Influence of Local Anesthetics on the Neuromuscular Blockade Produced by Rocuronium. Effects of Lidocaine and 50% Enantiomeric Excess Bupivacaine on the Neuromuscular Junction

Angélica de Fátima de Assunção Braga, TSA, M.D., Vanessa Henriques Carvalho, M.D., Franklin Sarmento da Silva Braga, M.D., Léa Rodrigues-Simioni, M.D., Yolanda Christina S. Loyola, M.D., Glória Braga Potério, TSA, M.D.

INTRODUCTION

The pharmacokinetic and pharmacodynamics properties of neuromuscular blockers can be modified by several factors like, for example, acid-base balance, temperature, monitoring, different diseases (burns, upper and lower motor neuron disorders), and drugs administered by different routes[1-12].

The interaction between local anesthetics and neuromuscular blockers observed in experimental studies[7,9] has also been reported in clinical assays, resulting in potentiation of the effects of neuromuscular blockers by local anesthetics administered by different routes[1,2,4-6,10-12]. However, although those effects have been demonstrated in experimental studies, in isolated preparations, and in clinical assays, the effects on neuromuscular transmission and in the neuromuscular blockade produced by non-depolarizing neuromuscular blockers has not been fully investigated. Understanding this type of interaction between local anesthetics and competitive neuromuscular blockers used in daily practice is important, since it allows their safe use.

The objective of the present study was to evaluate, in experimental models, the effects of lidocaine and 50% enantio-

meric excess bupivacaine on neuromuscular transmission, their influence on the neuromuscular blockade produced by rocuronium, and to investigate the probable mechanism of interaction between local anesthetics and rocuronium.

METHODS

This is an experimental *in vitro* study and the procedures followed the ethical principles of animal studies of the Brazilian College of Animal Studies (COBEA, from the Portuguese) and it was approved by the Ethics Commission on Animal Studies of the Biology Institute of Universidade Estadual de Campinas (protocol # 1204-1).

To evaluate the effects of lidocaine and 50% enantiomeric excess bupivacaine on neuromuscular transmission and their influence on the neuromuscular blockade produced by rocuronium, rat phrenic nerve-diaphragm, prepared according to the method proposed by Bulbrig, was used[13].

Twenty-five male Wistar rats weighing 180 to 250 g were used. Animals were anesthetized with urethane (1.2 $mg.kg^{-1}$, intraperitoneal administration); afterwards, they were exsanguinated by severing the neck vessel to facilitate the identification and removal of the left hemi-diaphragm and the corresponding section of the phrenic nerve. Preparations were fixed in 40 mL of Tyrode's solution, constantly aerated with carbogen (95% O_2 + 5% CO_2), and maintained at 37° C. The nerve was placed on platinum electrodes connected to a Grass S48 stimulator. Constant tension (5.0 g) was applied to the tendon of the diaphragm by a wire connected to the Load Cell BG50 GMS isometric transducer, and indirect stimulation of 0.1 Hz frequency and duration of 0.2 msec was applied; variations in tension produced by diaphragmatic contractions were recorded by the Gould RS 3400 physiograph.

Preparations were divided in five groups (n = 5) according to the drug added: Group I – lidocaine (20 $\mu g.mL^{-1}$); Group II – 50% enantiomeric excess bupivacaine (5 $\mu g.mL^{-1}$); Group III – rocuronium (4 $\mu g.mL^{-1}$); Group IV – rocuronium (4 $\mu g.mL^{-1}$) in preparations previously exposed to lidocaine (20 $\mu g.mL^{-1}$); Group V – rocuronium (4 $\mu g.mL^{-1}$) in preparations previously exposed to 50% enantiomeric excess bupivacaine (5 µg.ml). In groups IV and V, rocuronium was added 30 minutes after lidocaine and 50% enantiomeric excess bupivacaine, respectively. Muscular responses to indirect stimulation were recorded for 60 minutes after the addition of the drugs. The following parameter were evaluated in those groups: 1) the amplitude of the diaphragmatic response to indirect stimulation, before and 60 minutes after the isolate addition of lidocaine, 50% enantiomeric excess bupivacaine, and rocuronium; and 2) the amplitude of the diaphragmatic response after the addition of rocuronium to preparations previously exposed to lidocaine and 50% enantiomeric excess bupivacaine.

