Are You Overdosing Your (Older) Patients with Muscle Relaxants?

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Non-functioning Muscle – Think BOTOX!





- Cosmetic botulinum toxin A injections
 - Miller, et al-: Anesthesiology 2006; 105:862 (72-yr-old man)
 - Ward: Anaesthesia 2006; 61:726 (35-yr-old woman)

A Single Injection of Botulinum Toxin Decreases the Margin of Safety of Neurotransmission at Local and Distant Sites. Systemic Effect of Botox in Rat! Frick CG, et al. Anesth Analg 2012; 114:102-9

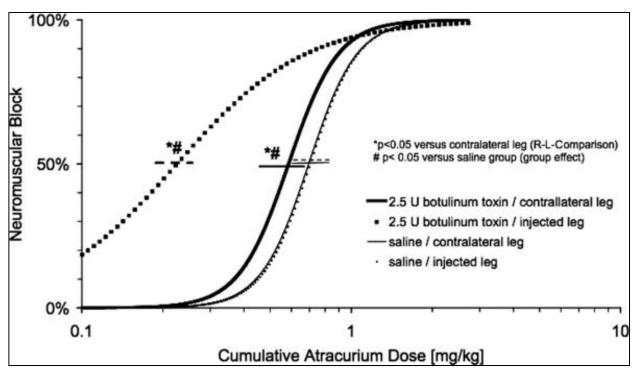


Figure 2 . Cumulative doseresponse curves to atracurium [mg/kg] at day 16. Doseresponse curve for atracurium was shifted to the left both on the toxin-injected and contralateral sides, resulting in significantly (P < 0.05) lower ED50 when compared with the saline-injected controls. The bars represent the confidence intervals.



Depth of Neuromuscular Block with Non-depolarizing NMBA

Classification

- Profound no response to PTF
- Deep PTF count of 1 or 2
- Moderate reappearance of T2 in TOF
- Shallow TOF ratio between 0.4-0.7

Unable to perceive fade when TOF ratio ≥ 0.5 with many current monitors

Schaller et al: *Anesthesiology* 2010; 113(5):1054-60

Kopman: Anesthesiology 2010; 113(5):1010-1 (Editorial)

What I Thought I Could Say

FACT: Postoperative morbidity: older > younger

ASSUMPTION: Anesthesia overdose contributes to anesthesia-related morbidity

HYPOTHESIS: If avoid overdose, reduce morbidity in older patients

But How Do You Define NMBA Overdose?

Block too deep to reverse at end of surgery Residual block after reversal and extubation

Dose dependent occurrence of adverse events due to side-effects of residual block

Extubation criteria not met in timely fashion despite reversal

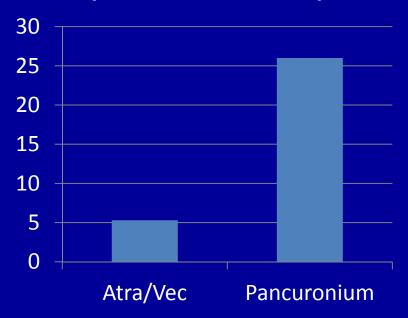
% Residual Neuromuscular Block & Postoperative Pulmonary Complications (POPC)

Berg: Acta Anaesthesiol Scand 1997; 41:1095

Neostigmine

Extubated in OR, TOF > 0.7

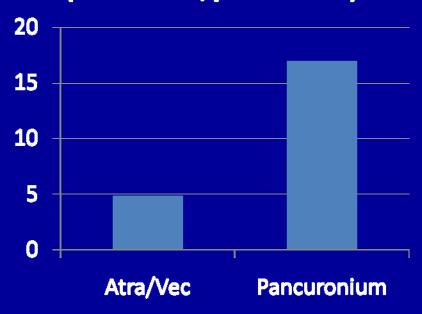
TOF < 0.7 (measured in PACU)



Age *sans* POPC 52 (38-66) yrs

Age with POPC 65 (56-76) yrs

POPC (atelectasis, pneumonia)



