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Interaction of Nondepolarizing Muscle Relaxants with M_2 and M_3 Muscarinic Receptors in Guinea Pig Lung and Heart

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Background: Neuromuscular blocking agents such as gallamine and pancuronium bind to muscarinic cholinergic receptors and alter parasympathetically mediated airway caliber and heart rate. In the lungs, acetylcholine induces bronchoconstriction via M_3 muscarinic receptors on airway smooth muscle, whereas in the heart M_2 muscarinic receptors mediate bradycardia. Moreover, release of acetylcholine from parasympathetic nerves in the lung is decreased by inhibitory M_2 receptors on the nerves, which represent a negative feedback system. Blockade of these receptors potentiates vagally induced bronchoconstriction, which may be clinically important if the M_3 receptors on airway muscle are not blocked. These experiments were designed to examine the effects of the newer, nondepolarizing muscle relaxants pipecuronium, doxacurium, and mivacurium on pulmonary and cardiac muscarinic receptors.

Methods: Guinea pigs were anesthetized with urethane, paralyzed with succinylcholine, and their lungs mechanically ventilated. Pulmonary inflation pressure and heart rate were measured before and after electrical stimulation of both vagus nerves to evaluate prejunctional M_2 muscarinic receptor function and after intravenous acetylcholine to evaluate postjunctional M_3 and M_2 receptor function in the presence of increasing concentrations of pancuronium, mivacurium, pipecuronium, and doxacurium.

Results: Pancuronium was an antagonist for M_2 and M_3 muscarinic receptors. Mivacurium was a more potent antagonist of M_3 than M_2 receptors. Pipecuronium was an antagonist of M_2 but not M_3 receptors. Doxacurium was not an antagonist of either M_2 or M_3 muscarinic receptors. Only pancuronium

and pipecuronium potentiated vagally induced bronchoconstriction. With pipecuronium, the potentiation occurred at concentrations greater than those used clinically.

Conclusions: Although pipecuronium is an M_2 receptor antagonist with no M_3 receptor antagonist properties, potentiation of reflex-induced bronchoconstriction is unlikely, because this effect occurred only at doses greater than those used clinically. (Key words: Muscarinic receptors: M_2 ; M_3 . Neuromuscular relaxants: doxacurium; mivacurium; pancuronium; pipecuronium.)

ALTHOUGH neuromuscular blocking drugs are designed to specifically block nicotinic cholinergic receptors at the neuromuscular junction, many bind to muscarinic cholinergic receptors on ganglia, nerve endings, and smooth muscle, and alter parasympathetically mediated airway caliber and heart rate.¹ At least three muscarinic receptor subtypes have been identified pharmacologically and five molecular forms have been delineated.² The heart contains a homogeneous population of M_2 muscarinic receptors, activation of which induces bradycardia.³ In the airways, acetylcholine (ACh) administered either exogenously or released from postganglionic parasympathetic nerve endings, induces bronchoconstriction by activating M_3 muscarinic receptors on airway smooth muscle.⁴ In addition, ACh release from parasympathetic postganglionic nerves is under local control of muscarinic M_2 receptors on prejunctional postganglionic parasympathetic nerves.⁵

Under physiologic conditions, M_2 muscarinic receptor activation inhibits ACh release, limiting vagally induced bronchoconstriction. Therefore, blockade of cardiac M_2 muscarinic receptors increases heart rate,⁶⁻⁸ while in the lungs, blockade of the prejunctional M_2 muscarinic receptors potentiates vagally induced bronchoconstriction.^{8,9} Conversely, blockade of M_3 muscarinic receptors on airway smooth muscle inhibits vagally induced bronchoconstriction.⁴ Gallamine, atracurium, and low concentrations of pancuronium are M_2 receptor blockers.^{8,9} Higher concentrations of

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pancuronium block M_3 receptors⁸ while vecuronium does not appear to have either M_2 - or M_3 -blocking properties.⁹

