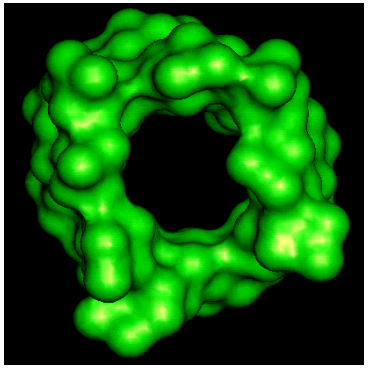
Colloque secteur URO-DIG

Mardi 22 mai 2012

HUG
Hôpitaux Universitaires de Genève
Département APSI
Service d'anesthésiologie

SUGGAMADEX (Bridion ®) état des lieux en 2012



DANGELSER G.

UNIVERSITÉ DE GENÈVE
FACULTÉ DE MÉDECINE

Remerciements

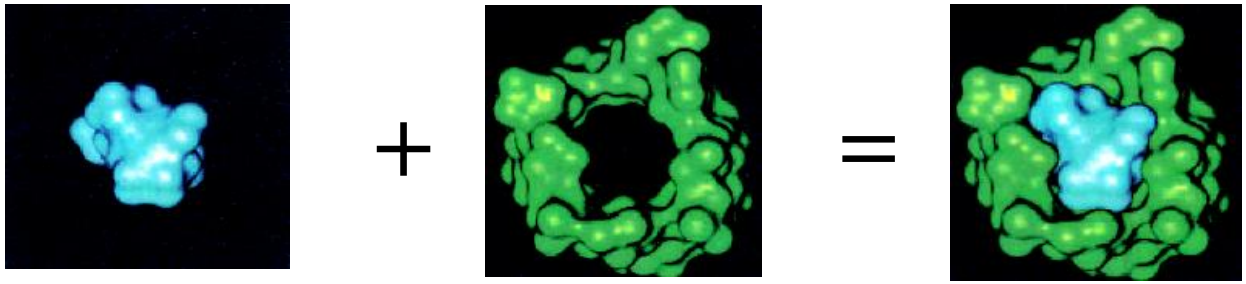
- Au **Pr Christophe BAILLARD**, praticien hospitalier d'Anesthésie-Réanimation à l'Hôpital Avicenne (Bobigny), pour sa documentation et avis sur le sujet (JEPU 2012)

- Au **Dr Philippe Dubois,** médecin anesthésiste des Cliniques Universitaires UCL de Mont Godinne pour ses conseils et sa relecture. Présentation CHU Mont Godinne 2008

- Merci à **Bidulz.com** pour ces illustrations.

Anesthesiology 2006; 104:631–3

Sugammadex: A Revolutionary Approach to Neuromuscular Antagonism



Curare stéroïde + Bridion ® =

Nouvelle classe de médicaments

Mécanisme d'action unique: Agent « encapsuleur »
Selective Relaxant Binding Agent (SRBD)

Antagoniste du Rocuronium +- autres curares non dépolarisants d'origine stéroïdienne

Steroidal neuromuscular blocking agents (NMBD)

SUGGAMADEX (ORG 25969)

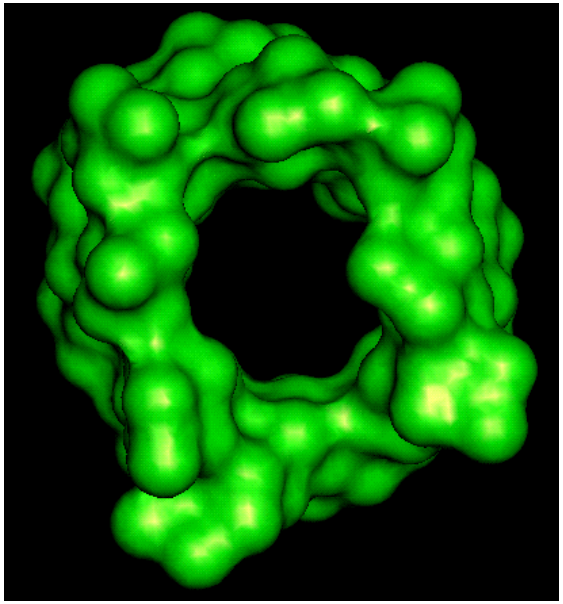
SU pour
SUGAR

SUGGAMADEX

GAMMADEX
pour
γ
CYCLO
DEXTRIN

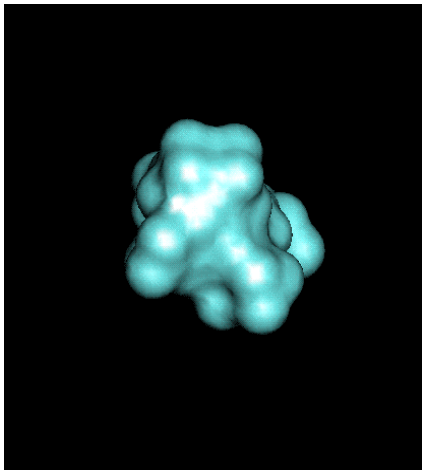
La structure tridimensionnelle du SUGAMMADEX ressemble à un beignet *(doughnut)* **avec une cavité hydrophobe** (the doughnut hole) **et une enveloppe externe hydrophile.**

