PROTOCOL

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

The breath study

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CONTENTS

1. Introduction

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 is 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:

[*] **TOF is a measure of muscle relaxation and is the response to 4 stimuli to the ulnar nerve. A moderately relaxed patient has no TOF responses (TOF = 0); Absence of muscle relaxation gives a TOF of 4. A very mild muscle block is observed by "fading" in which the strength of the 4 stimuli decreases. We can then calculate a TOF ratio. In the current study we will apply TOF ratios of 0.6 or greater, which indicate mild muscle relaxation.**

1. Dynamic effect of carotid body function as measured by the hypoxic ventilatory response at TOF ratio's slowly changing from 0.6 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.

2. Study objectives

To assess (i) the effect of partial neuromuscular blockade (NMB; TOF ratio 0.8 and 0.6) induced by low-dose rocuronium on the ventilatory response to isocapnic hypoxia and (ii) the effect over time (from TOF 0.6 to TOF 1.0) of the reversal by sugammadex, neostigmine or placebo in healthy volunteers.

To assess the effect of partial NMB (TOF ratio 0.6) induced by low-dose rocuronium on the ventilatory response to hypercapnia and effect over time (from TOF 0.6 to TOF 1.0) of the reversal by sugammadex, neostigmine or placebo in healthy volunteers.

3. Hypotheses

A. Rocuronium will induce impairment of carotid body function through blockade of cholinergic neurotransmission in carotid bodies resulting in a reduced or absent ventilatory response to isocapnic hypoxia.

B. Sugammadex will completely restore carotid body function following rocuronium administration with full reversal of the ventilatory response to isocpanic hypoxia within 2 min.

C. Neostigmine will cause a protracted reversal of the carotid body function following rocuronium administration with full reversal within 40-60 min.

4. Volunteers

We will study 30 healthy male volunteers. They will be randomized to receive low-dose rocuronium followed by one of three reversal treatments: placebo (normal saline), neostigmine (1 mg) or sugammadex (2 mg/kg). All volunteers will receive a physical examination prior to enrollment.

4.1 Inclusion criteria

Healthy male volunteers aged 18 and older with a body mass index < 30 kg/m^2.

4.2 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).

4.3 Drop out and replacements

Subjects that drop out will be replaced by a new subject. A subject may terminate the study at any moment, and will then receive sugammadex 2 mg/kg to ensure full reversal of the neuromuscular blockade. Subjects will then be paid (5 euros/h participation).

4.4 Reimburesement

Subjects will be paid euro 250 for the completion of an experimental session.

4.5 Pre-study requirements

All subjects will be asked to refrain from food 6 hours prior to the study and from drinks 2 hours prior to the study.

5. Study design

This is a randomized, double blind, 3-arm, placebo controlled parallel study on the influence of reversal of a partial NMB on carotid body function following rocuronium administration. Healthy volunteers will be randomized to receive either placebo (Group1, n = 12), neostigmine (1 mg. n =12) or sugammadex (2 mg/kg, n = 12) following a continuous rocuronium infusion for 120 min aimed at a TOF ratio of 0.8 for 1 h followed by 0.6 for another hour. Prior to the rocuronium infusion and during the infusion, ventilatory responses to isocapnic 2-min hypoxic pulses will be obtained as well as the (hyperoxic) ventilatory response to hypercapnia. After the 120 min infusion and the administration of reversal agents, the ventilatory response to hypoxic pulses will be obtained at 5 min interval for at least 60 min. In case the response has not returned to pretreatment control values, additional responses will be obtained. Hereafter, a final ventilatory response to carbon dioxide will be obtained (at hyperoxic conditions).

All procedures will be executed in compliance with the current revision of the Declaration of Helsinki and Good Clinical Practice guidelines. The trial starts after the medical ethical committee has approved the study protocol and will have a maximum duration of one year.

5.1 Rocuronium administration:

We will titrate rocuronium to effect followed by a target controlled infusion aimed at a TOF ratio of 0.8 and 0.6 (see Fig. 1). After 120 min the continuous infusion will be terminated. The plasma concentration and expected TOF ratio is simulated in Figure. 1.