Phrenic nerve-diaphragm preparations were also used to study the effects of local anesthetics in miniature end-plate potentials (MEPP) and membrane potentials (MP). The chick biventer cervicis preparation, also used in this study, was prepared according to the method described by Ginsborg and Warrimer[14]. Fourteen four- to eight-day old chicks weighing 40 to 80 g, were anesthetized with inhalational halothane, followed by the removal of the biventer cervicis muscle, which was suspended in a 5-mL container with Krebs solution. The preparation was aerated with carbogen and the temperature was maintained at 37° C. Experiments (n – 7/group) were undertaken to detect the acetylcholine curve (5 $\mu g.mL^{-1}$) before and after the addition of each local anesthetic: lidocaine (20 $\mu g.mL^{-1}$) and 50% enantiomeric excess bupivacaine (5 $\mu g.mL^{-1}$). Indirect stimuli with supramaximal pulses (duration of 0.2 msec and frequency of 0.1 Hz) were applied to the muscle. The responses to acetylcholine were recorded in the Gould RS 3400 physiograph, before and 30 minutes after the addition of lidocaine and 50% enantiomeric excess bupivacaine.

Results were expressed as means and standard deviation. The Student *t* test, Wilcoxon test, Kruskall-Wallis test, and Mann-Whitney test were used in the statistical analysis. A level of significance of 5% ($p < 0.05$) was used. The power of the test was calculated, showing $\beta > 20\%$ (power > 80%).

RESULTS

The isolate use of lidocaine and 50% enantiomeric excess bupivacaine in the concentrations used in the present study did not cause significant reduction in the amplitude of the muscular response to indirect electrical stimulation of the rat phrenic nerve-diaphragm preparation. Rocuronium alone produced a 73.12 ± 9.89% blockade (Figure 1). In prepara-

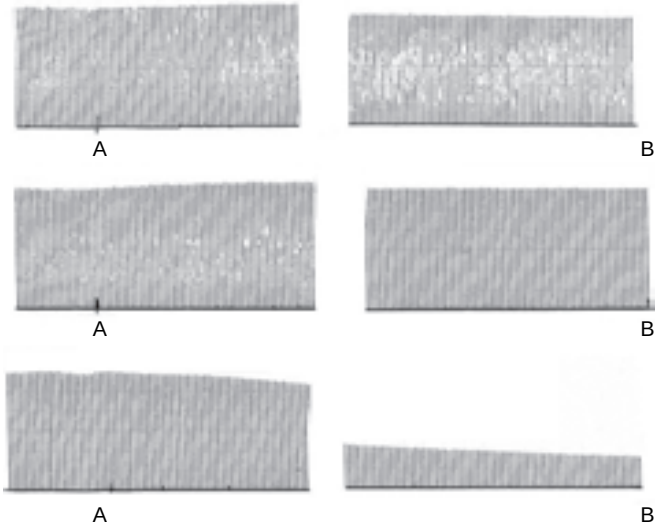

Figure 1 – Muscular responses to indirect stimulation of rat phrenic nerve-diaphragm preparations. Effects of lidocaine – 20 $\mu g.mL^{-1}$ (upper tracing), 50% enantiomeric excess bupivacaine – 5 $\mu g.mL^{-1}$ (mid-tracing), and rocuronium – 4 $\mu g.mL^{-1}$ (lower tracing) in neuromuscular transmission. A: Addition of the drug to the preparation; B: 60 minutes after adding the drug.

tions previously exposed to lidocaine and 50% enantiomeric excess bupivacaine, rocuronium produced a 90.10 ± 9.15% and 100% blockade, respectively, which was significantly different (p = 0.0037) than that produced by rocuronium alone. Rocuronium produced total (100%) blockade in preparations previously exposed to 50% enantiomeric excess bupivacaine, which occurred earlier (24.0 ± 6.74 min) than in preparations exposed to lidocaine (Figure 2).

The local anesthetics investigated did not cause significant changes in membrane potential. The effects of lidocaine on miniature end-plate potentials were initially characterized by an increase in frequency 30 minutes after adding the drug, which was followed by a blockade after 60 minutes. Bupivacaine (S75-R25) caused a reduction in the amplitude and frequency in MEPPs, which was followed by a blockade (Figure 3).