A new generation of nondepolarizing muscle relaxants is currently available for clinical use. Their effects on muscarinic receptors in heart and lung are not known. These experiments were designed to compare the effects of the new nondepolarizing muscle relaxants pipecuronium, doxacurium, and mivacurium to that of pancuronium on pulmonary and cardiac muscarinic receptors. We therefore determined the relative effects of prejunctional and postjunctional muscarinic receptor blockade with pancuronium, mivacurium, pipecuronium, and doxacurium on bronchoconstriction and the decrease in heart rate induced by vagal nerve stimulation and by intravenous ACh in anesthetized guinea pigs.

Materials and Methods

Dunkin-Hartley guinea pigs weighing 350–450 g were used. Guinea pigs were handled in accordance with the standards established by the United States Animal Welfare Acts set forth in the National Institutes of Health guidelines and the Policy and Procedures Manual published by the Johns Hopkins University School of Hygiene and Public Health Animal Care and Use Committee.

Animal Preparation

The guinea pigs were anesthetized with urethane (1.5 g/kg) injected intraperitoneally. The carotid artery was cannulated and connected to a Spectromed DTX pressure transducer (Spectromed, Oxnard, CA) for monitoring heart rate and blood pressure. Both jugular veins were cannulated for the administration of drugs. Both vagus nerves were cut and the distal ends were placed on shielded electrodes immersed in a pool of liquid paraffin. The animal's body temperature was maintained at 37°C using a heating blanket. The animals were treated with guanethedine (10 mg/kg intravenous) to deplete norepinephrine, paralyzed with succinylcholine (infused at $10 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$), and their lungs artificially ventilated *via* a tracheal cannula using a positive pressure, constant volume animal ventilator (Harvard Apparatus Co., South Natick, MA; tidal volume 2.5–3.5 ml, 100–120 breaths/min). In this preparation, succinylcholine has been shown previously to have no effect on baseline pulmonary inflation pressure

(Ppi), heart rate, or blood pressure⁵ and no effect on vagally induced increases in Ppi.⁵ Pulmonary inflation pressure was measured at the trachea with a Spectromed DTX pressure transducer. All signals were displayed on a Grass polygraph (Grass Instruments, Quincy, MA). Partial pressure of oxygen and partial pressure of carbon dioxide were measured from arterial blood samples at the beginning and the end of each experiment (Corning 170 pH/blood gas analyzer; Corning Glass, Medfield, MA).

Physiologic Measurements

Basal Ppi was produced by positive pressure ventilation of the guinea pigs' lungs. Bronchoconstriction was measured as an increase in Ppi over the basal pressure produced by the ventilator.¹⁰ The sensitivity of the method was increased by taking the output Ppi signal from the driver to the input of the preamplifier of a second channel on the polygraph. Thus, baseline Ppi was recorded on one channel and increases in Ppi above the baseline were recorded on a second channel at a greater sensitivity. With this method, increases in Ppi as small as 2–3 mmH₂O could be amplified and recorded accurately.

Electrical stimulation of both vagus nerves (15 Hz, 0.2 ms, 45 pulses/train) produced increases in Ppi and bradycardia. The voltage was selected within a range of 5–30 V to yield similar increases in Ppi between animals. The nerves were stimulated at 1-min intervals, and at regular intervals, ACh (1 or 2 $\mu\text{g}/\text{kg}$) was administered intravenously to monitor the function of the postjunctional muscarinic receptors on the heart and airway smooth muscle.

