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Neuromuscular interactions between mivacurium and esmolol in rabbits

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Summary

We compared the dose–response relationship and the neuromuscular blocking effects of mivacurium during infusions of esmolol in 40 anaesthetised rabbits. Train-of-four stimuli were applied every 10 s to the common peroneal nerve and the force of contraction of the tibialis anterior muscle was measured. Plasma cholinesterase activity decreased by 13% after esmolol infusion. The ED_{95} of mivacurium increased significantly from 29 (4.8) $\mu g.kg^{-1}$ with placebo to 61 (9.8) $\mu g.kg^{-1}$ during esmolol 100 $\mu g.kg^{-1}.min^{-1}$, 49 (8.2) $\mu g.kg^{-1}$ during esmolol 300 $\mu g.kg^{-1}.min^{-1}$ and 54 (7.3) $\mu g.kg^{-1}$ during esmolol 500 $\mu g.kg^{-1}.min^{-1}$, respectively ($p < 0.001$). The duration of neuromuscular block with mivacurium 0.16 $mg.kg^{-1}$ was prolonged by 30% with esmolol due to diminished plasma cholinesterase activity ($p < 0.05$). Heart rate and mean arterial blood pressure decreased by 15% with esmolol ($p < 0.05$). The results of this study show that, in rabbits, esmolol decreased plasma cholinesterase activity, antagonised the neuromuscular blocking potency of mivacurium and prolonged its neuromuscular blocking effect.

Keywords *Neuromuscular relaxants*; mivacurium. *Sympathetic nervous system*; β adrenoceptor antagonists, esmolol. *Interactions*; drug.

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Esmolol is a water-soluble, cardioselective β-adrenoceptor antagonist with a rapid onset and ultrashort duration of action due to its short elimination half-life of 9 min [1]. As an ester it is rapidly metabolised by esterases in the blood to a free acid metabolite which has a β-adrenergic blocking potency 1/1600 that of the parent drug. The hydrolysis reaction occurs mainly in the cytosol of red blood cells but not in plasma [2]. Esmolol is widely used as a treatment for various cardiovascular diseases, including supraventricular tachyarrhythmias, hypertension and angina pectoris [3].

Mivacurium is a nondepolarising muscle relaxant which has recently been introduced into clinical practice. Although chemically related to atracurium, it has a shorter duration of action [4, 5]. It is hydrolysed by plasma cholinesterase *in vitro* at 70–88% the rate of suxamethonium [6–8]. Esmolol is reported to inhibit human plasma cholinesterase activity by 50% *in vitro* [9]. There are no '*in vivo*' reports of pharmacological interactions between esmolol and mivacurium. The present study was undertaken to compare the dose–response relationships and the neuromuscular blocking effects of mivacurium during infusions of esmolol in anaesthetised rabbits.

Method

After approval by the Institutional Animal Care and Use Committee, we used 40 adult Korean white rabbits, weighing 2.5–3.0 kg. The animals were anaesthetised with propofol 1.5 $mg.kg^{-1}$ by intravenous injection using a marginal vein of the left ear and anaesthesia was maintained with propofol 0.2 $mg.kg^{-1}.min^{-1}$ [10]. A tracheostomy was performed and the lungs ventilated with an animal respirator (Shinano Co., Japan). End-tidal carbon dioxide (CO_2SMO, Novametrix Inc, USA) was monitored and maintained at 4.1–5.2 kPa. Rectal temperature was controlled at about 38 °C with a heated blanket (Blanketrol II, Cincinnati Sub-Zero Inc, USA) and a heating lamp. The right jugular vein was cannulated for esmolol infusion and the left for mivacurium administration. A common carotid artery was cannulated for monitoring of mean arterial pressure (MAP) and intermittent sampling for blood gas analysis (GEM-STAT, Mallinckrodt Co., USA). A four-limb ECG was employed for heart rate monitoring. Intravenous fluid administration using a syringe pump (Model No. STC-523, Termo Co.,

Japan) was maintained at 6 ml.kg^{-1}.h^{-1} (0.9% NaCl) during the experiment. Arterial samples (3 ml) for the plasma cholinesterase activity were drawn before and after the infusion of esmolol. The assays were performed using a Hitachi 747 chemical autoanalyser (Hitachi Co., Japan) according to the method of Garry [11].

