J Anesth (2000) 14:164–165

Journal of
Anesthesia

Short communications

A randomized, double-blind trial comparing the effect of mixing propofol with either lidocaine or nafamostat mesilate on injection pain

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Key words Propofol-induced pain, Lidocaine, Nafamostat mesilate

Propofol is widely used for the induction and maintenance of anesthesia, but it often causes local pain when administered into peripheral veins. To prevent this pain, it has been common practice to mix propofol with lidocaine [1]. Recently, we have demonstrated the effect of nafamostat mesilate (Torii Pharmaceutical, Tokyo, Japan) [2,3], which is not only a serine protease inhibitor but also a kallikrein inhibitor [4], in preventing the pain. The cause of the pain is attributed to the activation of the plasma kallikrein–kinin system by the lipid solvent of propofol, followed by bradykinin generation, which modifies the local vein injected. This modification increases contact between the aqueous-phase propofol and the free nerve endings of the vessel, resulting in aggravation of the pain [3]. Although propofol mixed with nafamostat produced a significant reduction of the pain [3], a definitive comparison between propofol mixed with lidocaine and propofol mixed with nafamostat has not yet been undertaken. In this report, we compared the effect of lidocaine and nafamostat in a randomized, double-blind study.

After approval of our institutional committee, 303 elective operative patients classified as ASA physical status 1 or 2 who provided informed consent were allocated in alternate weeks to the lidocaine (n = 153) or nafamostat (n = 150) group. The patients were premedicated with 0.005–0.008 mg·kg^{-1} atropine and 0.5–1.0 mg butorphanol i.m., 30 min before entering the operating room, where a 20-gauge intravenous catheter was inserted in the forearm. Either 2 ml of commercially available lidocaine 2% (ASTRA Japan, Osaka, Japan) or 2 ml of a solution containing 10 μg nafamostat diluted with 5% glucose was mixed with 20 ml of propofol 1% at room temperature before induction. The nafamostat solution was prepared by diluting a 10-mg vial with 5% glucose, stored at 4°C, and used within 48 h. In a double-blind manner, 1.5 mg·kg^{-1} of the prepared propofol was injected at a rate of 200 mg·min^{-1}. During induction, patients were repeatedly asked to grade any discomfort or pain as: none = 0; discomfort = 1, mild pain = 2; moderate pain = 3; or severe pain = 4.

Differences between the groups in age, weight, height, male/female ratio, ASA 1/2 ratio, and pain scores were analyzed by the unpaired t test or the Mann-Whitney U test. $P < 0.05$ was considered significant. Data are expressed as means ± SD or number of patients.

The lidocaine and nafamostat groups were similar in age [46 ± 18 (range, 10–87) *vs* 50 ± 18 (range, 12–87) years], weight (56 ± 10 *vs* 55 ± 9 kg), height (158 ± 9 *vs* 157 ± 9 cm), male/female ratio (52/101 *vs* 49/101), and ASA 1/2 ratio (108/45 *vs* 97/53). The pain scores are shown in Table 1. There was no significant difference in the pain scores between the groups.

The results demonstrate that mixing either lidocaine or nafamostat with propofol had the same effect on injection pain. We did not measure the pain with injection of propofol alone. However, previous reports [1–3,5] demonstrated a significant reduction of pain with the use of either lidocaine or nafamostat compared with propofol alone, in which the addition of lidocaine attenuated the intensity of pain from 65% to 36% [3] or from 67% to 13% [5], and the addition of nafamostat alternated the intensity from 65% to 27% [3]. Therefore, the results indicate that mixture with either lidocaine or nafamostat reduces propofol-induced pain on injection to the same degree, compared with injection of propofol alone, and suggest a promising use for nafamostat as an alternative to lidocaine.

Received: October 14, 1999 / Accepted: January 15, 2000

Table 1. Pain scores during injection of propofol mixed with either lidocaine or nafamostat mesilate

	Pain score				
Group	0	1	2	3	4
Lidocaine ($n = 153$)	61 (40%)	38 (25%)	22 (14%)	22 (14%)	10 (7%)
Nafamostat ($n = 150$)	61 (41%)	30 (20%)	28 (19%)	21 (14%)	10 (6%)

Number of patients (%). Pain scores are: 0 = no feeling, 1 = only discomfort, 2 = mild pain, 3 = moderate pain, and 4 = severe pain. There was no significant difference between the groups ($P > 0.05$)

Nafamostat is a synthetic serine protease inhibitor used clinically in Japan for treating patients with disseminated intravascular coagulation and acute pancreatitis, and as an anticoagulant during various extracorporeal circulation procedures [6,7]. Since nafamostat is hydrolyzed rapidly by blood esterases, its biological half-life is approximately 8 min [8]. When nafamostat is administered as a bolus injection, the concentration is highest immediately after injection and decreases subsequently [2]. Since the dose of nafamostat mixed with propofol in this study was very small, its blood concentration could not be detected using high-performance liquid chromatography [3], suggesting no systemic pharmacological effects [4]. Theoretically, one 10-mg vial of nafamostat can be used for 1000 injections. In Japan, a 5-ml ampoule of lidocaine 2% and a 10-mg vial of nafamostat cost 97 and 1966 yen, respectively, which works out to 39 yen for lidocaine and 2 yen for nafamostat per person. Although one vial of nafamostat can be used for only a limited number of patients, there would be no great economic dis-advantage in using nafamostat. Regarding potential complications, only one report so far has described an anaphylactic reaction induced by nafamostat [9], although previous anaphylactic reactions to drugs of this class, which includes gabexate mesilate and aprotinin in addition to nafamostat, may be considered a contraindication. The use of nafamostat in children and pregnant women has not been established, and there is one report [10] of its transfer into mother's milk in rats. Except for these situations, propofol mixed with nafamostat may be clinically safe.

In conclusion, the present study demonstrates that propofol mixed with either lidocaine or nafamostat reduces injection pain to the same degree. This result indicates a promising use for nafamostat as well as lidocaine to prevent propofol-induced pain on injection.

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