=

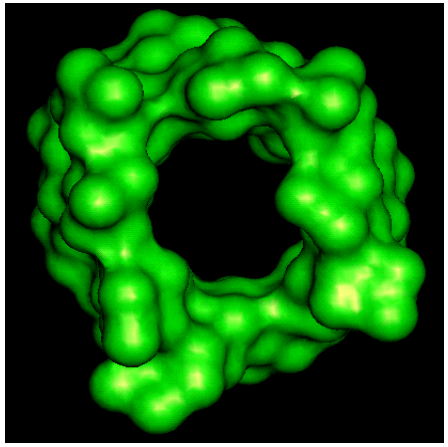


SUGGAMADEX: Mécanisme d'action

ROCURONIUM

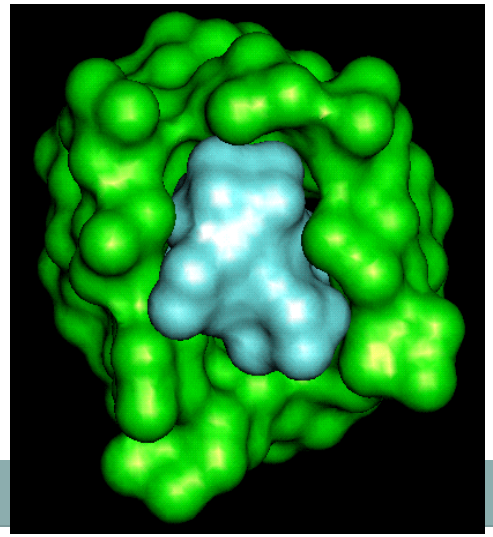


SUGAMMADEX

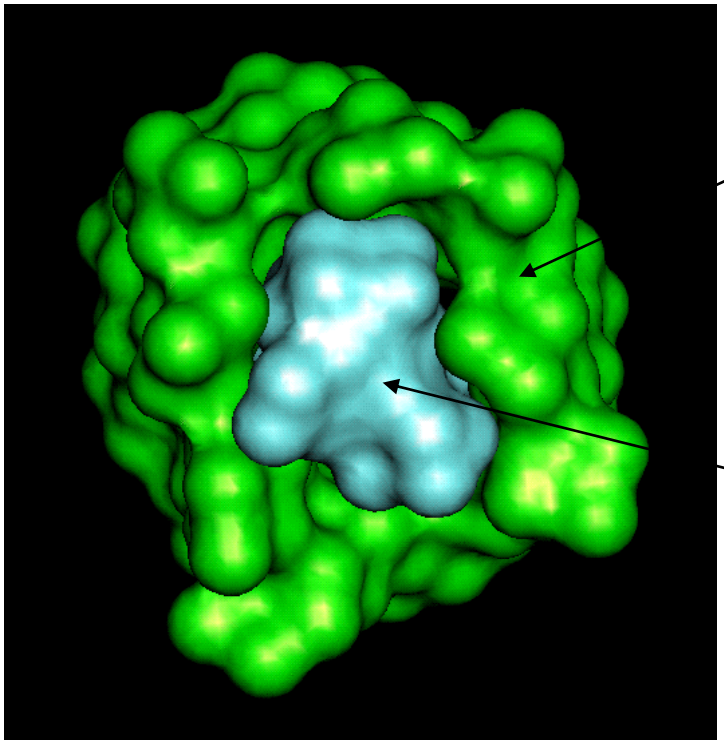


Hydrophobic and Electrostatic Interactions

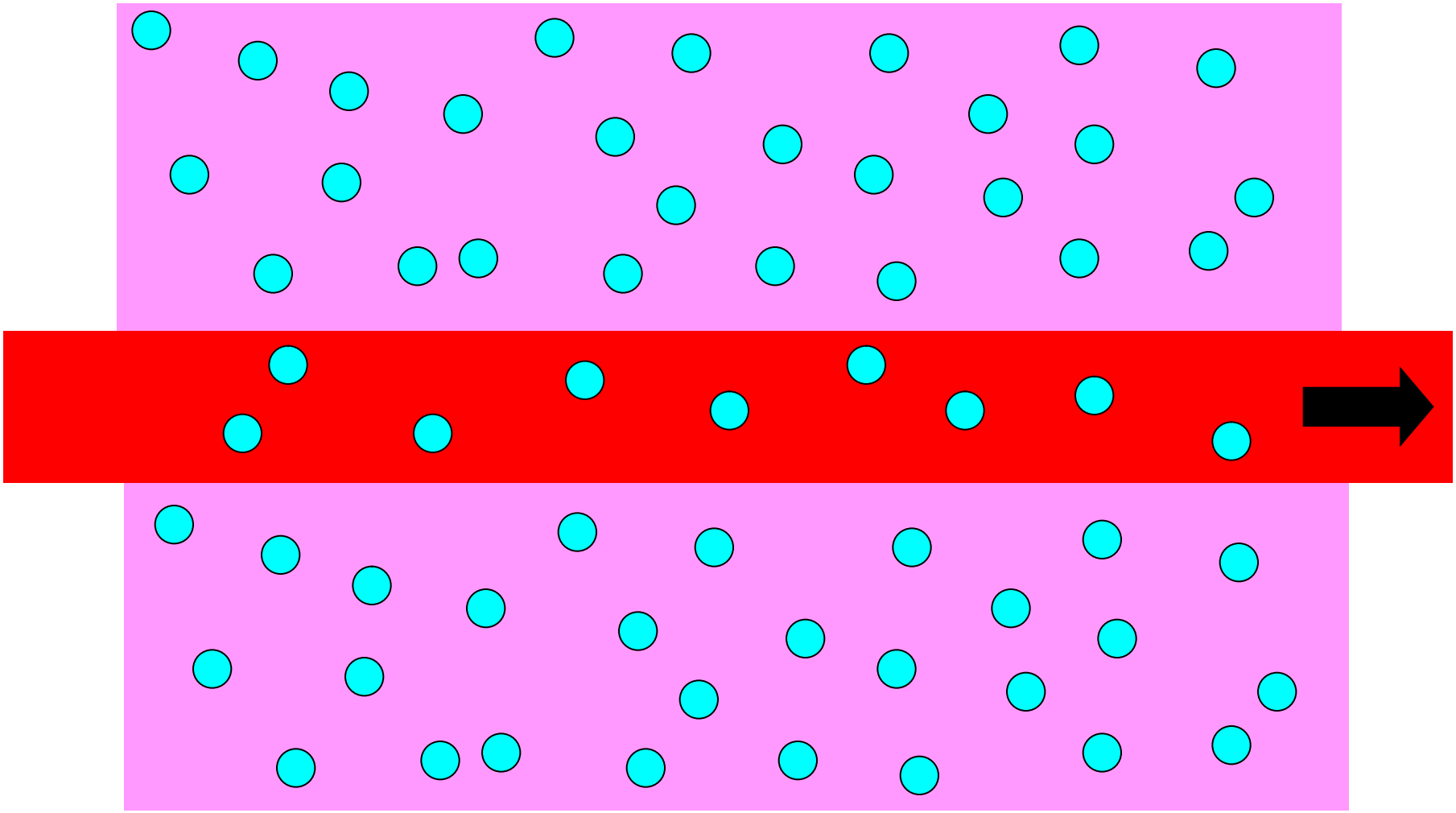
Encapsulation d'une molécule de Rocuronium par une molécule de Sugammadex