The common peroneal nerve was stimulated supramaximally at the posterolateral aspect of the knee with 0.2-ms pulses derived from a peripheral nerve stimulator (DualStim, Life-Tech Inc, USA). Train-of-four (TOF) stimuli (2 Hz) were applied once every 10 s. The tibialis anterior muscle was detached from its insertion and tied to a force transducer (Model No. 45196A, San-ei Co., Japan). The twitch response was quantified mechanomyographically with the preload tension and the mechanomyogram was recorded on a multichannel recorder. Neuromuscular block was quantified by the first twitch (T1) of the TOF.

Dose–response measurements

After stable recording of neuromuscular transmission had been established for a minimum of 30 min for the infusion of esmolol, rabbits were allocated randomly to one of four groups: infusion of placebo (0.9% NaCl) 3 ml.kg^{-1}.h^{-1} (group 1) and infusions of 100, 300 and 500 μg.kg^{-1}.min^{-1} of esmolol (groups 2, 3 and 4, respectively) ($n = 10$ for each group). Esmolol was given as a 1% solution by continuous infusion using a syringe pump. Any changes in MAP and heart rate were noted.

Each of the following predetermined doses of mivacurium were used to establish dose–response curves and were administered by random allocation: 10, 20 or 30 μg.kg^{-1} in group 1; 15, 25, 35 or 45 μg.kg^{-1} in groups 2, 3 and 4, respectively. The doses of mivacurium were different in group 1 from the other groups because of corrections which were possible after a pilot study. Each dose of mivacurium was withheld until the muscle twitch had recovered from the preceding dose and had remained at baseline value for at least twice the duration of block of the preceding dose. The neuromuscular response was recorded as the maximum depression of twitch tension, expressed as a percentage of the control value. The percentage values for twitch depression in each group were transformed to probits and plotted against the logarithm of the dose [12]. Regression lines were compared using the analysis of covariance. The effective doses resulting in 50% and 95% reduction of twitch tension (ED_{50}, ED_{95}) were calculated from the log-probit regression lines for each group.

Time-course measurements

Dose–response curves for mivacurium were determined during the infusion of placebo (0.9% NaCl) (group 1). The subsequent administration of mivacurium 0.16 mg.kg^{-1} was delayed by at least 1 h after complete recovery from the initial dose of mivacurium. The twitch recordings were evaluated for the following variables: time from end of injection of mivacurium to maximum twitch suppression (onset); time from end of injection of the initial dose to recovery of T1 in the TOF to a value of 1%, 25%, 75% and 95% of control twitch tension (T1(1, 25, 75, 95%)); time from 25–75% twitch recovery (recovery index, RI); time from end of injection of the initial dose to a TOF ratio (T4/T1) of 70% (TOF(70)). In groups 2, 3 and 4, individual dose–response curves of mivacurium and neuromuscular blocking effects of mivacurium 0.16 mg.kg^{-1} during infusion of esmolol 100, 300 and 500 μg. kg^{-1}.min^{-1} were determined as in group 1.

At the end of the experiments animals were given a lethal dose of thiopentone and potassium chloride by intravenous injection.

Data were analysed statistically using one-way analysis of variance with Bonferroni correction for multiple comparisons between groups and paired Student's *t*-tests for plasma cholinesterase activity. Differences were considered statistically significant at $p < 0.05$. Values are reported as mean (SD).

Results

Plasma cholinesterase activity after the infusion of esmolol decreased significantly from 362 (12) IU.l^{-1} (group 1) to 324 (11) IU.l^{-1} (group 2), 319 (8) IU.l^{-1} (group 3) and 314 (12) IU.l^{-1} (group 4), respectively ($p < 0.001$). There were no significant differences in plasma cholinesterase activity between the esmolol groups.

The ED_{50} and ED_{95} values of mivacurium according to the infusion doses of esmolol are shown in Table 1 and Fig. 1. There were no significant differences for ED_{50} and ED_{95} between the esmolol groups.

There were no significant differences in the rate of onset of block between groups. The duration of block in groups 2, 3 and 4 as reflected in the T1(75) and T1(95) was significantly prolonged compared with group 1 (Table 2). Similarly the times until T1(1) in group 3 and T1(25) in groups 3 and 4 were significantly increased compared to the control group. There were no significant differences in recovery index between groups (Table 2).

There were significant differences in heart rates between group 1 and groups 2, 3 and 4, and between group 2 and groups 3 and 4 (Fig. 2). Similarly, there were significant differences between group 1 and groups 2, 3 and 4 in mean arterial blood pressure (Fig. 3).

