Adenosine potentiation of neuromuscular blocking agents in guinea-pigs

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We have investigated the effects of adenosine i.v. on neuromuscular block induced by rocuronium, vecuronium and pipecuronium in an in vivo guinea-pig sciatic nerve–tibialis anterior preparation. The ED50 of each neuromuscular blocker was determined from cumulative log dose–response regression lines (n=14). In separate experiments, adenosine 0.1 mg kg⁻¹ min⁻¹ or the same volume of 0.9% NaCl was given i.v. via a constant infusion and the ED50 of each neuromuscular blocking agent was then administered (n=24). Adenosine 0.1 mg kg⁻¹ min⁻¹ increased significantly maximal block induced by the ED50 of these neuromuscular blockers (55–72%, 49–73% and 60–96%, respectively, for rocuronium, vecuronium and pipecuronium; P<0.05). Time to maximal block after rocuronium was significantly prolonged by adenosine (1.4–2.1 min; P<0.05) and time to maximal block after vecuronium and pipecuronium was unchanged by adenosine. Time to maximal recovery of twitch tension after administration of the ED50 of all neuromuscular blocking agents was prolonged significantly by adenosine (4.5–10.7 min, 8.2–15.8 min and 47.0–128.7 min, respectively, for rocuronium, vecuronium and pipecuronium; P<0.05). We conclude that continuous infusion of adenosine 0.1 mg kg⁻¹ min⁻¹ potentiated the effects of neuromuscular blocking agents in this in vivo guinea-pig preparation.

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Adenosine and its analogues modulate synaptic transmission in a variety of tissues via the purinergic receptor (receptors for adenosine and adenine nucleotides).1,2 At the neuromuscular junction, adenosine inhibits acetylcholine (ACh) release via the presynaptic inhibitory A₁ purinoceptor.1,3 Segerdahl and colleagues4 showed that continuous administration of adenosine i.v. had antinociceptive effects in patients during surgery. However, there have been no studies regarding the effects of systemically administered adenosine on the action of neuromuscular blocking agents.

To better understand the effects of systemically administered adenosine on neuromuscular blocking agents, we have investigated the effect of adenosine on neuromuscular block induced by different neuromuscular blocking agents, using an in vivo guinea-pig preparation. Previous work has shown that the potencies and time courses of neuromuscular effect of neuromuscular blocking agents in guinea-pigs and humans are similar.5

Methods and results

After obtaining approval from the Institutional Animal Care and Use Committee, 38 male guinea-pigs, weighing 300–500 g, were anaesthetized with pentobarbital and urethane i.p. The animals underwent tracheotomy and the lungs were ventilated with oxygen. Both jugular veins and one carotid artery were cannulated for injection of drugs and monitoring of arterial pressure and heart rate, respectively. Both sciatic nerves were isolated in the gluteal region, placed on bipolar platinum electrodes and crushed with a heavy ligature proximal to the electrode. The distal tendon of both tibialis anterior muscles was dissected, separated from its insertion and attached to FT03 transducers. Both sciatic nerves were stimulated with supramaximal square wave impulses of 0.2 ms duration at 0.1 Hz and the force of contraction of both tibialis anterior muscles was recorded continuously.

†Deceased
When twitch tension became stable, the ED50 of each neuromuscular blocking agent was determined in 14 guinea-pigs from cumulative log dose–response regression lines. The initial dose was 40 µg kg\(^{-1}\), 5 µg kg\(^{-1}\) and 3 µg kg\(^{-1}\) in the rocuronium (n=6), vecuronium (n=4) and pipecuronium (n=4) groups, respectively. The subsequent incremental dose was 20 µg kg\(^{-1}\), 2 µg kg\(^{-1}\) and 1 µg kg\(^{-1}\) in the rocuronium, vecuronium and pipecuronium groups, respectively. Each incremental dose was administered after three consecutive unchanged twitch responses were obtained after the previous dose of drug; additional doses were not given when at least 95% depression of twitch height occurred. Cumulative doses of each drug and neuromuscular responses were transformed to log-dose and probit-response values. ED50 values were derived from least square linear regression analysis.

