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Propofol injection pain is not alleviated by pretreatment with flurbiprofen axetil, a prodrug of a nonsteroidal antiinflammatory drug

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Abstract

Purpose. The effects of nonsteroidal antiinflammatory drugs (NSAIDs) on pain from propofol injection are controversial, partially because NSAIDs themselves cause injection pain. We evaluated the effects of flurbiprofen axetil (LFP), a prodrug of an NSAID, on pain induced by intravenous propofol injection, because LFP produces little pain on injection.

Methods. A randomized, double-blind, controlled trial was undertaken in patients who were assigned to one of three groups ($n = 50$ in each). Patients received either 5 ml of saline followed approximately 10 min later by propofol mixed with 0.4 ml of saline, LFP (50 mg, 5 ml) i.v. followed by propofol mixed with 0.4 ml of saline, or 5 ml of saline followed by propofol mixed with lidocaine (40 mg, 0.4 ml). Verbal rating scores for injection pain were assessed every 10 s during propofol administration at a rate of 0.05 $mg \cdot kg^{-1} \cdot s^{-1}$.

Results. None of the patients complained of pain during injection of LFP or saline. Admixture of lidocaine, but not of LFP, significantly reduced the incidence of pain and the severity of pain scores during propofol injection ($P = 0.0017$ and $P < 0.001$, respectively).

Conclusion. Lidocaine, but not LFP, is effective for controlling pain induced by propofol injection. This result suggests that NSAIDs have little effect on pain from propofol injection.

Key words Propofol · Injection pain · Nonsteroidal antiinflammatory agent · Flurbiprofen axetil · Lidocaine.

Propofol has the disadvantage of causing discomfort or pain during intravenous injection. Numerous methods have been used to reduce the pain, such as coadministration of lidocaine, alfentanil, and ketamine, or cooling of the propofol [1–5]. Although the underlying mechanism or etiology of pain induced by propofol injection is not clear, kinins might be involved [6]. Nonsteroidal antiinflammatory drugs (NSAIDs), therefore, might reduce the pain of propofol injection by reducing prostaglandin synthesis and/or inhibiting the kinin cascade [7]. In addition to these well-known peripheral effects of NSAIDs, in clinical settings they exert an antinociceptive effect via the central nervous system [8,9], including spinal effects [10].

Although administration of intravenous aspirin was reported to be effective for pain induced by propofol injection [11], pretreatment with intravenous ketorolac did not reduce pain during injection [12,13]. However, it may be difficult to assess the effects of NSAIDs on pain from propofol injection using ketorolac, because most NSAIDs, including ketorolac, have an irritant effect [14]. Therefore, we used flurbiprofen axetil [1-acetoxy-ethyo-2-(2-fluoro-4-biphenyl) propionate] (LFP) to evaluate the effects of NSAIDs on propofol injection pain. LFP is an injectable prodrug, formulated as a lipid emulsion of flurbiprofen ester, without irritant effects [15,16]. Therefore, the study was designed to evaluate whether intravenous administration of LFP reduces pain during propofol injection and offers any advantage over lidocaine admixture.

Patients and methods

This study was approved by the Ethics Committee of the National Defense Medical College. We recruited 150 patients (ASA physical status I or II) who were undergoing elective surgery and obtained written informed consent from each patient. Patients were randomly assigned to one of three treatment groups ($n = 50$ in each). Group S (placebo control) received 5 ml of 0.9% saline followed by propofol (Diprivan, Zeneka, Osaka, Japan) mixed with 0.4 ml of 0.9% saline. Group F received 5 ml of LFP (50 mg, Ropion, Kaken, Tokyo, Japan) followed by propofol mixed with 0.4 ml of 0.9% saline. Group L

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received 5 ml of 0.9% saline followed by propofol mixed with 0.4 ml of 10% lidocaine (Xylocaine, Astra, Osaka, Japan). The mixture of propofol with lidocaine or saline was injected within 15 min of preparation. A 20-gauge cannula was inserted into the cephalic vein in the wrist 2 h before induction of anesthesia. Approximately 10 min prior to induction of anesthesia with propofol, LFP or saline was injected slowly over 3 min. Ten minutes is considered to be sufficient to generate the active form of LFP [17]. All patients were given a questionnaire regarding injection pain.

Premedication was not administered. To induce anesthesia, propofol (2.0–2.5 $mg \cdot kg^{-1}$) was injected at 0.05 $mg \cdot kg^{-1} \cdot s^{-1}$. Every 10 s, the patients were asked to grade their level of pain on the following scale: 0 = none, 1 = mild (uncomfortable or a little painful), 2 = moderately painful, 3 = severely painful. Patients were told beforehand what questions would be asked by an anesthetist, who was unaware of the group to which the patient was assigned. The number of patients in each group with a pain score of more than 1 was totaled and was referred to as the "incidence of pain." In the postanesthetic care unit, patients whose pain score was more than 1 were asked whether they remembered any pain during the propofol injection. The number of patients in each group who answered "yes" was totaled as the "remembrance of pain."

On the basis of previous studies [1–3,18,19], the expected incidence of pain was 30% in group L and 60% in group S. A power analysis indicated that a sample size of 50 was sufficient to detect a large statistical difference with $\alpha = 0.05$ and power $1 - \beta = 0.8$. The Kruskal-Wallis test was used to compare the distribution of pain scores in the three groups, and with allowance for multiple comparisons, a RIDIT (relative to an identified distribution) analysis [20] was performed. The goodness test of fit for chi-square test and the chisquare test for independence were performed to compare incidence of pain and remembrance of pain. A P value of less than 0.05 was considered statistically significant.