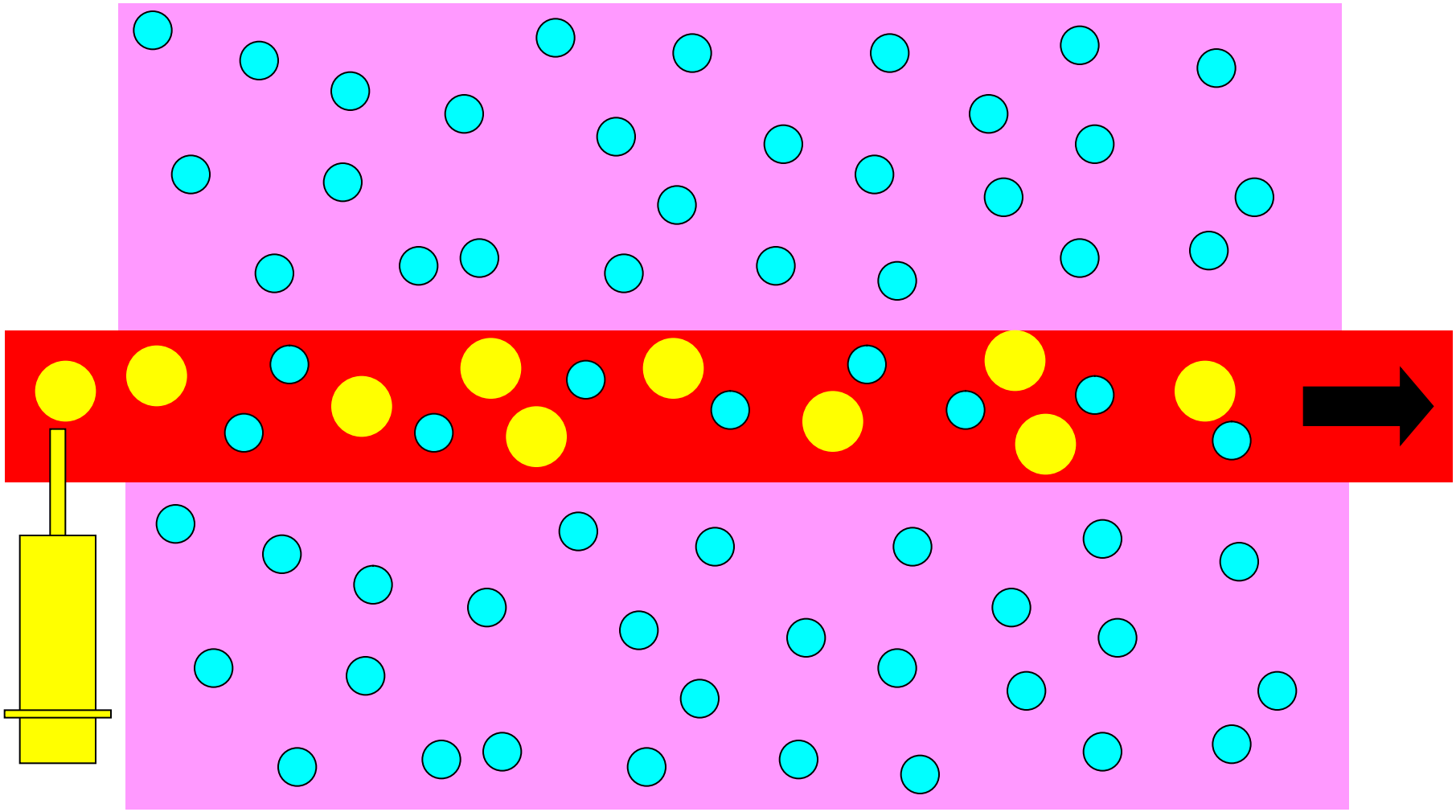
Complex Formation of Sugammadex and Rocuronium



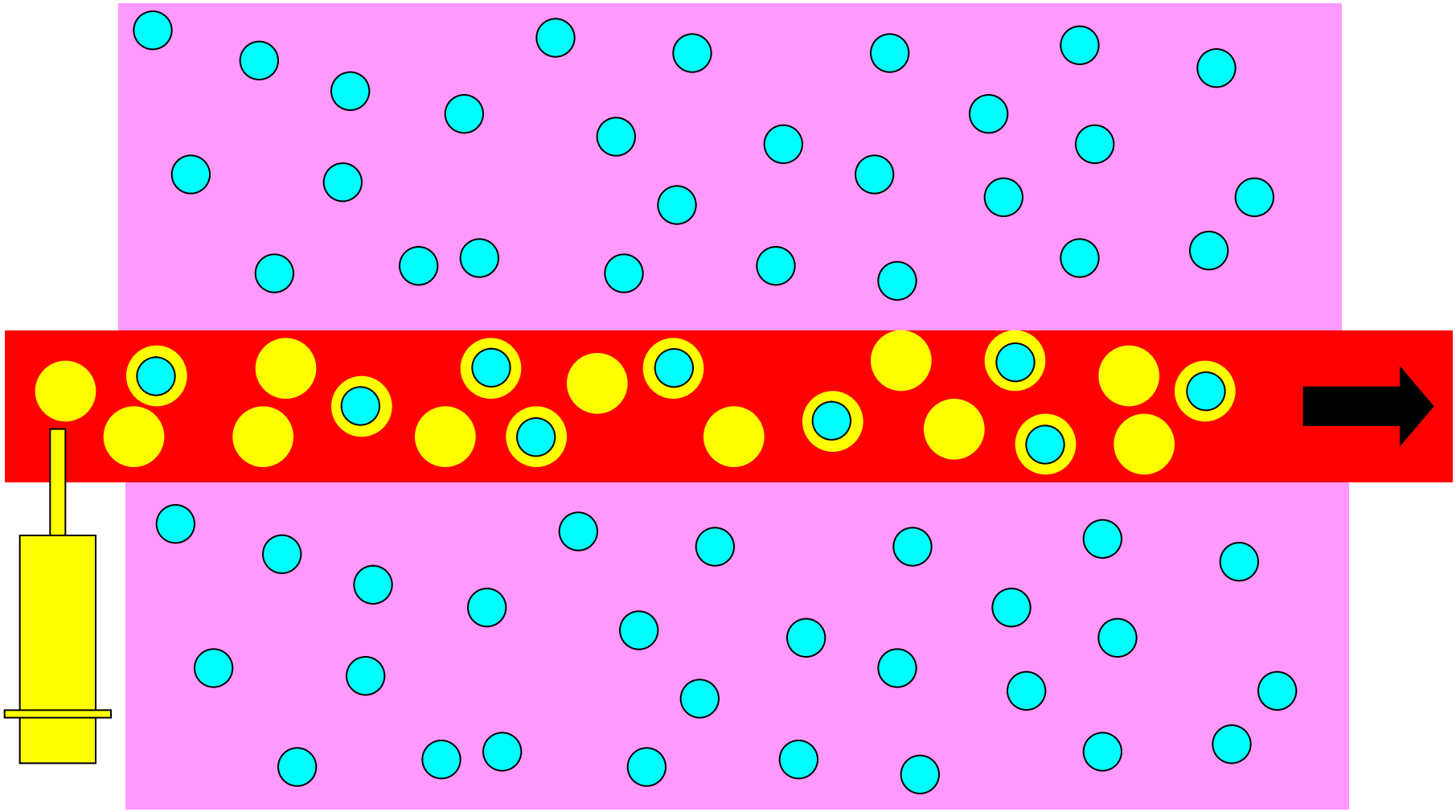
Very tight complex
Ratio 1:1
With steroidal neuromuscular blockings drugs
Rocuronium › Vecuronium › › Pancuronium
freely filtered by the glomerulus into the urine



