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Effect of low-dose infusion of prostaglandin E_1 on vecuronium-induced neuromuscular blockade

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Abstract: The effect of low-dose (20 ng·kg^{-1}·min^{-1}) infusion of prostaglandin E_1 (PGE_1) on vecuronium-induced neuromuscular blockade was studied. The study population consisted of 24 elderly patients (65–75 years old) and 24 younger adult patients (25–56 years old). They were randomly assigned to the control and PGE_1 groups. The steady-state dose requirement (SSDR) of vecuronium was derived from on-demand infusion of the drug which produced a stable twitch height of 20% of its baseline reading, and recovery time after steady-state infusion was defined as the time for recovery from twitch height from 25% to 75%. The patients in the PGE_1 group received an infusion of PGE_1 20 ng·kg^{-1}·min^{-1}, while those in the control group received an infusion of normal saline. The SSDR (23.2 ± 9.1 and 34.2 ± 5.9 μg·kg^{-1}·hr^{-1}, respectively; $P = 0.02$) was significantly less and the recovery time (35.0 ± 9.5 and 19.9 ± 4.2 min, respectively; $P = 0.01$) was significantly longer in the elderly than in the younger patients. However, low-dose infusion of PGE_1 significantly increased the SSDR (23.2 ± 9.1 to 37.4 ± 3.7 μg·kg^{-1}·hr^{-1}; $P = 0.01$) and shortened the recovery time (35.0 ± 9.5 to 23.5 ± 4.0 min; $P = 0.02$) in elderly patients. We concluded that low-dose infusion of PGE_1 is effective in preventing the prolonged action of vecuronium in elderly patients.

Key words: Age factors, Prostaglandin E_1, Vecuronium, Neuromuscular blockade

Introduction

Vecuronium has a prolonged duration of action in elderly patients, and it is thought to be one of the leading causes of prolonged apnea [1,2]. This prolonged action could be mainly due to an age-related decline in renal and hepatic elimination mechanisms [2,3]. Low-dose infusion of prostaglandin E_1 (PGE_1) has been shown to improve renal and hepatic hemodynamics by increasing renal and hepatic blood flow [4,5]. PGE_1 thus seems to affect the intensity and/or duration of the neuromuscular blocking effect of vecuronium by improving the metabolism of the drug, and therefore might prevent the prolonged action of vecuronium in elderly patients.

In this study, the effect of low-dose infusion of PGE_1 was assessed by measuring the dose requirement and recovery time of vecuronium in younger and elderly adults.

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Materials and methods

After receiving approval from our committee on human research and informed consent from all the patients, 24 younger adult patients (ages ranging from 25–56 years) and 24 elderly patients (ages ranging from 65–75 years) ASA physical status I or II scheduled for mastectomy, ear-nose-throat, or orthopedic surgery were studied. Patients known to have any history or laboratory evidence of renal, hepatic, or neuromuscular disease were excluded from the study. All patients had normal values for electrolytes, creatinine, blood urea nitrogen, serum glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, lactate dehydrogenase, and alkaline phosphatase. Patients were not given any medication known to cause alteration of response to muscle relaxants. Younger and elderly patients were randomly assigned to the PGE_1 and control groups.

Premedication with atropine 0.5 mg and famotidine 20 mg was given intramuscularly 1 h before surgery. Anesthesia was induced with thiopental 3–5 mg·kg^{-1} i.v. and vecuronium 0.1 mg·kg^{-1} i.v., and maintained with isoflurane (0.5%–2.0% end-tidal) and nitrous oxide 66% in oxygen. Ventilation was controlled to maintain end-tidal P_{CO_2} between 30 and 40 mmHg. Rectal temperature was maintained above 35.5°C by warming blankets and a heated humidifier. After the induction of anesthesia, the 24 patients in the PGE_1 group received low-dose (20 $ng \cdot kg^{-1} \cdot min^{-1}$) infusion of PGE_1 while the 24 patients in the control group received normal saline.

