Muscle Relaxants
Physiologic and Pharmacologic Aspects

With 125 Figures
## Contents

Preface ................................................................. V  
List of Contributors ............................................... XVII

### 1. History of Muscle Relaxants

Some Early Approaches to Relaxation in the United Kingdom  
J.P. Payne ............................................................... 3  
The Final Steps Leading to the Anesthetic Use of Muscle Relaxants  
F.F. Foldes ............................................................. 8  
History of Muscle Relaxants in Japan  
K. Iwatsuki ............................................................. 13

### 2. The Neuromuscular Junctions – Update

Mechanisms of Action of Reversal Agents  
W.C. Bowman .......................................................... 19  
Nicotinic Receptors  
F.G. Standaert ........................................................ 31  
The Neuromuscular Junction—Basic Receptor Pharmacology  
J.A. Jeevendra Martyn ............................................... 37  
Muscle Contraction and Calcium Ion  
M. Endo ................................................................. 48

### 3. Current Basic Experimental Works Related to Neuromuscular Blockade in Present and Future

Prejunctional Actions of Neuromuscular Blocking Drugs  
Approaches to Short-Acting Neuromuscular Blocking Agents
J.B. Stenlake ............................................................... 62

Effects Other than Relaxation of Non-Depolarizing Muscle Relaxants
E.S. Vizi ................................................................. 67

Regulation of Innervation-Related Properties of Cultured Skeletal Muscle
Cells by Transmitter and Co-Transmitters
R.H. Henning ............................................................ 82

4. Current Clinical Experimental Works Related to Neuromuscular
Blockade in Present and Future

Where Should Experimental Works Be Conducted?
R.D. Miller ............................................................... 93

Muscle Relaxants in the Intensive Care Unit
J.E. Caldwell ............................................................ 95

New Relaxants in the Operating Room
R.K. Mirakhur .......................................................... 105

Kinetic-Dynamic Modelling of Neuromuscular Blockade
C. Shanks ............................................................... 111

5. Basic Aspects of Neuromuscular Junction

Physiology of the Neuromuscular Junction
W.C. Bowman .......................................................... 117

Properties of $\alpha_7$-Containing Acetylcholine Receptors and Their Expression
in Both Neurons and Muscle
D.K. Berg, W.G. Conroy, R.A. Corriveau, P.C. Pugh, M.M. Rathouz,
S.J. Romano, S. Vijayaraghavan, and Z.W. Zhang .................. 128

Molecular Biology of Neuromuscular Transmission
C.S. Yost ............................................................... 135

Presynaptic Neuromuscular Blockade
H. Suzuki ............................................................... 142

The Function of the ACh Receptor Channel
Y. Kidokoro ............................................................ 150

6. Onset of Action

Differences of Onset of Different Muscles in Man and Their Consequences
on Monitoring of Neuromuscular Transmission
C. Meistelman .......................................................... 157
Structure-Onset Relationship of Steroidal Neuromuscular Blocking Agents
J.M.K.H. Wierda and J.H. Proost ........................................ 163

A Blueprint for a Fast Acting Non-Depolarizing Drug
F. Donati ................................................................. 167

7. Relaxants in ICU

Benzylisoquinolinium Compounds in the Critically Ill Patient
J.M. Hunter .............................................................. 173

The Long-Term Use of Pipecuronium in Cardiac and Esophageal Surgery Patients
T. Aoki ................................................................. 178

Mechanisms — Changes Induced by Long-Term High-Dose Muscle Relaxant Administration
R.D. Miller .............................................................. 186

8. Pharmacokinetics, Metabolism, and Metabolites

Metabolism and Metabolites of Benzylisoquinolinium Diester Compounds
J.J. Savarese, M.R. Belmont, and C.A. Lien .................................. 189

Conceptual Building Blocks in Developing a Pharmacodynamic Model for a Muscle Relaxant
V. Nigrovic and A. Banoub ............................................... 194

Structure-Pharmacokinetic and Pharmacodynamic Relationships of Steroidal Neuromuscular Blocking Agents

Pharmacokinetics and Pharmacodynamics of Aminosteroidal Neuromuscular Blocking Agents and Their Metabolites
N. Sugai and C. Yajima ................................................ 213

9. Uses in Special Groups

Pharmacokinetics of Muscle Relaxants in Children
D.M. Fisher .............................................................. 219

Muscle Relaxants in Elderly Patients
D.R. Bevan ............................................................. 224

Muscle Relaxants in patients with Renal or Hepatic Failure
P. Duvaldestin .......................................................... 232
The Influence of Temperature on the Adductor Pollicis Twitch Tension in the Presence and Absence of Vecuronium
T. Heier ................................................................. 249

