CLINICAL PHARMACOLOGY OF NEUROMUSCULAR BLOCKING AGENTS

Jerrold H. Levy, MD
Professor of Anesthesiology
Emory University School of Medicine
Division of Cardiothoracic Anesthesiology
and Critical Care
Emory Healthcare
Atlanta, Georgia

HISTORY OF NEUROMUSCULAR BLOCKING AGENTS AND CLINICAL DEVELOPMENT

HISTORY

1494 - Tales of travelers killed by poison darts

1551 - Ourari" or "cururu" meaning "bird killer"

1812 - Curarized cat kept alive by artificial respiration

1912 - Curare used to prevent fractures during ECT

1941 - Initial use by Griffith, Culler, and Rovenstine

1951 - Succinylcholine chloride first used in Stockholm

INTRODUCTION OF NEW DRUGS

1494 - 1942	Curare
1947 - 1951	Succinylcholine chloride, Gallamine, Metocurine, Decamethonium
1960's	Alcuronium
1970's	Pancuronium bromide, Fazadinium
1980's	Vecuronium bromide, Atracurium besylate
1990	Pipecuronium bromide
1991	Doxacurium chloride
1992	Mivacurium chloride
1994	Rocuronium bromide
1999	Rapacuronium bromide

STRUCTURAL CLASSES OF NONDEPOL.ARIZING RELAXANTS

- Steroids: Rocuronium bromide, Vecuronium bromide, Pancuronium bromide, Pipecuronium bromide

- Naturally occurring benzylisoquinolines: curare, metocurine

- Benzylisoquinoliniums: Atracurium besylate, Mivacurium chloride, Doxacurium chloride

THE IDEAL RELAXANT

- Nondepolarizing
- Rapid onset
- Dose-dependent duration
- No side-effects
- Elimination independent of organ function
- No active or toxic metabolites

ONSET OF PARALYSIS IS AFFECTED BY:

- Dose (relative to ED_{95})
- Potency (number of molecules)
- K_{eo} (chemistry/blood flow)
- Clearance
- Age

