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ORIGINAL ARTICLE

Pretreatment with nafamostat mesilate, a kallikrein inhibitor, to decrease withdrawal response associated with rocuronium

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Abstract
Purpose This randomized, double-blind, placebo-controlled study was conducted to examine the preventive effect of nafamostat mesilate, a kallikrein inhibitor, on the withdrawal response associated with rocuronium injection.
Methods Ninety American Society of Anesthesiology (ASA) physical status I or II patients, aged 18–65 years, were randomly divided into two groups that received either a 1.5-ml solution containing 1.5 mg nafamostat mesilate diluted in a 5% glucose solution or a 1.5-ml 5% glucose solution. Anesthesia was induced by 5 mg/kg 2.5% thiopental. After confirming loss of consciousness, a tourniquet was applied to the mid forearm and tightened to block venous flow. The test solution was then administered, 1 min after which the tourniquet was removed and 0.6 mg/kg rocuronium was administered. Each patient's response to rocuronium injection was graded on a four-point scale in a double-blind manner. Activated coagulation time and plasma potassium concentration were measured before and 5 and 10 min after nafamostat administration.
Results The incidence of withdrawal response was 68.9% in the control group and 24.4% in the nafamostat group ($P < 0.001$). The number of patients showing generalized movement (response 4) with the rocuronium injection was significantly lower in nafamostat group [1 (2.2%)] than the control group [15 (33.3%)], $P < 0.001$. Five and 10 min after nafamostat administration, measured potassium and activated coagulation time were similar to baseline values.
Conclusion Pretreatment with 1.5 mg nafamostat mesilate decreased withdrawal response associated with rocuronium injection.

Keywords Nafamostat · Movement · Rocuronium

Introduction

Following anesthetic induction with thiopental or propofol, a withdrawal response due to pain from rocuronium injection may occur in 22–84% of adults [1, 2] The mechanisms of rocuronium-induced injection pain are unclear. However, according to Borgeat and Kwiatkowski [2], after IV injection of rocuronium, the polymodal nociceptor present in the vascular wall is stimulated by the release of alogenic substances associated with the kallikrein–kinin system, such as bradykinin, which can lead to pain. The characteristics of rocuronium injection pain, such as immediate appearance after injection and a decrease in severity with repeated administration, are similar to the characteristics of pain induced by an IV injection of propofol. Therefore, mediators that are related to pain induced by IV propofol injections and that are similar to those involved in the kininogen cascade may also be involved in pain associated with rocuronium injection [2, 3].

Nafamostat mesilate is a synthetic kallikrein inhibitor that is administered to patients suffering from acute pancreatitis or disseminated intravascular coagulation [4]. Iwama et al. [5] reported that nafamostat mesilate significantly reduces the occurrence of propofol injection pain and suggested that the pain is associated with the plasma kallikrein–kinin system.

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This randomized, double-blind, placebo-controlled study examined the preventive effect of nafamostat mesilate, a kallikrein inhibitor, on the withdrawal response associated with rocuronium injection.

Patients and methods

The study was approved by the Ethics Committee of our institute, and informed consent was obtained from all patients. Ninety patients, aged 18–65 years, with American Society of Anesthesia (ASA) physical status I or II were allocated to one of two groups by computer-generated randomization. Exclusion criteria included a history of allergies to nafamostat mesilate, chronic pain, or pregnancy. Patients receiving analgesics or sedatives were also excluded. The control group received a 1.5 ml 5% glucose solution IV, whereas the nafamostat group received a 1.5-ml solution containing 1.5 mg nafamostat mesilate (Futhan®, Torii, Pharmaceutical Co. Ltd, Tokyo, Japan) diluted with 5% glucose solution. The nafamostat mesilate solution was prepared by diluting a 10-mg vial with 10 ml 5% glucose. The solution was then stored at 4°C and used within 48 h. The syringes of the test solution were prepared by another investigator and covered so that the investigator who assessed each patient's response was unaware of the solution administered. All patients were premedicated with 0.004 mg/kg glycopyrrolate IM 30 min before entering the operating room. All patients had an 18-gauge IV catheter placed on the dorsum of the hand. The free flow of lactated Ringer's solution was confirmed by administration of $\geq$20 ml by gravity. Routine noninvasive monitors were placed upon arrival in the operating room. Both groups of patients underwent IV induction of anesthesia by 5 mg/kg 2.5% sodium thiopental followed by free flow of IV fluid. Five seconds after loss of consciousness as assessed by standard clinical criteria (no verbal response and loss of eyelash reflex), the route of IV infusion was occluded by applying a rubber tourniquet to the middle of the forearm. If venous occlusion by the rubber tourniquet was not sufficient, manual compression was also applied. Study drugs at room temperature were administered, and the tourniquet was released after 1 min; IV infusion was sufficient to ensure the removal of residual effects. Rocuronium at 0.6 mg/kg was then IV injected for 10 s. No visible precipitation had occurred in the transparent part of the IV tubing. All medications were injected into a port connected directly to the IV catheter while the IV tubing was clamped above the injection site. The anesthesia was continued with an appropriate technique at the discretion of the attending anesthesiologist after assessment of withdrawal responses.

