Des cyclodextrines au Sugammadex

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Curarisation résiduelle

Incidence de la curarisation résiduelle

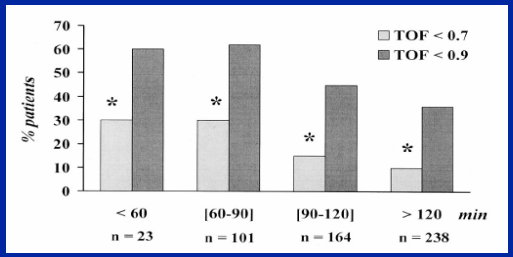
Vécuronium, atracurium

Canada	5-10%
Danemark	5-10%
France (pas d'anatagonisation et de monitorage)	33-42%

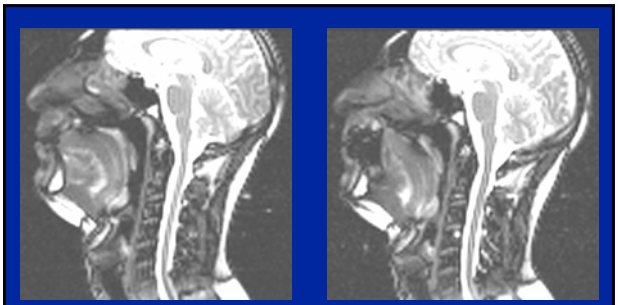
CURARISATION RESIDUELLE EN S.S.P.I.

	Décurarisés	*Curarisés*
n	329 *(58 %)*	239 *(42 %)*
âge	45 *(18-85)*	50 *(18-83)*
extubés à l'arrivée	290	145

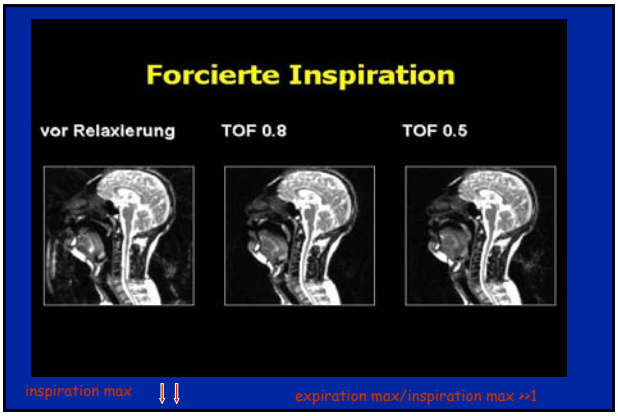
BAILLARD et al., Br. J. Anaesth., 2000; 84:394



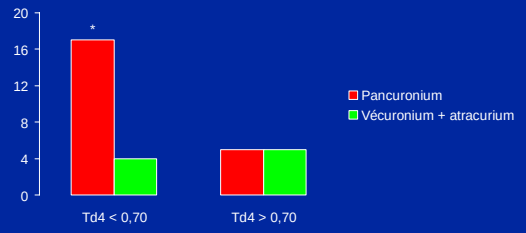
Debaene, Anesthesiology 2003; 98: 1042



Residual paralysis and UAO



Pancuronium : attention danger …
…complications respiratoires postopératoires



* : P < 0,05 *versus* Td4 > 0,70

Berg H et al. Acta Anaesthesiol Scand 1997;41:1095-103

Antagonisation du rocuronium par la néostigmine

		TOF 0.8 (min)
Spontané		66.5 (11.7)
T_1-10%	35 µg/kg	10.3 (4.3)
	50 µg/kg	10.5 (6.2)
T_1-25%	35 µg/kg	7.0 (4.8)
	50 µg/kg	6.4 (1.9)

Conférence de consensus (SFAR 1999)

1) La décurarisation pharmacologique est recommandée si la décurarisation complète ne peut être affirmée

2) Il n'existe pas de contre-indication à la décurarisation pharmacologique en dehors de:
- L'asthme sévère
- L'angor instable
- L'insuffisance cardiaque non contrôlée

Conférence de consensus (SFAR 1999)