Neuromuscular Blocking Agents and Patient Evaluation

Assessing Postoperative Neuromuscular Function

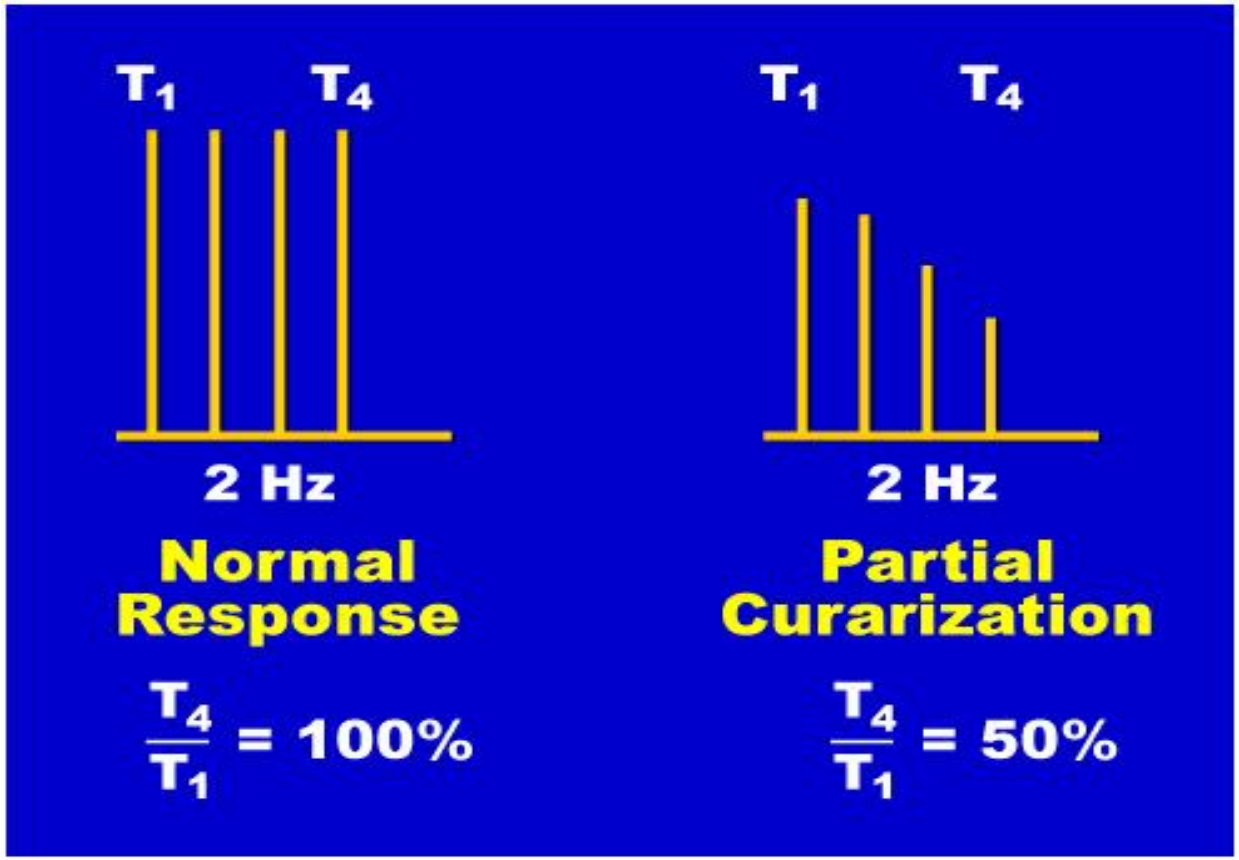
Assessing Postoperative Neuromuscular Function

CLINICAL ASSESSMENT

- Sustained 5-second head lift
- Ability to appose incisors (clench teeth)
- Negative inspiratory force > – 40 cm H_2O
- Ability to open eyes wide for 5 seconds
- Hand-grip strength
- Sustained arm/leg lift
- Quality of speaking voice
- Tongue protrusion

Assessing Postoperative Neuromuscular Function

Train-of-Four (TOF) Fade Ratio



Assessing Postoperative Neuromuscular Function

THE ORIGIN OF THE GOLD STANDARD

TOF Ratio	Vital Capacity	Inspiratory Force	Peak Exp. Flow Rate
Control =100	100	100	100
60%	91	70	95
70%*	97	82	92
80%	100	88	94
90%	100	91	95
100%	100	97	99

* Historically regarded as the Gold Standard

Ali HH, et al. *Br J Anaesth*. 1975;47:570

Assessing Postoperative Neuromuscular Function

NEW DATA SUGGEST THAT A TOF OF 0.90 MAY BE NEEDED TO ENSURE NORMAL FUNCTION

- Kopman: A TOF > 0.90 compatible with normal clinical tests (*Anesthesiology*. 1997;86:765)
- Eriksson: Pharyngeal function normal at TOF 0.90 (*Anesthesiology*. 1997;87:1035)

Assessing Postoperative Neuromuscular Function

ASSESSING TOF FADE RATIO

- Patients are often returned to the PACU with residual paralysis[1]
- The TOF ratio of 0.70 may be inadequate for discharge of an ambulatory patient[1]
- TOF ratios ≥ 0.40 are difficult to assess clinically[2]

[1]Viby-Mogensen J, et al. *Anesthesiology*. 1979;50:539

[2]Kopman AF, et al. *Anesthesiology*. 1994;81:1394

Assessing Postoperative Neuromuscular Function

TOF FADE RATIO: CONCLUSION

- Recovery is inadequate if fade is detected[1,2]
- Clinical trials are needed to demonstrate measurement techniques for TOF ratios of 0.90[2]