In separate experiments, cumulative doses of pancuronium (0.01–3.0 mg/kg), mivacurium (0.01–5.0 mg/kg), pipecuronium (0.01–3.0 mg/kg), and doxacurium (0.01–1.0 mg/kg) were administered to guinea pigs. The doses used were based on the ED₉₅ (effective dose, 95% of subjects) of each drug for neuromuscular relaxation. All drugs were administered intravenously at 5-min intervals and the effects were measured immediately after administration. The effects of each muscle relaxant on pulmonary and cardiac M_2 muscarinic receptor function were tested by comparing the magnitude of vagally induced bronchoconstriction and bradycardia before and after each dose of the drug. The effect of each drug on postjunctional M_3 muscarinic receptors was also tested by measuring ACh-induced bronchoconstriction and bradycardia responses before and after each dose of the muscle relaxant. Results are expressed as the ratio of

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the maximum bronchoconstriction (or bradycardia) after a particular dose of a muscle relaxant to the response before that dose of drug.

At the end of each experiment, intravenous atropine (1 mg/kg), was given to determine whether responses were mediated *via* muscarinic receptors. In the animals given mivacurium, the histamine-1 receptor antagonist pyrilamine (5 mg/kg intravenous) was administered after the atropine to determine whether the remaining airway and/or cardiac changes seen were related to the release of histamine by mivacurium.

Drugs

The drugs used in these experiments were: urethane, guanethidine, succinylcholine, pyrilamine, pancuronium, atropine, and ACh, all purchased from Sigma Chemical (St. Louis, MO). Pipecuronium was a gift from Organon (West Orange, NJ) and doxacurium and mivacurium were gifts from Burroughs Wellcome (Research Triangle Park, NC). All drugs were dissolved and diluted in 0.9% NaCl.

Statistics

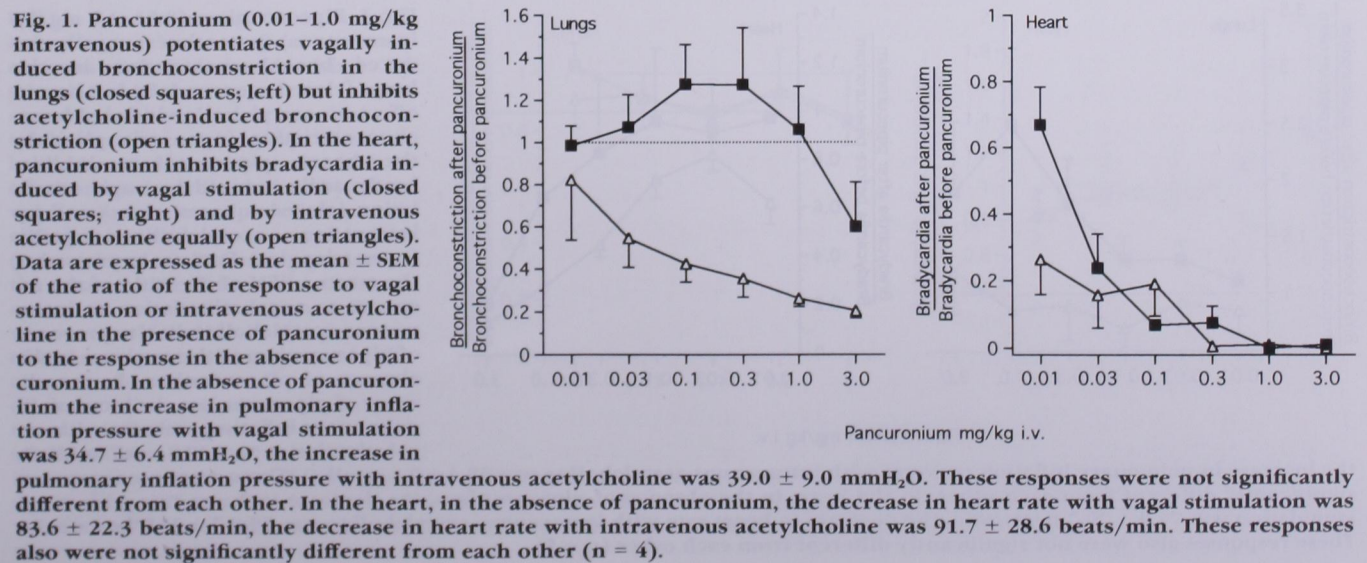
All data were expressed as mean \pm SEM. Control responses to vagal stimulation or ACh between groups of guinea pigs were compared using Student's *t* test for unpaired samples. Dose-response curves were analyzed by analysis of variance with repeated measures. A *P* value of less than 0.05 was considered significant. Appropriate ED₅₀'s (effective dose, 50% of subjects) were obtained from figures 1 through 4.