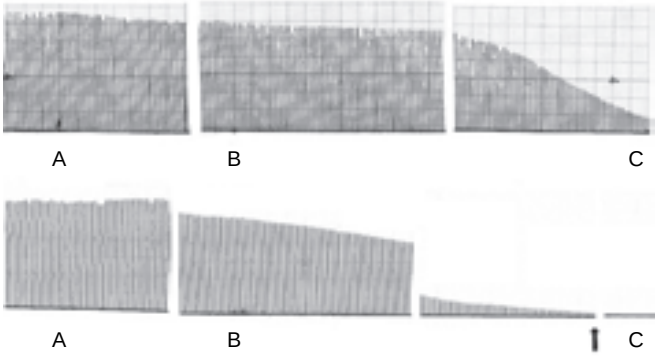

Figure 2 – Effects of rocuronium (4 μg.mL^{-1}) on the muscular response to indirect stimulation of rat phrenic nerve-diaphragm preparations exposed to lidocaine – 20 μg.mL^{-1} (upper tracing) and 50% enantiomeric excess bupivacaine – 5 μg.mL^{-1} (lower tracing). A: Addition of the local anesthetic; B: addition of rocuronium 30 minutes after the local anesthetic; C: 60 minutes after rocuronium. The arrow (lower tracing) shows complete blockade with rocuronium (24.0 ± 6.75 minutes).

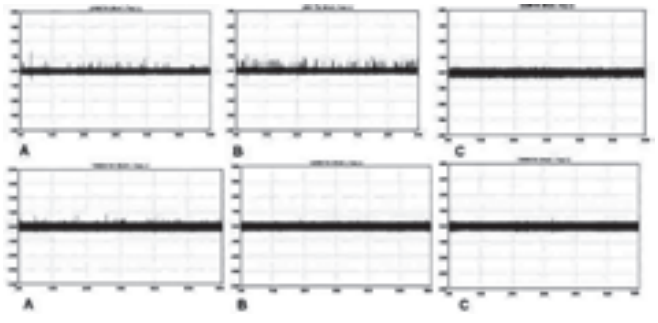

Figure 3 – Effects of lidocaine – 20 μg.mL^{-1} (upper tracing) and 50% enantiomeric excess bupivacaine – 5 μg.mL^{-1} (lower tracing) on miniature end-plate potentials (MEPP in rat phrenic nerve-diaphragm preparation). A: Control; B: 30 minutes after the addition of the local anesthetic; C: 60 minutes after the addition of the local anesthetic.

In chick biventer cervicis preparations, lidocaine (20 μg.mL^{-1}) and 50% enantiomeric excess bupivacaine (5 μg.mL^{-1}) caused a significant reduction, 28.77± 19.65% and 33.2 ± 11.69%, respectively, in the contracture provoked by acetylcholine. Statistical analysis demonstrated that the percentage reduction in the contraction in response to acetylcholine was similar (p = 0.2550) with both local anesthetics.

DISCUSSION

Lidocaine and 50% enantiomeric excess bupivacaine are frequently used in different types of blockade. Additionally, lidocaine is commonly used to suppress reflexes during laryngoscopy and tracheal intubation, and it is also a first-line drug in the treatment of ventricular arrhythmias, with great advantages over quinidine and procainamide due to its fast onset of action and easy titration[6,12,15].

The present study demonstrated that, in the concentrations used, lidocaine and 50% enantiomeric excess bupivacaine, isolated or not, did not have significant effects in the neuromuscular junction, but they did potentiate the blockade induced by rocuronium. Those results are similar to those of other authors who also reported the lack of effects of local anesthetics in neuromuscular transmission, but who observed potentiation of the effects of different neuromuscular blockers when local anesthetics were administered by different routes[1,2,4-7,9,10,16].

In studies with cats, the neuromuscular blockade induced by the lidocaine-pancuronium association was 20% greater than that of pancuronium alone, which was statistically significant[16].

In vitro studies with rat phrenic nerve-diaphragm preparations, the authors also observed potentiation of rocuronium-induced blockade in preparations previously exposed to procainamide and lidocaine[7,9]. It is possible that prolonged exposure to local anesthetics can cause a reduction in the number of nicotinic receptors in the neuromuscular junction, with the consequent reduction in the safety margin[9,17].

In humans, the effects of vecuronium and atracurium were prolonged by the epidural administration of bupivacaine, and the duration of action of rocuronium was increased by the intravenous administration of lidocaine[1,2,6].

The interaction between local anesthetics and neuromuscular blockers is not completely understood, and several mechanisms can be responsible for the potentiation observed. In theory, those agents can interfere with any step of the neuromuscular transmission. The pre-synaptic effects of local anesthetics can cause selective depression of motor fiber conduction and decrease the release of acetylcholine during nerve stimulation[18-20]. Their post-synaptic effects include binding to different acetylcholine-specific sites, resulting in the desensitization of those receptors, besides the temporary occlusion of ion channels in nicotinic receptors[9,21,23].