[1]Eriksson, LI, et al. *Anesthesiology*. 1997;87:1035

[2]Bevan, DR, et al. *Anesthesiology*. 1988;69:272

Neuromuscular Blockers: Chemical Structure & Key Characteristics

Aminosteroids

- Vagolytic
  - Partially block cardiac muscarinic receptors involved in heart rate slowing, resulting in increased heart rate:
    - rapacuronium > pancuronium > rocuronium > vecuronium
- Generally do not promote histamine release
  - Exception: rapacuronium
- Organ-dependent elimination
  - Kidneys and liver

Neuromuscular Blockers: Chemical Structure & Key Characteristics

Benzylisoquinolines

- Absence of vagolytic effect
  - these drugs do not block cardiac-vagal (muscarinic) receptors
- Histamine release
  - dTc > atracurium > mivacurium > cisatracurium
  - can cause rare bronchospasm, decreased blood pressure, increase of heart rate
- Generally organ-independent elimination[1]
  - esp: atracurium, cisatracurium, mivacurium
- Noncumulative[2]

[1]Stenlake JB, et al. *Br J Anaesth.* 1983;55;3S
[2]Ali HH, et al. *Br J Anaesth.* 1983;55:107S

Classification of Neuromuscular Blockers by Duration of Action (Minutes)

	Ultra-Short	Short	Intermediate	Long
Clinical duration (injection to T_{25})	6 - 8	12 - 20	30 - 45	>60
Recovery time (injection to T_{95})	<15	25 - 30	50 - 70	90 -180
Recovery index (T_{25} to T_{75})	2 - 3	6	10 -15	>30
Examples	succinyl-choline [1]	mivacurium [2]	cisatracurium [3]	doxacurium [4]

Assumes bolus dose = 2x ED_{95}

[1]**Anectine® (succinylcholine chloride) Package Insert**
[2]**Mivacron® (mivacurium chloride) Package Insert**
[3]**Nimbex® (cisatracurium besylate) Package Insert**
[4]**Nuromax® (doxacurium chloride) Package Insert**

DURATION OF ACTION OF NEUROMUSCULAR BLOCKING AGENTS

- Ultra-Short: Succinylcholine chloride
- Short: Mivacurium chloride
- Intermediate: Rocuronium bromide, Vecuronium bromide, Atracurium besylate
- Long: Pancuronium bromide, curare, metocurine, Pipecuronium bromide, Doxacurium chloride

CARDIOVASCULAR PROFILE OF NEUROMUSCULAR BLOCKING AGENTS

Hemodynamics, histamine release, and other aspects

HISTAMINE RELEASING POTENTIAL

Significant		Insignificant	
Tubocurarine	+ + +	Rocuronium bromide	±
Metocurine	++	Vecuronium bromide	±
Atracurium besylate	+	Pancuronium bromide	±
Mivacurium chloride	+	Pipecuronium bromide	±
Succinylcholine chloride	+	Doxacurium chloride	±

Muscle Relaxants

Pancuronium

- Vagolytic: increases heart rate, may require beta blockade
- Easy to use
- Intermediate duration of action
- Slower onset
- Not reversed at end of case

