

## Supplementary appendix

### Resistance towards non-depolarizing muscle relaxants: prolonged onset time -a systematic review

#### Supplementary Appendix S1: Literature Search

##### Search strategy for PubMed (Ovid SP)

- 1 exp Neuromuscular Nondepolarizing Agents/ or Vecuronium Bromide/ or Atracurium/ or Pancuronium/ or (nondepolarizing adj3 (agent\* or drug\*)).mp. or (rocuronium or vecuronium or pavulon or atracurium or cisatracurium or mivacurium or tubocurare).ti,ab. or (neuromuscular adj3 block\*).mp.  
(22931)
- 2 ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or (case adj3 (report\* or study)).mp. or prospective.ti,ab. or multicenter.ti,ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.  
(4760261)
- 3 (hyposensitive\* or resist\* or onset or ((patient\* or remain\*) adj3 unparalysed) or ((lack or absence or insufficien\*) adj4 (response or effect\* or block\*)) or (increase\* adj3 requir\*)).mp. or (muscle adj3 relaxation).ti,ab. or Drug Resistance/  
(1195637)
- 4 1 and 2 and 3 (1442)

##### Search strategy EMBASE (Ovid SP)

- 1 exp neuromuscular blocking agent/ or vecuronium/ or pancuronium/ or atracurium besilate/ or alcuronium/ or (nondepolarizing adj3 (agent\* or drug\*)).mp. or (rocuronium or vecuronium or pavulon or atracurium or cisatracurium or mivacurium or tubocurare).ti,ab. or (neuromuscular adj3 block\*).mp.  
(49332)
- 2 (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random\* or cross?over\* or multicenter\* or factorial\* or placebo\* or volunteer\* or (case adj3 (report\* or study)).mp.).mp. or ((singl\* or doubl\* or trebl\* or tripl\*) adj3 (blind\* or mask\*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.  
(8130791)
- 3 (hyposensitive\* or resist\* or onset or ((patient\* or remain\*) adj3 unparalysed) or ((lack or absence or insufficien\*) adj4 (response or effect\* or block\*)) or (increas\* adj3 requir\*)).mp. or (muscle adj3 relaxation).ti,ab. or drug resistance/  
(1686320)
- 4 1 and 2 and 3 (3013)

#### Supplementary Appendix S2: Data extraction sheet.

Title:	
Publication year:	
Authors:	
Journal:	
Purpose of study:	
Sample Size/Patients:	
Age Groups:	
Type of Study:	
NMBA used and dosage:	
Premedication:	
Induction of Anesthesia	
Maintenance of Anesthesia	
Other relevant study population descriptions:	
Outcome(s)	
Mention of Possible Dropouts:	
Blinding of staff:	
Neuromuscular monitoring:	
Methods and Setup:	
Number of patients analyzed:	
Results:	
Authors Comments:	
Conclusion:	
Own Comments:	