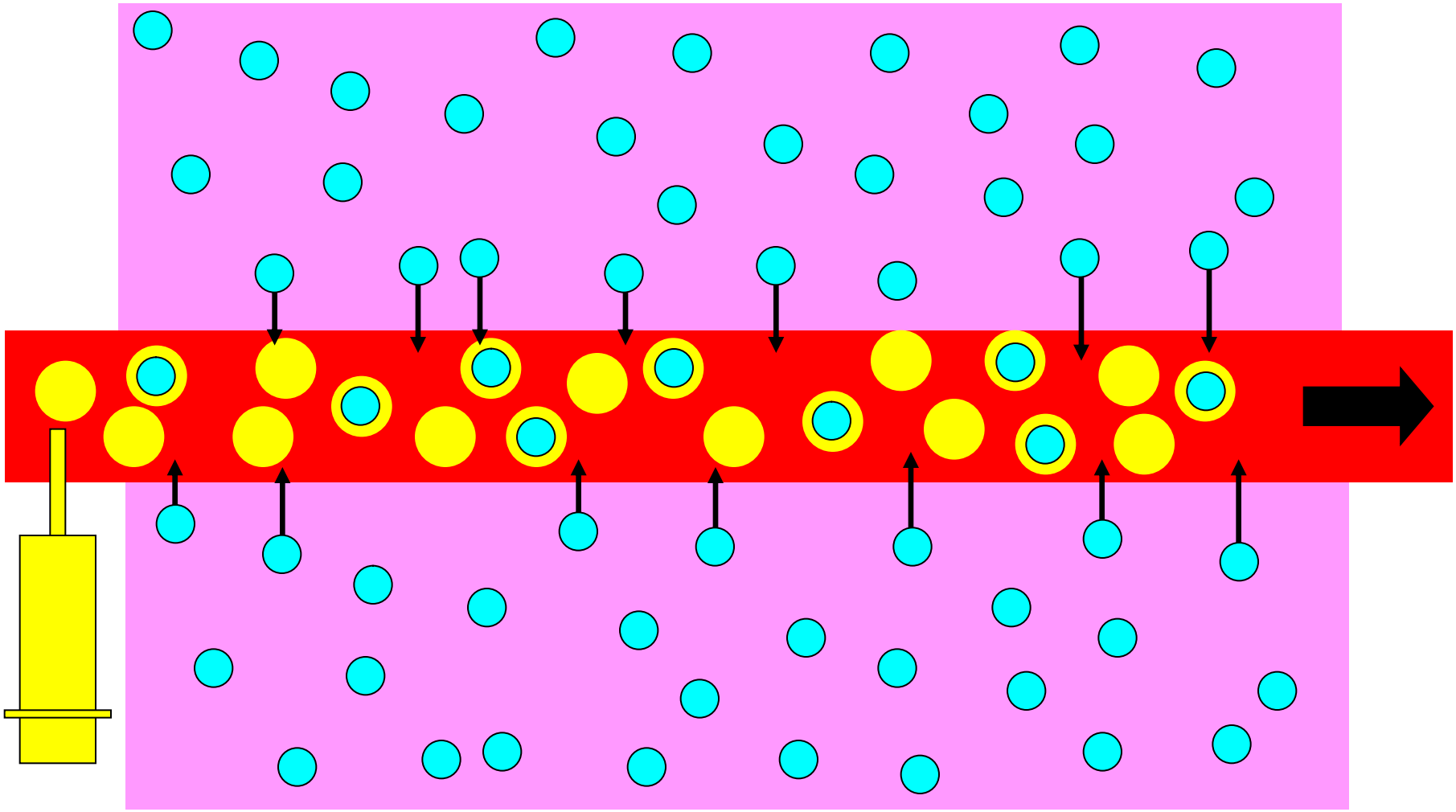
Concentration plasmatique et tissulaire du rocuronium en équilibre