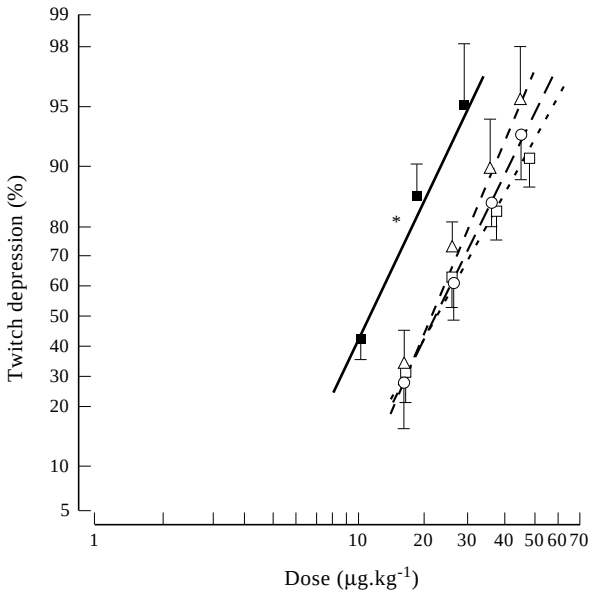

Figure 1 Log dose-probit plot for twitch depression (95% confidence intervals) for mivacurium during the infusion of esmolol in rabbits. (■) Placebo; (□) $100\,\mu g.kg^{-1}.min^{-1}$; (△) $300\,\mu g.kg^{-1}.min^{-1}$; (○) $500\,\mu g.kg^{-1}.min^{-1}$; * $p<0.05$ compared with groups 2, 3 and 4 ($n=10$ each group).

Discussion

We found that esmolol decreased plasma cholinesterase activity, reduced mivacurium potency and prolonged the neuromuscular effects of mivacurium in rabbits. We also noted that heart rate and MAP were decreased by approximately 15% during the infusion of esmolol.

Plasma cholinesterase activity in rabbits is reported as approximately 10% of that in humans [13]. Esmolol has been reported to inhibit human plasma cholinesterase activity by 50% *in vitro* [9], but pre- and postinfusion plasma cholinesterase activities were not significantly different *in vivo*. In our study, esmolol decreased plasma cholinesterase activity by 11–13% depending on the infusion doses. Steady-state plasma concentrations of esmolol were attained within 30 min of starting an infusion and new steady-state blood concentrations were re-established within 30 min of changing the infusion rates [14]. Arterial samples for estimation of plasma cholinesterase activity were taken approximately 40 min after starting the esmolol infusion.

The ED_{95} and ED_{50} values of mivacurium ($29.1\,\mu g.kg^{-1}$ and $16.4\,\mu g.kg^{-1}$) in rabbits are 30–40% of those reported for humans [4, 15]. Similarly, the ED_{90} and ED_{50} values in rats are $197\,\mu g.kg^{-1}$ and $144\,\mu g.kg^{-1}$ [16]. Our findings indicate that mivacurium is approximately three and seven times more potent in rabbits than in humans or rats, respectively.

Esmolol caused significantly rightward shifts in the mivacurium dose–response curves (Fig. 1). The mechanism of this antagonism is unclear, but one explanation might be that esmolol antagonises the β-adrenergic effects of noradrenaline [17]. Noradrenaline inhibits nicotinic transmission in the rabbit vesical parasympathetic ganglia and may reduce acetylcholine release from presynaptic nerve terminals [18]. It also reduces the amplitude of slow postsynaptic currents induced by acetylcholine. In bullfrogs the inhibition of muscarinic transmission induced by noradrenaline is reported to be due to direct suppression of the muscarinic current at the postsynaptic membrane of sympathetic ganglia [19]. So the antagonised β-adrenergic effects induced by esmolol may cause the enhancement of potential amplitude of acetylcholine during neuromuscular transmission.

In our study, the ED_{95} values were no different between groups 2 and 4 (Table 1). The explanation for this is not clear.

