Effect of ropivacaine combined with pancuronium on neuromuscular transmission and effectiveness of neostigmine and 4-aminopyridine for blockade reversal: experimental study

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Abstract

Background and objectives: The local anesthetic effects on neuromuscular junction and its influence on blockade produced by nondepolarizing neuromuscular blockers are still under-investigated; however, this interaction has been described in experimental studies and in humans. The aim of this study was to evaluate in vitro the interaction between ropivacaine and pancuronium, the influence on transmission and neuromuscular blockade, and the effectiveness of neostigmine and 4-aminopyridine to reverse the blockade.

Methods: Rats were divided into groups (n=5) according to the study drug: ropivacaine (5 μg mL⁻¹); pancuronium (2 μg mL⁻¹); ropivacaine + pancuronium. Neostigmine and 4-aminopyridine were used at concentrations of 2 μg mL⁻¹ and 20 μg mL⁻¹, respectively. The effects of ropivacaine on membrane potential and miniature endplate potential, the amplitude of diaphragm responses before and 60 min after the addition of ropivacaine (degree of neuromuscular blockade with pancuronium and with the association of pancuronium-ropivacaine), and the effectiveness of neostigmine and 4-aminopyridine on neuromuscular block reversal were evaluated.
Results: Ropivacaine did not alter the amplitude of muscle response (the membrane potential), but decreased the frequency and amplitude of the miniature endplate potential. Pancuronium blockade was potentiated by ropivacaine, and partially and fully reversed by neostigmine and 4-aminopyridine, respectively.

Conclusions: Ropivacaine increased the neuromuscular block produced by pancuronium. The complete antagonism with 4-aminopyridine suggests presynaptic action of ropivacaine.

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Introduction

Local anesthetics, particularly amino amides, are a group of drugs widely administered by different routes, such as topical, subcutaneous infiltration, peripheral nerve block, neuraxial anesthesia alone or combined with general anesthesia.1-4

There is evidence that these drugs may interfere with neuromuscular transmission and increase the effects of neuromuscular blockers.1-7

Ropivacaine is an amino-amide local anesthetic with similar physicochemical properties to bupivacaine (550%–R50%), except for the lower potency and lesser degree of motor blockade, with greater selectivity for sensory nerve fibers, characteristics attributed to its lower lipid solubility and pure S- isomer structure as opposed to the racemic mixture of bupivacaine.8,9

These characteristics are also responsible for less cardiac and central nervous system toxicity, ropivacaine advantages over bupivacaine (550%–R50%).1-9 Pancuronium is a long acting nondepolarizing aminoesteroid neuromuscular blocker, which justifies its use in prolonged surgery and intensive care.10

The aim of this study was to evaluate in an experimental model the effect of ropivacaine on neuromuscular transmission, its influence on the neuromuscular block produced by pancuronium, and the effectiveness of neostigmine and 4-aminopyridine on blockade reversal.

Method

This is an in vitro experimental study in which the procedures used were in accordance with the ethical principles
The effects of local anesthetics on neuromuscular junction and its influence on the blockade produced by nondepolarizing neuromuscular blockers are still under-investigated; however, this interaction has been described in experimental and human studies. 1-3,7,13 Experimental studies serve as the basis for the results observed in the clinic, with the

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advantage of eliminating bias, which is the great individual variability in response to neuromuscular blockers.\textsuperscript{10,14}

Although local anesthetics can only produce neuromuscular blockade at high doses, interactions with neuromuscular blockers, particularly non-depolarizing, become clinically relevant, and careful observation is required when using these agents simultaneously, or in situations where the safety margin of neuromuscular transmission is reduced.\textsuperscript{1-4,12,14,15}

Several mechanisms are admitted to explain the interaction between local anesthetics and neuromuscular blockers: in the presynaptic region, it selectively depresses conduction in motor fibers and inhibits the acetylcholine release during nerve stimulation; at the postsynaptic level, local anesthetics may bind to different specific acetylcholine sites, resulting in desensitization of receptors, and may cause temporary occlusion of nicotinic receptor channels; furthermore, a stabilizing action of postjunctional membrane and the interference with the muscular fiber excitation-contraction mechanism are described.\textsuperscript{5-7,11,13,16-19}

