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ORIGINAL ARTICLE

Interaction between rosuvastatin and rocuronium in rat sciatic-gastrocnemius nerve-muscle preparation

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Abstract
Purpose Long-term use of rosuvastatin may be associated with myotoxicity. Statins are one of the groups commonly found to be associated with neuromuscular weakness. The present study was designed to investigate the interaction between rosuvastatin and rocuronium in vivo by using a sciatic-gastrocnemius nerve-muscle preparation of rat.
Methods In our study groups, animals received rosuvastatin 2 mg/kg for 14 and 28 days. Train of four (TOF) stimulation was applied to the sciatic nerve, and gastrocnemius muscle contractions were recorded in Wistar albino rats. Intravenous infusion of rocuronium was given until the twitch responses were abolished. We ultimately compared the effective dose required for a desired effect in 95% of the population (ED_{95}), duration 25 %, deep block, recovery index, and time for returning of TOF ratio to 0.9 between the active control and study groups.
Results Chronic administration of rosuvastatin at a dose of 2 mg/kg for 28 days significantly reduced the ED_{95} of rocuronium as compared to the active control group. Deep block and duration 25 % were increased by 3.5 and 2.5 times, respectively, compared to the active control group. The spontaneous recovery of neuromuscular block was delayed, as evidenced by the prolonged recovery index and increase in time required for a return of the TOF ratio to 0.9.
Conclusion The neuromuscular blocking potency of rocuronium is increased and recovery is delayed in rats that pre-treated with rosuvastatin.

Keywords Rosuvastatin · Rocuronium · Drug interaction · Rat sciatic-gastrocnemius nerve-muscle preparation · Neuromuscular junction

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Introduction

Statins are widely used in the prevention of ischemic heart disease due to their effectiveness in reducing cardiovascular morbidity and mortality [1]. They inhibit the formation of mevalonate, a precursor of cholesterol produced by 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Among all the available statins, rosuvastatin (10–80 mg) reduces the plasma LDL-C level more than other statins, and is also more effective in achieving the European LDL cholesterol goal of <3 mmol/L [2]. Cholesterol is an essential component of the nicotinic acetylcholine receptor (nAChR) at the postsynaptic membrane. It stabilizes the receptor protein in the membrane. A reduction in cholesterol by statins may lead to the internalization and endocytosis of nAChR [3]. Long-term treatment with statins is associated with myotoxicity, ranging from asymptomatic elevation of creatinine kinase to rhabdomyolysis [4]. The mechanism of myotoxicity is not clear, but it may be due to muscle membrane dysfunction caused by the inhibition of glycoprotein synthesis, mitochondrial

dysfunction caused by decreasing endogenous coenzyme Q10 levels [5], deficiency of the chloride channel [6], and increased intracellular calcium concentrations leading to impaired membrane function [7]. Statin-induced myotoxicity is dose- and duration-dependent [8]. Concomitant use of fibrates [9], nicotinic acid, calcium channel blockers, ciclosporin, amiodarone, thiozolidinediones, macrolide antibiotics, azole antifungals, and protease inhibitors [10] increases the risk of statin-induced myopathy [11]. The development of severe muscle weakness may require the discontinuation of statins. If the function of the motor nerve or skeletal muscle is impaired, the action of neuromuscular relaxants may be exaggerated [12]. Statins are one of the key factors responsible for acquired neuromuscular weakness in patients admitted to the intensive care unit [13]. Therefore, particular attention should be given to the analysis of cumulative drug dosage and drug interaction during the use of neuromuscular blockers. Patients who are on long-term statin therapy, going for minor or major surgery, and who receive neuromuscular blockers pre- or intra-operatively should be cautioned on and monitored for the possibilities of drug interaction. There is also the possibility of altered neuromuscular response from neuromuscular blockers in patients with statin-induced muscle weakness. To the best of our knowledge, no such data are available on altered neuromuscular response in patients receiving statin therapy. The present experimental study was designed to evaluate the impact of rosuvastatin on the neuromuscular blocking property of rocuronium in rats pretreated with rosuvastatin.

Methods

All experiments were performed after prior permission from the Institutional Animal Ethics Committee of Government Medical College, Bhavnagar, Gujarat, India, protocol no. 20/2011, dated 13/09/2011. This committee is constituted in accordance with the guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), Ministry of Environment and Forests (Animal Welfare Division), Government of India, New Delhi, India.