The integrated electromyogram (EMG) was monitored using a relaxograph (Datex Instrumentarium, Helsinki, Finland). The ulnar nerve was stimulated supramaximally at the wrist with repetitive train-of-four stimulation (2 Hz for 2 s at 20-s intervals) through surface electrodes. The evoked compound electromyogram (EMG) of the adductor pollicis muscle was recorded. After induction of anesthesia but before administration of vecuronium, calibration of the relaxograph was performed and the basal EMG (100%) was obtained. An intravenous bolus of 0.1 $mg \cdot kg^{-1}$ of vecuronium was injected. The maximum neuromuscular blocking effect was recorded, and the trachea was intubated. When the first response of the EMG signal (T_1) returned to 10% of baseline, an administration of vecuronium 0.5 $mg \cdot ml^{-1}$ in normal saline was started with an infusion pump (Terumo, Tokyo, Japan). The infusion rate was manually adjusted to maintain T_1 at 20% of its baseline reading (80% neuromuscular blockade) for at least 120 min or for as long as required for the surgical procedure. The amount of vecuronium required to maintain 80% neuromuscular blockade was obtained every 5 min by measuring the displacement of the piston, and the vecuronium steady-state dose requirement (SSDR) was calculated on the basis of body weight ($\mu g \cdot kg^{-1} \cdot h^{-1}$). After the surgical procedure, the time for recovery from T_1 25% to T_1 75% (T_1 25–75) period or recovery time was also measured. Standard deviations are shown for all mean values. Statistical analysis of the results was performed using unpaired Student's t-test and chi-square analysis for the intergroup and the intragroup comparisons. Differences were considered significant when $P < 0.05$.

Results

There was no statistical difference in terms of distribution of sex, body weight, body height, duration of anesthesia, duration of operation, bleeding volume, total amount of fluid during anesthesia, or isoflurane concentration among the four groups of patients studied (Table 1). Urine output during anesthesia was less in the elderly than in the younger patients ($P = 0.03$). However, in the elderly patients, the urine volume was increased significantly in the PGE1 group compared with the control group ($P = 0.01$).

The results with SSDR and recovery time are listed in Table 2. The SSDR of vecuronium in younger adults did not significantly differ between the control and PGE_1 group ($P = 0.72$), while in the elderly patients, the SSDR was increased significantly in the PGE_1 group compared with the control group ($P = 0.01$). The SSDR in elderly patients was approximately 30% less than in the younger patients ($P = 0.02$). However, with prostaglandin E_1 administration, there was no significant difference between elderly and younger patients in the SSDR ($P = 0.17$).

The recovery time showed no significant difference between the control and PGE_1 groups in the younger patients ($P = 0.48$), but in the elderly patients, the recovery time was reduced significantly in the PGE_1 group compared with the control group ($P = 0.02$). The recovery time in the elderly patients was approximately 75% longer than in the younger patients ($P = 0.01$), while

Table 1. Patient characteristics of the four groups and variables in anesthesia

	Younger		Elderly	
	Control	PGE_1	Control	PGE_1
Number of patients	12	12	12	12
Sex: male/female	5/7	4/8	4/8	6/6
Age (years)	44.9 ± 8.5	40.1 ± 8.7	69.9 ± 3.4*	69.6 ± 6.7*
Weight (kg)	51.0 ± 6.3	53.9 ± 7.5	57.4 ± 11.8	55.1 ± 9.2
Height (cm)	156.4 ± 6.6	159.6 ± 10.6	153.3 ± 8.0	154.3 ± 8.9
Anesthesia time (min)	217.8 ± 73.1	229.0 ± 54.4	197.5 ± 53.7	214.0 ± 99.6
Operation time (min)	161.6 ± 69.7	167.7 ± 45.2	128.7 ± 51.7	149.3 ± 107.1
Blood loss during anesthesia (g)	217.2 ± 152.8	204.0 ± 120.2	212.3 ± 202.5	193.5 ± 190.6
Infused volume during anesthesia ($ml \cdot kg^{-1} \cdot h^{-1}$)	7.3 ± 1.7	7.2 ± 2.2	6.1 ± 1.3	6.5 ± 1.4
Urine volume during anesthesia ($ml \cdot min^{-1}$)	1.8 ± 1.5	2.7 ± 1.7	0.8 ± 0.4*	2.5 ± 1.2#
Isoflurane concentration (%)	1.4 ± 0.5	1.2 ± 0.4	1.3 ± 0.3	1.1 ± 0.3

Values are mean ± SD.
*$P < 0.05$ vs. younger patients.
#$P < 0.05$ vs. control group.
PGE_1, Prostaglandin E_1

Table 2. Steady-state dose requirement (SSDR) and recovery time after steady-state infusion of vecuronium

	Younger		Elderly	
	Control	PGE_1	Control	PGE_1
SSDR ($\mu g \cdot kg^{-1} \cdot h^{-1}$)	34.2 ± 5.9	33.0 ± 8.5	23.2 ± 9.1*	37.4 ± 3.7#
Recovery time (min)	19.9 ± 4.2	21.8 ± 5.5	35.0 ± 9.5*	23.5 ± 4.0#

Values are mean ± SD.
*$P < 0.05$ vs. younger patients.
#$P < 0.05$ vs. control group.

with administration of PGE_1 there was no significant difference between elderly and younger patients in the recovery time ($P = 0.45$).