### Supplementary Appendix S3: Thermal injury

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T1<sub>max</sub>, Onset time T1<sub>10</sub>, Onset time T1<sub>5</sub> and Onset time T1<sub>0</sub> (Time between administration of NDMR to maximal, 90 %, 95 % or 100 % depression of baseline twitch height in the first time in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	Age group	NDMR (dose)	$\Delta$ Onset time T1 <sub>max</sub>	$\Delta$ Onset time T1 <sub>10</sub>	$\Delta$ Onset time T1 <sub>5</sub>	$\Delta$ Onset time T1 <sub>0</sub>	Quality assessment	Association
Han et al. (2004)	Cohort study	109 (9)	>18 years	Rocuronium (0.9 or 1.2 mg/kg)			<b>0,9 mg/kg:</b> 69 % (47 sec) (20 sec; 74sec)  <b>1,2 mg/kg:</b> 29 sec (51 %) (20 sec; 38 sec)		2++	Yes
Han et al. (2009)	Cohort study	154(3)	>18 years	Rocuronium (0.06+0.94 mg/kg or 1.0 mg/kg)		<b>0.06+0.94 mg/kg:</b> 33 % (15 sec) (4 sec; 26 sec)  <b>1.0 mg/kg:</b> 167 % (75 sec) (55 sec; 95 sec)		<b>0.06+0.94 mg/kg:</b> 80 % (60 sec) (38 sec; 82 sec)  <b>1.0 mg/kg:</b> 180 % (135 sec) (95 sec; 175 sec)	2++	Yes, in patients given 1.0 mg/kg
Han et al. (2011)	Cohort study	61 (0)	>18 years	Mivacurium (0.2 mg/kg)		25 % (20 sec) (-4 sec; 44 sec)		28 % (25 sec) (-5 sec; 55 sec)	2++	Yes
Uyar et al. (1999)	Cohort study	26 (0)	2-13 years	Vecuronium (0.1 mg/kg)			94 % (91 sec) (44 sec; 138 sec)		2+	Yes
Martyn et al. (2000)	Cohort study	36 (7)	2-12 years	Mivacurium (0.2 mg/kg)	<b>&lt;6 days, 10-30 % TBSA:</b> 0 sec (-59 sec; 59 sec )  <b>&lt; 6 days, &gt; 30 % TBSA:</b> -33 % (-60 sec) (-119 sec; -12 sec)  <b>1-12: weeks, 10-30 % TBSA:</b> 0 sec (-54 sec; 54 sec)  <b>1-12 weeks, &gt; 30 % TBSA:</b> -33 % (-60 sec) (-111 sec; -9 sec)			2+	No	

### Supplementary Appendix S3: Thermal injury

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T_{1_{max}}$ , Onset time  $T_{1_{10}}$ , Onset time  $T_{1_5}$  and Onset time  $T_{1_0}$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	Age group	NDMR (dose)	$\Delta$ Onset time $T_{1_{max}}$	$\Delta$ Onset time $T_{1_{10}}$	$\Delta$ Onset time $T_{1_5}$	$\Delta$ Onset time $T_{1_0}$	Quality assessment	Association	
Martyn et al. (2002)	Cohort study	27 (8)	13-18 years	Mivacrium (0.15 mg/kg)	<b>&lt;6 days, 10-30 % TBSA:</b> -28 % (-78 sec) (-207 sec; 51 sec)					2+	No
					<b>&lt; 6 days, &gt;30 % TBSA:</b> -26 % (-72 sec) (-184 sec; 40 sec)						
					<b>1-12: weeks, 10-30 % TBSA:</b> -30 % (-84 sec) (-181 sec; 13 sec)						
					<b>1-12 weeks, &gt;30 % TBSA:</b> -33 % (-90 sec) (-182 sec; 2 sec)						
TBSA: Total burned surface area											

### Supplementary Appendix S4: Anesthetic Technique and temperature regulation

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T1<sub>max</sub>, Onset time T1<sub>10</sub> Onset time T1<sub>5</sub> and Onset time T1<sub>0</sub> (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a “Train-Of-Four”). A positive association was defined as a reported significant prolonged *Onset time* (p < 0.05) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

<i>Reference</i>	<i>Type of study</i>	<i>n (dropouts)</i>	<i>NDMR (dose)</i>	<i><math>\Delta</math>Onset time T1<sub>5</sub></i>	<i><math>\Delta</math>Onset time T1<sub>0</sub></i>	<i>Quality assessment</i>	<i>Association</i>
<b>Time sequence of drug administration of remifentanyl and rocuronium</b>							
<b>Na et al. (2012)</b>	RCT	136(0)	Rocuronium (0.6 mg/kg)	44 % (40 sec) (37 sec; 43 sec)		1+	Yes
<b>Pre-operative rehydration</b>							
<b>Ishigaki et al. (2016)</b>	RCT	46(6)		32 % (23 sec) (5 sec; 40 sec)		1+	Yes
<b>Hypothermia</b>							
<b>Eriksson et al. (1991)</b>	Cohort study	7 (0)	Vecuronium (0.05 mg/kg)		29 % (40 sec) <sup>1</sup>	2+	Yes
<sup>1</sup> Cases served as their own controls							