Results

At the beginning of each experiment, baseline pulmonary inflation pressure (range 9.6–11.5 cm H₂O), heart rate (range 260–300 beats/min) and blood pressure (systolic range 43–50 mmHg; diastolic range 21–26 mmHg) were not different between groups. None of the drug treatments, except mivacurium, had any effect on these parameters.

Electrical stimulation of the vagus nerves (15 Hz, 0.2 ms, 5–40 V, 45 pulses/train) caused an increase in Ppi. Intravenous injection of ACh (1 or 2 μ g/kg) also caused an increase in Ppi. Atropine (1 mg/kg intravenous) given at the end of each experiment blocked increases in Ppi induced by both electrical stimulation of the vagus nerves and intravenous ACh, indicating that these responses are mediated by muscarinic receptors. In the heart, vagal stimulation and intravenously administered ACh caused bradycardia (measured as a decrease in heart rate) *via* stimulation of M₂ muscarinic receptors on cardiac muscle.

Pancuronium at doses of 0.01–1.0 mg/kg potentiated the vagally induced increase in Ppi (*P* = 0.05). However, at the highest concentration used, 3.0 mg/kg, pancuronium inhibited vagally induced increases in Ppi by 40% (fig. 1, left). This inhibition is probably a result of the large, coincident blockade of M₃ muscarinic receptors because at this dose, increases in Ppi induced by intravenous ACh (and therefore mediated solely by M₃ receptors) are almost completely inhibited (open triangles). At all doses used, pancuronium