3) La décurarisation n'est envisageable qu'à partir du moment où il existe au moins deux réponses au train de quatre

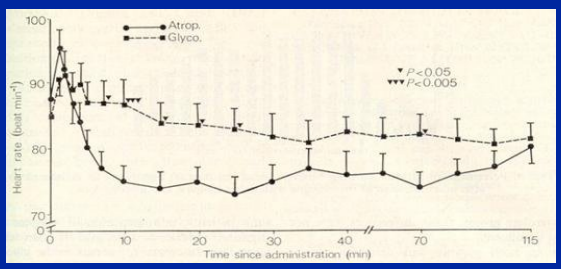
4) Elle repose sur la néostigmine à la dose de 40 à 50 µg/kg. La néostigmine est associée à l'atropine à la dose de 15 à 20 µg/kg

Inconvénients

- Nécessité de réapparition de 2 réponses au train de quatre
- Effet plafond: néostigmine (70 µg/kg)

- Bradycardie
- Bronchoconstriction
- Crampes abdominales
- Nausées, vomissements?

Heart rate changes following neostigmine administered with atropine or glycopyrrolate



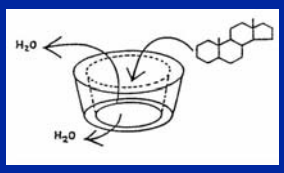
Nécessité d'un nouvel agent pharmacologique

- Action rapide
- Peu d'effets secondaires
- Possibilité d'antagoniser un bloc profond
- Action indépendante des agents anesthésiques

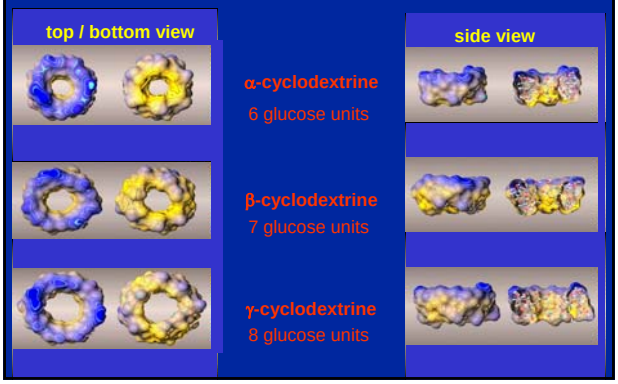
Cyclodextrines

- Molécules glucidiques disposées en anneau
- Centre hydrophobe
- Extérieur hydrophyle

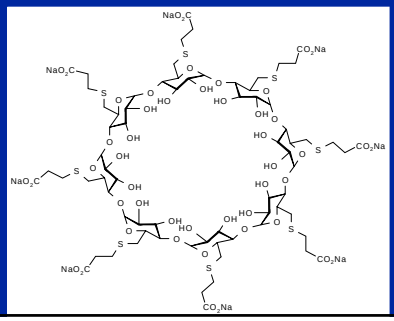
- Agents solubilisants



Cyclodextrines



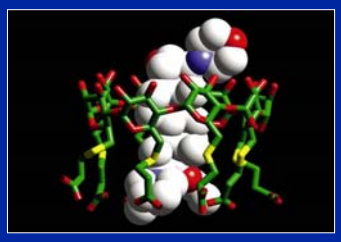
Sugammadex, a Selective Relaxant Binding Agent (SRBA)



Quelle cyclodextrine ?

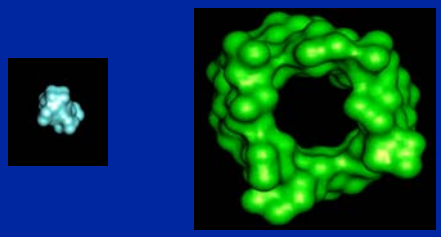
	maximum reversal	EC_{50}
γ-cyclodextrine	94.1 %	34.6 µM
sugammadex	95.1 %	1.2 µM

ORG 29569, a Selective Relaxant Binding Agent (SRBA)

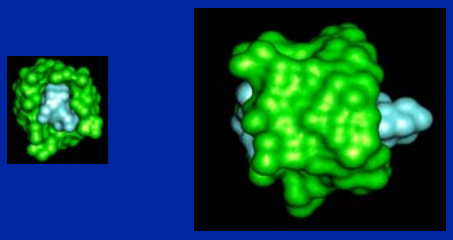


Bom. *Angew Chem* 2002:41; 265.