Avoid Pancuronium in Older Patients

%: [TOF < 0.9] > [TOF < 0.7] > POPC > acute CRE

50%

25%

15%

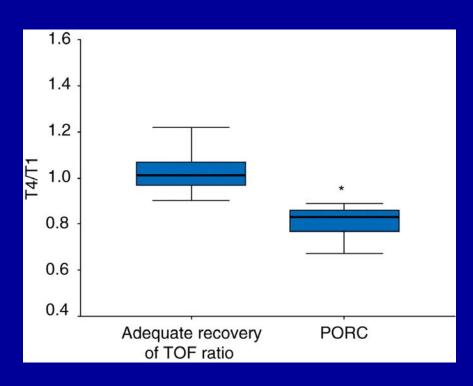
5%

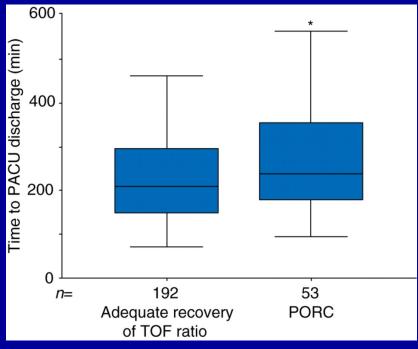
Unacceptable incidence of residual block

- Critical respiratory events (CRE) (transport, PACU)
 - Swallowing dysfunction, aspiration
 - Upper airway obstruction, laryngospasm
 - Panic reactions: "I can't breathe!"
 - Hypoxemia, CV stimulation
- Postoperative pulmonary complications (POPC) (days 2-6)
 - Atelectasis, pneumonia

Postoperative Residual Curarization (PORC) from Cisatracurium or Vecuronium Delays PACU Discharge

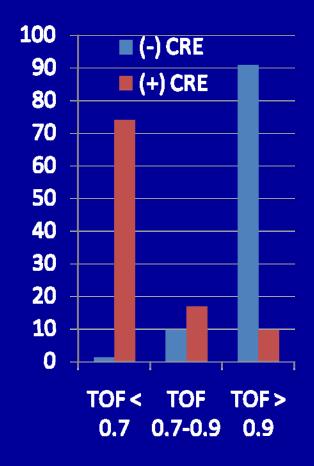
Butterly, et al. *Br J Anaesth* 2010; 105:304-9





Rocuronium and Critical Respiratory Events (CRE) in PACU

Murphy: Anesth Analg 2008; 107:130-7



CRE's ≤ 15 min in PACU 0.8%

- 61 patients with CRE's, age 63.7 yrs (± 14.2)
- Control group from 7399 adult patients without CRE's, matched for age, sex, surgical procedure,

Sevoflurane, isoflurane, or desflurane

Rocuronium

CRE's associated with TOF < 0.9 after reversal of rocuronium

Pancuronium vs Rocuronium in Older Patients after Reversal with Neostigmine

%: [TOF < 0.9] > [TOF < 0.7] > POPC > acute CRE

Panc 50% 25% 15% 5%

Roc 40% 12% 5% 1%

Ratio 1.25 2 3 5

But How Do You Define NMBA Overdose?

Residual block after reversal and extubation

Dose dependent occurrence of adverse events due to side-effects or residual block

Extubation criteria not met in timely fashion despite reversal

Reasonable Anesthetic with Rocuronium

75-yr-old 120 kg woman for partial colectomy for colon cancer. Adequately controlled diabetes mellitus type 2. Serum creatinine 2.4 mg/dL

Induction: modified rapid sequence, rocuronium 100 mg

Maintenance: isoflurane, **rocuronium** [20 mg x 2 (maintained 0-1 T in TOF)]

Emergence: spontaneous ventilation, esophageal temp 35.5° C

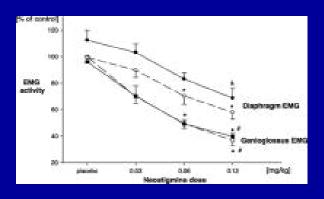
Unable to extubate 15 min after neostigmine 5 mg