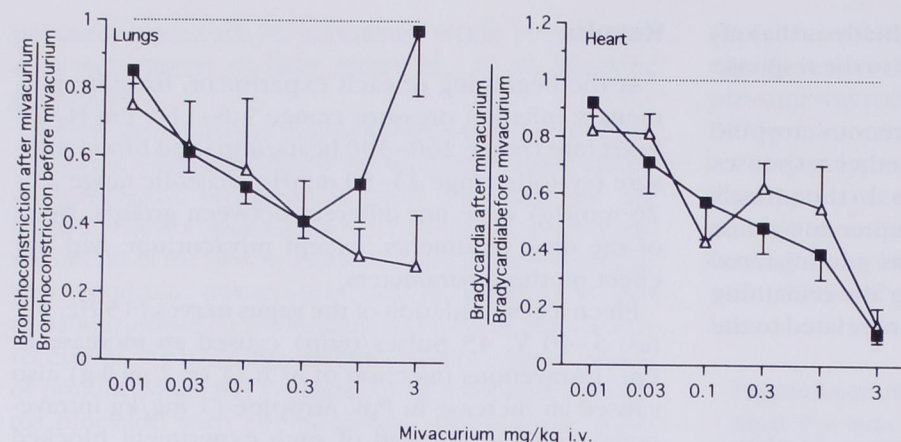


Fig. 2. Mivacurium (0.01–0.3 mg/kg intravenous) inhibits both vagally induced (closed squares; left side) and acetylcholine-induced (open triangles) bronchoconstriction in the lungs. Doses higher than 1.0 mg/kg increase only vagally induced bronchoconstriction. In the heart, mivacurium (0.01–3.0 mg/kg intravenous) inhibits bradycardia induced by vagal stimulation (closed squares; right) or by intravenous acetylcholine equally (open triangles). Data are expressed as the mean \pm SEM of the ratio of the response to vagal stimulation or intravenous acetylcholine in the presence of mivacurium to the response in the absence of mivacurium. In the absence of mivacurium the increase in pulmonary inflation pressure with vagal stimulation was 35.8 ± 6.4 mmH₂O, the increase in pulmonary inflation pressure with intravenous acetylcholine was 46.7 ± 9.6 mmH₂O. These responses were not significantly different from each other. In the heart, in the absence of mivacurium, the decrease in heart rate with vagal stimulation was 80.9 ± 31.2 beats/min, the decrease in heart rate with intravenous acetylcholine was 128 ± 37.5 beats/min. These responses also were not significantly different from each other ($n = 8$).

caused an inhibition of ACh-induced increase in Ppi ($P = 0.009$). This effect of pancuronium on M₃ receptors was dose-dependent with a maximal inhibition (at 3 mg \cdot kg⁻¹ pancuronium) of 74%. In the heart, pancuronium (0.01–3.0 mg \cdot kg⁻¹ intravenous) inhibited both vagally induced ($P = 0.0001$) and ACh-induced ($P = 0.0001$) bradycardia (fig. 1, right). This effect of pancuronium in the heart was dose-related. After administration of 1 mg/kg or more of pancuronium, no

bradycardia could be elicited either by vagal stimulation or by intravenous ACh. Atropine (1 mg/kg) abolished the vagally induced and ACh-induced increase in Ppi and bradycardia provoked by pancuronium.

Mivacurium, at doses of 1–5 mg/kg, increased baseline Ppi (table 1). Pyrilamine, but not atropine, prevented the increase in baseline Ppi (table 1), indicating that this increase was mediated *via* histamine release, rather than *via* a muscarinic receptor. In separate ex-

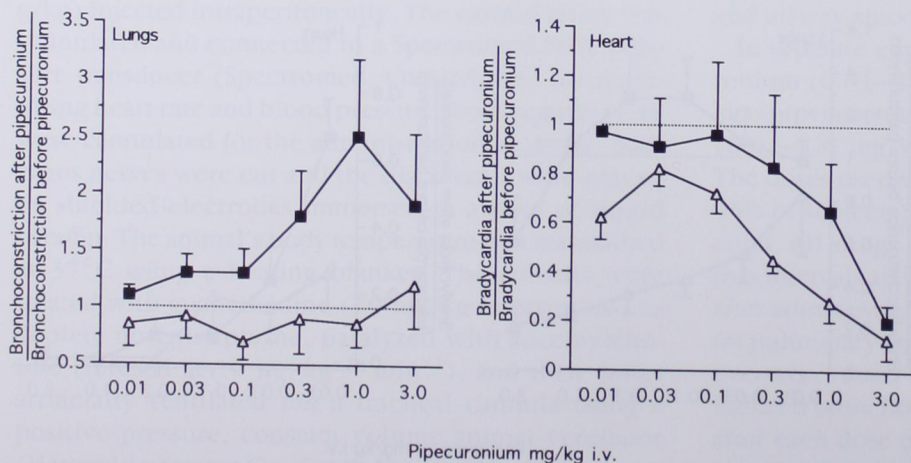


Fig. 3. Pipecuronium (0.01–3.0 mg/kg intravenous) potentiates vagally induced bronchoconstriction in the lungs (closed squares; left) but has no effect on acetylcholine-induced bronchoconstriction (open triangles). In the heart, pipecuronium inhibits bradycardia induced by vagal stimulation (closed squares; right) and by intravenous acetylcholine equally (open triangles). Data are expressed as the mean \pm SEM of the ratio of the response to vagal stimulation or intravenous acetylcholine in the presence of pipecuronium to the response in the absence of pipecuronium. In the absence of pipecuronium the increase in pulmonary inflation pressure with vagal stimulation was 30.8 ± 0.7 mmH₂O, the increase in pulmonary inflation pressure with intravenous acetylcholine was 28.4 ± 7.4 mmH₂O. These responses were not significantly different from each other. In the heart in the absence of pipecuronium, the decrease in heart rate with vagal stimulation was 74.9 ± 20.7 beats/min, the decrease in heart rate with intravenous acetylcholine was 79.8 ± 33.7 beats/min. These responses also were not significantly different from each other ($n = 5$).