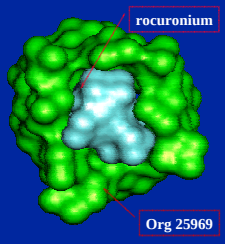
2 Molécules …..



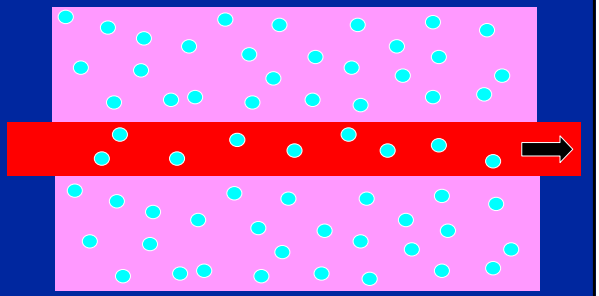
….qui sont parfaitement complémentaires



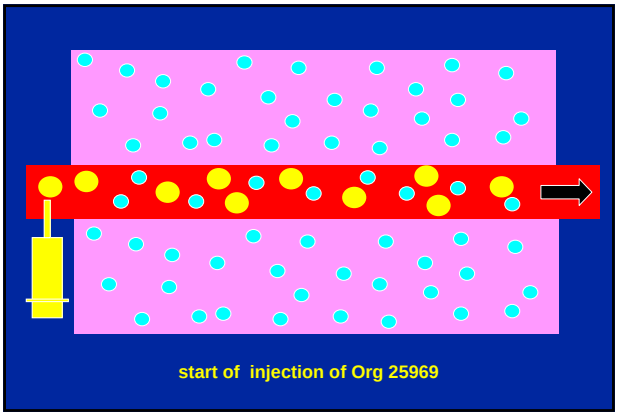
Sugammadex: quels objectifs?



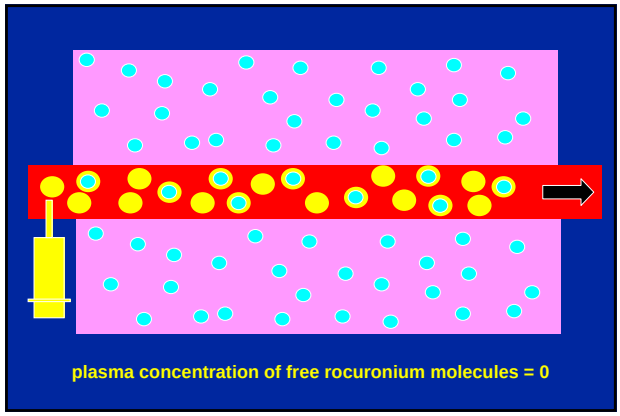
- raccourcissement de la décurarisation
- moins d'effets secondaires que la néostigmine)
- Possibilité d'un bloc profond jusqu'à la fin de l'intervention
- effet "on/off"



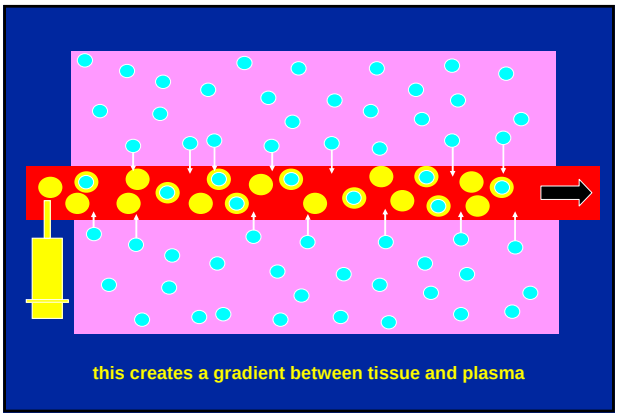
plasma rocuronium in equilibrium with tissue