Lidocaine can block completely nerve conduction and can also cause depression of pre- and post-junctional impul-

ses[24]. A study that correlating the molecular structure of different lidocaine byproducts with their ability to inhibit muscular transmission and local anesthetic potency, demonstrated that the molecular properties of those byproducts associated with changes in neuromuscular transmission are similar to those involved in the activation of acetylcholine receptors and not with their local anesthetic potency. Those results suggest that lidocaine produces neuromuscular blockade by different mechanisms than those involved with its local anesthetic effects[24].

In the present study, it was also observed that, in experiments in which bupivacaine (S75-R25) was used, rocuronium induced complete neuromuscular blockade, which developed earlier than in preparations exposed to lidocaine, in approximately 24.0 ± 6.74 minutes. Bupivacaine (S75-R25), an amphiphilic molecule, has great affinity for excitable cellular membranes, inactivating voltage-gated sodium channels and, therefore, block the influx of ions necessary for membrane depolarization. It is believed that two mechanisms are responsible for the reduction in membrane permeability to sodium ions: general changes in membrane fluidity with conformational modifications in the protein of voltage-gated sodium channels and/or by the specific interaction of local anesthetics with sodium channels[25-27]. On the other hand, the direct correlation between hydrophobicity and anesthetic potency indicates that nonspecific partition of a large amount of local anesthetic in the lipid bilayer is important to facilitate the access of the molecule to voltage-gated sodium binding sites[28,29].

The structure and physical-chemical characteristics of 50% enantiomeric excess bupivacaine can fundamental for such findings, since the potency of this drug is greater than that of lidocaine. This property can be attributed to the greater hydrophobicity of this agent, indicating an alternative access pathway to hydrophobic sites in the sodium channel protein. On the other hand, lipid solubility is crucial for drug partition in the axon to guarantee that enough amounts of local anesthetic penetrate in the membrane and inactivate the sodium channel[29,30].

Racemic bupivacaine, enantiomeric excess bupivacaine, ropivacaine, and mepivacaine contain a chiral center in their piperidinium ring, which is responsible for the optical isomers with S (-) and R (+) configurations. Besides receptor affinity, this stereoisomery also contributes for fluidization of cellular membranes[27].

The effects of local anesthetics were also evaluated in other preparations looking for probable mechanisms of this interaction. The characteristics of the chick biventer cervicis preparation are different from mammal preparations and, due to the peculiar behavior in the presence of nicotinic receptor agonists, it allowed the evaluation of the affinity of lidocaine and bupivacaine (S75-R25) for post-synaptic nicotinic receptors. Post-synaptic activity of different drugs, such as local anesthetics, can be identified by the absence of response to cholinergic agonists without affecting the response to the increase in potassium concentration or direct stimulation[31].

Due to the high density of receptors in bird musculature, agonists cause sustained depolarization of muscle fibers, leading to muscular contracture (shortening of muscle fibers) secondary to the influx of calcium ions in those cells. This type of behavior is different from normal muscular contraction, since, in the latter, fast end-plate depolarization generates an action potential that spreads throughout the muscle fiber, while contracture is a sustained and slow depolarization and that does not spread, but it is seen on every site of the fiber that contains acetylcholine receptors[14,32].

The results observed in this preparation demonstrated that different local anesthetics, in the concentrations used here, cause significant and similar reductions in contracture in response to acetylcholine, which suggests that the interaction with rocuronium might be due to a competitive mechanism between local anesthetics and the neurotransmitter. Those results can be explained by the results of Ueta et al.[33] who studied, *in vitro*, the antagonistic activity of racemic bupivacaine and its two enantiomers, S (-) and R (+), in nicotinic cholinergic receptors, gamma-aminobutyric acid (GABA) receptors, 5-hydroxitryptamine (5-HT), and N-methyl-d-aspartate (NMDA). The authors concluded that racemic bupivacaine and its isomers cause similar and concentration-dependent antagonism of the activity of those receptors.

Similarly to other authors, we observed that the local anesthetics in the concentrations used here did not produce changes in the membrane potential of muscular fibers, demonstrating that lidocaine and bupivacaine (S75-R25), in those concentrations, do not cause depolarization of the muscle fiber, and that their mechanism of action in the neuromuscular junction is not related with their ability to stabilize the muscular membrane.