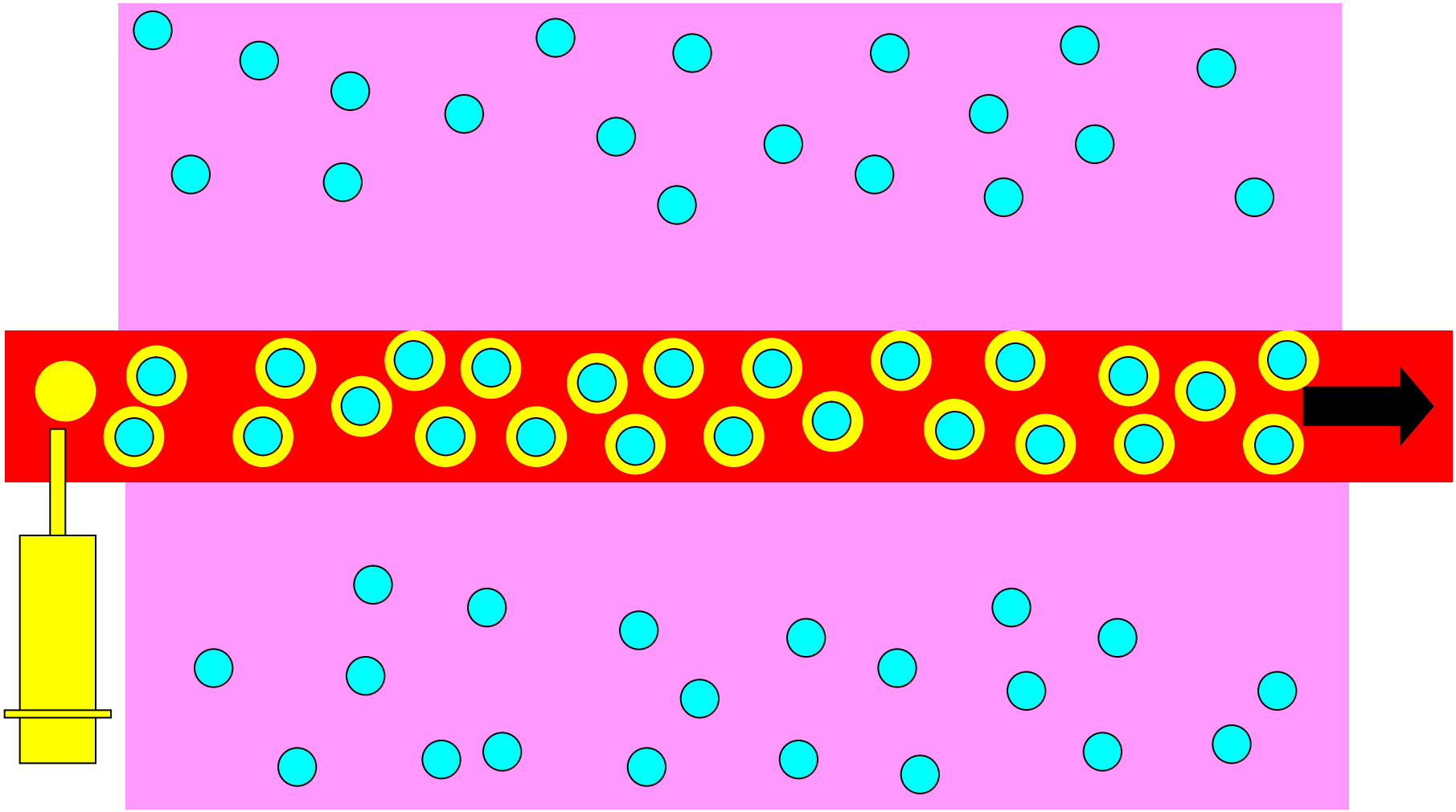
Début de l’injection du Sugammadex



Concentration plasmatique du rocuronium libre = 0



Création d’un gradient entre tissu et plasma



Sugammadex is biologically inactive, does not bind to plasma proteins, and appears to be safe and well tolerated.

Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First Human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. Anesthesiology 2005;103:695-703

Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006;104:667-74

Bridion® et bloc modéré

Anesthesiology 2007; 106:283–8

Fev 2007

Effective Reversal of Moderate Rocuronium- or Vecuronium-induced Neuromuscular Block with Sugammadex, a Selective Relaxant Binding Agent

Koen Suy, M.D., Karl Morias, M.D.,* Guy Cammu, M.D., Ph.D.,* Pol Hans, M.D.,† Wilbert G. F. van Duijnhoven, M.Sc.,‡ Marten Heeringa, Ph.D.,§ Ignace Demeyer, M.D.**

Table 2. Summary of Mean (SD) Recovery Times (in Minutes) for the T_4/T_1 Ratios after Sugammadex Administration: Per-protocol Population

		Sugammadex					
NMBA Group	Placebo	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	3.0 mg/kg	4.0 mg/kg	8.0 mg/kg
Rocuronium (0.60 mg/kg), n	3	8	7	8	3	8	—
T_4/T_1 ratio to 0.9	31.8 (21.0)*	3.7 (1.0)	2.3 (0.6)	1.7 (0.6)	1.9 (1.2)	1.1 (0.3)	—
T_4/T_1 ratio to 0.8	26.8 (17.5)*	2.7 (0.5)	1.8 (0.6)	1.4 (0.4)	1.6 (1.0)	1.0 (0.2)	—
T_4/T_1 ratio to 0.7	21.8 (12.9)*	2.3 (0.5)	1.5 (0.4)	1.4 (0.4)	1.4 (0.9)	1.0 (0.2)	—
Vecuronium (0.10 mg/kg), n	4	7	8	8	—	7	4
T_4/T_1 ratio to 0.9	48.8 (27.9)	7.7 (2.6)†	2.5 (0.8)	2.3 (0.8)	—	1.5 (0.5)	1.4 (0.5)
T_4/T_1 ratio to 0.8	44.8 (28.2)	5.3 (1.8)†	1.9 (0.5)	1.7 (0.4)	—	1.3 (0.5)	1.3 (0.5)
T4/T_1 ratio to 0.7	33.7 (16.7)	3.7 (1.0)	1.7 (0.4)	1.5 (0.3)	—	1.2 (0.5)	1.2 (0.3)

2 réponses au Td4

Anesthesiology 2007; 106:283–8

Fev 2007

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Koen Suy, M.D., Karl Morias, M.D.,* Guy Cammu, M.D., Ph.D.,* Pol Hans, M.D.,† Wilbert G. F. van Duijnhoven, M.Sc.,‡ Marten Heeringa, Ph.D.,§ Ignace Demeyer, M.D.**

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2 réponses au Td4

Anesthesiology 2007; 106:283–8

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T_4/T_1 ratio to 0.8	44.8 (28.2)	5.3 (1.8)†	1.9 (0.5)	1.7 (0.4)	—	1.3 (0.5)	1.3 (0.5)
T4/T_1 ratio to 0.7	33.7 (16.7)	3.7 (1.0)	1.7 (0.4)	1.5 (0.3)	—	1.2 (0.5)	1.2 (0.3)

2 réponses au Td4

Bridion® et bloc profond

Ou

Ce que ne peux pas faire la prostigmine……..