10. Monitoring

The Iceberg Theory — Fact or Fiction? Implication for Monitoring
S.A. Feldman .......................................................... 257

New Aspects of Double Burst Stimulation
N. Ueda ................................................................. 262

11. Drug Interactions

Interactions of Volatile Anesthetics with Non-Depolarizing Neuromuscular Blocking Agents
K. Fukushima .......................................................... 269

Interaction Between Calcium Antagonists and Muscle Relaxants
H. Nagashima, E.S. Vizi, and F.F. Foldes ........................................ 275

Dexamethasone Induces nAChRs Upregulation in C2C12 Mouse Myotubes
E. Maestrone ........................................................... 280

Interaction Between Muscle Relaxants
K. Ono, Y. Ohta, and M. Hirakawa ................................................. 283

12. Methods of Administration

The Pharmacokinetics of the Three Isomers of Mivacurium Chloride in Healthy, Renal and Hepatic Patients Given Short or Prolonged Infusions of the Drug
J.M. Hunter ............................................................. 295

Methods of Administration of Neuromuscular Blocking Drugs
T.A. Torda ............................................................... 299

Pharmacodynamics and Pharmacokinetics of Different Modes of Rocuronium Administration

Making the Administration Simple and Safe
J. Norman ............................................................... 311

13. Reversal of Blockade

Problems with Reversal in Adults
J. Norman ............................................................... 317
14. Future of Muscle Relaxants

Future Goals of the Benzylisoquinolinium Ester Program
J.J. Savarese, C.A. Lien, M.R. Belmont, R.B. Maehr, and W.B. Wastila ............................................... 335

Is a Non-Depolarising Suxamethonium an Achievable Target?
R.J. Marshall and A.W. Muir .................................................. 342

The Future of Muscle Relaxants Outside the Operating Room
R.D. Miller .......................................................... 348

15. Scientific Presentations

Recovery Characteristics After Early Administration of Anticholinesterases During Intense Mivacurium-Induced Block
M. Abdulatif .................................................. 351

Assessment of the Optimal Interval of Tetanic Stimulation for Post-Tetanic Count
K.S. Kim, J.U. Han, and S.U. Chon ................................................. 352

Clinical Assessment of a New Neuromuscular Monitoring System: TOF Guard® — A Comparison with the Conventional Method
Y. Masuda, N. Ueda, and T. Muteki .............................................. 353

Onset and Duration of Rocuronium and Succinylcholine at the Adductor Pollicis and Laryngeal Adductor Muscles in Patients Anesthetized with Fentanyl and Propofol
P.M.C. Wright, J.E. Caldwell, and R.D. Miller ................................ 354

The Mechanisms of the Differential Sensitivity to Non-Depolarizing Muscle Relaxants of the Adductor and Abductor Laryngeal Muscles in Rat
M. Igarashi, H. Iwaskai, I. Ohta, E. Narimatsu, and A. Namiki .................. 355

Rocuronium Neuromuscular Blockade at Guinea Pig Intrinsic Laryngeal Muscles and the Cranial Tibial Muscle
A. Sauberer, E. Stanek, and H. Gilly .............................................. 356
Fibers, Endplates and Acetylcholine Receptors in Limb, Abdominal, Laryngeal and Diaphragm Muscles in the Cat
C. Ibebunjo, C. Srikant, and F. Donati ........................................... 357

Recovery and Reversal of Mivacurium Neuromuscular Blockade with Neostigmine and Edrophonium in Paediatric Patients
J.C. Bevan, C. Stephenson, M.F. Smith, E.J. Reimer, L. Blackman, and D.R. Bevan ......................................................... 358

Neuromuscular Effects of Mivacurium When Preceded by Succinylcholine in Children
L. Jalkanen, O.A. Meretoja, and T. Taivainen....................................... 359

Isobolographic Analysis of the Interaction Between Hexamethonium and Decamethonium

Synergism Between Atracurium and Vecuronium with Mivacurium
O.A. Meretoja, L. Jalkanen, T. Taivainen, B.W. Brandom, and B. Dayal ......................................................... 361

Influence of Bambuterol on the Duration of Action of Mivacurium Induced Neuromuscular Blockade
D. Østergaard, U. Bang, N.A. Pedersen, and J. Viby-Mogensen ............... 362

Onsets of Train-of-Four Responses and Discomfort Associated With the Ulnar Nerve Stimuli at Varying Currents
Y. Saitoh, H. Toyooka, and K. Amaha ............................................. 363

A Method for Studying Interaction Between Non-Depolarizing Neuromuscular Blockers and Other Drugs in Vivo

Time Course of Neuromuscular Block of Vecuronium Analogues and d-Tubocurarine in the Chick Biventer Cervicis Muscle
J.M. Ward, H. Fajrak, and C. Prior .................................................. 365