### Supplementary Appendix S5: Mediastinal infection

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T1_{max}$ , Onset time  $T1_{10}$  Onset time  $T1_5$  and Onset time  $T1_0$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

<i>Reference</i>	<i>Type of study</i>	<i>n (dropouts)</i>	<i>NDMR (dose)</i>	<i><math>\Delta</math>Onset time <math>T1_{max}</math></i>	<i>Quality assessment</i>	<i>Association</i>
<b>Mediastinal infection</b>						
<b>Knuttgen et al. (1999)</b>	Cohort study	30 (0)	Atracurium (0.6 mg/kg)	61 % (120 sec) (20 sec; 219 sec)	2+	Yes

## Supplementary Appendix S6: Neurological and neuromuscular disorders

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T1<sub>max</sub>, Onset time T1<sub>10</sub> Onset time T1<sub>5</sub> and Onset time T1<sub>0</sub> (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* (p < 0.05) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	Age group	NDMR (dose)	$\Delta$ Onset time T1 <sub>max</sub>	$\Delta$ Onset time T1 <sub>5</sub>	$\Delta$ Onset time T1 <sub>0</sub>	Quality assessment	Association
<b>Cerebral Palsy</b>									
<b>Hepaguslar et al. (1999)</b>	Cohort study	21 (0)	4-8 years	Vecuronium (0.1 mg/kg)	<b>CP without ACT:</b> 37 % (35 sec) (3 sec; 67 sec)  <b>CP with ACT:</b> 38 % (35 sec) (-4 sec; 75 sec)			2+	No
<b>Duchennes Muscular Dystrophy (DMD)</b>									
<b>Schmidt et al. (2005)</b>	Cohort study	24 (0)	5-14 years	Mivacurium (0.2 mg/kg)		-6 % (-9 sec) (-34 sec; 18 sec)		2+	No
<b>Ihmsen et al. (2009)</b>	Cohort study	38 (0)	6-9 years or 12-16 years	Mivacurium (0.2 mg/kg)	<b>Children with DMD:</b> 10 % (12 sec) (-19 sec; 43 sec)  <b>Adolescents with DMD:</b> 60 % (90 sec) (46 sec; 134 sec)			2+	Yes, in adolescents with DMD
<b>Wick et al. (2005)</b>	Cohort study	24 (0)	10-16 years	Rocuronium (0.6 mg/kg)		126 % (113 sec) (65 sec; 161 sec)		2++	Yes
<b>Muenster et al. (2006)</b>	Cohort study	24 (0)	10-18 years	Rocuronium (0.3 mg/kg)		62 % (120 sec) (66 sec; 174 sec)		2++	Yes
<b>Ihmsen et al. (2009)</b>	Cohort study	25 (0)	10-18 years	Rocuronium (0.3 mg/kg)			76 % (132 sec) (55 sec; 208 sec)	2+	Yes
<b>Oculopharyngeal Muscular Dystrophy</b>									
<b>Caron et al. (2005)</b>	Cohort study	40 (0)	>18 years	Cisatracurium (0.1 mg/kg)		29 % (60 sec) (15 sec; 104 sec)		2+	Yes
CP: cerebral palsy									

## Supplementary Appendix S7: Congenital heart defects

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T1_{max}$ , Onset time  $T1_{10}$ , Onset time  $T1_5$  and Onset time  $T1_0$  (Time between administration of NDMR to maximal, 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

<i>Reference</i>	<i>Type of study</i>	<i>n</i> (dropouts)	<i>NDMR</i> (dose)	$\Delta$ <i>Onset time</i> $T1_0$	<i>Quality assessment</i>	<i>Association</i>
<b>Wu et al. (2016)</b>	Cohort study	42 (0)	Cisatracurium (0.15 mg)	<b>VSD:</b> 125 % (163 sec) (144 sec; 181 sec)  <b>ASD:</b> 129 % (167 sec) (141 sec; 194 sec)	2+	Yes