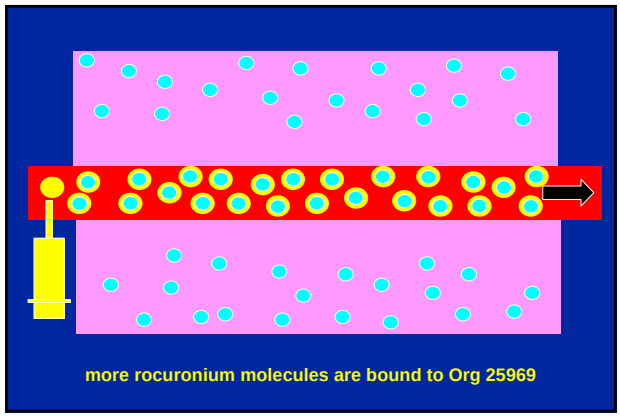
start of injection of Org 25969



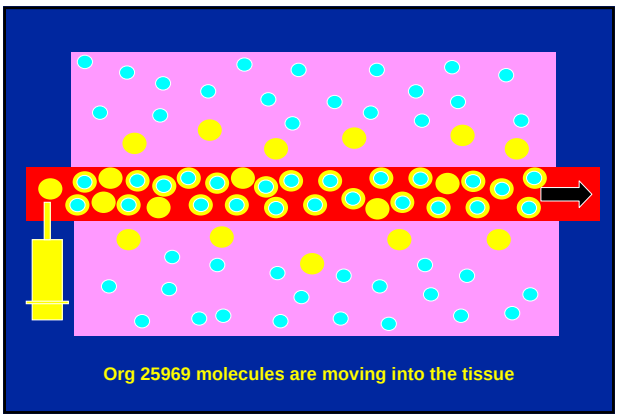
plasma concentration of free rocuronium molecules = 0



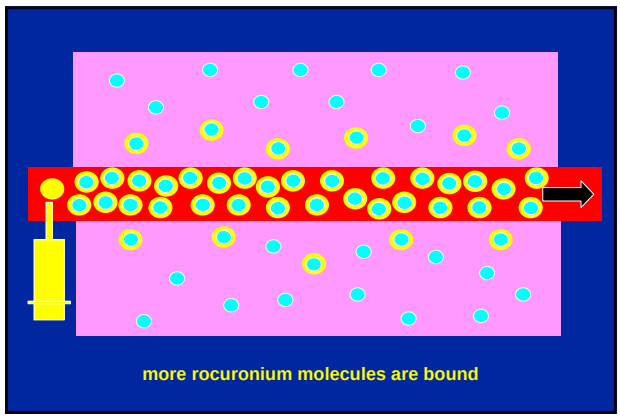
this creates a gradient between tissue and plasma



more rocuronium molecules are bound to Org 25969

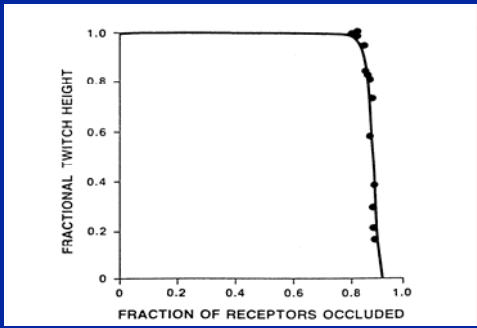


Org 25969 molecules are moving into the tissue



more rocuronium molecules are bound

Marge de sécurité



Waud B, Anesthesiology 1971; 35:456

Sorgenfrei et al, Anesthesiology 2006; 104: 667

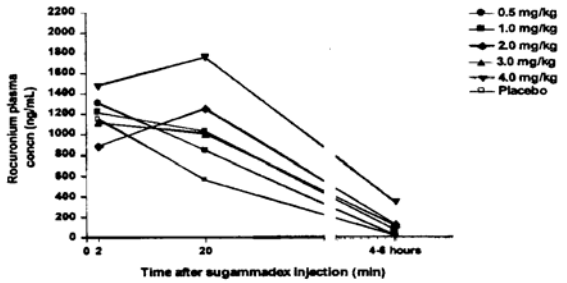


Fig. 4. Median plasma concentrations of rocuronium (sum of free and sugammadex bound) *versus* time after administration of sugammadex (0.5, 1.0, 2.0, 3.0, or 4.0 mg/kg) or placebo.