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periments, mivacurium (0.01–1.0 mg/kg) inhibited both vagally induced and ACh-induced increases in Ppi (fig. 2, left). Larger doses of mivacurium (1 and 3 mg/kg) reversed the inhibition of vagally induced, but not ACh-induced increases in Ppi (fig. 2, left). Vagally induced changes in Ppi were not measured at doses larger than 3 mg/kg because of large postjunctional effects of atracurium at these doses. In the heart, mivacurium inhibited both vagally induced ($P = 0.0001$) and ACh-induced ($P = 0.0002$) bradycardia similarly in a dose-related manner (fig. 2, right).

Pipecuronium (0.01–3.0 mg/kg) potentiated vagally induced increases in Ppi ($P = 0.02$) but did not alter ACh-induced increases in Ppi (fig. 3, left). The maximum effect, a 2.5-fold potentiation, was obtained in response to 1.0 mg/kg pipecuronium. Both vagally ($P = 0.0001$) and ACh-induced ($P = 0.0001$) bradycardia were inhibited in a dose-related fashion by pipecuronium (fig. 3, right). Atropine (1 mg/kg) abolished vagally induced and ACh-induced increases in Ppi and bradycardia provoked by pipecuronium. Doxacurium (0.01–1.0 mg/kg) had no significant effect on either vagally induced or ACh-induced increases in Ppi or bradycardia (fig. 4).

The relative order of potency for the M₂ receptor was pancuronium > pipecuronium > mivacurium > doxacurium (table 2). The relative order of potency for the M₃ receptor was pancuronium > mivacurium. Pipecuronium and doxacurium had no effect on M₃ muscarinic receptors at the doses used (table 2).

Table 1. Effect of Mivacurium of Baseline Pulmonary Inflation Pressure

Mivacurium Dose (mg/kg)	Increase in Ppi mm H ₂ O (mean \pm SEM)
0.01	0.0 \pm 0.0
0.03	0.0 \pm 0.0
0.10	0.0 \pm 0.0
0.30	0.5 \pm 0.5
1.00	5.8 \pm 2.9
3.00	22.7 \pm 10.4
5.00	86.0 \pm 18.5
5.00 + 1 mg/kg atropine	73.3 \pm 9.8
5.00 + 5 mg/kg pyrilamine	0.0 \pm 0.0

Discussion

Vagal nerve stimulation in animals is an accepted model to study drug effects on bronchoconstriction.^{8,9} The increase in pulmonary inflation pressure over the basal inflation pressure produced by the ventilator was used as our measure of bronchoconstriction,^{10,11} because increases in pulmonary inflation pressure during vagal stimulation reflect primarily an increase in lung resistance with little change in dynamic compliance.^{12,13} Cholinergic efferent nerve fibers of the parasympathetic nervous system pass down the vagus nerve and synapse in the smooth muscle of the airway wall. In the human lung, the parasympathetic nervous system regulates airway caliber, both in the baseline state and after mechanical, chemical, or physical stimulation,