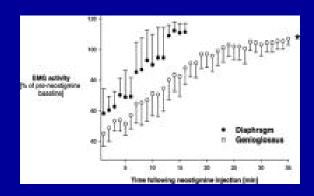
Extubation Criteria Not Met

- Seeking TOF in non-functioning muscle
- Inappropriate dose of neostigmine
 - Too little
 - Too much
- When compared with suggamadex, neostigmine is not that good!
- Inappropriate NMBA
- Appropriate NMBA

"Over-reversal" with Neostigmine Impairs Genioglossus and Diaphragm

Eikermann: Anesthesiology 2007; 107:621-9 (rats)





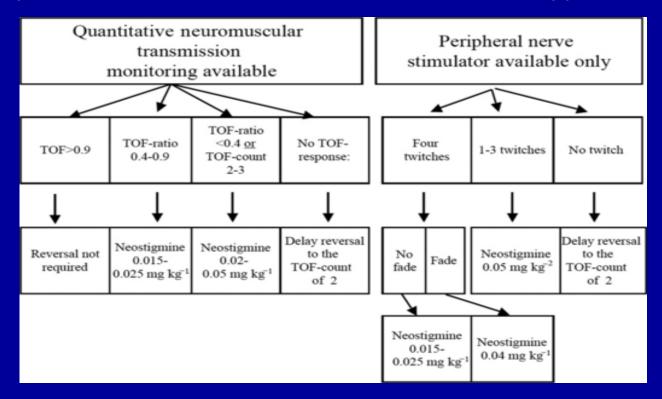
Left: open symbols—after TOF recovery from vecuronium; closed – no previous vecuronium

Dose-dependent impairment from neostigmine

Genioglossus: greater decline, longer time to recovery than diaphragm

Algorithm for Reversal Intermediate-acting NMBA

Kopman AF, Eikermann M: Anaesthesia 2009; 64(Suppl 1):22-30



Less neostigmine if less blockade

Neostigmine Dose – Lien *Anesthesiology* 2010; 112:16-8 [Editorial]

- "Clinicians can be reassured that administration of 50
 µg/kg is not necessary if patient has four equal
 responses to TOF stimulation"
- "A dose of 30 μg/kg is sufficient"

Neostigmine Dose – Brull & Murphy

Anesth Analg 2010; 111:129-40

- TOF count ≤ 1: delay reversal
- TOF count 2-3: 50 μg/kg
- TOF count 4 with fade: 50 μg/kg
- TOF count 4, no perceived fade: 20 μg/kg

Dose of Neostigmine to Reverse Shallow Neuromuscular Block

TOF Reversal	Placebo — (n = 9)	Neostigmine Groups by Dose (N = 51)				
		5 μg/kg (n = 8)	8 μg/kg (n = 8)	15 μg/kg (n = 9)	25 μg/kg (n = 9)	40 μg/kg (n = 8)
≥ 0.7	-	_	_	-	_	-
Median						
[min]	5.9	2.7	1.9	1.5	1.3	1.1
Range (min-max)						
[min]	(3.5-9.8)	(1.8-3.5)	(1.5-2.3)	(1.2-2.5)	(1.0-2.3)	(0.7-1.5)
≥ 0.8	200	922	(2)	_	320	_
Median						
[min]	10	4.9	2.8	2.3	1.8	1.4
Range (min-max)						
[min]	(7.2-16)	(3.3-6.0)	(2.5-3.3)	(1.7-3.7)	(1.2-3.2)	(1.2-2)
≥ 0.9		_	_	_		_
Median						
[min]	19	9.3	5.3	4.0	3.2	2.0
Range (min-max)						
[min]	(12-33)	(5.8-15)	(3.5 - 8.7)	(2.8-6.0)	(1.7-6.2)	(1.7-4.2)

A per-protocol population (i.e., all treated patients without any major protocol violations) was used. Placebo values also presented in table