The ropivacaine concentration used was established in a pilot study and determined from data presented in studies carried out in Brazil, where other amino-amide local anesthetics with similar characteristics to ropivacaine were used.\textsuperscript{5,7} Matsuo et al.\textsuperscript{12} evaluated, in preparation similar to that used in this study, the association of d-tubocurarine with different local anesthetics and found that, even in ineffective concentrations, local anesthetics potentiated neuromuscular block, as evidenced by significant decrease in the ED50. Regarding the influence of neuromuscular blockers on the effects local anesthetics, these authors also reported that ineffective concentrations of d-tubocurarine caused a similar decrease of ED50 and increase of local anesthetic potency.

In a clinical trial, Sahin et al.\textsuperscript{4} evaluated the characteristics of neuromuscular block produced by vecuronium in patients undergoing general anesthesia combined with epidural block with 0.5% levobupivacaine (15 mL) and observed a significant increase in the rate of recovery and total duration of vecuronium effect, without, however, influencing its clinical duration (CD25%). These findings may be explained by the fact that levobupivacaine metabolism, when used in epidural space, only occurs in approximately 30 min when the drug reaches the circulation.\textsuperscript{1}

The present study showed that ropivacaine, at the concentration studied, administered alone had no effect on neuromuscular junction; however, it potentiated the blockade produced by pancuronium. These results are similar to those of other authors, who found no clinical impairment in neuromuscular transmission in experimental studies with the isolated use of different local anesthetics. However, a clear potentiation of the effect of various neuromuscular blockers has been described as a result of these drugs combination, an interaction that may be consequential to the true potentiation at different locations of the neuromuscular junction,\textsuperscript{1,2,4-7,12,13,20} caused by the action of the two drugs.

It is believed that the greatest degree of neuromuscular blockade caused by pancuronium in rat diaphragm preparations previously exposed to ropivacaine, and evidenced by a greater reduction in the extent of muscle responses to phrenic nerve stimulation, is due to a presynaptic action of ropivacaine and not to the muscular fiber depolarizing action, as it was found in electrophysiological studies that bupivacaine at the concentration used did not modify the membrane potential of muscle fibers. The presynaptic action was demonstrated by the decrease in the frequency and amplitude of miniature endplate potentials (MEPP) caused by ropivacaine, being the result of changes in quantal release of acetylcholine.

The neuromuscular blockade caused by ropivacaine combined with pancuronium was completely reversed by 4-aminopyridine and, to a lesser extent, with neostigmine. These results were also described by Sahin et al.\textsuperscript{2} who observed greater efficacy of 4-aminopyridine in humans compared to neostigmine on blockade reversal caused by vecuronium in patients receiving levobupivacaine in the epidural space. In experimental studies, similar results were found regarding reversal of blockade caused by lidocaine–rocuronium combination.\textsuperscript{5}

By inhibiting the acetylcholinesterase, neostigmine increases the neurotransmitter concentration in the synaptic cleft, competitively displacing the agents causing blockage. The partial antagonism of neostigmine reinforces this finding, as cholinesterase inhibitors are only effective in reversing the postsynaptic block. The 4-aminopyridine, in addition to its inhibitory effect of endplate nicotinic receptor desensitization, causes increased quantal acetylcholine. This increase is the result of actions in the membrane of nerve endings, such as potassium channel inhibition, which produces an increase in the duration of the action potential and increased influx of calcium ions to motor nerve endings during membrane depolarization.\textsuperscript{21-23} The complete antagonism achieved with 4-aminopyridine suggested that ropivacaine interaction with pancuronium has presynaptic component related to decreased acetylcholine release.

Ropivacaine alone did not compromise neuromuscular transmission, but potentiated the blockade produced by pancuronium, which was reversed by neostigmine and 4-aminopyridine. These findings are important for clinical practice because it provides guidance on the need for monitoring, particularly when combined with other drugs.

Conflicts of interest

The authors declare no conflicts of interest.
References