The neuromuscular blocking onset time of mivacurium $0.15\,mg.kg^{-1}$ has been reported in the range 3.3–3.7 min in healthy adult patients receiving nitrous oxide opioid anaesthesia [4, 20]. Increasing the dose to more than twice ED_{95} accelerated the rate of onset of nondepolarising relaxants [21]. In our study, the onset time of mivacurium $0.16\,mg.kg^{-1}$ was 1.1 (0.4) min and we suspect that this relatively rapid onset was due to the larger dose ($5\times ED_{95}$) than that ($2\times ED_{95}$) used in the human investigations.

In urethane anaesthetised rats, esmolol almost doubled the time to 75% block with mivacurium [12]. In our

Table 1 Mean (SD) dose–response data for mivacurium during infusion of esmolol.

		Esmolol		
	Group 1 Placebo	Group 2 $100\,\mu g.kg^{-1}.min^{-1}$	Group 3 $300\,\mu g.kg^{-1}.min^{-1}$	Group 4 $500\,\mu g.kg^{-1}.min^{-1}$
ED_{50} ($\mu g.kg^{-1}$)	16 (4.5)	29 (7.9)*	26 (6.1)*	29 (6.9)*
ED_{95} ($\mu g.kg^{-1}$)	29 (4.8)	61 (9.8)*	49 (8.2)*	54 (7.3)*

* $p<0.001$ compared with placebo group.

Table 2 Onset of block (min) and its duration (min) in rabbits given mivacurium $0.16\,mg.kg^{-1}$ with concurrent infusions of esmolol. Data are mean (SD).

Group	Onset	T1(1)	T1(25)	T1(75)	T1(95)	RI	TOF(70)
1 ($n=10$)	1.1 (0.4)	19.6 (4.3)	22.0 (4.1)	29.7 (3.9)	33.1 (4.5)	6.4 (3.1)	32.4 (3.7)
2 ($n=10$)	1.1 (0.2)	22.5 (3.1)	29.1 (5.7)	36.9 (5.9)*	42.3 (6.3)*	7.7 (3.4)	41.5 (5.7)*
3 ($n=10$)	1.0 (0.3)	25.7 (2.9)*	31.3 (3.9)*	38.1 (3.7)*	41.4 (3.6)*	7.6 (2.8)	40.8 (4.9)*
4 ($n=10$)	1.0 (0.4)	23.4 (3.6)	29.9 (4.5)*	37.2 (3.5)*	44.3 (3.5)*	7.4 (2.5)	41.3 (3.5)*

T1(1, 25, 75, 95) – time interval (min) between administration of mivacurium and recovery of the first twitch in the train-of-four (T1) to 1%, 25%, 75%, 95% of control. RI – recovery index – time interval between T25% and 75%. TOF(70) – time interval (min) between injection of mivacurium and a train-of-four ratio of 70%. Group 1 received a placebo (0.9% NaCl) infusion. Groups 2, 3 and 4 received 100, 300 and $500\,\mu g.kg^{-1}.min^{-1}$ infusions of esmolol. * $p<0.05$ compared to Group 1.

study, the onset of mivacurium was similar whether or not esmolol was given concurrently. Our initial dose of mivacurium ($0.16\,mg.kg^{-1}$) was more than three times that of the ED_{95} of mivacurium with esmolol whereas the dose used in rats was $1\times$ ED_{90}. This may explain the difference in the findings of these studies.

When competitive neuromuscular blocking drugs are used for reversal, attainment of a TOF ratio of 0.7 is widely believed to equate with clinically adequate recovery [22, 23], although protective airway reflexes may not be fully effective [24]. Spontaneous recovery of mivacurium $0.15\,mg.kg^{-1}$ to a TOF(70) is quoted as 17 min in humans [20], approximately 50% as long as that shown in rabbits. This difference in recovery times may reflect the much higher initial dose in rabbits (ED_{95} $\times 5$) than in humans (ED_{95} $\times 2$). Esmolol has been reported to prolong recovery from suxamethonium-induced neuromuscular blockade by less than 3 min [25]. Since enzymatic hydrolysis is the major route of mivacurium clearance, its duration of action might be prolonged if plasma cholinesterase activity was inhibited [4]. We found that the duration of block to TOF(70) with esmolol was longer with esmolol than without it. We interpreted this as evidence of inhibition of plasma cholinesterase activity by esmolol; the lack of difference between groups 2, 3 and 4 was perhaps surprising and suggests that the upper end of the dose–response curve was achieved even at the lowest esmolol dosage.

Cumulation of neuromuscular blocking drugs is often defined as the recovery index, i.e. T25–T75% [4]. We found that the recovery indices of mivacurium were similar with or without the infusion of esmolol. Cumulation, therefore, did not occur.