Muscle Relaxants

Vecuronium

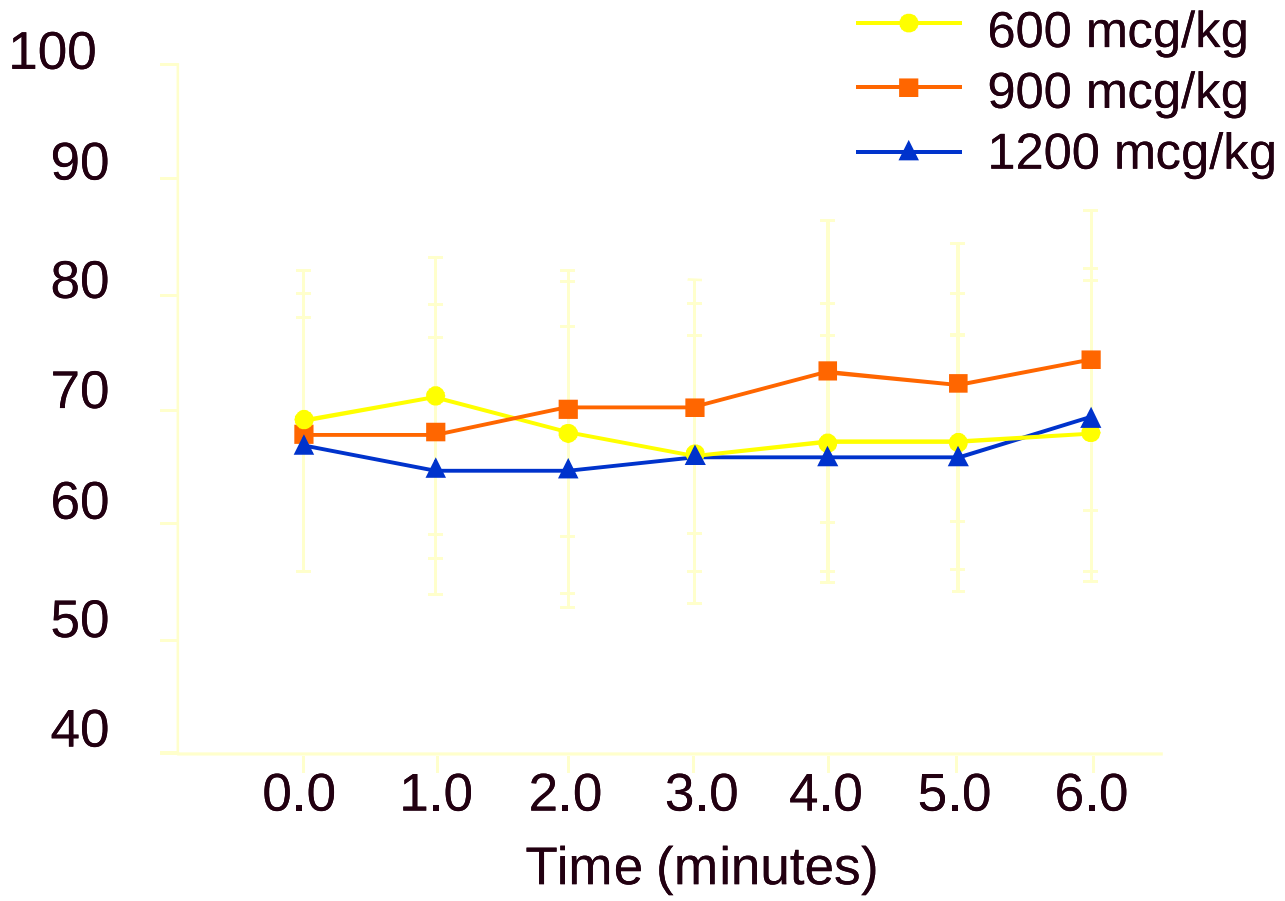
- No effects on HR, BP
- Requires reconstitution
- Reliable and controllable duration of action
- Slower onset
- Stable hemodynamics/no histamine release

