Effect of neuromuscular blockade and reversal by sugammadex versus neostigmine on breathing when hypoxic or hypercapnic in volunteers

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To assess (i) the effect of partial neuromuscular blockade (NMB; TOF ratio 0.7) induced by low-dose rocuronium on the ventilatory response to isocapnic hypoxia and (ii) the effect of the reversal by sugammadex, neostigmine or placebo in healthy...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON46872

Source ToetsingOnline

Brief title Breath

Condition

Other condition

Synonym perioperative muscle relaxation

Health condition

perioperatieve verslapping

Research involving

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Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Neuromuscular block, respiration, reversal

Outcome measures

Primary outcome

Magnitude of the hypoxic and hypercapnic ventilatory responses.

Secondary outcome

NA

Study description

Background summary

The carotid bodies, located at the bifurcation of the common carotid artery, play a crucial and life-saving role in the control of breathing in humans. The carotid bodies contain type 1 cells that are primarily sensitive to low oxygen concentrations in arterial blood. In response to low oxygen the carotid bodies send information to the brainstem respiratory centers and a brisk hyperventilatory response will be initiated ensuring an increase in uptake of oxygen via the lungs. Following surgery, a rapid return of the carotid body function is vital and persistent loss of carotid body function may result in respiratory complications that occur independent of the effects of anesthetics (incl. muscle relaxants) on respiratory muscles. Respiratory complications that are related to the loss of carotid body function include the inability to respond properly to hypoxia as well the inability to overcome upper airway obstruction. The latter is especially important in patients with sleep disordered-breathing and obese patients. These patients rely on the optimal function of their carotid bodies in response to hypoxia or upper airway closure.

Important neurotransmitters involved in the carotid body response to hypoxia include acetylcholine, which acts through local nicotinergic acetylcholine receptors. Apart from the observation that muscle relaxants (which are blockers

of the acetylcholine receptors) affect the proper functioning of the carotid bodies (see Eriksson et al. Anesthesiology 1993; 78: 693-9), we have no knowledge on the dynamic effects of muscle relaxants on carotid body function over time or on the relationship between carotid body function and Train-of-Four (TOF) ratio over time. Additionally, there is no data on the link between the use of NMB antagonists and return of carotid body function. Linking TOF ratio to carotid body function is of clinical importance as a possible relationship will allow clinicians to predict carotid body function from the TOF ratio. The latter is highly relevant as we show in the Neuropa trial that a large proportion of patients is extubated at TOF ratio*s < 0.7. Apart from the carotid bodies, chemoreceptors in the brainstem exist that are sensitive to hypercapnia. This response system is not under control of cholinergic neurotransmission. Since we may assume that the hypercpanic ventilatory response is not influenced by muscle relaxants we can use this response to calibrate the hypoxic ventilatory response as both responses are equally affected by the effect of muscle relaxants on muscle function (Eriksson et al. Anesthesiology 1993; 78: 693-9).

As stated there are data on the effect of muscle relaxants on carotid body function at one fixed TOF ratio (TOF ratio fixed at 0.7; Eriksson et al. 1993). No data are available on:

1. Dynamic effect of carotid body function as measured by the hypoxic ventilatory response at TOF ratio*s changing from 0.7 to 1.0;

2. Dynamic effect of reversal of NMB by sugammadex versus neostigmine. Sugammadex and neostigmine are both reversal agents of neuromuscular blockade. At LUMC we use both agents in clinical practice but remain without knowledge on their effects on carotid body function. Our current proposal is designed to study items 1 and 2 in healthy awake volunteers.

Study objective

To assess (i) the effect of partial neuromuscular blockade (NMB; TOF ratio 0.7) induced by low-dose rocuronium on the ventilatory response to isocapnic hypoxia and (ii) the effect of the reversal by sugammadex, neostigmine or placebo in healthy volunteers.

To assess the effect of partial NMB (TOF ratio 0.7) induced by low-dose rocuronium on the ventilatory response to hypercapnia and effect of the reversal by sugammadex, neostigmine or placebo in healthy volunteers.

Study design

Double blind, placebo-controlled and randomized

Intervention

- 1) low dose rocuronium administration;
- 2) administration of either sugammadex, neostigmine or placebo
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3) exposure to mild hypercapnia and mild hypoxia.

Study burden and risks

Due to the mild level of relaxation some subjects may experience some muscle weakness and dysarthria. This is frequently seen in postoperative patients and is well accepted, especially when subjects are well coached during the period of mild muscle relaxation. In case the subject indicates that his discomfort is unacceptable the level of relaxation will be reduced, as discussed in paragraph 6 of the protocol. In case the subjects demands termination of the study the reversal agent Sugammadex will be administered.

Contacts

Public

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age

Adults (18-64 years) Elderly (65 years and older)

Inclusion criteria

Healthy male volunteers aged 18 and older with a body mass index < 30 kg/m2.

Exclusion criteria

Known or suspected neuromuscular disorders impairing neuromuscular function; allergies to muscle relaxants, anesthetics or narcotics; a (family) history of malignant hyperthermia or any other muscle disease; any medical, neurological or psychiatric illness (including a history of anxiety).

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL	
Recruitment status:	Recruitment stopped
Start date (anticipated):	01-05-2017
Enrollment:	36
Туре:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Bridion
Generic name:	sugammadex
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Esmeron
Generic name:	rocuronium
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	neostigmine
Generic name:	neostigmine
Registration:	Yes - NL intended use

Ethics review

Approved WMO	
Date:	13-07-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO	
Date:	14-07-2016
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl
Approved WMO	
Date:	27-08-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
	metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-005222-19-NL
ССМО	NL55794.058.15

Study results

Date completed:	11-12-2018
Actual enrolment:	36

Summary results

Trial is onging in other countries