

Investigation of the Cardiac Effects of Pancuronium, Rocuronium, Vecuronium, and Mivacurium on the Isolated Rat Atrium

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ABSTRACT

BACKGROUND: Pancuronium, vecuronium, rocuronium, and mivacurium are nondepolarizing neuromuscular blocking agents that affect the cardiovascular system with different potencies. Their cardiovascular effects are clinically significant in the anesthetic management of patients, particularly those undergoing cardiac surgery.

OBJECTIVE: We aimed to compare the cardiac effects of these compounds, such as heart rate and developed force, in one species under identical experimental conditions in isolated rat atria.

METHODS: The left or right atria of rats were removed and suspended in organ baths. Pancuronium, vecuronium, rocuronium, or mivacurium were added cumulatively (10^{-9} – 10^{-5} M) in the presence and absence of the nonselective β -blocker propranolol (10^{-8} M) and the noradrenaline reuptake inhibitor desipramine (10^{-7} M), and heart rate changes were recorded in spontaneously beating right atria. Left atrial preparations were stimulated by electrical field stimulation using a bipolar platinum electrode, and the effects of cumulative concentrations of these nondepolarizing neuromuscular blocking agents on the developed force in the presence and absence of propranolol (10^{-8} M) and desipramine (10^{-7} M) were recorded.

RESULTS: Pancuronium increased heart rate in a dose-dependent manner compared with the control group ($P < 0.027$). Vecuronium, rocuronium, and mivacurium also increased heart rate in a dose-dependent manner, but the changes were not statistically significant. Although propranolol decreased the pancuronium heart rate effect ($P < 0.05$), it did not change the heart rate effects with vecuronium, rocuronium, or mivacurium. Desipramine did not change the heart rate effects of vecuronium, rocuronium, mivacurium, or pancuronium. All 4 drugs increased developed force in a dose-dependent manner; the increases were significant at 10^{-5} M concentration for pancuronium and at 10^{-6} and 10^{-5} M concentrations for vecuronium, rocuronium, and mivacurium ($P < 0.038$). These increases in developed force were

abolished with the addition of propranolol. Desipramine did not change the developed force effects of any of the 4 drugs.

CONCLUSIONS: The heart rate effect of pancuronium and developed force effects of pancuronium, vecuronium, rocuronium, and mivacurium may occur via direct stimulation of β receptors. Although our investigation was an in vitro study, the effects found may be important especially under pathologic conditions, such as hypertension, in which patients usually use β -blocking agents, which cause β receptor upregulation. (*Curr Ther Res Clin Exp.* 2011;72:195–203) © 2011 Elsevier HS Journals, Inc. All rights reserved.

KEY WORDS: atrium, mivacurium, neuromuscular blockers, pancuronium, rat, rocuronium, vecuronium.

INTRODUCTION

Pancuronium, vecuronium, rocuronium, and mivacurium are nondepolarizing neuromuscular blocking agents that affect the cardiovascular system with different potencies.¹ Their cardiovascular effects are clinically significant in the anesthetic management of patients, particularly those undergoing cardiac surgery. Although neuromuscular blocking drugs are designed to specifically block nicotinic cholinergic receptors at the neuromuscular junction, many bind to muscarinic cholinergic receptors on ganglia, nerve endings, and smooth muscle and alter parasympathetically mediated heart rate.²

The cardiovascular effects of these neuromuscular blocking agents have been investigated in different studies. Both positive inotropic and chronotropic effects have been reported after pancuronium administration^{3,4} by increased heart rate and arterial blood pressure.^{5,6} In patients with coronary artery disease, pancuronium caused tachycardia, which may result in myocardial ischemia.⁷ These effects of pancuronium on heart rate were reported to be due to the increased release and decreased reuptake of catecholamines at the adrenergic nerve terminal.⁸ Vecuronium has been reported to possess sympathomimetic properties that are less pronounced than those produced by pancuronium,⁹ and, in contrast to pancuronium, it has been reported to induce bradycardia.^{10–12} Vecuronium has been used more often than pancuronium because it has a relatively short duration of action, minimal cardiovascular effects, and an apparent lack of histamine-releasing properties.^{13–14}