### Supplementary Appendix S8: Hepatic disease

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T1_{max}$ , Onset time  $T1_{10}$  Onset time  $T1_5$  and Onset time  $T1_0$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	NDMR (dose)	Type of hepatic disease	$\Delta$ Onset time $T1_{max}$	$\Delta$ Onset time $T1_{10}$	$\Delta$ Onset time $T1_5$	$\Delta$ Onset time $T1_0$	Quality assessment	Association
Khalil et al. (1994)	Cohort study	18(0)	Rocuronium (0.6 mg/kg)	Cirrhosis	50 sec (46 %) (2 sec; 98 sec)				2+	Yes
Magorian et al. (1995)	Cohort study	20 (0)	Rocuronium (0.6 mg/kg)	Cirrhosis and hepatoma				-10 sec (-14 %) (-34 sec;14 sec)	2+	No
Saitoh et al. (2002)	Cohort study	45 (0)	Vecuronium (0.1 mg/kg)	Cirrhosis				<b>Cirrhosis + ulinastatin treatment:</b> 26 % (56 sec) (15 sec; 97 sec)  <b>Cirrhosis + placebo (saline):</b> -2 % (-4 sec) (-34 sec; 26 sec)	2+	Yes, in patients with cirrhosis treated with ulinastatin



## Supplementary Appendix S9: Renal disease

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T1_{max}$ , Onset time  $T1_{10}$  Onset time  $T1_5$  and Onset time  $T1_0$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	Age groups	NDMR	$\Delta$ Onset time $T1_{max}$	$\Delta$ Onset time $T1_5$	Quality assessment	Association
<b>Driessen et al. (2002)</b>	Cohort study	30 (1)	9 months- 14 years	Rocuronium (0.3 mg/kg)	59 % (52 sec) (7 sec; 97 sec)		2+	Yes
<b>Robertson et al. (2005)</b>	Cohort study	34 (0)	> 18 years	Rocuronium (0.6 mg/kg)	18 % (21 sec) (-51 sec; 93 sec)		2+	No
<b>Cooper et al (1993)</b>	Cohort study	18 (0)	> 18 years	Rocuronium (0.6 mg/kg)	-6 % (-4 sec) (-25 sec; 17 sec)		2+	No
<b>Robertson et al. (2005)</b>	Cohort study	36 (0)	> 18 years	Rocuronium (0.3 mg/kg)	-6% (-15 sec) (-75 sec; 46 sec)		2+	No

**Supplementary Appendix S10: Urinary Trypsin Inhibitors (Ulinastatin)**

General characteristics of the included studies. Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T1<sub>max</sub>, Onset time T1<sub>10</sub> Onset time T1<sub>5</sub> and Onset time T1<sub>0</sub> (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch hight in the first twice in a “*Train-Of-Four*”). A positive association was defined as a reported significant prolonged *Onset time* (p < 0.05) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

<i>Reference</i>	<i>Type of study</i>	<i>n (dropouts)</i>	<i>NDMR (dose)</i>	<i><math>\Delta</math>Onset time T1<sub>0</sub></i>	<i>Quality assessment</i>	<i>Association</i>
Saitoh et al. (2002) <sup>1</sup>	Cohort study	45 (0)	Vecuronium (0.1 mg/kg)	26 % (56 sec) (15 sec; 97 sec)	2+	Yes