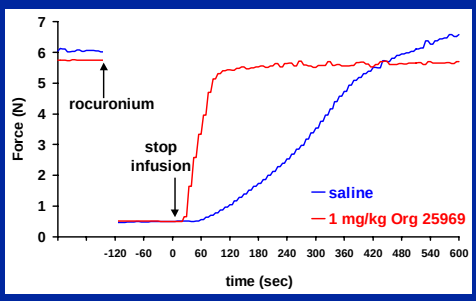
Spécificité du sugammadex

Table 1. 25–75% recovery index

	Spontaneous recovery (min)	Recovery after 1 mg kg^{-1} Org 25969 (min)
Rapacuronium	2.1 ± 0.4	0.3 ± 0.0*
Rocuronium	2.5 ± 0.3	0.3 ± 0.0*
Pancuronium	7.4 ± 1.8	0.3 ± 0.0*
Vecuronium	12.9 ± 3.1	0.4 ± 0.0*
Succinylcholine	4.2 ± 0.7	4.4 ± 0.4
D-Tubocurarine	4.5 ± 0.4	5.7 ± 1.2
Atracurium	7.2 ± 1.2	9.3 ± 2.4
Mivacurium	34.4 ± 6.2	16.3 ± 4.6

Mean ± SEM; $n = 4$; *$P < 0.05$ vs. spontaneous recovery.

Antagonisation d'un bloc induit par le rocuronium chez le chat (n = 3)



Sugammadex: phase I

Anesthesiology 2005; 103:695–703

First Human Exposure of Org 25969, a Novel Agent to Reverse the Action of Rocuronium Bromide

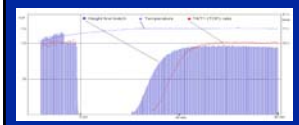
Francois Gijsenbergh, M.D.,* Steven Ramael, M.D.,† Natalie Houwing, M.Sc.,‡ Thijs van Iersel, M.D.§

0.1-8.0 mg/kg

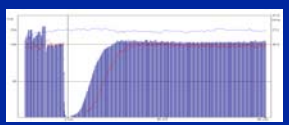
Phase I: pas de rocuronium

Phase II: 3 min après le rocuronium

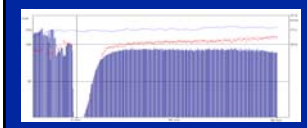
0.6 mg/kg rocuronium and Org 25969



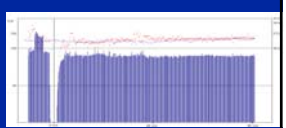
Placebo (>45 min)



1.0 mg/kg Org 25969 (23 min)



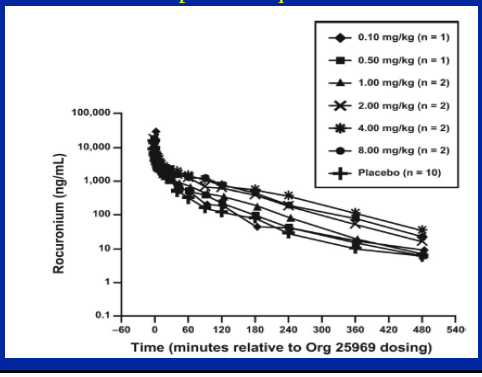
2.0 mg/kg Org 25969 (13 min)



4.0 mg/kg Org 25969 (3.2 min)