Muscle Relaxants

Rocuronium

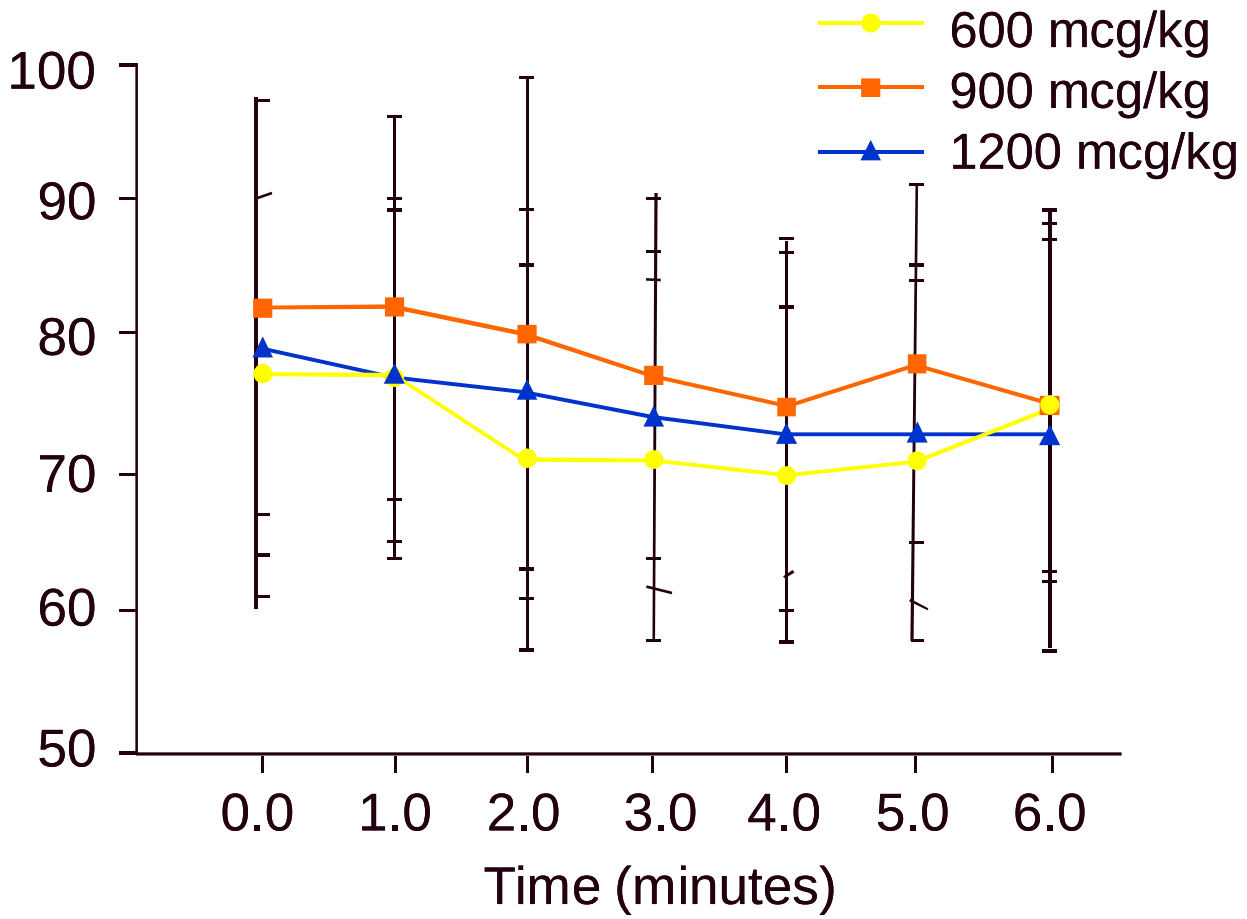
- No effects on HR, BP
- Easy to use, liquid, no refrigeration
- Reliable and controllable duration of action
- Fast onset
- Stable hemodynamics/no histamine release