Mars 2007

A Randomized, Dose-Finding, Phase II Study of the Selective Relaxant Binding Drug, Sugammadex, Capable of Safely Reversing Profound Rocuronium-Induced Neuromuscular Block

Groudine SB et al.

(Anesth Analg 2007;104:555–62)

Variabilité si <4mg/Kg

Table 2. Time from Start of Administration of Sugammadex to Recovery of the Train-of-Four (TOF) Ratio to 0.9 by Dose Group (Per-Protocol Population)

	Time to recovery of TOF ratio to 0.9 (min) Sugammadex dose group (mg/kg)				
	0.5	1.0	2.0	4.0	8.0
Rocuronium 0.6 mg/kg					
n	3	2	5	2	4
Mean ± SD	44.2 ± 34.6	19.1 ± 20.0	5.4 ± 5.7	3.3 ± 1.6	1.5 ± 0.6
Range	22.4–84.1	5.0–33.2	1.8–15.2	2.2–4.7	1.0–2.1
Rocuronium 1.2 mg/kg					
n	1	3	3	2	4
Mean ± SD	20.6 ± 0.0	11.5 ± 11.6	4.3 ± 0.5	1.9 ± 0.7	1.0 ± 0.2
Range		4.5–25.0	3.8–4.8	1.5–2.4	0.8–1.3

→ PTC:1-2

Anesthesiology 2007; 106:935–43

Mai 2007

Early Reversal of Profound Rocuronium-induced Neuromuscular Blockade by Sugammadex in a Randomized Multicenter Study

Efficacy, Safety, and Pharmacokinetics

Harald J. Sparr, M.D., Karel M. Vermeyen, M.D.,† Anton M. Beaufort, M.D.,‡ Henk Rietbergen, M.Sc.,§ Johannes H. Proost, Pharm.D.,‖ Vera Saldien, M.D.,# Corinna Velik-Salchner, M.D.,** J. Mark K. H. Wierda, M.D.††*

Table 2. Time Interval (Minutes) from Administration of Sugammadex or Placebo to a Train-of-four Ratio of 0.7, 0.8, and 0.9 for the Various Time and Dose Groups (Per-protocol Population)

		Placebo	Sugammadex Dose Group, mg/kg				
Time of Administration of Sugammadex or Placebo	Time to Train-of-four Ratio	(n = 3)	1.0 (n = 6)	2.0 (n = 6)	4.0 (n = 6)	6.0 (n = 6)	8.0 (n = 6)
3 min	0.7	46.0 (8.0)	17.8 (8.8)	4.1 (1.3)*	2.1 (0.5)	1.3 (0.5)†	1.2 (0.3)†
	0.8	48.2 (8.0)	20.0 (10.7)	4.5 (1.5)*	2.3 (0.6)	1.6 (0.5)†	1.2 (0.4)†
	0.9	52.1 (8.8)	22.7 (11.6)	4.9 (1.3)*	6.3 (9.0)	1.9 (0.6)†	1.8 (0.9)†
5 min	0.7	45.2 (7.8)	22.8 (5.9)	4.8 (1.3)	1.8 (0.7)	1.4 (0.5)	1.1 (0.3)
	0.8	46.8 (8.4)	24.8 (5.7)	6.4 (3.1)	2.0 (0.7)	1.7 (0.7)	1.1 (0.3)
	0.9	51.7 (13.1)	27.4 (6.4)	8.9 (7.8)	2.3 (0.7)	2.1 (0.9)	1.5 (0.6)
15 min	0.7	31.2 (6.6)	4.7 (1.3)	2.2 (0.6)	1.2 (0.3)‡	1.1 (0.5)	1.1 (0.1)
	0.8	33.4 (8.1)	5.5 (1.4)	2.4 (0.7)	1.3 (0.5)‡	1.2 (0.5)	1.2 (0.2)
	0.9	35.6 (9.1)	6.5 (1.7)	2.7 (0.7)	2.1 (1.2)	2.1 (2.0)	1.4 (0.2)

Rocuronium 0,6mg/kg

Anesthesiology 2008; 109:188–97

Aout 2008

Reversal of Profound, High-dose Rocuronium–induced Neuromuscular Blockade by Sugammadex at Two Different Time Points

An International, Multicenter, Randomized, Dose-finding, Safety Assessor– blinded, Phase II Trial

Friedrich K. Pühringer, M.D.,* Christopher Rex, M.D.,† Andreas W. Sielenkämper, M.D.,‡ Casper Claudius, M.D.,§ Per Bo Larsen, M.D.,‖ Martine E. Prins, M.Sc.,# Matthias Eikermann, M.D.,** Karin S. Khuenl-Brady, M.D.††

Table 4. Recovery Times after an Initial Bolus Dose of 1.2 mg/kg Rocuronium, with Sugammadex or Placebo Given 3 min after Rocuronium

		Sugammadex Dose				
	Placebo	2 mg/kg	4 mg/kg	8 mg/kg	12 mg/kg	16 mg/kg
Recovery to TOF 0.7, min						
n	5	10	8	11	10	11
Mean (SD)	122.9 (36.2)	54.4 (17.3)	7.5 (2.8)	2.4 (0.9)	1.6 (0.8)	1.2 (0.2)
Median	107.5	53.5	7.4	2.6	1.3	1.3
Min–max	81.3–173.1	33.6–92.5	2.8–11.5	0.8–4.0	1.0–3.6	0.8–1.5
Recovery to TOF 0.9, min						
n	4	9	8	11	10	11
Mean (SD)	123.0 (28.5)	65.7 (24.6)	13.8 (7.6)	3.2 (1.0)	2.1 (0.9)	1.3 (0.4)
95% CI for the mean	[78; 168]	[47; 85]	[7.4; 20.2]	[2.6; 3.9]	[1.5; 2.7]	[1.0; 1.6]
Median	124.3	63.3	11.3	3.6	1.9	1.3
Min–max	87.3–156.1	36.3–117.2	5.3–28.5	1.5–4.7	1.2–4.1	0.8–2.3

