

Evaluation of the antimicrobial effects of atracurium, rocuronium and mivacurium. Antimicrobial effects of muscle relaxants

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Abstract

Some anaesthetic agents may be contaminated with microorganisms during the process of preparing an infusion. For this reason, it is important to understand the antimicrobial effects of various anaesthetic agents, which have been investigated to some degree in previous studies. However, studies specifically focusing on antibacterial effects of neuromuscular blocking drugs (anaesthetic agents) are very rare. Herein, we analysed the antimicrobial effects of atracurium, rocuronium, and mivacurium, on four different microorganisms. The *in vitro* antimicrobial activities of atracurium, rocuronium and mivacurium were investigated using the broth microdilution method. The pH of the test solutions was determined using a pH meter. The test microorganisms included *Staphylococcus aureus* ATCC 29213, *Enterococcus fecalis* ATCC 29212, *Escherichia coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853. The pH of the test solutions ranged between 7.20 and 7.32. The minimum inhibitory concentrations of atracurium, rocuronium and mivacurium for *S. aureus*, *E. fecalis*, *E. coli* and *P. Aeruginosa* were all found to be 512 µg/mL. Atracurium, rocuronium and mivacurium inhibit the growth of common intensive care unit pathogens at the same concentration (512 µg.mL⁻¹). Thus, the neuromuscular blocking drugs, atracurium, rocuronium and mivacurium should be administered at a minimum concentration of 512 µg/mL in intensive care units to achieve this antibacterial effect. In our opinion, when used systemically, atracurium, rocuronium and mivacurium do not cause a systemic antibacterial effect. However, their antibacterial effects may be advantageous for inhibiting the spread of bacterial contamination during the preparation of the infusion solutions.

Introduction

Some anaesthetic agents are known to support the growth of microorganisms, while other anaesthetic agents neither support nor inhibit microbial growth. The antibacterial effects of anaesthetic agents may be beneficial for reducing the spread of some types of infections brought about by contaminated compounds that are destined to be delivered into patients.¹

Atracurium, rocuronium and mivacurium are neuromuscular blocking agents that are commonly used in intensive care units (ICUs).^{2,5} However, to date, only one previous study has focused on the antibacterial effects of atracurium.⁶

The aim of this study was to evaluate the antimicrobial effects of atracurium, rocuronium and mivacurium on microorganisms that are frequently isolated in our ICU. The test microorganisms chosen were *S. aureus* American Type Culture Collection (ATCC) 29213, *E. fecalis* ATCC 29212, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853.

Materials and Methods

The antibacterial activities of atracurium, rocuronium and mivacurium were investigated using the broth microdilution method according to the procedures outlined by the Clinical and Laboratory Standards Institute (CLSI).⁷

Briefly, each neuromuscular blocking drug was diluted with 0.9% sterile saline to final concentrations of 512 µg/mL, 256 µg/mL, 128 µg/mL, 64 µg/mL, 32 µg/mL, 16 µg/mL, 8 µg/mL, 4 µg/mL, 2 µg/mL, 1 µg/mL and 0.5 µg/mL. For each neuromuscular blocking drug, the pH values of all the dilutions were determined with a pH meter (Mettler MP 220, Toledo, Switzerland). *S. aureus* ATCC 29213, *E. fecalis* ATCC 29212, *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853 were used as control microorganisms. The bacteria [5×10⁵ colony-forming units per millilitre; (CFU/mL)], CAMHB (cation-adjusted Mueller-Hinton broth) and the neuromuscular blocking drugs in the specified concentrations were incubated in the wells on microplates at 35°C for 20 hours. The minimal inhibitory concentrations (MIC) were determined by observing the lowest concentration of the agent that inhibited visible growth of the bacterium. Haze or turbidity in the wells were indicators of bacterial growth.

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Results

The MIC values of atracurium, rocuronium and mivacurium for *S. aureus*, *E. coli*, *P. aeruginosa* and *E. fecalis* were all determined to be 512 µg/mL. The pH values of the tested agent solutions are listed in Table 1.

Discussion

In this study, we have found that atracurium, rocuronium and mivacurium have antimicrobial properties with regard to the microorganisms studied. The MIC of the antibacterial neuromuscular blocking drugs were found to be higher in concentration than the plasma concentrations required to produce a 50% inhibition in humans and lower than their recommended clinical use concentrations.