Gijsenbergh F, et al. Anesthesiology 2005; 103: 695

Concentrations plasmatiques de rocuronium



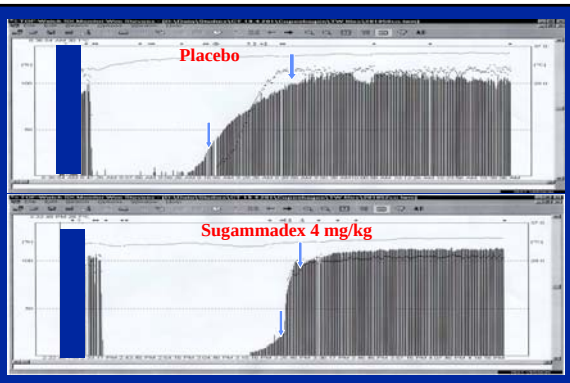
Anesthesiology 2006; 104:667–74

Reversal of Rocuronium-induced Neuromuscular Block by the Selective Relaxant Binding Agent Sugammadex

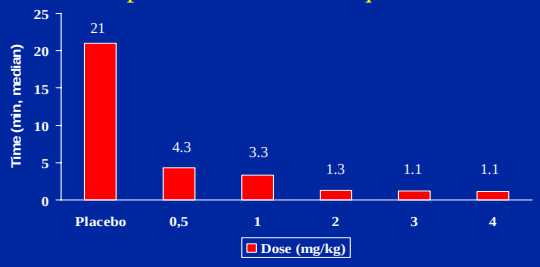
A Dose-finding and Safety Study

Iben F. Sorgenfrei, M.D.,* Kathrine Norrild, M.D.,* Per Bo Larsen, M.D.,† Jakob Stensballe, M.D.,* Doris Østergaard, M.D.,† Martine E. Prins, M.Sc.,‡ Jørgen Viby-Mogensen, M.D., D.M.Sc., F.R.C.A.§

Rocuronium	0.6 mg/kg
Antagonisaton:	2 réponses au train-de-quatre
Dose de sugammadex	Placebo, 0.5, 1.0, 2.0, 3.0 or 4.0 mg/kg



Rocuronium 0.6 mg/kg et sugammadex à 2 réponses au train-de-quatre



670 SORGENFREI *ET AL.*

Table 1. Time from Start of Administration of Sugammadex or Placebo at Reappearance of T_4 to Recovery of the TOF Ratio to 0.9, 0.8, and 0.7: Per-Protocol Population

		Sugammadex Dose Group				
	Placebo	0.5 mg/kg	1.0 mg/kg	2.0 mg/kg	3.0 mg/kg	4.0 mg/kg
TOF 0.9						
n	4	5	4	3	5	3
Median	21.0	4.3	3.3*	1.3	1.2	1.1
Range (min–max)	(15.0–35.4)	(1.3–8.5)	(1.4–4.9)	(0.9–1.7)	(0.7–3.2)	(1.0–1.4)
TOF 0.8						
n	3	5	5	3	5	3
Median	15.8*	3.7	1.7	1.1	1.2	1.1
Range (min–max)	(13.0–16.7)	(1.1–7.5)	(1.1–2.6)	(0.9–1.6)	(0.7–2.4)	(0.7–1.1)
TOF 0.7						
n	4	5	5	3	5	3
Median	14.8	2.8	1.4	0.9	1.0	0.9
Range (min–max)	(11.5–26.4)	(1.1–5.7)	(1.1–1.8)	(0.8–1.5)	(0.7–2.2)	(0.7–1.1)

Values are reported in minutes.
* Data for one subject excluded.
TOF = train-of-four.

BJA
CLINICAL PRACTICE

Org 25969 (sugammadex), a selective relaxant binding agent for antagonism of prolonged rocuronium-induced neuromuscular block

M. Shields[1], M. Giovannelli[2], R. K. Mirakhur[1,*], I. Moppett[1], J. Adams[1] and Y. Hermens[1]

- Rocuronium 0.6 mg/kg suivi de réinjections pour maintenir un bloc profond (PTC < 10)
- Antagonisation après plus de 2 heures de curarisation à T2
- Doses d'Org 25969
  - 0.5, 1.0, 2.0, 4.0 and 6.0 mg/kg