Neostigmine: 34 µg/kg reverses rocuronium block at TOF 0.5 to \geq 0.9 within 5 min in 95% of patients [18-65 yrs]

With lower doses of neostigmine, longer time to TOF 0.9

Anesthesia: propofol, remifentanil, rocuronium (no volatiles)

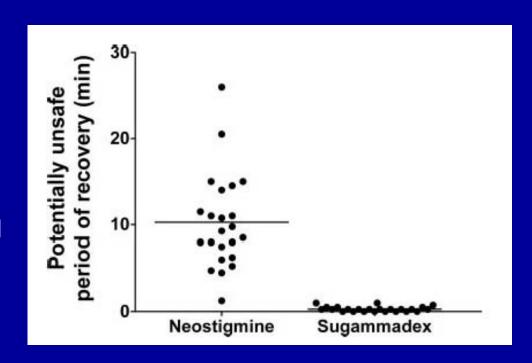
Schaller, et al: Anesthesiology 2010; 113:1054-60

Duration of Residual NMB (TOF ≤ 0.9) after Administration of Neostigmine or Sugammadex at 2 Visible Twitches During TOF Monitoring

Illman, et al. Anesth Analg 2011; 112:63-8

Neostigmine 50 µg/kg Sugammadex 2 mg/kg TOF ≤ 0.9:

- Pharyngeal, respiratory muscle weakness
- ↓ ability to maintain normal hypoxic ventilatory response
- ↑ Critical respiratory events
- ↑ Postoperative pulmonary complications



Key Points re Neostigmine

Neostigmine takes more time than previously appreciated and typically allowed to reverse NMB

Suggamadex reversal of rocuronium is superior to neostigmine

- 1) supports the conclusion that neostigmine incompletely reverses NMB more commonly than previously appreciated
- 2) specific (forms tight 1:1 complexes) for rocuronium > vecuronium>> pancuronium; ineffective for cisatracurium

Despite above, important to reduce neostigmine dose when possible to avoid the previously under-appreciated neostigmine-induced impairment of neuromuscular function, especially if residual inhaled agent present.

Neostigmine Dosing for reversal of rocuronium

My <u>New</u> Practice with Peripheral Nerve Stimulator Using Subjective (Visual, Tactile) Assessment

≤ 2 twitch in TOF — wait until non-subtle 3rd twitch

Kim, et al. *Anesth Analg* 2004; 99:1080-5

Non-subtle 3 twitches in TOF – 50 μg/kg

Non-subtle 4th twitch – 40 μg/kg

No fade in TOF (? detectability) – 30 μg/kg

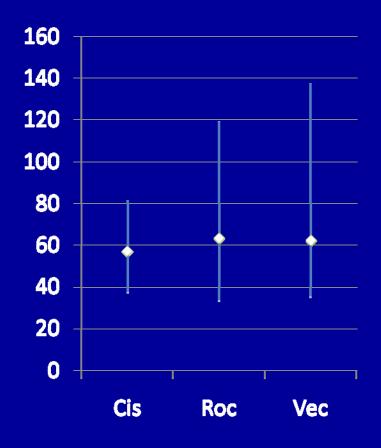
No apparent fade in TOF for > 15 min $- 20 \mu g/kg$

Extubation Criteria Not Met

- Seeking TOF in non-functioning muscle
- Inappropriate dose of reversal agent
- Inappropriate NMBA
 - Longer-acting vs shorter-acting: pancuronium
 - Higher vs lower variability in duration
 - Rocuronium or vecuronium vs cis-atracurium
- Appropriate NMBA