The interaction of adenosine and the neuromuscular blocking agents was studied in the other 24 guinea-pigs. Adenosine 0.1 mg kg\(^{-1}\) min\(^{-1}\) or the same volume of 0.9% NaCl (control) was administered via a constant i.v. infusion throughout the experiment and the ED50 of rocuronium, vecuronium or pipecuronium was given as a single i.v. dose (n=4 per group). After administration of each neuromuscular blocking agent, maximal block of twitch tension, time to maximal block, maximal recovery of twitch tension and time to maximal recovery were recorded.

Data were analysed using the unpaired Student’s t test and significance was assumed when P<0.05. Data are presented as mean (SEM).

The ED50 of each neuromuscular blocking agent was 64 (8.7) µg kg\(^{-1}\) for rocuronium, 7 (1.9) µg kg\(^{-1}\) for vecuronium and 4 (0.7) µg kg\(^{-1}\) for pipecuronium.

Table 1 summarizes the effects of adenosine on the neuromuscular blocking agents. Continuous infusion of adenosine 0.1 mg kg\(^{-1}\) min\(^{-1}\) alone had no effect on the height of the twitches, but significantly increased the maximal block of twitch tension induced by all blocking agents (P<0.05). Time to maximal block after vecuronium and pipecuronium was unchanged by adenosine, but after rocuronium, it was significantly prolonged by adenosine (P<0.05). Time to maximal recovery of twitch tension after all neuromuscular blocking agents was significantly prolonged by adenosine (P<0.05).

**Comment**

We investigated the effects of adenosine on three neuromuscular blocking agents used commonly in clinical practice on a guinea-pig *in vivo* sciatic nerve–tibialis anterior preparation.

Adenosine increased maximal block and prolonged the duration of block induced by all of the neuromuscular blocking agents. *In vitro* studies using mouse hemidiaphragm and frog sartorius muscle revealed that adenosine potentiated the effects of neuromuscular blocking agents by inhibiting ACh release via a presynaptic inhibitory A1 purinoceptor. Therefore, it seems likely that potentiation of neuromuscular blocking agents in our study was caused by A1 receptor mediated inhibition of ACh release.

Time to maximal block after rocuronium was prolonged and that after vecuronium and pipecuronium was unchanged by adenosine. The explanation of this finding is that the pharmacokinetic effects of adenosine (haemodynamic depressant effect, that is increase in the time of delivery of neuromuscular blocking agent) affected the onset time of rocuronium as it has the fastest baseline onset time. In a study of magnesium sulphate, potentiation of the neuromuscular blocking effects of blockers with shorter baseline onset times was less affected by magnesium sulphate. Although it was not statistically significant, adenosine shortened the time to maximal block after pipecuronium. As pipecuronium has the longest baseline onset time, the pharmacodynamic effects of adenosine influenced the onset time of this blocker.

While adenosine increased neuromuscular block induced by neuromuscular blocking agents, it alone had no effect on twitch tension. This could be explained by a high margin of safety of neuromuscular transmission. Adenosine inhibited twitch tension only when the margin of safety was reduced by rocuronium, vecuronium or pipecuronium. In a mouse hemidiaphragm study, it has also been reported that adenosine or its stable analogues inhibited nerve stimulation-evoked twitches only when the margin of safety was reduced by neuromuscular blocking agents or high [Mg\(^{2+}\)].

In summary, adenosine potentiated the neuromuscular blocking effects induced by rocuronium, vecuronium and pipecuronium and prolonged the time to maximal block.
after rocuronium in the in vivo sciatic nerve–tibialis anterior guinea-pig preparation. This study indicates that perioperative administration of adenosine or its analogues may increase the potency of neuromuscular blocking agents. Therefore, careful monitoring of neuromuscular block is appropriate in such cases.

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