The study of miniature end-plate potentials contributed to the investigation of the pre- and post-synaptic influence of the drugs used, by their interference in the process of mediator production or release[34]. As described previously by other authors, lidocaine, initially, caused an increase in the frequency of miniature end-plate potentials followed by a blockade[7], which might suggest that lidocaine has pre-synaptic activity, leading to a discrete increase in the release of acetylcholine. It is possible that this initial increase in the concentration of the neurotransmitter in the synaptic cleft and its prolonged contact with the end-plate terminal could cause desensitization of those receptors and consequent blockade.

Unlike lidocaine, preparations exposed to bupivacaine (S75-R25) showed progressive blockade of MEPP, with reduction in their frequency and amplitude, until it disappeared completely. The results of electrophysiologic studies demonstrated that those drugs, in the concentrations used in the present study, interfere with the release of acetylcholine.

According to the literature, the results of the present study showed that the mechanisms responsible for the interaction

between the local anesthetics investigated here and rocuronium are differentiated and controversial. The changes in miniature end-plate potentials indicate a pre-synaptic effect modifying the quantal release of acetylcholine. The absence of changes in membrane potentials demonstrates that, in the concentrations used here, those drugs do not depolarize muscle fibers and the reduction in the amplitude of the response to acetylcholine probably reflects post-synaptic effects, especially in the motor end-plate.

Isolated lidocaine and 50% enantiomeric excess bupivacaine did not compromise neuromuscular transmission, but they potentiated rocuronium-induced neuromuscular blockade. Those results indicate that the neuromuscular blockade should be monitored and the dose of neuromuscular blockers should be reduced when used in combination with those agents.

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RESUMEN

Braga AFA, Carvalho VH, Braga FSS, Rodrigues-Simioni L, Loyola YCS, Potério GB - Influencia de Anestésicos Locales sobre el Bloqueo Neuromuscular Producido por el Rocuronio. Acción de la Lidocaína y de la Mezcla Enantiomérica en Exceso de 50% de Bupivacaína en la Junción Neuromuscular.

JUSTIFICATIVA Y OBJETIVOS*: Los efectos de los anestésicos locales (AL), en la transmisión neuromuscular y su influencia en el bloqueo neuromuscular producido por bloqueadores neuromusculares competitivos, todavía no se ha investigado lo suficiente. El objetivo del estudio, fue evaluar in vitro los efectos de la lidocaína y de la mezcla enantiomérica en exceso de 50% de bupivacaína (S75-R25) en el bloqueo neuromuscular producido por el rocuronio.*

MÉTODOS*: Algunos ratones se distribuyeron en cinco grupos (n = 5) de acuerdo con el fármaco estudiado: lidocaína, bupivacaína (S75-R25), rocuronio, aisladamente (Grupos I, II, III); rocuronio en preparaciones previamente expuestas a los AL (Grupos IV, V). Las concentraciones utilizadas fueron: 20 µg.mL^{-1}, 5 µg.mL^{-1} y 4 µg.mL^{-1}, para lidocaína, bupivacaína (S75-R25), y rocuronio, respectivamente. Se evaluó: 1) la fuerza de contracción muscular del diafragma a la estimulación eléctrica indirecta, antes y 60 minutos después de la adición de los AL y rocuronio aisladamente, y la asociación AL – rocuronio; 2) efectos de los AL sobre el potencial de la membrana (PM) y potenciales de placa terminal en miniatura (PPTM). En una preparación biventer cérvicis de pollito, se evaluó el efecto de los AL en la respuesta de contracción a la acetilcolina.*

RESULTADOS: *La lidocaína y la bupivacaína (S75-R25) aisladamente, no alteraron las respuestas musculares y los valores del PM. En las preparaciones expuestas a los AL, el bloqueo por el rocuronio fue significativamente mayor con relación al producido por el rocuronio aisladamente. En una preparación biventer cervicis de pollito, la lidocaína y la bupivacaína (S75-R25), redujeron la respuesta de contracción a la acetilcolina. La lidocaína aumentó la frecuencia de los PPTM, seguido de bloqueo; la bupivacaína (S75-R25) generó una disminución seguida de bloqueo.*

CONCLUSIONES: *Los anestésicos locales potenciaron el bloqueo neuromuscular causado por el rocuronio. Los resultados mostraron una acción presináptica y postsináptica.*