Experimental animals

Wistar albino rats (300 ± 50 g, 30 ± 2 weeks) of either sex were procured from the Central Animal House of the institute. The animal house is registered in the CPCSEA, New Delhi with registration no. 577/GO/c/02/CPCSEA, dated 17th November 2011. The rats were housed in standard polypropylene cages with husk bedding and kept under controlled room temperature with humidity (24 ± 2 °C; 40 ± 5 %) in a 12-h light–dark cycle. The rats were given a standard laboratory diet and water ad libitum. The food was withdrawn 12 h prior to commencement of the experiment, but glucose water was provided to experimental animals.

Drugs

Rosuvastatin (Torrent Pharma Ltd., Ahamedabad, Gujarat, India) and rocuronium bromide (Neon Laboratories Ltd., Mumbai, India) were used. Rosuvastatin suspension was freshly prepared daily in distilled water for oral administration. Rocuronium (400 μg/ml) solution was freshly prepared in normal saline at the time of slow infusion.

Sciatic-gastrocnemius nerve-muscle preparation of rat

Wistar albino rats were anaesthetized by aqueous solution of urethane in the dose of 100 mg/100 g of body weight intraperitoneally. Body temperatures (35.9–37.5 °C by digital rectal thermometer) of the rats were maintained throughout the experiment with a heating bulb under the rat operation table platform and by an overhead lamp. The left common jugular vein was cannulated for the slow infusion of rocuronium. A tracheostomy was performed for artificial respiration at the rate of 60 strokes/minute with air volume 8–10 ml/kg body weight, using a rodent respiratory pump (Biodevice, Ambala, India). The right side of the sciatic-gastrocnemius nerve-muscle of each rat was mounted, as described by Mishra and Ramzan [14]. For the stimulation of the sciatic nerve, a bipolar electrode (Daxtre's electrode; Biodevice, Ambala, India) was used. After 30 min of rest period [15] with a maintenance temperature of 35.9–37.5 °C, the sciatic nerve was stimulated by train of four (TOF) stimulations, with 2-Hz square-wave pulses of 0.5 s duration every 10 s [16], with an amplitude of 2 V, by a research stimulator RS 48 (Labotech, Ambala, India). Baseline twitch responses of the gastrocnemius muscle were recorded through the force displacement transducer, which was connected to a student's physiograph (Sensitivity—50 μv/cm, paper speed—2 mm/s, gain—maximum. Bio Device, Ambala, India). Rocuronium was infused at a rate of 50 μg/min through a digital infusion pump (Infusomat-P; B. Braun, Mumbai, Maharastra, India) until all four twitch responses were abolished. Muscle paralysis was quantified by comparing the height of T_1 after starting infusion to that of the initial height of T_1 before starting an infusion of rocuronium. The disappearance of T_1 was considered as complete paralysis. After stopping the infusion, we allowed a recovery phase in which the spontaneous recovery of the twitch

responses was observed for 30 min in each experiment. At the end of the experiment, rats were sacrificed by injecting a high dose of ketamine through the venous cannula in the jugular vein.

To evaluate interactions between rosuvastatin and rocuronium, experiments were performed in the following groups ($n = 6$ in each group). The rats were allocated randomly into each group.

Group 1: active control group (received rocuronium infusion only).

Interaction groups

Group 2: rats pre-treated with oral rosuvastatin 2 mg/kg for 14 days received an infusion of rocuronium.

Group 3: rats pre-treated with oral rosuvastatin 2 mg/kg for 28 days received an infusion of rocuronium.

The following parameters of neuromuscular block were calculated in all the groups. The TOF ratio was calculated by dividing the twitch height of T_4 by the twitch height of T_1.

1. ED_{95}: dose (μg/kg) of rocuronium required to produce 95 % inhibition of the first twitch response (T_1).
2. Duration 25 % (in s): time from the start of rocuronium infusion to 25 % of the first twitch response (T_1) recovery.
3. Deep block (in s): time from the disappearance of T_1 (complete block) to the appearance of the first twitch response (T_1) during the recovery phase.
4. Recovery index (in s): time interval during which T_1 is recovered from 25 to 75 % of control.
5. Time required (in s) for the return of the TOF ratio to 0.9 after stopping the rocuronium infusion.

Statistical analysis

Data are expressed as mean ± standard error of mean. Data were checked for normal distribution using the Kolmogorov–Smirnov test. ED_{95} of rocuronium, duration 25 %, deep block, recovery index, and time for the TOF ratio to return to 0.9 in the active control and interaction study groups were compared using one-way analysis of variance (ANOVA) supported by Dunnett's multiple comparison test, as the data were normally distributed. All the statistical analyses were performed by using SPSS 20.0 demo version software. A p value <0.05 was considered as statistically significant.