Fig. 4. Doxacurium (0.01–1.0 mg/kg intravenous) had no effect on bronchoconstriction induced either by stimulation of the vagus nerve (closed squares; left) or by intravenous acetylcholine (open triangles). Likewise, in the heart, doxacurium also had no effect on bradycardia induced by either vagal stimulation (closed squares; right) or by intravenous acetylcholine (open triangles). Data are expressed as the mean \pm SEM of the ratio of the response to vagal stimulation or intravenous acetylcholine in the presence of doxacurium to the response in the absence of doxacurium. In the absence of doxacurium, the increase in pulmonary inflation pressure with vagal stimulation was 29.8 ± 1.0 mmH₂O, the increase in pulmonary inflation pressure with intravenous acetylcholine was 49.0 ± 16.5 mmH₂O. These responses were not significantly different from each other. In the heart in the absence of doxacurium the decrease in heart rate with vagal stimulation was 46.9 ± 7.5 beats/min, the decrease in heart rate with intravenous acetylcholine was 83.6 ± 45.7 beats/min. These responses also were not significantly different from each other ($n = 5$).

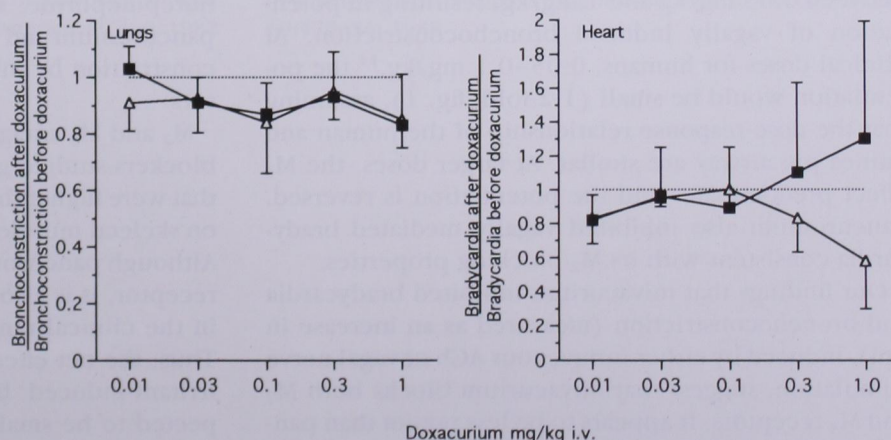


Table 2. Approximate ED₅₀ of Nondepolarizing Muscle Relaxants at Postjunctional M₂ and M₃ Muscarinic Receptors in Guinea Pig Heart and Lung and ED₉₅ at Skeletal Muscle Nicotinic Receptors in Humans

Muscle Relaxant	~ ED ₅₀ M ₂ (heart) (mg/kg)	~ ED ₅₀ M ₃ (smooth muscle lung) (mg/kg)	~ ED ₉₅ Nicotinic Receptor (skeletal muscle) (mg/kg)
Pancuronium	0.01	0.03	0.07 ¹⁴
Mivacurium	0.30	0.1	0.08 ¹⁷
Pipecuronium	0.25	>3.0	0.05 ¹⁸
Doxacurium	>1.0	>1.0	0.025 ¹⁹

via release of ACh onto postjunctional muscarinic M₃ receptors of airway smooth muscle. However, previous studies from this laboratory have demonstrated the presence of prejunctional M₂ receptors, which inhibit ACh release, thus limiting vagally induced bronchoconstriction.⁵ Thus, blockade of M₃ receptors inhibits bronchoconstriction induced by either vagal nerve stimulation or intravenous ACh, whereas blockade of M₂ receptors potentiates bronchoconstriction induced by vagal nerve stimulation. The net effect of a muscarinic antagonist on bronchoconstriction provoked by vagal nerve stimulation depends on its relative potency as an M₂ or M₃ antagonist. M₂, but not M₃, antagonists inhibit bradycardia induced by either vagal nerve stimulation or intravenous ACh.

Our current study demonstrates that pancuronium is a potent antagonist for both M₂ and M₃ receptors, thus confirming previous studies in guinea pigs⁸ and dogs.⁹ In the lungs, the M₂ antagonist effect must predominate between 0.03 mg/kg and 1 mg/kg, resulting in potentiation of vagally induced bronchoconstriction. At clinical doses for humans, 0.05–0.1 mg/kg,¹⁴ the potentiation would be small (1.2-fold; fig. 1), assuming that the dose-response relationship of the human and guinea pig airway are similar. At larger doses, the M₃ effect predominates and the potentiation is reversed. Pancuronium also inhibited vagally mediated bradycardia consistent with its M₂-blocking properties.