The absence of cardiovascular effects has led investigators to propose using a large dose of vecuronium to achieve a shorter onset of action,^{15–17} and it has been offered as a better alternative to pancuronium for long-lasting neuromuscular blockade in patients with coronary artery disease during opioid anesthesia.¹⁸

Clinical use of rocuronium has shown that it does not produce significant cardiac effects,⁶ except minor hemodynamic changes.¹⁹ Mivacurium has been reported to cause transient tachycardia and hypotension,^{20,21} and has been offered in patients who require hemodynamic stability throughout the surgical procedure.²²

In the present study we aimed to compare the cardiac effects of neuromuscular blockers pancuronium, vecuronium, rocuronium, and mivacurium under identical

experimental conditions. We evaluated the cardiac effects of heart rate and developed force and the possible underlying mechanisms at rat atrial tissue after exposure to cumulative doses of these drugs.

METHODS

ANIMALS

All experimental procedures were performed in accordance with the recommendations of the Guide for the Care and Use of Laboratory Animals and approved by the Animal Care Committee of Cumhuriyet University Medical Faculty. Twenty male albino Wistar rats (weighing 180–220 g) were allocated into 3 groups: control ($n = 6$), right atrium for heart rate measurement ($n = 7$), and left atrium for developed force measurement ($n = 7$). The rats were injected with pentobarbital sodium (100 mg/kg) and sodium heparin (5000 IU/kg) intraperitoneally, and each heart was rapidly and carefully excised and placed into Ringer solution at room temperature. The left or right atrium was then removed and suspended in a water-jacketed organ bath containing 10 mL of Ringer solution at 37°C with an applied preload of 600 mg. The Ringer solution contained (mmol/L): 144 Na⁺ (sodium ion), 5.3 K⁺ (potassium ion), 1.98 Ca²⁺ (calcium ion), 1.18 Mg²⁺ (magnesium ion), 123.93 Cl⁻ (chloride ion), 2.35 H₂PO₄⁻ (dihydrogen phosphate ion), 25 HCO₃⁻ (bicarbonate ion), 1.18 SO₄²⁻ (sulfate ion), and 10 glucose. The pH of the solution was 7.4, and the solution was gassed with a mixture of 95% oxygen and 5% carbon dioxide.

ISOMETRIC MEASUREMENTS

The investigators measuring the effects of these agents were blind to the treatment groups. After mounting in the organ bath, each preparation was allowed to stabilize for 60 minutes. During this period, the solution in the bath was changed every 15 minutes. The control group received no treatment. The spontaneously beating right atria received cumulative concentrations (10^{-9} – 10^{-5} mol/L) of pancuronium, vecuronium, rocuronium, or mivacurium in the presence and absence of nonselective β -blocker propranolol (10^{-8} M) and noradrenaline reuptake inhibitor desipramine (10^{-7} M). These antagonists had no effect on heart rate or developed force in these concentrations during preliminary experiments (data not shown). The right atrium preparations were exposed to each concentration for 20 minutes, and the heart rate changes were recorded. After the exposure of the highest concentration, the preparation was washed by Ringer solution and rested for 20 minutes before the next drug exposure. Left atrial preparations were stimulated by electrical field stimulation using a bipolar platinum electrode with 2-millisecond constant current square pulses. The intensity of these stimuli was set at 75 mA, and the applied frequency was 1 Hz (60 beats per minute).¹ Every preparation was exposed to electrical impulses for 30 minutes, 5 minutes of exposure for each concentration of drugs. Biological response of heart tissue (heart rate and developed force) was converted to electrical stimulus and recorded on a Grass model 79E polygraph (Grass Technologies, Astro-Med, Inc., West Warwick, Rhode Island).

DRUGS

Drugs used were propranolol and desipramine (Sigma Chemical, St. Louis, Missouri); vecuronium and rocuronium (NV Organon, Oss, Netherlands); mivacurium (GlaxoSmithKline, Parma, Italy); and pancuronium (Organon Teknika, Istanbul, Turkey). All drugs were dissolved in deionized water freshly on the day of the experiment. Stock solutions were stored at -20°C .