Discussion

Vecuronium is a nondepolarizing neuromuscular blocking agent with a short duration of action with minimal cumulative effects following repeated administration. These properties suggest that a continuous infusion of the drug, at an appropriate dose, could produce stable neuromuscular blockade [6,7]. We measured the SSDR and recovery time after steady-state infusion of vecuronium with respect to age, and found that the dose required to keep T_1 at 20% was smaller and the recovery time was increased in the elderly patients compared with the younger patients. This could be due to age-related changes in the pharmacokinetics and pharmacodynamics of vecuronium. With this in mind, the reduction in SSDR in patients over 65 years old could be attributed to either reduced plasma clearance or increased sensitivity of the neuromuscular junction. Studies of vecuronium [3] and pancuronium [3,8] have demonstrated no significant age difference in neuromuscular junction sensitivity to these nondepolarizing neuromuscular blocking agents. Additionally, the reduced plasma clearance without a change in neuromuscular junction sensitivity provides a better explanation for the reduced SSDR in elderly patients found in our study.

After an infusion approaches steady-state, the recovery of neuromuscular blockade is predominantly dependent on both plasma clearance and steady-state volume of distribution (Vdss). The prolonged recovery time in elderly patients could be attributed to either reduced plasma clearance or increased Vdss compared with younger patients. Rupp et al. [3] reported that Vdss of vecuronium was reduced in elderly versus younger populations. Consequently, the duration of action for vecuronium prolonged in a given elderly patients is more likely due to reduced clearance of the drug than to a change in volume of distribution. The elderly patients in our study were healthy individuals. In the absence of systemic disease, organ function remained adequate to meet basal requirements, but the functional reserve of the organ system and the capacity to tolerate surgical stress were considered to be reduced [1]. The age-related difference in plasma clearance seems to result from progressive decrease in organ function, hepatic and renal function, which decrease the elimination or biotransformation of the drug, or both [2,3].

Administration of low-dose (20 $ng \cdot kg^{-1} \cdot min^{-1}$) PGE_1 increased the dose requirement of vecuronium and shortened the recovery time in elderly patients. The infusion rate in this study was much less than that which induces hypotension for the purpose of reduction of intraoperative blood loss [9–11], and the low-dose infusion of PGE_1 has been reported to maintain organ blood flow without affecting blood pressure [4,5]. PGE_1 acts directly on the vascular smooth muscle and increases renal and hepatic blood flow [9–11], and it has been shown to produce cytoprotection of kidney and liver following surgical procedure [4,5]. In a recent investigation [4], it was demonstrated in elderly patients that, with administration of PGE_1, urinary output increased during and after anesthesia, and renal and hepatic function tests showed no notable changes before and after operation. The present results also showed that infusion of PGE_1 increased urine volume in the elderly patients by as much as three times, implying that PGE_1 attenuated the decrease in renal plasma flow and the glomerular filtration rate which occurred due to surgical stress. Ishii et al. [12] studied the pharmacokinetics of vecuronium, and showed that plasma clearance tended to increase with low-dose infusion of PGE_1. The mean value for plasma clearance of vecuronium was increased by 16% by the administration of PGE_1. PGE_1 thus seems to affect age-related changes in plasma clearance of vecuronium by improving renal and hepatic elimination and/or metabolism of vecuronium.

In conclusion, this study shows a reduced steady-state dose requirement and prolonged recovery time after steady-state infusion of vecuronium in patients over 65 years old compared with younger adults. The reduced plasma clearance in elderly patients was thought to be the cause. However, low-dose ($20\,ng \cdot kg^{-1} \cdot min^{-1}$) infusion of PGE_1 increased the dose requirement and shortened the recovery time in elderly patients. PGE_1 is effective in preventing the prolonged action of vecuronium in elderly patients by improving renal and hepatic hemodynamics.

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