Our findings that mivacurium inhibited bradycardia and bronchoconstriction (measured as an increase in Ppi), induced by either intravenous ACh or vagal nerve stimulation, suggest that mivacurium blocks both M₂ and M₃ receptors. It appears to be less potent than pancuronium as an M₂ antagonist. Thus, mivacurium does not potentiate vagally induced bronchoconstriction at doses between 0.03 and 0.3 mg/kg. The potentiation of vagally induced, but not ACh-induced, bronchocon-

striction at 1- and 3-mg/kg doses could be caused by blockade of M₂ receptors. However, it is more likely caused by enhanced ACh release by histamine,^{15,16} because this effect occurred at doses at which histamine was released¹⁷ and was prevented by atropine. The increase in baseline airway tone at these same concentrations is likely a result of the direct effects of histamine on H₁ receptors on airway smooth muscle, because this effect occurred at doses at which histamine is released¹⁷ and was prevented by pyrilamine, an H₁ receptor antagonist.

Our findings that pipecuronium potentiated bronchoconstriction induced by vagal stimulation, with no effect on bronchoconstriction induced by intravenous ACh, and inhibited bradycardia, suggest that pipecuronium is selective for M₂ muscarinic receptors. Pipecuronium, however, is less potent than pancuronium as an M₂ antagonist, only producing significant potentiation of vagally induced bronchoconstriction at doses greater than 0.3 mg/kg. Because the concentrations of pipecuronium used clinically are tenfold less, it is unlikely that pipecuronium will have any clinically relevant effects on muscarinic receptors. Our results with doxacurium showing neither potentiation nor inhibition of bronchoconstriction or bradycardia suggest that doxacurium has no effect on either M₂ or M₃ receptors at doses up to 1 mg/kg.

ACh release from vagal nerve stimulation may be inhibited by prejunctional β -adrenoceptors.¹³ Thus, inhibition of these receptors by pancuronium and pipecuronium could explain our results. However, all animals were pretreated with guanethidine to deplete norepinephrine, which rules out the possibility that pancuronium and pipecuronium potentiated bronchoconstriction by inhibiting prejunctional β adrenoceptors.

M₂ and M₃ antagonist activity by the neuromuscular blockers studied generally occurred at concentrations that were higher than the ED₉₅ for the nicotinic receptor on skeletal muscle, except for pancuronium (table 2). Although pancuronium is a potent antagonist of the M₂ receptor, it is also a potent antagonist of M₃ receptors in the clinical range, inhibiting bronchoconstriction. Thus, the net effect of pancuronium on any potential irritant-induced bronchoconstriction would be expected to be small. Mivacurium is a more potent M₃ than M₂ antagonist, and should not potentiate irritant-induced bronchoconstriction in the clinical range. In contrast, pipecuronium is not an antagonist for M₃ receptors but does inhibit M₂ receptor function. How-

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ever, this occurs only at doses larger than are used clinically.

In summary, the most important findings of this study are: mivacurium is a muscarinic antagonist with similar potencies for both M₂ and M₃ receptors; pipecuronium is an antagonist for M₂ but not M₃ muscarinic receptors; and doxacurium has no effect on either M₂ or M₃ receptors. Although pipecuronium is an M₂ receptor antagonist and can potentiate reflex-induced bronchoconstriction, this effect occurs only at doses that are larger than those used clinically. If these studies in the guinea pig are relevant to the clinical situation in humans, pipecuronium, mivacurium, and doxacurium, in concentrations in the clinical range, should have few adverse effects on airway tone and reactivity in humans.

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