STATISTICAL ANALYSIS

All data are expressed as mean (SEM). Groups were compared statistically using general linear models of ANOVA followed by Newman-Keuls test and *t* test, when appropriate. Differences were considered to be significant at $P < 0.05$. All analyses were performed with Statistica for Windows 6.0 (Statsoft, Inc, Tulsa, Oklahoma).

RESULTS

Pancuronium increased heart rate in a dose-dependent manner compared with the control group, especially at 10^{-7} , 10^{-6} , and 10^{-5} M concentrations ($P < 0.05$). This increase was even more obvious at 10^{-6} and 10^{-5} M concentrations. Vecuronium, rocuronium, and mivacurium also increased heart rate in a dose-dependent manner, but the changes were not statistically significant. Although propranolol (10^{-8} M), a nonselective β -blocker, decreased the pancuronium heart rate effect ($P < 0.05$), it did not change that of vecuronium, rocuronium, or mivacurium. Desipramine (10^{-7} M), a noradrenaline reuptake inhibitor, did not change the heart rate effect of vecuronium, rocuronium, mivacurium, or pancuronium (Figure 1).

Separately, all 4 drugs increased developed force in a dose-dependent manner; the increases were significant at 10^{-5} M concentration for pancuronium and 10^{-6} and 10^{-5} M concentrations for vecuronium, rocuronium, and mivacurium ($P < 0.05$). The increases in developed force were abolished by the addition of propranolol. Desipramine (10^{-7} M) did not change the developed force effects of pancuronium, vecuronium, rocuronium, or mivacurium (Figure 2).

The maximum effects of these drugs on heart rate and developed force are summarized in the Table.

DISCUSSION

The cardiovascular effects of nondepolarizing muscle relaxants have been studied in different animals and also in humans. The isolated heart muscle preparation is useful in evaluation of the effects of drugs upon myocardial contractility, because such a preparation allows preload and afterload to be controlled and because it is free of the influence of neurohumoral responses.³ Pancuronium produced tachycardia and increased arterial pressure; this cardiac stimulation has been attributed to vagolytic action, a release of norepinephrine from the sympathetic nerve terminals, or inhibition of neuronal uptake of norepinephrine.⁹ In another study, the effect of pancuronium on heart rate was connected to, in part, increased release and decreased reuptake of catecholamines at the adrenergic nerve terminal.⁸ Plasma adrenaline and noradrenaline concentrations increased when pancuronium was administered to facilitate tracheal intubation²³ or after administration of pancuronium to ill neonates.²⁴

