Nafamostat mesilate, a kallikrein inhibitor, prevents pain on injection with propofol

H. IWAMA, M. NAKANE, S. OHMORI, T. KANEKO, M. KATO, K. WATANABE and A. OKUAKI

Summary

We have examined the preventative effect of nafamostat mesilate, a kallikrein inhibitor, on pain on injection with propofol in a randomized, double-blind study. A control group (n=110) and a nafamostat (n=103) group received 5% glucose 0.02 ml kg⁻¹ and nafamostat 0.02 mg kg⁻¹ diluted with 5% glucose, respectively, followed 1 min later by 1% propofol injected at a rate of 200 mg min⁻¹. Pain scores recorded during injection of propofol were significantly less in the nafamostat than in the control group. In another 10 patients, blood concentrations of nafamostat were measured after administration of nafamostat 0.02 mg kg⁻¹ i.v. Mean nafamostat concentration 1 min after injection was 0.1 (sd 0.05) μmol litre⁻¹, which is sufficient to inhibit plasma kallikrein activity. We conclude that pretreatment with nafamostat 0.02 mg kg⁻¹ significantly reduced pain on propofol injection and this effect may be caused by a reduction in kallikrein activity. (Br. J. Anaesth. 1988; 81: 963–964).

Keywords: pharmacology, nafamostat; anaesthetics i.v., propofol; pain, injection

The mechanism whereby propofol causes pain on i.v. injection is still unclear, although Scott, Saunders and Norman have suggested an effect on an enzymatic cascade, possibly the plasma kallikrein-kinin system. In this cascade, kallikrein converts kininogens to kinins which are chemical mediators of pain. Nafamostat mesilate (Torii Pharmaceutical Co., Tokyo, Japan) is a synthetic serine protease inhibitor used clinically in Japan which inhibits kallikrein activity. If propofol-induced pain is attributed to kinins, this drug should decrease the pain via an inhibitory effect on kallikrein activity. This study was designed to test this hypothesis.

Methods and results

This study was approved by the Institutional Committee and all patients (ASA I–II) gave informed consent. In this randomized, double-blind study, 213 adult patients undergoing elective surgery were allocated to control (n=110) and nafamostat (n=103) groups. Patients were premedicated with atropine 0.008 mg kg⁻¹ i.m. and butorphanol 1 mg, 30 min before entering the operating room where a 20-gauge intravenous catheter was inserted in the forearm. A 10-ml vial of nafamostat was diluted with 10 ml of 5% glucose, and this solution was stored at 4°C and used within 72 h. One minute after injection of 5% glucose 0.02 ml kg⁻¹ (control group) or nafamostat 0.02 mg kg⁻¹ (nafamostat group), 1% propofol at room temperature was administered at a rate of 200 mg min⁻¹. During induction, patients were repeatedly asked to report and grade any discomfort or pain as: none = 0; only discomfort = 1; mild pain = 2; moderate pain = 3; and severe pain = 4. Data are presented as mean (sd) or number of patients.

The groups were similar in age (mean 48 (range 19–78) vs 49 (18–83) yr), weight (mean 57 (sd 9) vs 58 (10) kg), height (158 (9) vs 158 (9) cm), male/female ratio (38/72 vs 36/67) and ASA I/II ratio (80/30 vs 67/36). The injected doses of propofol in the control and nafamostat groups were 83 (17) and 87 (22) mg (P>0.05, unpaired t test). Pain scores recorded during propofol injection are shown in table 1. The nafamostat group had a significantly lower incidence of propofol-induced pain (P<0.01, Mann–Whitney U test).

Another 10 adult patients undergoing major surgery and requiring monitoring of arterial pressure during anaesthesia were studied. Mean age, weight, height, male/female and ASA I/II ratios were 61 (range 59–76) yr, 59 (sd 14) kg, 157 (8) cm, 6/4 and 4/6. Before induction of anaesthesia, a 22-gauge arterial catheter was inserted into the radial artery. Subsequently, nafamostat 0.02 mg kg⁻¹ diluted with 5% glucose was administered i.v., and arterial blood was collected from the catheter. Nafamostat concentrations in blood 1 and 5 min after injection were assayed using high pressure liquid chromatography. Activated coagulation time (ACT) and plasma potassium concentration were measured before, and 1, 5 and 10 min after injection. ACT was measured using ACTester (Quest Medical Inc., TX, USA). Nafamostat concentrations 1 and 5 min after injection were 100 (50) and 16 (7) mmol litre⁻¹. ACT was 110.6 (10.5) s before injection, and 114.3 (9.5), 112.7 (8.6) and 116.3 (8.3) s, 1, 5 and 10 min after injection. Potassium concentrations were 3.803 (0.390) mmol litre⁻¹ before injection, and 3.868 (0.456), 3.809 (0.373) and 3.792 (0.364) mmol litre⁻¹, 1, 5 and 10 min after injection. There were no significant changes:

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in ACT and potassium measurements \((P>0.05,\) repeated measures one-way analysis of variance).

**Comment**

According to the inhibitory effect of nafamostat on kallikrein, 50% inhibition is obtained at concentrations of 1–100 nmol litre\(^{-1}\). As this drug is hydrolysed rapidly by blood esterase, its biological half-life is approximately 8 min. We speculated that the i.v. dose of nafamostat to transiently inhibit kallikrein activity would be approximately 1.0 mg. We have demonstrated in our randomized, double-blind study, that nafamostat 0.02 mg kg\(^{-1}\) had a significant effect on propofol-induced pain.

We subsequently examined blood concentrations of nafamostat, and also ACT and plasma potassium concentrations after administration of nafamostat 0.02 mg kg\(^{-1}\). Arterial nafamostat concentrations were within the range necessary to inhibit the activity of plasma kallikrein.

Nafamostat is used clinically as an antithrombotic agent but at the dose used in our study, there was no change in ACT. This is consistent with a previous report. The most harmful adverse effect of nafamostat is hyperkalaemia, although this complication appears in only 4.53% of patients with DIC receiving a continuous infusion of nafamostat (data on nafamostat mesilate, 1996, Torii Pharmaceutical Co., Tokyo, Japan). The mechanism of hyperkalaemia is by reduced urinary excretion of potassium, and it has been suggested that intermittent administration may prevent this effect. We found no change in potassium concentration using a bolus dose of nafamostat 0.02 mg kg\(^{-1}\).

In summary, pretreatment with nafamostat 0.02 mg kg\(^{-1}\), 1 min before propofol injection significantly inhibited pain on injection. Blood concentrations of nafamostat indicated values sufficient to inhibit plasma kallikrein activity, suggesting kinin generation as a cause of pain.

**References**


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<th>Group</th>
<th>Pain score</th>
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<td></td>
<td>0</td>
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<tr>
<td>Control ((n=110))</td>
<td>26 (24%)</td>
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<tr>
<td>Nafamostat ((n=103))</td>
<td>56 (54%)</td>
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