An investigator blinded to the contents of the test solution was responsible for scoring the observed responses during rocuronium injection as follows: 1 = no response, 2 = movement at the wrist only, 3 = movement/withdrawal involving the arm only (elbow/shoulder), and 4 = generalized response (withdrawal response or movement in more than one extremity, cough, or breath-holding). Local side effects such as redness, tenderness, or hardness were assessed immediately in the arm receiving the injection and 1 and 24 h after anesthetic recovery by a study-blinded anesthesiologist. In the nafamostat group (15 men and 15 women in whom intra-arterial pressure monitoring was required due to major surgery), a 22-gauge arterial catheter was inserted in the radial artery prior to the induction of anesthesia. Arterial blood sampling was performed three times through this arterial catheter. Activated coagulation time (ACT; Hemochron® Jr. Signature, ITC, USA) and plasma potassium concentration were measured before and 5 and 10 min after nafamostat administration.

Statistical analysis was performed using SPSS 15.0 for Windows (SPSS Inc., Chicago, IL, USA). Based on an estimated incidence of approximately 80% of patients showing withdrawal response, the sample size required to detect a 30% difference in frequency at the 5% level of significance and a power of 80% was 44 patients per group. Patients' age, weight, and height were compared using an independent t test, and genders were compared using a Fisher's exact test. The incidence and degree of withdrawal movement associated with rocuronium injection were compared using a Fisher's exact test. The changes in ACT and potassium concentration were compared using a repeated measures analysis of variance (ANOVA) test. Statistical significance was defined as $P < 0.05$.

Results

There were no significant differences in patient characteristics between the two groups (Table 1). The incidence of withdrawal response was 68.9% in the control group and 24.4% in the nafamostat group ($P < 0.001$). Three (6.7%) patients showed wrist-only movements in the control group, and seven (15.6%) in the nafamostat group. Thirteen (28.9%) and three (6.7%) patients in the control and

Table 1 Patient characteristics

	Control group ($n = 45$)	Nafamostat group ($n = 45$)
Age (years)	43.5 ± 10.6	40.3 ± 11.4
Gender (M/F)	23/22	22/23
Weight (kg)	63.0 ± 8.4	65.7 ± 6.1
Height (cm)	164.7 ± 8.1	162.1 ± 6.5

Values are the number of patients and mean ± standard deviation (SD). There were no significant differences between groups

nafamostat groups, respectively, showed arm-only movement (response 3; $P < 0.05$).

Only one patient (2.2%) in the nafamostat group showed generalized movement (response 4) with rocuronium injection compared to 15 patients (33.3%) in the control group ($P < 0.001$; Table 2).

ACT was 129.9 ± 10.0 s before injection and 131.2 ± 8.0 s and 129.1 ± 9.0 s at 5 and 10 min, respectively, after injection. Potassium concentration was 3.7 ± 0.4 mmol/L before injection, 3.7 ± 0.2 mmol/L 5 min after injection, and 3.6 ± 0.5 mmol/L 10 min after injection. Five and 10 min after nafamostat administration, ACT and potassium concentrations were similar to baseline values ($P > 0.05$). The observations made 1 and 24 h postoperatively revealed no local side effects, such as redness, tenderness, or hardness.