NMBA Variability in Duration in Elderly

Arain: Acta Anaesthesiol Scand 2005; 49:312



Median ages: 70-75 yrs

Creatinine: 1.2-1.3

Dose: 2 x ED95

Time (min): inject \rightarrow 25% T1

Sevoflurane 1 MAC

Median duration: no Δ

Variability: Vec ≥ Roc >> Cis

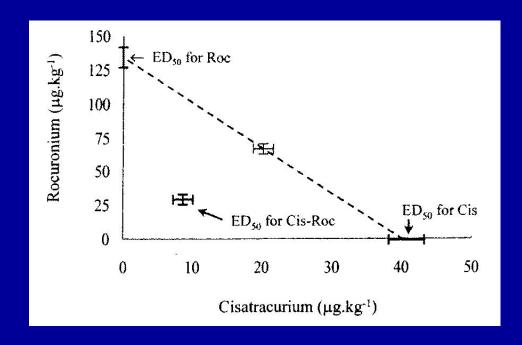
NMBA "Trap"

- Rocuronium preferred for intubation
- Cisatracurium may be better for maintenance
- But rocuronium + cisatracurium = synergistic
- Switching from rocuronium to cisatracurium may produce a long, profound block
 - Kim, et al. Anaesthesia 1998; 53:872-8
 - Liu, et al. *Anesth Analg* 2008; 107:525-33

Synergism: Rocuronium + Cisatracurium

Do not administer cisatracurium to a patient who has received rocuronium during same anesthetic.

Kim, et al. *Anaesthesia* 1998; 53:872-8



Extubation Criteria Not Met

- Seeking TOF in non-functioning muscle
- Inappropriate dose of reversal agent
- Inappropriate NMBA
- Appropriate NMBA
 - Dose too high
 - Appropriate dose

Possible Contributors to Rocuronium "Overdose" in this Patient

Patient factors

- Age 75
- Gender female
- Obesity 25 ≤ BMI < 30
- Diabetes mellitus type 2
- Creatinine 2.4 mg/dL

Patient Factor - AGE

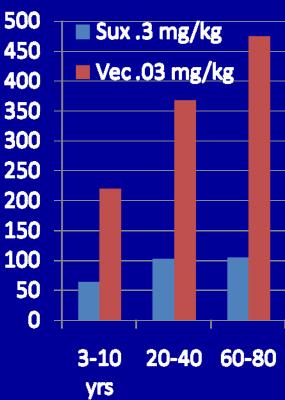
ED95 unaffected by age Advancing age increases

- Time to peak effect (onset time)
- Duration
- Interpatient variability

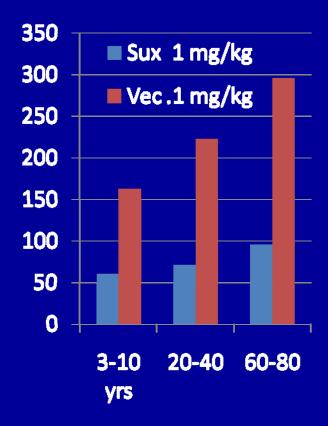
Age & Onset Time (sec)

Koscielniak-Nelson. Anesthesiology 1993; 79:229



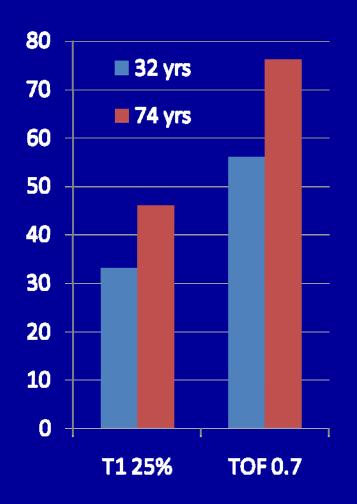


Dose: 2-3 x ED95



Age & Rocuronium Duration

Kocabas: Eur J Anaesthesiol 2008;1-7



Time (min) from injection

Rocuronium 0.6 mg/kg (2xED95)

Creatinine 1.0 mg/dL

N₂O-opioid anesthesia

Normothermia (36°-36.5° C)

Normocarbia (P_{ET}CO₂ 35-40 mmHg)