Results

Animals were comparable in terms of age, gender, and weight between all the groups (Table 1). There was a significant reduction in the ED_{95} of rocuronium in rats pre-treated with rosuvastatin for 28 days ($p = 0.033$; Table 2, Fig. 1). The ED_{95} was reduced 1.5 times as compared to the active control group. However, a significant prolongation of duration 25 % and deep block were noted in rats treated with rosuvastatin for 28 days compared to the active control group ($p = 0.02$; Table 2). Duration of deep block and duration 25 % block was increased by 3.5 and 2.5 times, respectively, compared to the active control. The TOF ratio was recovered to 0.9 in all the groups within a 30-min recovery period. The recovery of neuromuscular block was delayed in the group 3 animals, as evidenced by a prolonged recovery index and prolonged duration required for the return of the TOF ratio to 0.9 ($p = 0.0007$; Table 3). In group 1 and 2, a final recovery level of 100% was achieved for T_1, compared to the initial T_1 value, whereas it was up to 85 % for the group 3 animals.

Discussion

In the present study, pre-treatment with rosuvastatin 2 mg/kg for 28 days in rats significantly decreased the ED_{95} value of rocuronium, prolonged the duration 25 % and deep block durations, and delayed the recovery of twitch responses. ED_{95} describes the potency of the neuromuscular blocking agent [17]. The reduced ED_{95} of rocuronium suggests that tracheal intubating conditions can be achieved earlier with the same dose of rocuronium, or that the required dose to produce deep block should be less in the presence of rosuvastatin. Moreover, the requirement of maintenance doses may be delayed, as duration 25 % and

Table 1 Baseline comparison of animals in the study groups

Groups	Active control	Rosuvastatin 2 mg/kg (14 days)	Rosuvastatin 2 mg/kg (28 days)	F value	p value (ANOVA)
Weight (g)	286.6 ± 6.6 (0.2)	290 ± 5.7 (0.2)	275 ± 4.2 (0.1)	4.2	0.151
Gender					
Male	3	2	3		
Female	3	4	3		

Data are expressed as mean ± SEM (standard error of mean). Values in brackets show p values measured by Kolmogorov–Smirnov test

Table 2 Comparison of ED_{95}, deep block, and duration 25 % in active control and interaction study groups

Groups	ED_{95} (μg/kg)	Deep block duration (s)	Duration 25 % (s)
Active control	679.2 ± 91.9 (0.2)	125.7 ± 34.6 (0.06)	245.7 ± 41.1 (0.2)
Rosuvastatin 2 mg/kg (14 days)	528.8 ± 6.4 (0.2)	208.5 ± 67.9 (0.11)	366.5 ± 100.8 (0.2)
Rosuvastatin 2 mg/kg (28 days)	436.1 ± 77.3* (0.08)	443.7 ± 103.1* (0.14)	618.4 ± 105.4* (0.2)
F value (*df*)	3.11 (2.15)	4.96 (2.15)	4.72 (2.15)
p value (ANOVA)	0.03	0.02	0.02

Data are expressed as mean ± SEM (standard error of mean). *df* degree of freedom. Values in brackets show *p* values measured by Kolmogorov–Smirnov test. (*$p < 0.05$ by Dunnett's multiple comparison test as compared to the active control group)

Table 3 Comparison of time required for the return of the TOF ratio to 0.9, and the recovery index for rocuronium in the active control and interaction study groups

Groups	Time for returning of TOF ratio to 0.9	Recovery index (second)
Active control	519.8 ± 86.2 (0.13)	198.3 ± 16.0 (0.2)
Rosuvastatin 2 mg/kg (14 days)	459.2 ± 127.5 (0.2)	226.5 ± 58.5 (0.2)
Rosuvastatin 2 mg/kg (28 days)	928.7 ± 83.3* (0.2)	442 ± 60.4* (0.1)
F value (*df*)	6.94 (2.15)	4.99 (2.15)
p value (ANOVA)	0.0007	0.004

Data are expressed as mean ± SEM (standard error of mean). *df* degree of freedom. Values in brackets show *p* values measured by Kolmogorov–Smirnov test. (*$p < 0.05$ by Dunnett's multiple comparison test as compared to active control group)