Female Rats are More Sensitive to the Neuromuscular Blocking Action of Rocuronium than Male Rats

The Effect of Cardiac Output on the Onset of Neuromuscular Blockade of Vecuronium and Pancuronium
H. Iwasaki, M. Igarashi, M. Yamauchi, and A. Namiki .......................... 367

Correlation of the Speed of Onset of the Effective Relaxation with Vecuronium 0.15 mg/kg with Body Mass and the Size of the Priming Dose
T. Takaya, M. Takiguchi, and Y. Yamasaki ....................................... 368
Functional Heterogeneity of Murine Mucosal and Connective Tissue Mast Cells in Response to Six Kinds of Muscle Relaxants in Vitro
  R. Ozawa, H. Saito, Y. Ikura, M. Kobayasi, H. Yanagi, Y. Iwao, and H. Sankawa ................................................. 369

Hemodynamic Evaluation of Pancuronium Bromide by the Transesophageal Echocardiography
  S. Toyota, M. Kumagai, and Y. Amaki ........................................ 370

Neuromuscular Blocking Effects of Org-9487 in the in Vitro Rat Hemidiaphragm/phrenic Nerve Preparation

Neuromuscular Refractoriness, Prejunctional Block and MgSO₄ in the Pig
  C. Lee, X. Zhang, and W.-F. Kwan ........................................... 372

Comparative Studies of Picrocuronium and Tubocurarine on Releases of Histamine and N-Methylhistamine in Surgical Patients
  'E. Ueda, J. Takeda, J. Takahashi, and K. Fukushima ......................... 373

The Effects of Rocuronium in Infants, Children and Adults
  T. Taivainen, O.A. Meretoja, O. Erkola, P. Rautoma, and M. Juvakoski .... 374

Augmentation of Succinylcholine on the Neuromuscular Blocking Effect of Vecuronium in Pediatrics
  S. Yasuda, J. Takeda, H. Sekiguchi, and K. Fukushima ........................ 375

Efficient Method for Administration of Neostigmine to Antagonize Neuromuscular Blockade by Vecuronium
  N. Yasuda, M. Kumagai, H. Niwa, and Y. Amaki ................................ 376

Antagonism of Mivacurium-Induced Neuromuscular Blockade in Man: Edrophonium Dose Requirements at Threshold Train-of-Four Count of Four

Edrophonium Antagonism of Constant Mivacurium Infusion

Comparison of the Neuromuscular Effects of SZ1676, SZ1677 and Vecuronium in Beagle Dogs
  F.F. Foldes, P.D. Thut, and C.T. Cordes ..................................... 379

The Protein Binding of SZ1676, SZ1677 and Rocuronium and Their Inhibitory Effect on Human Cholinesterases
  I.A. Chaudhry, F.F. Foldes, and H. Nagashima ................................ 380

Comparison of the Neuromuscular Effects of SZ1676 and Vecuronium in Guinea-Pig
  K. Tomizawa, J. Takeda, J. Oshida, K. Watanabe, and K. Fukushima ...... 381
Postsynaptic Nicotinic Receptor Desensitized by Non-Contractile Ca\textsuperscript{2+} Mobilization (Ramie) via Protein Kinase-C Activation at the Mouse Neuromuscular Junction
I. Kimura, K. Dezaki, H. Tsuneki, and M. Kimura ........................................ 382

The Influence of Cold on the Recovery Index of Vecuronium and Decamethonium in Man

Discrepancy of Recovery Times Related to Potency Between Atracurium and Mivacurium Simultaneously Administered into the Isolated Forearms
S.-Y. Kim, K.-H. Hwang, S.-Y. Ok, S.-I. Kim, S.-C. Kim, and W. Park .......... 384

Disposition of Mivacurium Isomers in Patients Undergoing Hypothermic Cardiopulmonary Bypass
M. Abel, C. Diefenbach, G. Aydincioglu, M. Theisohn, and W. Buzello ......... 385

The Duration of Vecuronium Action Shortened After Kidney Transplantation
A. Okuyama, K. Takita, O. Kemmotsu .................................................. 386

Evaluation of 51W89 for Endotracheal Intubation and Repeated Doses
H. Deriaz, E. Schmautz, M. Vrillon, and A. Lienhart .......................... 387

A New Technique for the Facilitation of Rapid Sequence Intubation: “The Prime Time Principle”
H. Nagashima, H.D. Nguyen, M. Doss, K. Torigoe, and F.F. Foldes ...... 388

Pharmacodynamics of Pipecuronium in Patients with Decreased Renal Function
G. Mitterschiffthaler and F.K. Puhringer .............................................. 389

The Sensitivity of the Neonatal Rat to Mivacurium Relative to Mature Rats
H.S. Yang, N.G. Goudsouzian, and J.A.J. Martyn ............................... 390