Délai pour obtenir un TOF > 90% après injection à 2 réponses au TOF

Dose (mg/kg)	Temps (Médiane (range))
0.5	5:29 (4:50-11:26)
1.0	2:42 (1:49-3:40)
2.0	1:46 (1:00-2:31)
4.0	1:04 (0:57-2:19)
6.0	2:41 (1:08-3:56)

Shields et al, Br j Anaesth 2006; 96: 36

Antagonisation d'un bloc profond

- Rocuronium: 0,6 ou 1,2 mg/kg
- Antagonisation lors d'un bloc profond: 1 à 2 réponses au TOF
- Sugammadex: 0,5 – 1,0 – 2,0 – 4,0 ou 8,0 mg/kg

Antagonisation d'un bloc profond

	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

Groudine et al, Anesth Analg 2007; 104: 555

Sugammadex versus néostigmine ou édrophonium

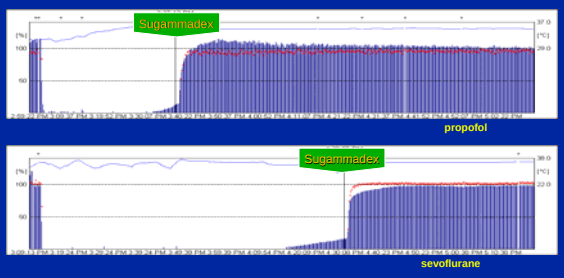
Table 2. The Times from Reversal Administration to Achieve a Train-of-Four (TOF) Ratio of 0.7, 0.8, and 0.9, as well as the Percentage of Patients who Achieved a TOF of 0.9 in ≤2 min and ≤5 min in the 3 Reversal Groups

	Edrophonium (n = 20)	Neostigmine (n = 20)	Sugammadex (n = 20)
Initial TOF ratio after reversal administered (%)*	30 ± 14*	16 ± 7*	73 ± 16
Time to achieve TOF ratio (s)*			
0.7	202 ± 171*	625 ± 341*	71 ± 25
0.8	248 ± 132*	960 ± 456*	79 ± 33
0.9	331 ± 27*	1044 ± 590*	107 ± 61
No. of patients achieved TOF ratio			
0.7	7	9	20
0.8	5	5	20
0.9	2	5	20
No. of patients achieved TOF ratio of 0.9			
≤2 min	0 (0%)*	0 (0%)*	15 (75%)
≤5 min	0 (0%)*	1 (5%)*	20 (100%)

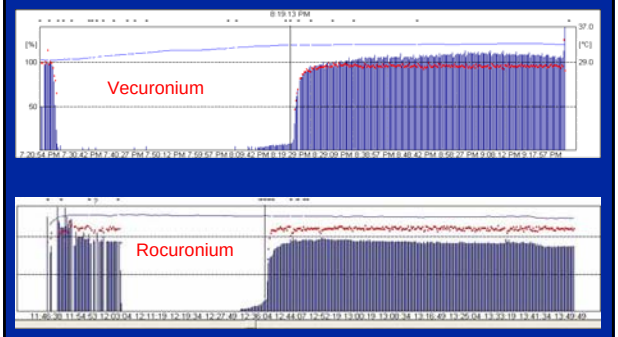
* Values are expressed as means ± SD.
* $P < 0.05$ when compared with sugammadex group.

Sacan et al, Anesth Analg 2007; 104: 569

Antagonisation lors d'anesthésie utilisant le propofol ou le sévoflurane



Sugammadex: 2.0 mg/kg



Anesthesiology 2007; 106:283–8

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.**

NMBA Group	Placebo	Sugammadex 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 (0.6)	2.3 (0.6)	—	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)

Antagonisation immédiate du rocuronium par le sugammadex

(étude 202)