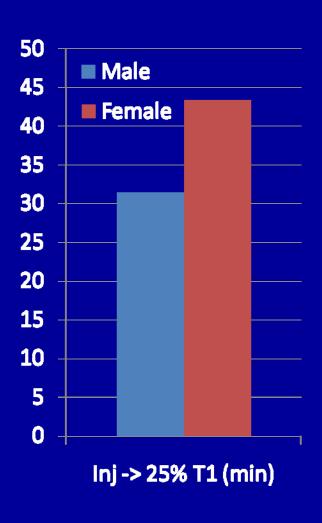
35-40% prolongation in elderly

Intermediate -acting NMB in elderly

= long-acting NMB in young

Patient Factor - GENDER

Adamus M, et al: Eur J Anaesthesiol 2008; 25:589-95



Gender

Healthy 50-yr-olds

TIVA

Rocuronium .6 mg/kg (2 x ED95)

35-40% increase in women (P <.001)

Cisatracurium - no Δ

Patient Factor – OBESITY

Leykin Y, et al: *Anesth Analg* 2004; 99:1086



Healthy 35-yr-old women

TIVA (propofol, remifentanil)

Rocuronium dose (3 groups): 0.6 mg/kg

Normal (BMI 22): dose based on lean body wt

Obese (BMI 43): dose based on lean body wt

Obese (BMI 44): dose based on real body wt

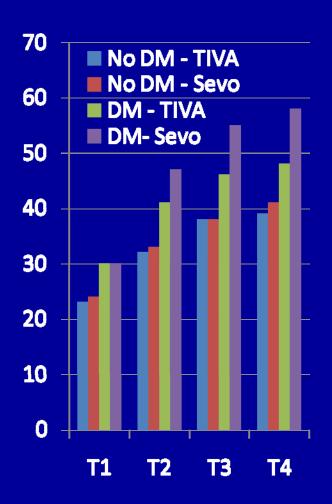
Significantly prolonged duration if base rocuronium dose on total body weight of obese patient

"Old rule": base dose on LBW + .33 (RBW-LBW)

Patient Factor - DIABETES MELLITUS

Effect on Duration of Vecuronum

Saitoh. Can J Anesth 2005; 52:467



60-yrs old

DM Type 2

Sevoflurane or TIVA

Vecuronium .1 mg/kg

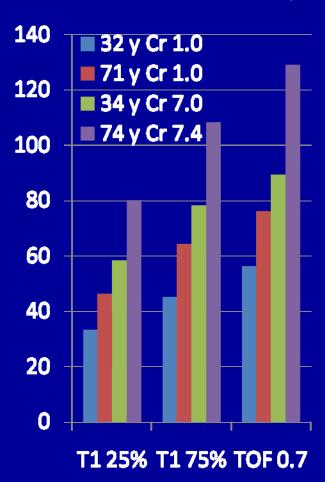
Duration (min):

DM > No DM

Sevo (30-40%) > TIVA (20-30%)

Patient Factor — RENAL INSUFFICIENCY Rocuronium Duration & Renal Failure

Kocabas S, et al: Eur J Anaesthesiol 2008; 1-7



Serum creatinine unchanged in healthy aging

 Creatinine clearance decreases despite normal serum creatinine in elderly

†serum creatinine in elderly is sign of significant renal impairment

Rocuronium duration increases with both 个 creatinine and 个 age

Extubation Criteria Not Met

- Seeking TOF in non-functioning muscle
- Inappropriate dose of reversal agent
- Inappropriate NMBA
- Appropriate NMBA
 - Dose too high
 - Appropriate dose Management factors

Possible Contributors to Rocuronium "Overdose" in this Patient

Management factors that potentiated block

- Used large intubating dose
 3.3 x ED95 based on TBW; 6.7 x ED95 based on LBW
- Maintained deep block
 Maintained 0-1 T in TOF rather than 1-2 T
- Used longer- vs shorter-acting NMBA
 Rocuronium vs cisatracurium