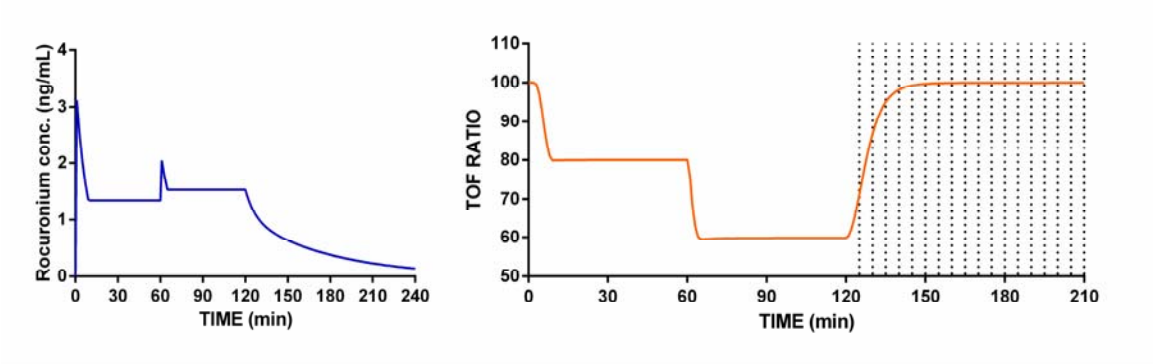


Figure 1. Simulated plasma concentration (LEFT) and expected TOF ratio (RIGHT). A continuous infusion of rocuronium for 120 min (1st hours aimed at TOF ratio 0.8, 2nd hour TOF ratio 06). Additionally during the 1 hour period after reversal the timing of hypoxic challenges are given (vertical dotted lines).

5.2 Reversal

At t = 120 min, all subjects will receive a reversal agent which is placebo (NaCl 0.9%) for Group 1, neostigmine 1 mg/atropine 0.5 mg for Group 2 and sugammadex 2 mg/kg for Group 3.

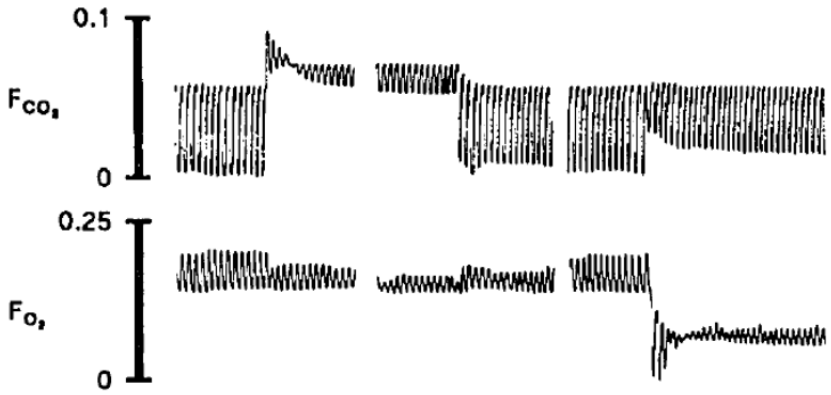


Figure 2. Examples of hypercapnic (left and middle) and hypoxic challenges in a healthy volunteer. From Dahan et al. Anesthesiology 1994.

5.3 Ventilatory tests

We will apply hypoxic and hypercapnic challenges and measure ventilation on a breath-to-breath basis using the Dynamic End-tidal Forcing (DEF) technique. This technique allows the manipulation of inspired gas concentrations to steer the end-tidal concentrations of O_2 and CO_2 independent of the ventilatory response or the concentrations of O_2 and CO_2 in mixed venous blood. The technique allows a reliable assessment of carotid body function (in this case hypoxia) without the confounding effects of variations in end-tidal CO_2. Additioanlly we will obtained the ventilatory response to hypercapnia at hyperoxic conditions. This allows assessment of the response activity of the central chemoreceptors in the brainstem.

HYPOXIA: Hypoxic responses will be obtained (1) prior to administration of rocuronium; (2) During administration of rocuronium at a TOF of 0.6; (3) at 5 min intervals following the end of the administration of rocuronium and the administration of the reversal agent.

Hypoxia will be induced by lowering the end-tidal PO_2 in a step-wise fashion from 14.5 kPa (110 mmHg) to 7 kPa (53 mmHg) for 2 min. Thereafter the end-tidal concentration will be returned to normoxic values. The target arterial oxygen saturation of this challenge is 80 ± 2%. This method allows assessment of the hypoxic ventilatory sensitivity (HVR) as defined by: HVR = [Delta ventilation from normoxia to