The following points must be considered in assessing the clinical relevance of our results. Firstly, species differences are such that blood esmolol esterase activity may be greater in rabbits than in humans [26]. Secondly, plasma cholinesterase activity in rabbits has been reported as

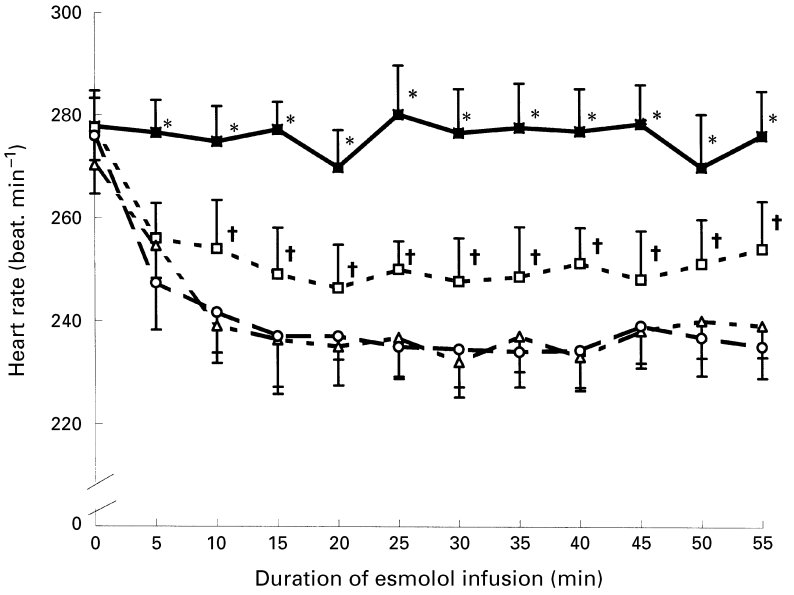

Figure 2 Heart rate (95% confidence intervals) during the infusion of esmolol in rabbits. (■) Placebo; (□) $100\,\mu g.kg^{-1}.min^{-1}$; (△) $300\,\mu g.kg^{-1}.min^{-1}$; (○) $500\,\mu g.kg^{-1}.min^{-1}$; * $p<0.05$ compared with groups 2, 3 and 4; † $p<0.05$ compared with groups 3 and 4 ($n=10$ each group).

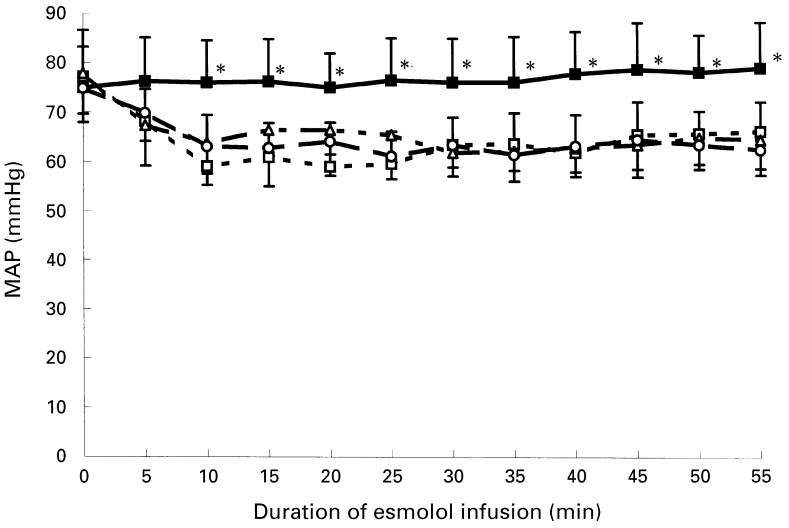

Figure 3 Mean arterial blood pressure (MAP) (95% confidence intervals) during the infusion of esmolol in rabbits. (■) Placebo; (□) 100 $\mu g.kg^{-1}.min^{-1}$; (△) 300 $\mu g.kg^{-1}.min^{-1}$; (○) 500 $\mu g.kg^{-1}.min^{-1}$; * $p < 0.05$ compared with groups 2, 3 and 4 ($n = 10$ each group).

approximately 10% of that in humans [10]. Thirdly, the effect of esmolol on plasma cholinesterase activity did not seem to be dose-dependent (see above).

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