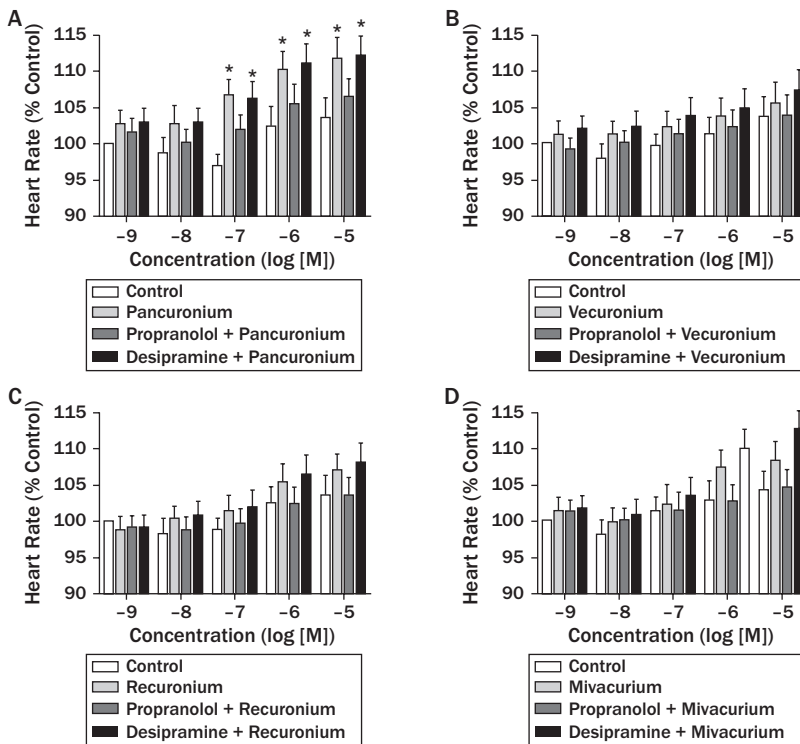


Figure 1. The effects of (A) pancuronium (10^{-9} – 10^{-5} M), (B) vecuronium (10^{-9} – 10^{-5} M), (C) rocuronium (10^{-9} – 10^{-5} M), and (D) mivacurium (10^{-9} – 10^{-5} M) on heart rate at rat atrial tissue. Data are expressed as mean (SEM) ($n = 5$ for each drug). * $P < 0.05$ denotes significant difference from the pancuronium control group.

In contrast, vecuronium has been reported to have minimal effects on the cardiovascular system in experimental animals and in clinical practice.^{4,25} However, vecuronium has been suggested to have positive chronotropic and inotropic effects, but it is much less potent than pancuronium in some experimental animals.⁹ It has been suggested that the bradycardia effect of vecuronium was due to its direct action or the increase in vagal tone induced by either surgical procedures or other drugs.⁹ In patients undergoing coronary artery bypass grafting, rocuronium administration was associated with significant increases in cardiac index and stroke volume index, but not with a change in heart rate.²⁶ In a study performed in elderly patients, the authors reported that rocuronium did not cause tachycardia or hypertension.²⁷ However, Booth et al²⁸ demonstrated a marked tachycardia after administration of rocuronium. Appadu and Lambert²⁹ showed an interaction with cardiac muscarinic receptors with a potency rank order of pancuronium, vecuronium, and rocuronium, respectively. Savarese et al²⁰ showed a transient decrease in blood pressure after mivacurium administration, but Okanlami et al³⁰ reported that mivacurium inhibited bradycardia

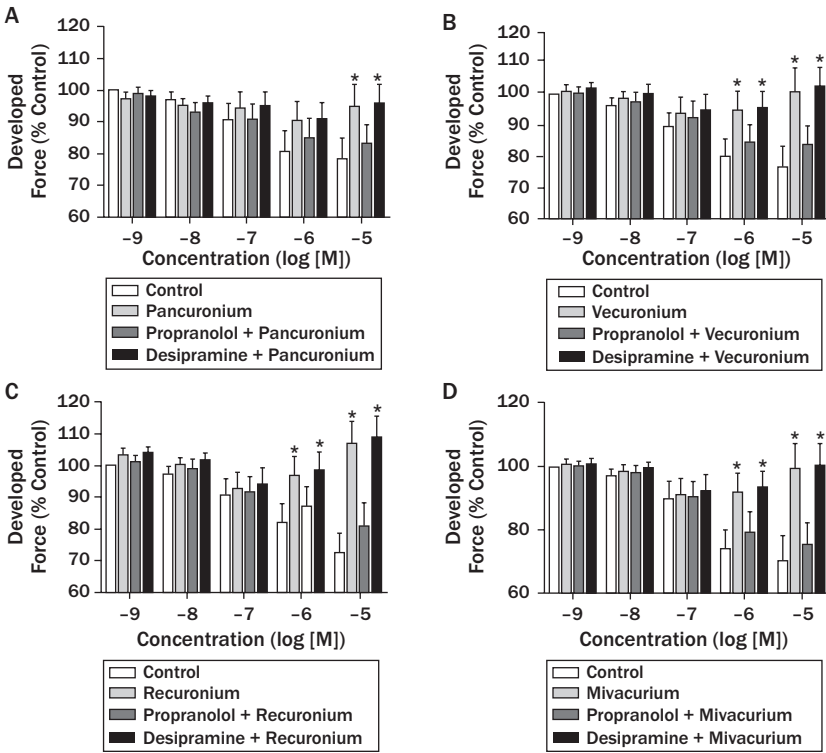


Figure 2. The effects of (A) pancuronium (10^{-9} – 10^{-5} M), (B) vecuronium (10^{-9} – 10^{-5} M), (C) rocuronium (10^{-9} – 10^{-5} M), and (D) mivacurium (10^{-9} – 10^{-5} M) on developed force at rat atrial tissue. Data are expressed as mean (SEM) ($n = 5$ for each drug). * $P < 0.05$ denotes significant difference from each control group.

and bronchoconstriction induced by either intravenous acetylcholine (Ach) or vagal nerve stimulation. They suggested that mivacurium blocks both M_2 and M_3 receptors and that it is a muscarinic antagonist with similar potencies for both M_2 and M_3 receptors.