<sup>1</sup>Cases were suffering from hepatic cirrhosis

## Supplementary Appendix S11: Studies evaluated as *low quality studies* (1- or 2-)

General characteristics of the studies allocated as low quality (1- or 2-). Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T<sub>1max</sub>, Onset time T<sub>10</sub>, Onset time T<sub>15</sub> and Onset time T<sub>10</sub> (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* (p < 0.05) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	NDMR (dose)	$\Delta$ Onset time T <sub>1max</sub>	$\Delta$ Onset time T <sub>10</sub>	$\Delta$ Onset time T <sub>15</sub>	$\Delta$ Onset time T <sub>10</sub>	Quality assessment	Association
<b>Thermal injury</b>									
Dwersteg et al. (1986)	Cohort study	45 (0)	Atracurium (0.5 mg/kg)	<b>&lt;6 days, all TBSA:</b> -15 % (-34 sec) (-86 sec; 17 sec)  <b>6-60 days, &lt;33 % TBSA:</b> 21 % (47 sec) (-68 sec; 162 sec)  <b>6-60 days, 33-66% TBSA:</b> 101 % (227 sec) (97 sec; 358 sec)  <b>6-60 days, &gt;66 % TBSA:</b> 132 % (297 sec) (207 sec; 387 sec)  <b>&gt;60 days, all TBSA:</b> 44 % (99 sec) (-18 sec; 216 sec)				2-	Yes, in patients examined at 6-60 post-injury and with 33-66 % TBSA)
<b>Undernourished patients</b>									
Sinha et al. (1998)	Cohort study	70 (0)	Vecuronium (0.1 mg/kg)	<b>Mild undernutrition:</b> 4 % (12 sec) (-35 sec; 59 sec)	<b>Moderate undernutrition:</b> 20 % (54 sec) (4 sec; 103 sec)	<b>Severe undernutrition:</b> 42 % (114 sec) (74 sec; 153 sec)		2-	Yes, in patients with moderate and severe under-nutrition
Jain et al. (1999)	Cohort study	60 (0)	Vecuronium (0.1 mg/kg)	<b>Mild undernutrition:</b> 39 % (54 sec) (22 sec; 86 sec)	<b>Moderate undernutrition:</b> 61 % (84 sec) (51 sec; 117 sec)	<b>Severe undernutrition:</b> 265 % (366 sec) (319 sec; 412 sec)		2-	Yes
<b>Mediastinal infection</b>									
Knuttgen et al. (1998)	Cohort study	52 (0)	Atracurium (0.6 mg/kg)	117 % (204 sec) (120 sec; 287 sec)				2-	Yes
<b>Accuired immune deficiency syndrome (AIDS)</b>									
Fassoulaki et al. (1994)	Cohort study	8 (0)	Vecuronium (0.08 mg/kg)	114 sec (127%) (76 sec; 151 sec)				2-	Yes
<b>Hepatic disease</b>									

### Supplementary Appendix S11: Studies evaluated as *low quality studies* (1- or 2-)

General characteristics of the studies allocated as low quality (1- or 2-). Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T_{1\max}$ , Onset time  $T_{10}$ , Onset time  $T_{15}$  and Onset time  $T_{10}$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	NDMR (dose)	$\Delta$ Onset time $T_{1\max}$	$\Delta$ Onset time $T_{10}$	$\Delta$ Onset time $T_{15}$	$\Delta$ Onset time $T_{10}$	Quality assessment	Association
Bell et al. (1985)	Cohort study	76 (0)	Atracurium (0.5 mg/kg) or Vecuronium (0.1 mg/kg)	<b>Atracurium:</b> 76 sec (70 %) (39 sec; 115 sec)  <b>Vecuronium:</b> 63 sec (44 %) (-17 sec; 169 sec)				2-	Yes, in patients given atracurium, negative in patients given vecuronium
Head-Rapson et al. (1994)	Cohort study	21 (0)	Mivacurium (0.15 mg/kg)	42 sec (6 %) (-43 sec; 127 sec)	54 sec (15 %) (-16 sec; 124 sec)	60 sec (15 %) (-27 sec; 147 sec)		2-	No
De Wolf et al. (1996)	Cohort study	25 (2)	Cisatracurium (0.1 mg/kg)	-54 sec (-27 %) (-100 sec; -8 sec)				2-	No
Devlin et al. (1993)	Cohort study	35 (0)	Mivacurium (0.15 mg/kg)	54 sec (17 %) (-101 sec; 209 sec)		-18 % (-30 sec) (-71 sec; 11 sec)		2-	No
Arden et al. (1988)	Cohort study	20 (0)	Vecuronium (0.1 mg/kg)				47 % (54 sec) (22 sec; 86 sec)	2-	Yes
van Miert et al. (1997)	Cohort study	38 (0)	Rocuronium (0.6 mg/kg)		-5 % (-3 sec) (-20 sec; 14 sec)			2-	No
Renal disease									