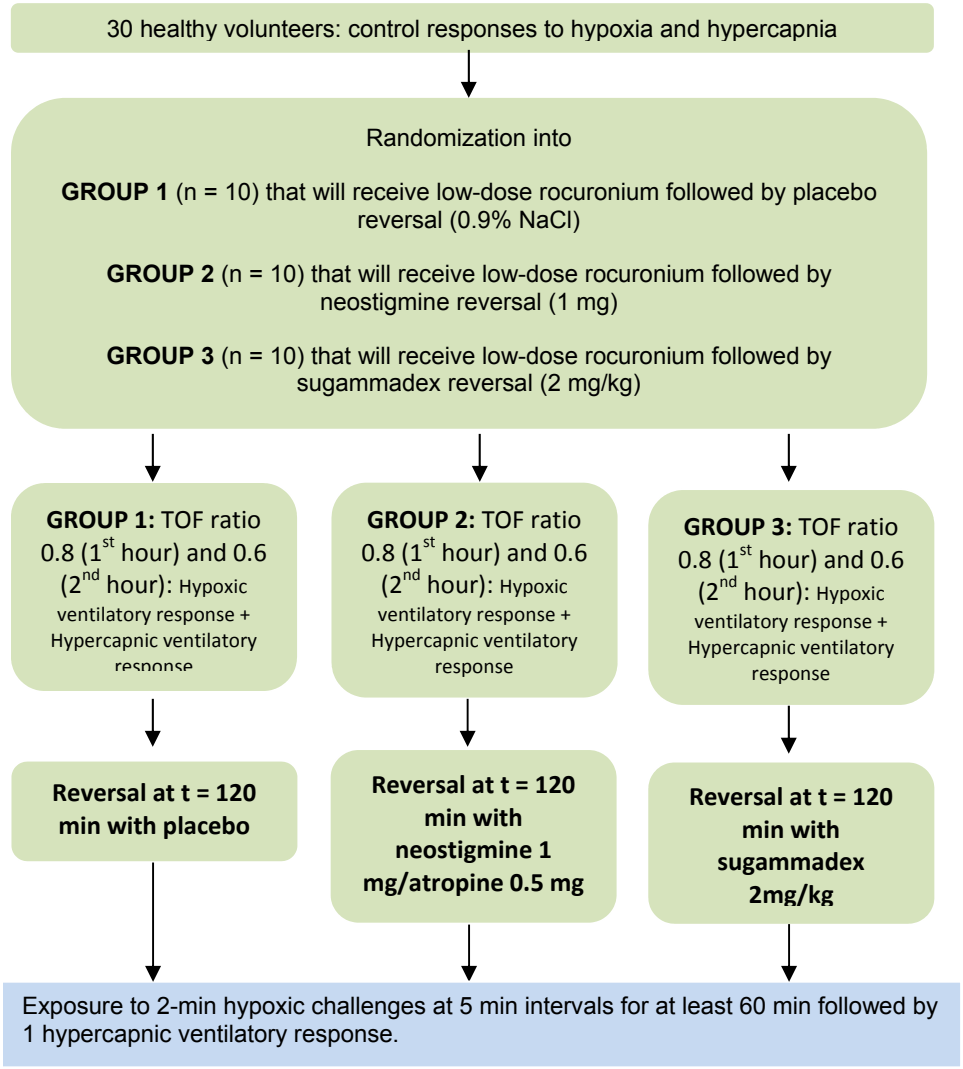
hypoxia]/[Delta saturation from normoxia to hypoxia]. (Dahan et al., Anesthesiologu 1996)

HYPERCAPNIA: We will apply two 7 min steps in end-tidal PCO_2 at the background of a hyperoxic gas mixture. At the end-of each step a ventilation and arterial oxygen saturation will be obtained. This allows assessment of the hypercapnic ventilatory response slope (S) which is calculated by linear regression of Ventilation to PCO_2. (Dahan et al. PLoS Med 2007). Hyperoxic conditions are used to silence the carotid bodies.

See for example of hypoxic and hypercapnic challenges Figure 2.

Additionally we will measure the diaphragm EMG activity to get an indication of diaphragm contribution to the measured responses.

6. Study procedures



After approval of the protocol by the Human Ethics Committee a total of 30 volunteers will be recruited and tested in the Clinical Research Unit of the Department of Anesthesiology at Leiden University Medical Center. Each volunteer will undergo a physical examination first and only healthy volunteers without a (family) history of neuromuscular disease will be included in the study.

The subjects are not allowed to eat or drink for at least 8 hours before the experiment.

After arrival in the laboratory all subjects will be connected to monitors including ECG, pulse oximeter and two EMG electrodes to measure diaphragmatic EMG activity; next an iv line is placed. The subjects are comfortably seated in a semirecumbant position. Next, the control ventilatory responses are obtained. A facemask will be used to administer specific gas mixtures.

Following the control ventilator responses and after a short break the rocuronium will be titrated to a TOF ratio of 0.8 for 1 hour followed by 0.6 for the next hour. In case the TOF ratio of 0.6 has a large effect on the subject in terms of oxygen saturation (values < 94%) or increases in end-tidal PCO_2 > 9 kPa, we will increase the TOF ratio to 0.7 and if this has no effect to 0.8. The experiment is then continued. After the desired TOF ratio is reached, the ventilatory challenges are repeated. The TOF ratio will be measured with the TOF Cuff/TOF watch device at 25 mA. We know from experience that this is an acceptable current.