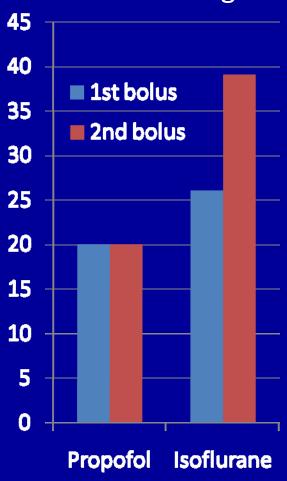
Possible Contributors to Rocuronium "Overdose" in this Patient

Management factors that potentiated block

- Used inhaled agent rather than TIVA
 - Did not discontinue early enough
- Permitted spontaneous ventilation
 - Created respiratory acidosis
- Allowed mild hypothermia
- Allowed insufficient time for reversal agent to act

Management Factor INHALED AGENT vs TIVA

Dragne: *Can J Anaesth* 2002; 49:353



Age: 57 yrs ASA I-II

Rocuronium

1st bolus 0.5 mg/kg

2nd bolus 0.3 mg/kg 1 hr after 1st

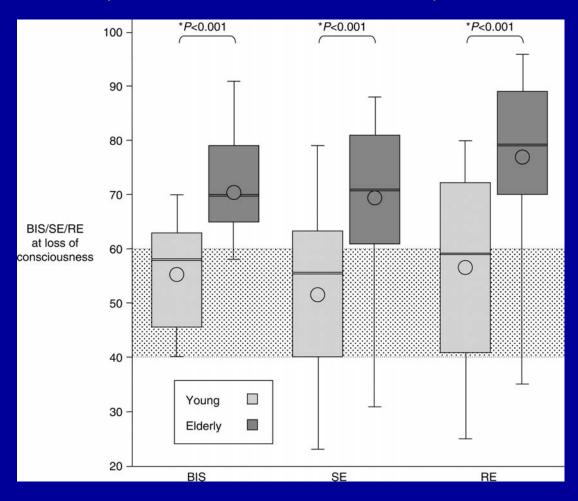
Time (min): inject \rightarrow 25% T1

Duration:

TIVA - no Δ

Isoflurane – significant ↑

Lysakowski, et al. Br J Anaesth 2009; 103:387-93



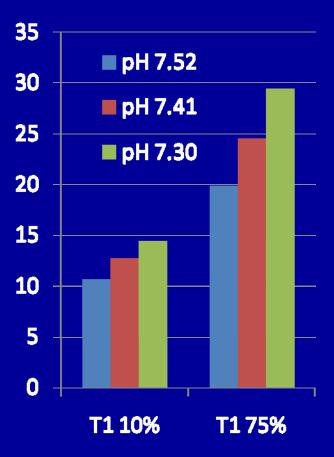
End-tidal anesthetic concentration associated with BIS 50 decreases with advancing age.

Matsuura et al: *Br J Anaesth* 2009; 102:331 *P<0.05, **P<.01 vs middle age

Age yrs	Age range	Isoflurane	Isoflurane (95% conf)	Sevoflurane	Sevoflurane (95% conf)
30	20-39	0.82%*	.7688	1.28%*	1.24-1.32
56	44-67	0.67%	.6173	0.97%	0.89-1.05
75	70-88	0.56%**	.5161	0.87%**	0.84-0.90

Management Factor RESPIRATORY ACIDOSIS

Yamauchi et al: J Clin Anesth 2002; 98-101

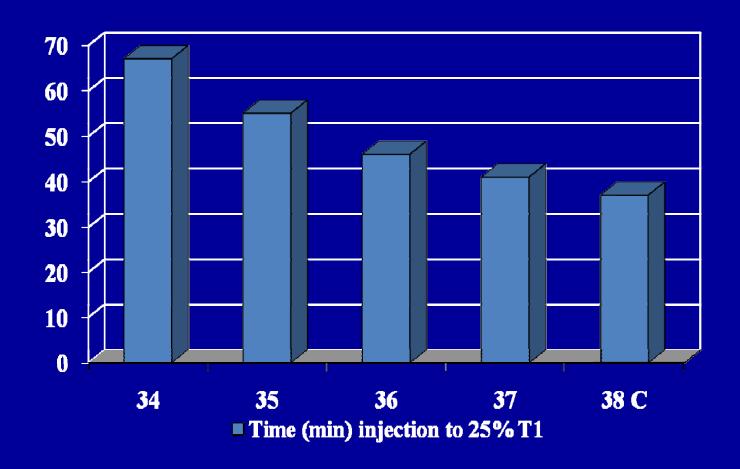


45-yr olds
vecuronium .08 mg/kg (1.6 x ED95)
creatinine 1.0 mg/dL
spinal-N₂O-fentanyl-midazolam
esophageal T 35.5° C
acidosis prolongs recovery