### Supplementary Appendix S11: Studies evaluated as *low quality studies* (1- or 2-)

General characteristics of the studies allocated as low quality (1- or 2-). Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time  $T_{1_{max}}$ , Onset time  $T_{1_{10}}$ , Onset time  $T_{1_5}$  and Onset time  $T_{1_0}$  (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* ( $p < 0.05$ ) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	NDMR (dose)	$\Delta$ Onset time $T_{1_{max}}$	$\Delta$ Onset time $T_{1_{10}}$	$\Delta$ Onset time $T_{1_5}$	$\Delta$ Onset time $T_{1_0}$	Quality assessment	Association
Hunter et al. (1984)	Cohort study	154 (0)	Vecuronium (0.1 mg/kg) or Atracurium (0.5 mg/kg) or Tubocurarine (0.6 mg/kg)	<b>Vecuronium:</b> 8 % (14 sec) (-83 sec; 111 sec)  <b>Atracurium:</b> 67 % (74 sec) (48 sec; 100 sec)  <b>Tubocurarine:</b> 32 % (71 sec) (-33 sec; 174 sec)				2-	Yes, for atracurium and tubocurarine, negative for vecuronium
<b>Sickle cell disease</b>									
Duvaldestin et al. (2008)	Cohort study	30 (0)	Atracurium (0.5 mg/kg)		96 % (158 sec) (93 sec; 223 sec)			2-	Yes
<b><math>\beta</math>-adrenoreceptor blocking drugs</b>									
Loan et al. (1997)	Cohort study	74 (0)	Rocuronium (0.6 mg/kg)	21 % (13 sec) (-6 sec; 32 sec)				2-	No
Szmuk et al. (2000)	RCT	60 (0)	Rocuronium (0.6 mg/kg)		27 % (25 sec) (19 sec; 31 sec)			1-	Yes
Ezri et al. (2003)	RCT	33 (0)	Rocuronium (0.6 mg/kg)		31 % (27 sec) (19 sec; 35 sec)			1-	Yes
<b>Phosphodiesterase Inhibitors III</b>									
Nakajima et al. (2003)	RCT	30 (0)	Vecuronium (0.1 mg/kg)				25 % (74 sec) (12 sec; 136 sec)	1-	Yes

### Supplementary Appendix S11: Studies evaluated as *low quality* studies (1- or 2-)

General characteristics of the studies allocated as low quality (1- or 2-). Results are expressed as the change( $\Delta$ ) in *Onset time* between cases and controls in percentage and seconds including a 95 % confidence interval in seconds of the difference in mean or median value between cases and controls. Onset time T1<sub>max</sub>, Onset time T1<sub>10</sub>, Onset time T1<sub>5</sub> and Onset time T1<sub>0</sub> (Time between administration of NDMR to maximal , 90 %, 95 % or 100 % depression of baseline twitch height in the first twice in a "Train-Of-Four"). A positive association was defined as a reported significant prolonged *Onset time* (p < 0.05) in cases compared to controls including a  $\Delta$ *Onset time* of at least 25 %.

Reference	Type of study	n (dropouts)	NDMR (dose)	$\Delta$ Onset time T1 <sub>max</sub>	$\Delta$ Onset time T1 <sub>10</sub>	$\Delta$ Onset time T1 <sub>5</sub>	$\Delta$ Onset time T1 <sub>0</sub>	Quality assessment	Association
Katayama et al. (2007)	RCT	30 (0)	Vecuronium (0.1 mg/kg)				9 % (20 sec) (-18 sec; 58 sec)	1-	No
Urinary trypsin inhibitor									
Kim et al. (2012)	RCT	44 (0)	Rocuronium (0.6 mg/kg)				77 % (117 sec) (84 sec; 150 sec)	1-	Yes