Anesthesiology 2009; 110:1020–5

Reversal of Profound Neuromuscular Block by Sugammadex Administered Three Minutes after Rocuronium

16mg/Kg

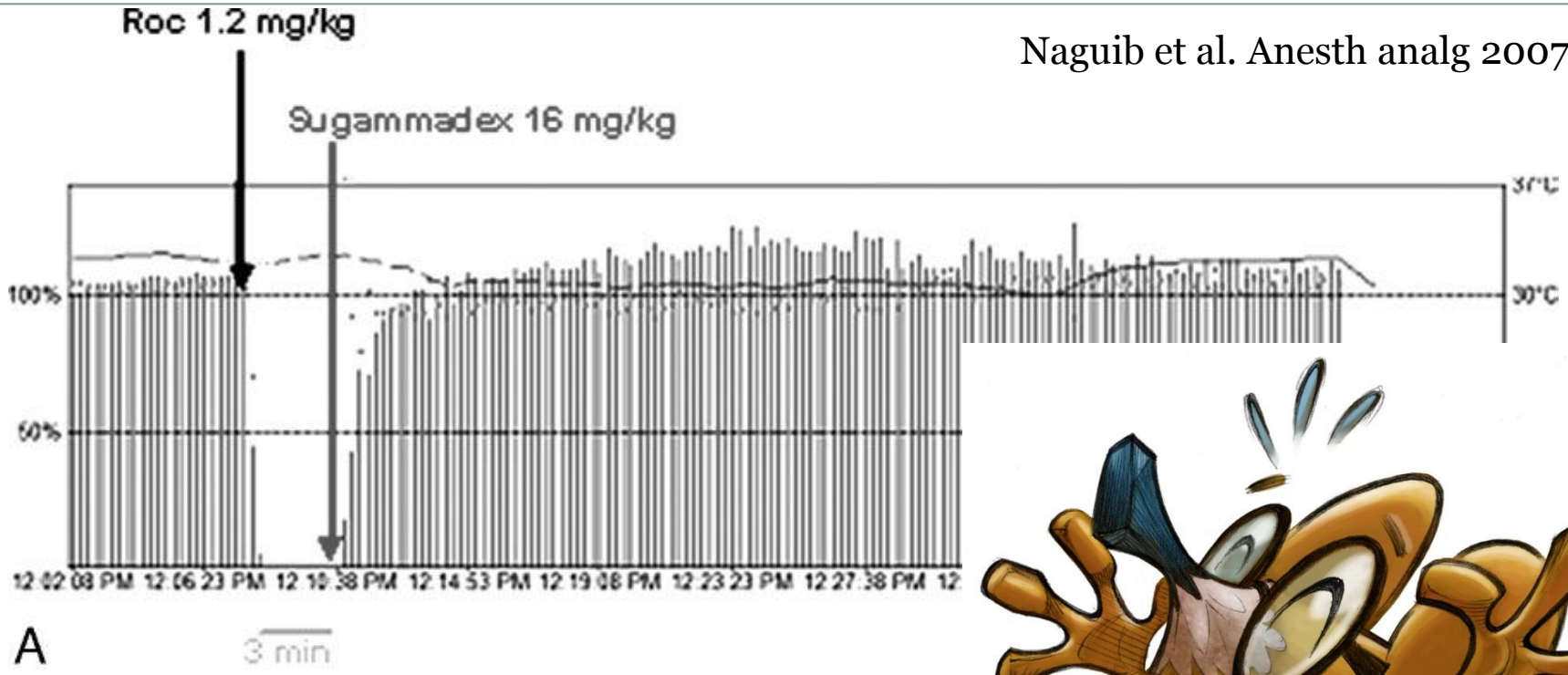
A Comparison with Spontaneous Recovery from Succinylcholine

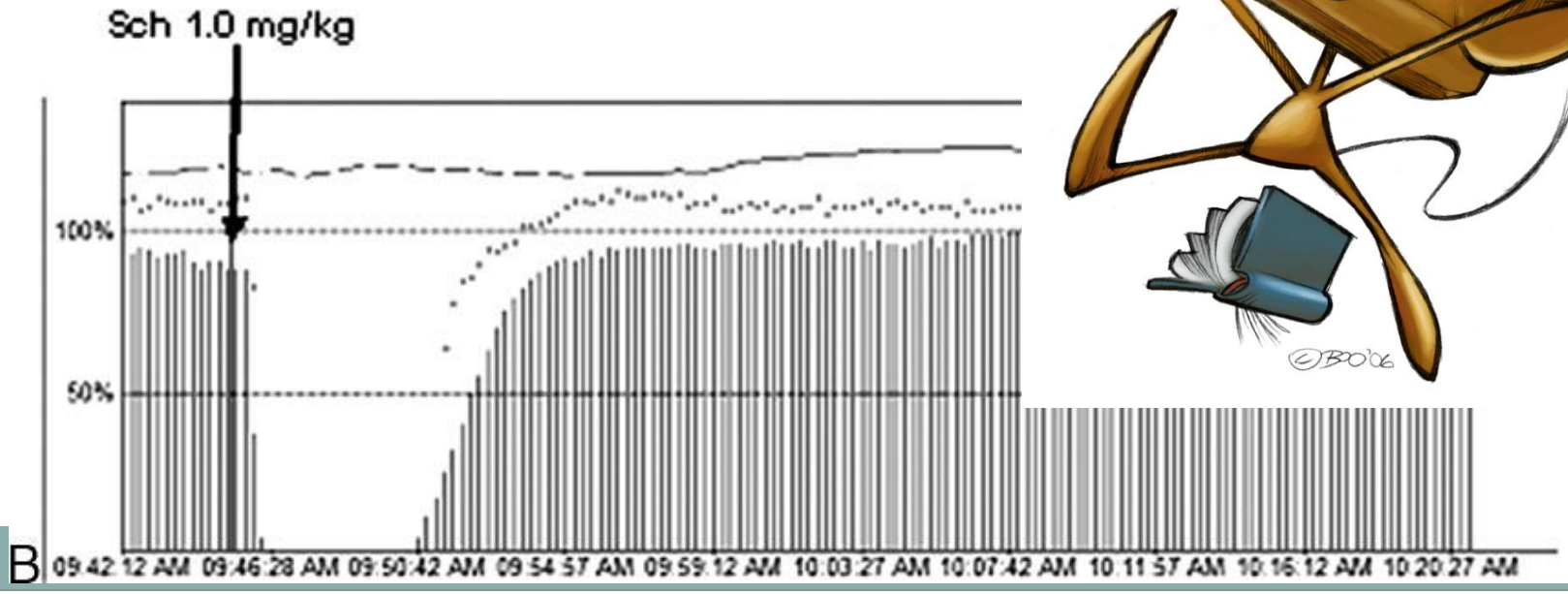
Chingmuh Lee, M.D., Jonathan S. Jahr, M.D.,† Keith A. Candiotti, M.D.,‡ Brian Warriner, M.D.,§ Mark H. Zornow, M.D.,|| Mohamed Naguib, M.D.#*