Discussion

The results of this study demonstrate that nafamostat mesilate, a kallikrein inhibitor, decreased the withdrawal response associated with rocuronium injection and suggest a relationship between rocuronium-induced pain and the kallikrein–kinin system. A range of mechanisms responsible for the pain experienced during rocuronium injection have been postulated, but the precise mechanism has remained unclear [6]. One possible mechanism for rocuronium injection pain, which is characterized by immediate but short movements, might be the local release of mediators associated with the kallikrein–kinin system. Activation of the kallikrein–kinin system in plasma involves the activation of coagulation factor XII, which converts prekallikrein to kallikrein. Kallikrein, in turn, cleaves the high molecular weight kininogen to release bradykinin [7]. Bradykinin is a very effective endogenous excitatory agent of polymodal nociceptors in human beings [8], producing burning pain after an intradermal injection into the skin as well as after IV infusion into an isolated hand-vein segment [9]. Bradykinin has a biological half time of 15 s [10].

Nakane and Iwama [7] found propofol injection pain was significantly lower in a group pretreated with 0.02 mg/kg nafamostat mesilate than in a placebo-controlled group; bradykinin concentration was also relatively lower in the nafamostat mesilate group They also found that serum concentration 1 min after administering 0.02 mg/kg nafamostat mesilate was 100 nm/L, which is high enough to inhibit plasma kallikrein activity by 50% [11–13]. The dose of nafamostat mesilate used in our study (1.5 mg) is similar to that used by Nakane and Iwama [7] because the mean weight of the patients was approximately 60 kg. Nafamostat mesilate is not only fast acting [7], it is also short acting because it is promptly hydrolyzed by blood esterase. Its biological half-life is 8 min [14]. In our study, the use of a tourniquet likely helped decrease the occurrence of withdrawal response even after pretreatment with a small dose of nafamostat mesilate.

Nafamostat mesilate is used clinically as an antithrombotic agent. At the doses used in this study, there was no change in ACT, which was measured 5 and 10 min later. This is also in agreement with other studies [5, 12]. Nafamostat mesilate may also be associated with hyperkalemia due to decreased urinary potassium excretion, suppression of aldosterone secretion, and direct inhibition of apical sodium conductance in the collecting ducts [15]. There were no significant changes in the serum potassium concentration at the doses used in this study, which is also in agreement with other studies [5].

Several methods have been attempted to reduce rocuronium-induced withdrawal movement and pain, with variable results. These include pretreatment with ondansetron [16], lidocaine [17], tramadol [18], fentanyl [18], remifentanil [19], and an injection of a rocuronium and sodium bicarbonate mixture [20]. Although several studies have reported positive results, lidocaine allergy is a contraindication of lidocaine use; in addition, opioids have several well-known side effects, such as hypotension, bradycardia, chest rigidity, and coughing. In our study, the effects of preventing rocuronium-associated withdrawal responses with nafamostat mesilate were comparable with the effects of lidocaine [18, 21], therefore making it a useful alternative. However, the cost of nafamostat mesilate is relatively high, and other than preventing rocuronium-associated pain, there seems to be no additional clinical advantage, thus making it less cost effective than other drugs. Also, more research is needed to determine the concentration of bradykinin that should be used to assess the activity of the kallikrein–kinin system. In conclusion, pretreatment with 1.5 mg nafamostat mesilate decreases the withdrawal response associated with rocuronium injection.

Table 2 Incidence and grade of withdrawal response associated with rocuronium injection

Grade of response	Control group ($n = 45$)	Nafamostat group ($n = 45$)	P value
1 No response	14 (31.1)	34 (75.6)	0.000
2 Wrist only	3 (6.7)	7 (15.6)	0.315
3 Elbow/shoulder	13 (28.9)	3 (6.7)	0.011
4 Generalized	15 (33.3)	1 (2.2)	0.000
Overall incidence	31 (68.9)	11 (24.4)	0.000

Values are the number (%) of patient responses

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