However, some anaesthetic agents may be contaminated by microorganisms during the preparation of an infusion. For this reason, the antimicrobial effects of various anaesthetic agents have been deemed important, and they have been investigated in previous studies. There are also published reports of systemic bacteremias and wound infections involving *S. aureus* that are linked to the use of intravenous propofol.⁸ Notably, propofol is known to support the growth of microorganisms.^{6,9-15} Yet, previous studies have shown that morphine sulphate, thiopental sodium, fentanyl citrate, dexmedetomidine and midazolam all have antimicrobial effects.^{1,6,14-16} However, studies on the antimicrobial effects of neuromuscular blocking drugs, which are commonly used in ICUs, are very rare.^{6,11} Graystone *et al.*⁶ showed that atracurium demonstrates antibactericidal effects and also

Table 1. The pH values of tested dilutions of atracurium, rocuronium and mivacurium.

Dilution of agents $\mu\text{g mL}^{-1}$	pH values		
	Atracurium	Rocuronium	Mivacurium
512	7.22	7.24	7.26
256	7.25	7.27	7.28
128	7.28	7.29	7.29
64	7.30	7.30	7.30
32	7.30	7.30	7.30
16	7.30	7.30	7.31
8	7.30	7.31	7.31
4	7.30	7.31	7.31
2	7.30	7.31	7.31
1	7.30	7.31	7.31
0.5	7.30	7.31	7.31

reduces fungal growth. However, a study by Durak *et al.*¹¹ did not support the aforementioned claims of atracurium's bactericidal effect. In our study, we found that rocuronium, atracurium and mivacurium have antimicrobial properties with respect to the growth of *S. aureus*, *E. coli*, *P. aeruginosa* and *E. fecalis*.

However, the mechanisms of the antibacterial activity of these three compounds have not been clarified. Several studies have established that the antimicrobial effects of some anaesthetics may depend on their molecular weight, pH and thermodynamic activity.^{1,6,11} Yet, other studies revealed an interaction between the cytoplasmic membrane and a macromolecule component of the anaesthetic agent.^{17,18}

The bactericidal property of thiopental is thought to be related to its high pH (10.55).¹⁹ In several studies, the pH range of midazolam was shown to be responsible for its bacterial inhibitory effect.^{6,20} Keles *et al.*¹⁶ concluded that the antimicrobial effect of midazolam may be due to the fact that this compound includes HCl as a preservative.

Most pathogenic bacteria prefer a fairly narrow pH range, between 6 to 8, for survival.^{12,14} However, the growth of *S. aureus* (ATCC 25923), *E. coli* (ATCC 25922) or *P. aeruginosa* (ATCC 27853) were not affected by growth conditions in which the pH was between 5.0 and 8.0.²¹

In our study, prior to performing the recommended dilution, the pH of the atracurium, rocuronium, and mivacurium solutions were 3.5, 4.1, and 4.0 respectively. However, the diluted drugs all had a pH between the narrow range of 7.20 to 7.32. For this reason, the bactericidal properties of the three compounds in our study could not be due to their pH.

Lipid-based emulsions and preservative-free forms have been shown to support various microorganisms by inhibiting the reticuloendothelial system and thereby suppressing the host's natural immunity.^{1,10} Atracurium, rocuronium and mivacurium would then be deemed to be advantageous in that they do not contain

lipid-based emulsions. Moreover, the pH values of the undiluted solutions may prevent contamination at clinically relevant concentrations. However, based on a review of the literature, there were no publications addressing the effects of atracurium, rocuronium, and mivacurium on human neutrophil functions, immune function or the inflammatory response.

It is important that strict guidelines regarding the need for sterile equipment and deliverables be adhered to during all procedures performed in the ICU. In some circumstances neuromuscular blocking drugs may be contaminated with microorganisms that can then lead to infections.¹ Thus, the antimicrobial effect of neuromuscular blocking drugs in these types of settings is of paramount importance.

The emerging problem of bacterial resistance in the hospital and in the ICU limits the use of antimicrobials because of the risk of the positive selection of resistant bacteria. Although the neuromuscular blocking drugs atracurium, rocuronium and mivacurium are known to have antibacterial effects, these effects are concentration dependant. However, we have found that the working antibacterial concentration of atracurium, rocuronium and mivacurium was higher than the concentration corresponding to a 50% inhibition in their activity (EC_{50}) (454 ng/mL^{-1} , 1008 ng/mL^{-1} and 130 ng/mL^{-1} , respectively).^{22,25}

In our opinion, when used systemically, atracurium, rocuronium and mivacurium do not cause a systemic antibacterial effect. However, their antibacterial effects may be sufficient to inhibit contamination during the preparation of the infusion solutions.

As a result, we have shown that atracurium, rocuronium and mivacurium have antibacterial effects on some microorganisms frequently encountered in hospital settings, but when these compounds are administered as an infusion, they should be used at concentrations equal to or greater than 512 $\mu\text{g/mL}$.

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