Effects of Rocuronium on Heart Rate



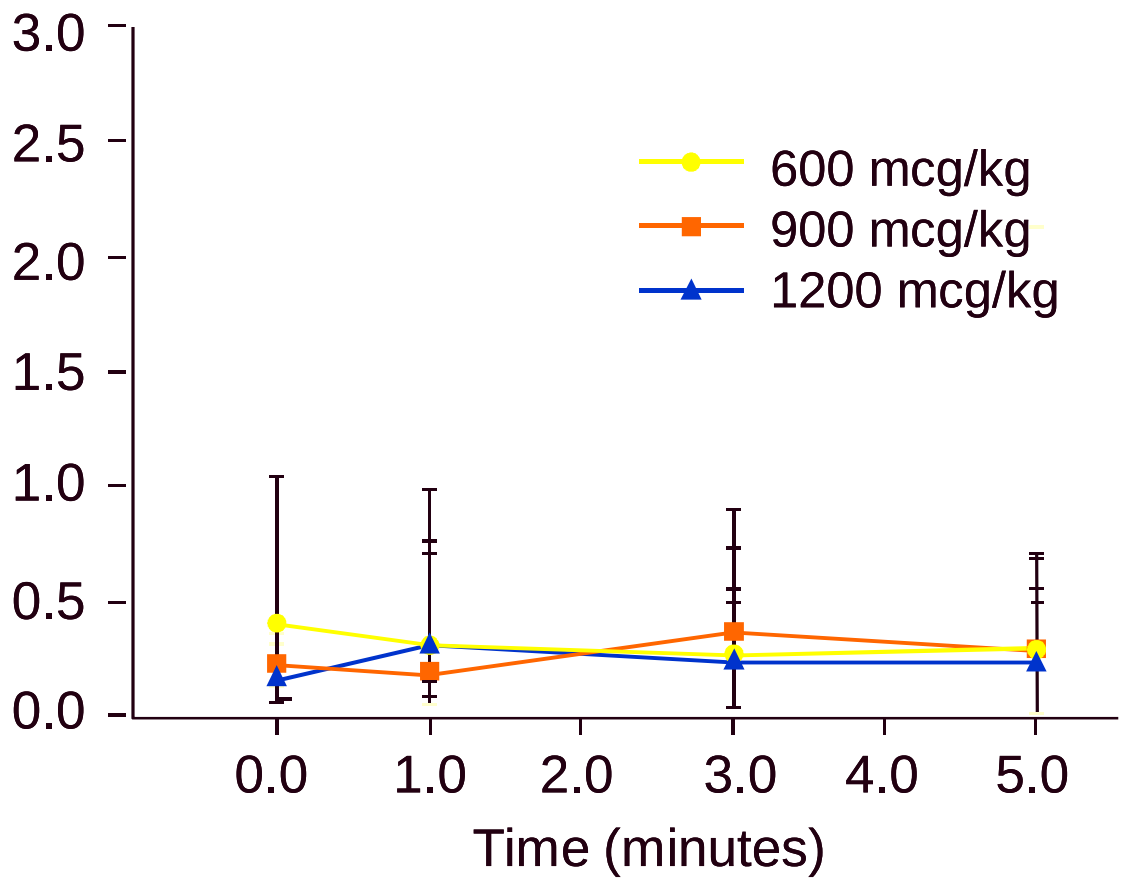
Levy et al. Anesth Analg 1994;78,318-321.

Effects of Rocuronium on Mean Arterial Pressure



Levy et al. Anesth Analg 1994;78,318-321.

Effects of Rocuronium on Histamine Release



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Muscle Relaxants

Rapacuronium

- Minimal effects on HR, BP
- Controllable duration of action
- Fast onset
- Stable hemodynamics/minimal histamine release
- Potential for bronchospasm led to its removal in 2001

COSTS OF NEUROMUSCULAR BLOCKING AGENTS AND SELECTION CRITERIA

Neuromuscular Agents: Costs of Care

- Cost of care ≠ acquisition cost
- The real, substantial savings accrue from use of intermediate- and short-acting drugs because:
  - Inexpensive, long-acting drugs are associated with prolonged postoperative recovery [1]
  - Fast recovery means shorter risk periods of residual blockade. This translates into fewer postoperative complications, as shown in the Berg study[2]
  - Postoperative complications are <u>very expensive</u> Avoiding these is where the real cost savings accrue

Rationale for Selection of NMBAs:

- Cardiovascular stability
- Nondepolarizing vs depolarizing
- Organ-independent elimination
- Clinically significant active or toxic metabolites
- Predictability of duration
- Cumulative effects
- Reversibility
- Time to onset
- Stability of solution
- Cost