Results

The three groups were similar in regard to age, sex, and weight (Table 1). Neither pain on injection nor adverse effects attributable to LFP were observed in any patients. Table 2 shows the pain score and the number of patients in each group reporting various levels of pain. There was a significant difference in the distribution of pain scores among groups (P = 0.0016, Kruskal-Wallis test). The severity of pain scores in group F was not significantly different from that in group S but was significantly higher than in group L ($P < 0.01$, RIDIT analysis; Table 2). The incidence of pain during propofol injection was 50% (25/50), 56% (28/50), and 20% (10/50) in groups S, F, and L, respectively. The incidence of pain in groups S and F was significantly higher than in group L (P = 0.0017 and 0.0002, respectively, chi-square test for independence), whereas there was no difference between groups S and F (P = 0.55, chi-square test for independence). The remembrance of pain was 36% (9/25), 21% (6/28), and 30% (3/10) in groups S, F, and L, respectively (P = 0.50, goodness test of fit for chi-square test).

Table 1. Characteristics of patients pretreated with saline (group S), flurbiprofen (group F), or lidocaine (group L)

Characteristic	Group S	Group F	Group L
N	50	50	50
Age (yr)	51 ± 3	58 ± 2	49 ± 3
Sex (M/F)	28/22	25/25	27/23
Weight (kg)	56.6 ± 1.7	57.6 ± 1.6	59.4 ± 1.9

Values are expressed as numbers or means ± SD.

Table 2. Distribution of pain scores (no. of patients) during propofol injection in patients pretreated with saline (group S), flurbiprofen (group F), or lidocaine (group L)

Pain score[a]	Group S	Group F	Group L[b]
0	25	22	40
1	12	16	8
2	12	12	2
3	1	0	0

[a] Pain score: 0 = nil, 1 = mild, 2 = moderate, 3 = severe pain.
[b] $P < 0.001$ (*vs* group S) or 0.01 (*vs* group F), by RIDIT analysis.

Discussion

In this study, LFP administered 10 min before propofol injection did not reduce the pain induced by propofol. LFP is a prodrug of an NSAID, which is metabolized and converted to an active form (flurbiprofen). LFP (50 mg) used in this study is effective for postoperative pain relief [16], and the maximum plasma concentration of the active form is attained 6.7 min after injection [17]. The maximum plasma concentration of flurbiprofen after LFP (50 mg) injection is higher than that after oral flurbiprofen (40 mg; Froben, Kaken, Tokyo, Japan), which is used clinically for the treatment of inflammatory disorders. Therefore, we chose 50 mg of LFP to evaluate the inhibition of the injection pain of propofol in this study.

The effects of NSAIDs on propofol injection pain have been controversial. Intravenous administration of aspirin [11] was previously reported to reduce the incidence of severe pain following injection of propofol (1% solution in 16% Cremophor EL). A kinin cascade is implicated in the mechanism of propofol injection

pain [6], although the exact mechanism remains to be elucidated. The effect of aspirin, however, is limited, because Cremophor itself causes pain during injection. On the other hand, Smith et al. [13] reported that ketorolac (10 mg, i.v.) did not reduce the incidence of propofol injection pain. However, the interval (15 s) between ketorolac and propofol injections may have been too short in their study. Furthermore, Dexter [14] suggested that ketorolac might increase the pain of propofol injection, because many NSAIDs have an irritant effect. We considered it important to avoid NSAID injection pain to evaluate the effects of NSAIDs on propofol injection pain. In the present study, administration of LFP did not have an irritant effect, probably because LFP is a prodrug. Our results are consistent with the report by, Eriksson [12] that ketorolac (30 mg, i.m.) administered 45–60 min prior to propofol did not reduce pain on injection. Therefore, pretreatment with NSAIDs has little effect on pain relief during propofol injection, suggesting that prostanoids and kinin have little to do with the genesis of propofol injection pain.

In this study the administration of lidocaine mixed with propofol reduced pain induced by propofol injection. We used only the cephalic vein in the wrist to administer propofol, because the incidence of pain has been shown to be dependent on the size of the vein used for injection of propofol [1,6]. Furthermore, a constant infusion rate of propofol was adopted in this study to avoid affecting the incidence of pain. The incidence of pain during propofol injections in our control group (group S) was 50%, which falls within the range of previously reported percentages (40%–86%) [18,19]. In the present study, 20% of the patients complained of pain during propofol injection with 40 mg (0.4 ml) of 10% lidocaine. This is consistent with a previous report [1–3].

The memory of propofol injection pain fades postoperatively, and propofol, but not benzodiazepine, may reduce the incidence of recall of pain [3,21]. Impairment of memory of pain with time might be beneficial for patients. Although the underlying mechanism remains to be elucidated, it has been reported that propofol impairs explicit memory, but that implicit memory is preserved following propofol sedation [22]. The incidence of recall of pain (approximately 30%) in this study seems lower than previously reported values [3,21], but the reason for the difference in incidence is not clear. Further studies are necessary to evaluate the reduced incidence of pain recall.

In conclusion, LFP, a prodrug of an NSAID, administered intravenously before propofol injection was ineffective in reducing the pain induced by propofol injection per se. Administration of lidocaine mixed with propofol would be a simple way of reducing propofol injection pain.

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