The Effects of Sevoflurane, Halothane and Balanced Anaesthesia on Vecuronium-Induced Neuromuscular Blockade in Children
T. Taivainen and O.A. Meretoja ..................................................... 391

The Effects of Succinylcholine-Induced Fasciculation on Energy Metabolism in Rat Denervated Skeletal Muscle Studied by \textsuperscript{31}P-NMR
M. Mizogami, T. Fujibayashi, and Y. Goto ........................................ 392

The Potency and Time Course of the Neuromuscular Effects of SZ1676 and Its Hydroxy Analogs in Guinea-Pigs
F.F. Foldes, H. Nakatsuka, K. Nitahara, K. Oe, and E. Umeda ............. 393

Comparison of the Neuromuscular and Circulatory Effects of SZ1676, SZ1677 and Rocuronium in Cats
E.S. Vizi, M. Doda, H. Nagashima, and F.F. Foldes ................................. 394
Comparative Pharmacodynamics of SZ1677 and Rocuronium in Laryngeal Muscles of the Guinea Pig
E. Stanek, A. Sauberer, H. Gilly, and E.S. Vizi ............................... 395

Do Antiarrhythmic Dose of Magnesium Have Prejunctional Neuromuscular Block in Human Being
S.-M. Lin, S.-K. Tsai, and T.-Y. Lee ................................. 396

The Roles of the Equilibrium Dissociation Constant and the Receptor Concentration on the Time Course of Neuromuscular Block
V. Nigrovic, A. Banoub, and F.G. Standaert ............................... 397

Safety and Efficacy of Surgeon-Controlled Mivacurium Administration During Elective Caesarean Section
M. Abdulatif and E. Taylouni ........................................ 398

Dose Response Relationship of Mivacurium in Patients Homozygous for the Atypical Cholinesterase Gene
D. Østergaard, F.S. Jensen, L.T. Skovgaard, and J. Viby-Mogensen .... 399

Hyperparathyroidism in Patients with Chronic Renal Failure Shortens the Action of Vecuronium
A. Okuyama, K. Takita, Y. Goda, H. Kawahigashi, and O. Kemmotsu .. 400

Mivacurium-Induced Neuromuscular Blockade (NB) Is Not Affected by Chronic Anticonvulsant Therapy with Carbamazepine

Does Chronic Anticonvulsant Therapy with Carbamazepine Affect the Atracurium — Induced Neuromuscular Blockade?

An Anesthesia for the Patient Who Was Suspected the Lambert-Eaton Syndrome by an Unexpected Prolongation of Vecuronium
K. Minami, T. Sata, and A. Shigematsu .................................. 403

Quantifying the Effect of Enflurane on Infusion Requirements of Atracurium and Vecuronium
M. Kansanaho and K.T. Olkkola ..................................... 404

Effect of Isoflurane and Sevoflurane on the Potencies of the Neuromuscular Blocking Agents in Rat in Vivo

Comparative Neuromuscular Inhibition of Volatile Anesthetics Using Repetitive Stimulation

Potentiation of Vecuronium by Desflurane vs. Isoflurane
Neuromuscular Recovery During Washout of Desflurane vs. Isoflurane
D.M. Fisher, P.S. Hart, P.M.C. Wright, M. Lau, R. Brown, and M. Sharma .......................................................... 408

Pharmacodynamics of Rocuronium in Comparison with that of Vecuronium
C. Yajima, N. Sugai, K. Hanaoka, S. Nitta, and H. Suzuki ............... 409

Co-Administration of Two Muscle Relaxants: When Are the Effects Supra-Additive?
V. Nigrovic ........................................................................ 410

Neuromuscular Interaction Between Succinylcholine and Esmolol in the Rat
S.-C. Chern, R.-Y. Chang, and S.-K. Tsai ........................................... 411

Intubating Conditions and Haemodynamic Effects of Rapid Sequence Induction with Fentanyl, Propofol and Rocuronium
A. Sauberer, T. Publig, and I. Schindler ........................................ 412

The Usefulness of Neuromuscular Monitoring in the Intensive Care Unit — A Report of Three Cases
K. Terui, N. Fuke, Y. Uno, M. Ozawa, S. Tokutake, T. Ehara, and S. Morita ................................................................. 413

Comparison of Respiratory Sparing Effect on Pancuronium, Vecuronium and Rocuronium in Rats in Vivo
T. Matsumoto, S. Nitta, H. Itoh, and T. Kobayashi ....................... 414

Difference of Recovery of Neuromuscular Function in Adductor Pollicis and Flexor Hallucis Brevis Following Muscle Relaxation with Vecuronium
Y. Hirose, H. Ito, and S. Jinno .................................................. 415