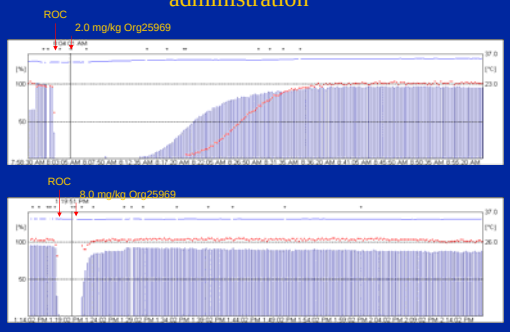
- Rocuronium 0.6 mg/kg
- Antagonisation à 3, 5 ou 15 min après le rocuronium
- Dose de sugammadex:
  - Placebo, 1.0, 2.0, 4.0, 6.0, or 8.0 mg/kg

Antagonisation immédiate

(médiane pour obtenir un TOF à 90%)

	3 min après rocuronium	5 min après rocuronium	15 min après rocuronium
2 mg/kg	5.1 min	5.8 min	2.5 min
4 mg/kg	2.7 min	2.0 min	1.5 min
6 mg/kg	1.7 min	2.1min	1.1 min
8 mg/kg	2.0 min	1.3 min	1.3 min

Antagonisation de 1.0 mg/kg de rocuronium 3 min après son administration



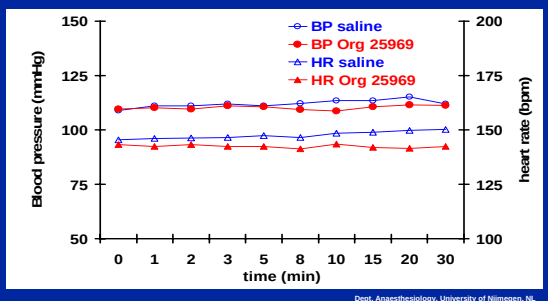
Sugammadex et antagonisationd'une haute dose de rocuronium

Dose de rocuronium: 1.2 mg/kg
Sugammadex: 3 min après le rocuronium

Dose de Sugammadex	TOF à 90% (min (SD))
8.0 mg/kg	3.2 (1.0)
12.0 mg/kg	2.1 (0.9)
16.0 mg/kg	1.3 (0.4)

Effets hémodynamiques de l' Org 25969

chez le singe (n = 4)



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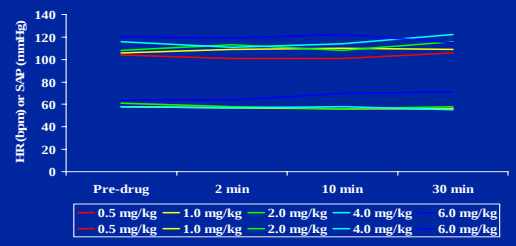
SBP et FC



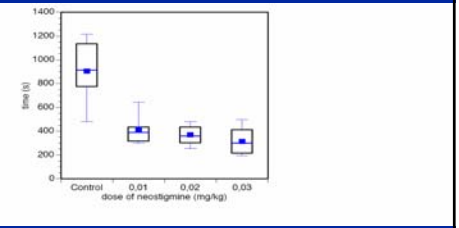
Sugammadex

- Effectif pour tous les niveaux de bloc
- Permet une curarisation profonde jusqu'à la fin de l'intervention (coelioscopie)
- Pas d'effets muscariniques, vagolytiques
- Pas d'effets secondaires significatifs
  - (plus de 1 500 administrations chez l'homme)

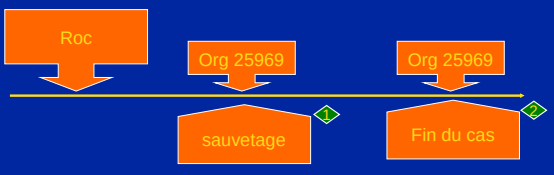
Utilisation clinique

- Bloc du au rocuronium ou au vécuronium
- Antagonisation dès la fin de l'acte
- Posologie: 4 mg/kg
- En cas de réintervention utiliser l'atracurium ou le ciasatracurium
- Intubation impossible après rocuronium
- Posologie: 16 mg/kg
- Décurarisation complète en moins de 2 minutes

Is neostigmine dead ?



Utilisaton du sugammadex



1. cannot intubate - cannot ventilate (3 minutes)
2. quel que soit le niveau de bloc