Table 1. Time (min) from Start of Administration of Neuromuscular Blocking Agent to Recovery of T_1 to 10% and T_1 to 90%

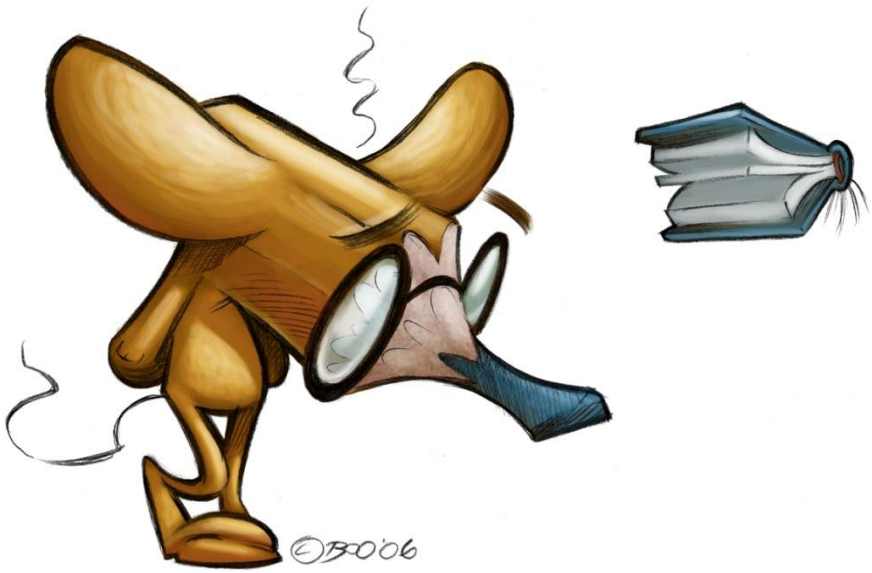
	Treatment Group	
	Rocuronium + Sugammadex* (n = 55)	Succinylcholine Only (n = 55)
Recovery to T_1 10% (primary endpoint)		
Mean (SD)	4.4 (0.7)	7.1 (1.6)†
Median	4.2	7.1
Min–max	3.5–7.7	3.8–10.5
Recovery to T_1 90%		
Mean (SD)	6.2 (1.8)	10.9 (2.4)†
Median	5.7	10.7
Min–max	4.2–13.6	5.0–16.2

Naguib et al. Anesth analg 2007





Side Effects of SUGGAMADEX



- **Hypotension**
- **Toux**
- **Mouvement**
- **Nausées**
- **Vomissements**
- **Sécheresse bouche**
- **Dysgueusie**
- **Augmentation N-acétylglucoaminidase dans les urines**
- **Allongement QT corrigé**

Gijsenbergh F, Ramael S, Houwing N, van Iersel T. First Human exposure of Org 25969, a novel agent to reverse the action of rocuronium bromide. Anesthesiology 2005;103:695-703

Sorgenfrei IF, Norrild K, Larsen PB, et al. Reversal of rocuronium-induced neuromuscular block by the selective relaxant binding agent sugammadex: a dose-finding and safety study. Anesthesiology 2006;104:667-74

Sparr HJ, Vermeyen KM, Beaufort AM et al. Early reversal of profound rocuronium induced neuromuscular blockade by sugammadex in a randomized multicenter study. Anesthesiology 2007;106:935-43

Hunter JM, Flockton EA. The doughnut and the hole: a new pharmacological concept for anaesthestists. British Journal of Anaesthesia 2006;97:123-6

Vanacker BF, Vermeyen KM, Struys MMRF et al.Reversal of Rocuronium-Induced Neuromuscular Block with the Novel Drug Sugammadex Is Equally Effective Under Maintenance Anesthesia with Propofol or Sevoflurane. Anesth Analg 2007;104:563-8.

Bridion® en pratique
Résumé

Anesthesiology 2006; 104:631–3

Sugammadex: A Revolutionary Approach to Neuromuscular Antagonism

- Le Bridion® est un nouvel antagoniste de la curarisation

- Ne concerne que les blocs induits par les curares stéroïdes : rocuronium, vecuronium.

Anesthesiology 2006; 104:631-3

Sugammadex: A Revolutionary Approach to Neuromuscular Antagonism

- L'efficacité du Bridion® est supérieure à la prostigmine en terme de délai d'action, de maniabilité (profondeur du bloc NM), et d'effets indésirables.

- L'efficacité du Bridion® n'est pas modifiée sous sévoflurane.

- Les effets indésirables possibles du Bridion® sont encore insuffisamment évalués.

En pratique

Rocuronium (Esmeron®) Ou Vécuronium (Norcuron®)	Bloc modéré (≥ 2 réponses au Td4 à l'AP)	2 mg/kg
	Bloc profond (≥ 2 réponses au PTC à l'AP)	4 mg/kg

Rocuronium (Esmeron®)	Décurarisation immédiate	16 mg/kg