Concern: spontaneous ventilation before reversal of NMBA at end of procedure

Management Factor – HYPOTHERMIA

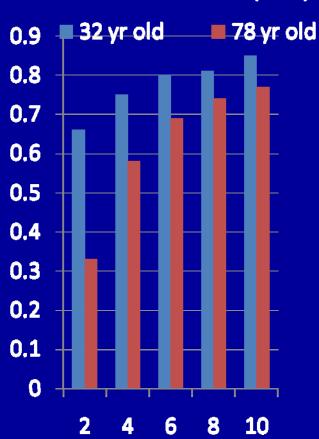
Effect of Temperature on Duration of Vecuronium Caldwell: *Anesthesiology* 2000; 92: 84



Management Factor SUFFICIENT TIME FOR NEOSTIGMINE TO ACT

McCarthy GJ, et al: *Br J Anaesth* 1992; 69:281-3

TOF RATIO vs TIME (min)



Vecuronium .08 mg/kg, Halothane

Time: inj \rightarrow 10% T1

32 yr olds – 24 min

78 yr olds – 33 min

Neostigmine 45 µg/kg at 10% T1

Elderly required longer time to achieve lower TOF ratio

TO AVOID NMBA OVERDOSE IN OLDER PATIENTS:

- Patient factors
 - Calculate dose based on lean body weight (LBW)
 - Understand that age increases
 - Onset time
 - Duration
 - Interpatient variability
 - Incidence of potentiating pathologic conditions
 - Diabetes mellitus
 - Renal insufficiency
 - Advanced age

TO AVOID NMBA OVERDOSE IN OLDER PATIENTS:

Management factors

- Use lower dose, longer dosing intervals whenever possible
 - ≥ 2 twitches in TOF
 - Be aware of impending end-of-surgery avoid that last dose
- Choice of non-depolarizing NMBA agent
 - Avoid pancuronium
 - Use rocuronium when need rapid onset
 - Keep dose ≤ 2 x ED95 based on LBW
 - Consider (succinylcholine +) cisatracurium when ↑creatinine, DM, longer surgery
 - Least interpatient variability, fewest patients with prolonged response
 - Do <u>not</u> start with rocuronium and switch to cisatracurium

TO AVOID NMBA OVERDOSE IN OLDER PATIENTS:

Management factors

- Allow for longer onset times –NMBA, neostigmine
- Minimize potentiating pharmacologic interactions
 - Less inhaled agent: none (TIVA) $\leftrightarrow \downarrow$ MAC, \uparrow BIS (55-65)
 - ↓/turn off inhaled agent sooner near end of case, treat ↑BP with labetalol
- Minimize potentiating physiologic situations
 - Respiratory acidosis, hypothermia
- Recognize that even if "do everything right", can still have:
 - TOF ≤ 0.9 after reversal, CRE's, POPC

Suggamadex Could Eliminate the Problem of NMBA Overdose

McDonagh, et al. Efficacy, safety, and pharmacokinetics of suggamadex for the reversal of rocuronium-induced neuromuscular blockade in elderly patients.

Anesthesiology 2011; 114:318-29

- Rocuronium 0.6 mg/kg induction, 0.15 mg/kg repeat
- Suggamadex 2.0 mg/kg when TOF ≥ 2 twitches
- TOF ratio ≥ 0.9 in 2.3 min in 65-74 yr-olds and 2.9 min (range 2.7-3.2) in those ≥ 75 yrs-old