The plasma concentration of pancuronium administered to humans during the first 3 hours is reportedly 500 to 100 ng/mL ($\sim 90\%$ free form), which is equivalent to 7×10^{-7} and 1.4×10^{-7} M, respectively.^{31,32} In the present study we used all neuromuscular blocking drugs at concentrations harmonious with the study of Cannon et al.¹⁷

In the present study, pancuronium increased heart rate in a dose-dependent manner compared with the control group, especially at high concentrations, but vecuronium, rocuronium, and mivacurium did not cause a significant increase. Although propranolol decreased the heart rate effect of pancuronium, desipramine did not. All 4 drugs increased developed force in a dose-dependent manner. The increases

Table. Maximum effects of all 4 drugs on heart rate and developed force. Data are given as mean (SEM).

| Group | Heart Rate | Developed Force |
|---------------------------|--------------|-----------------|
| Control | 103.6 (2.9) | 78.2 (7.2) |
| Pancuronium | 111.7 (3.0)* | 90.4 (6.0)* |
| Pancuronium + Propranolol | 106.4 (2.5) | 83.2 (6.4) |
| Pancuronium + Desipramine | 112.2 (2.6)* | 91.0 (5.1)* |
| Control | 103.6 (2.7) | 76.6 (6.8) |
| Vecuronium | 105.6 (2.7) | 93.7 (5.3)* |
| Vecuronium + Propranolol | 103.8 (2.8) | 84.0 (6.2) |
| Vecuronium + Desipramine | 107.2 (2.8) | 95.0 (5.0)* |
| Control | 103.7 (2.3) | 72.4 (6.1) |
| Rocuronium | 106.9 (2.4) | 92.5 (5.1)* |
| Rocuronium + Propranolol | 103.7 (2.3) | 80.8 (7.4) |
| Rocuronium + Desipramine | 108.2 (2.4) | 94.0 (5.0)* |
| Control | 104.1 (2.6) | 70.2 (8.1)* |
| Mivacurium | 108.2 (2.6) | 91.2 (5.4) |
| Mivacurium + Propranolol | 104.4 (2.5) | 75.5 (7.2) |
| Mivacurium + Desipramine | 112.6 (2.4) | 92.6 (4.9)* |

* $P < 0.05$ denotes significant difference from control of each group.

in developed force were abolished by the addition of propranolol, but desipramine did not change the developed force effect of any of the 4 drugs.

The decreased heart rate effect of pancuronium and developed force effects of all 4 agents in the presence of propranolol points to the effects occurring via β receptor stimulation. If we had not used desipramine, we might hypothesize that the effects may occur by direct stimulation of β receptors, increased release of endogenous noradrenaline from sympathetic nerve terminals, and/or decreased reuptake of noradrenaline at nerve terminals. Desipramine did not change their effects, so the effects may be due to direct stimulation of β receptors.

CONCLUSIONS

Cardiovascular effects of nondepolarizing muscle relaxants are clinically significant in the anesthetic management of patients in whom long-duration neuromuscular blockade is usually required. Pancuronium increased heart rate, and pancuronium, vecuronium, rocuronium, and mivacurium had positive inotropic effects. A positive inotropic effect of pancuronium was seen at a higher concentration. These effects may be due to direct stimulation of β receptors. The effects may be important, especially under pathologic conditions such as hypertension, in which patients usually use β -blocking agents causing β receptor upregulation. A limitation of the present study is that it was an in vitro investigation. Further in vivo experimental studies and controlled clinical trials are needed to determine whether these findings are correct.

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