deep block durations were prolonged. Pre-treatment with rosuvastatin delayed the recovery of twitch responses. The delayed return of a normal TOF ratio, an increased recovery indexed, and up to 85 % final recovery of T_1 suggests that there may have been pre-existing muscular impairment due to rosuvastatin in the group 3 animals [18]. However, we could not confirm pre-existing muscle damage by laboratory and/or histopathological evaluation. For this study, we selected a human dose (20 mg for 70 kg male) that is the most efficacious and used clinically. It was extrapolated for a rat model (0.39 mg for 200 g of rat ≈2 mg/kg) [19]. A maximum effect on plasma cholesterol levels with rosuvastatin is achieved within 7–10 days [20]. In rats, repeated daily dosing of statin for 10–16 days produces evident myopathy [21]. Thus, we selected two different durations for treatment of rosuvastatin. In rats treated with rosuvastatin for 14 days, alterations in parameters were there, but could not achieve the level of significance as observed in rats treated for 28 days. This may be due to the possible impact of the duration of rosuvastatin therapy on the development of myopathy [21]. Type II B fibers are very sensitive to statin-induced myopathy [21]. They are glycolytic, fast-contracting fibers with a low content of mitochondria and myoglobin. Statin inhibits the mitochondrial electron transport and produces muscle necrosis [21]. Gastrocnemius muscle is rich in type II B fibers. The mixed portion contains almost 68 % of type II B fibers, while the white portion, which is the largest part, contains only type II B fibers.

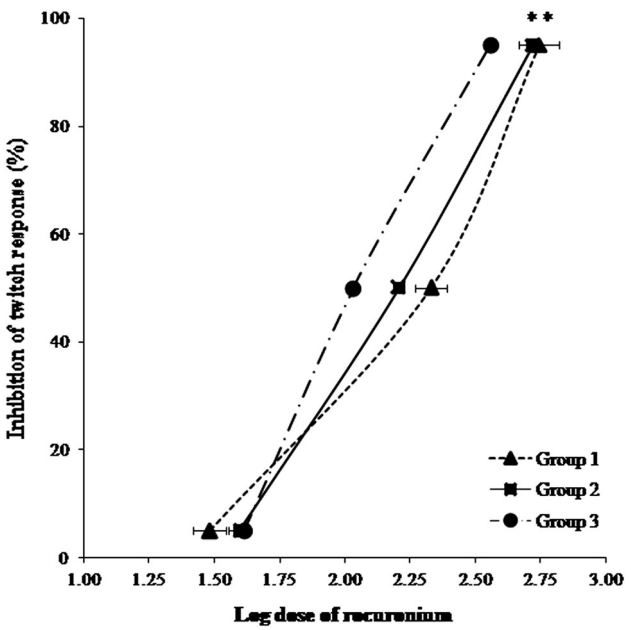

Fig. 1 Comparison of log dose of rocuronium and percentage of inhibition between the active control group and interaction study groups. *$p < 0.05$ as compared to the control using ANOVA, followed by Dunnett's multiple comparison test

Interaction between these drugs may be at the pharmacokinetic or pharmacodynamic level. Rosuvastatin is 88 % and rocuronium is 30 % bound to plasma proteins, mainly albumin. The major metabolite of rosuvastatin is N-desmethyl rosuvastatin, which is formed by CYP2C9 [22]. The action of rocuronium on neuromuscular blockade is rapidly terminated because of rapid redistribution. Moreover, the elimination of rocuronium occurs through biliary excretion, while the elimination of rosuvastatin occurs through feces following oral administration [23]. With different routes of administration, distribution, and metabolic, and excretion properties, the possibility of pharmacokinetic interaction seems less likely. Rosuvastatin acts by inhibiting the cholesterol synthesis [24]. Cholesterol is required to maintain

stability and proper functioning of nAChR at the cell surface [25]. It regulates the nAChR function probably by affecting the conformational state of the receptor and altering the biophysical properties of the cell membrane [3]. A reduction in cholesterol level results in internalization and changes in the ionic activity of nAChR [26, 27]. It also affects the presynaptic release of the neurotransmitter [28]. The development of myopathy may also be the possible reason for the observed exaggerated response of rocuronium in the present study [13]. Thus, the interaction between rosuvastatin and rocuronium is possibly at the pharmacodynamic level.

We could not confirm the observed differences for different durations of treatment by measuring the plasma concentration of rosuvastatin, serum cholesterol level, and/or histopathologically confirmed myopathy. These are the limitations of our study. Further studies can be conducted to find out the correlation between the plasma concentration of rosuvastatin, cholesterol level, degree of myopathy, and the neuromuscular blocking effect of rocuronium. Turan et al. [29] observed statistically significant, but clinically limited consequences of statin-induced muscular injury with succinyl choline. However, they excluded the group of patients who were at risk for neuromuscular complications. Similarly, a rocuronium-induced neuromuscular blockade may have clinical consequences in patients with hepatic, renal, or neuromuscular pathologies, orthopedic and spinal surgeries, and any other procedures requiring extensive muscle manipulations only. The findings of this study can be extrapolated to humans after conducting clinical studies.

Conclusion

The neuromuscular blocking potency of rocuronium is increased and recovery is delayed in rats pre-treated with rosuvastatin 2 mg/kg for 28 days.

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Conflicts of interest The authors declare that they have no conflicts of interest to report.

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