence was not apparent for Dipri compared with Lipuro, although the decrease in the free propofol concentration shown by FA in Dipri (i.e., $3.8\,\mu g \cdot ml^{-1}$) was comparable with that in Lipuro (i.e., $4.3\,\mu g \cdot ml^{-1}$)

Our study has some limitations. First, the ratio of propofol and FA in the mixture was limited, because the maximum dose of FA per injection was limited to 5 ml (50 mg). Consequently, the decreases in the free propofol concentration in the samples were 31% for Dipri and 40% for Lipuro. Further studies are necessary to investigate the pain incidence over a wide range of free propofol concentrations. Second, we injected the solution about 10 min after preparing the mixture, and it has not been determined whether the free propofol concentrations would have reached equilibrium during this short period. The free propofol concentration of Dipri in the present study ($15.6\,\mu g \cdot ml^{-1}$) was in the same range as that in previous reports (18.6 and $14.8\,\mu g \cdot ml^{-1}$) [7,23]. However, the free propofol concentration in situ injected in the present study may not have been the same as that shown in vitro. Thirdly, no apparent relationship was found between the intensity of injection pain and the extent of dilution. Three patients in the Lipuro-S group experienced severe pain, but the difference from other groups was not significant. Finally, the study was performed at room temperature and the temperature of the propofol solution during the infusion was not controlled. Temperature is an important factor in determining injection pain [17,24,25]. Further investigations are required to clarify the effects of free propofol concentrations on injection pain at different temperatures.

In conclusion, admixture with FA significantly decreased propofol injection pain with Lipuro emulsions. A Good relationship was found between pain incidence and the free propofol concentration. The pain reduction produced by the mixture of FA with Lipuro may be reasonably explained, at least in part, by a reduction in the free propofol concentration.

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