After the 120-min infusion, the subject is reversed with either placebo (normal saline), or neostigmine 1 mg, or sugammadex 2 mg/kg. We will then repeat the 2-min hypoxic challenges at 5 min interval. When the hypoxic response has returned to control values but not before 60 min have elapsed since reversal we will perform one final hypercapnic ventilatory response.

We expect that all values will normalize within 90 min. The iv line is then removed and after another break of 1 hours (observation period) the subjects is discharged.

The duration of one single experiment is about 4 hours (incl. post experiment observation period). The complete study requires 30 experiment days and will last about 6 months (incl. data analysis)

7. Data and sample size calculation

7.1 Data analysis

We will obtain HVR and S under control conditions (HVRc and Sc) and under rocuronium conditions at TOF 0.6 (HVRr and Sr). The ratio of HVRr/HVRc and Sr/Sc will be calculated. This will give an indication of the effect of rocuronium on respiratory muscles per se (Sr/Sc = S') and on the combined effect of rocuronium on respiratory muscles and carotid bodies (HVRr/HVRc = HVR'). To compute the effect of rocuronium on just the

carotid bodies F' is calculated which is the ratio of HVR'/S'. In other words the effect of rocuronium on hypercapnic ventilation is used to correct for the effect of rocuronium on respiratory muscles (as well as other influences such as drowsiness, discomfort, etc). A value of F' < 1 is the effect of rocuronium on the carotid bodies. See also Eriksson et al. 1993.

The dynamics of return of the HVR towards control values following reversal is our main end-point. We are aware that the absolute value of the HVR is contaminated by effects from the respiratory muscles next to an effect of rocuronium at the carotid bodies. However, the calculation made on HVR and S obtained before and during rocuronium infusion give us an indication on the distribution of muscle vs. carotid body effects. We will take this into account in our analysis. The HVR-time data will be analyzed by taking time, HVR and TOF ratio into account. This HVR-time data will be analyzed using an exponential function allowing assessment of a half-life for HVR return (and hence for return of carotid body function). The HVR-TOF ratio data will be analyzed by linear regression and allows assessment whether HVR return follows TOF ratio or whether it deviates from the TOF ratio.

7.2 Sample size calculation

We decided not to use a crossover design as we do not want to expose one person to multiple awake rocuronium infusions. Hence we chose a parallel design. We powered the study on the speed of reversal of HVR from TOF ratio 0.6 to TOF ratio 1.0 between sugammadex and neostigmine. Assuming a return of carotid body function within 3-5 min for sugammadex and at least 10-20 min for neostigmine with a SD of the difference of 4-5 min we calculate the need for 12 subjects per group giving a power of > 90% (alpha = 0.05). The power calculation was performed in SigmaPlot.

8. Monitoring

The subject will be closely monitored by measurement of the TOF ratio using the TOFF Cuff/TOF watch system, oxygen saturation, respiratory rate, tidal volume, and ECG. In case of an emergency sugammadex will be administered to overcome the muscle blockade.

9. Subject discomfort

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. In case the subjects demands termination of the study the reversal agent Sugammadex will be administered.

There are multiple studies on the use of muscle relaxants in volunteers, such as the Eriksson et al. (1993) study. Here we give some examples:

Schuller et al. **Response of bispectral index to neuromuscular block in awake volunteers.** Br J Anaesth 2015; 115: i95-i103: Rocuronium 0.7 mg/kg was administered causing full paralysis in unsedated volunteers.

Blokland et al. **Detection of attempted movement from the EEG during neuromuscular block: proof of principle study in awake volunteers.** Sci Rep 2015; 5:12815: Complete relaxation in awake volunteers. Study performed at RadboudMC.

Cedborg et al. **Pharyngeal function and breathing pattern during partial neuromuscular block in the elderly: effects on airway protection.** Anesthesiology 204; 120: 312-25: TOF ratios of 0.7 in elderly (>70 yrs) unsedated volunteers.

Heier et al. **Sex-related differences in the relationship between acceleromyographic adductor pollicis train-of-four ratio and clinical manifestations of residual neuromuscular block: a study in healthy volunteers during near steady-state infusion of mivacurium.** Br J Anaesth 2012; 108: 444-51: NMB in unsedated volunteers.

Banzett et al. **'Air hunger' from increased PCO2 persists after complete neuromuscular block in humans.** Respir Physiol 1990; 81: 1-17: Complete paralysis in unsedated volunteers.

Gandevia et al**. Respiratory sensations, cardiovascular control, kinaesthesia and transcranial stimulation during paralysis in humans.** J Physiol 1993; 470: 85-107: Complete paralysis in unsedated volunteers.

Note that we will perform a study according to the design of Eriksson et al (1993), i.e., mild paralysis.

10. SAFETY

10.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product, including placebo, and which does not necessarily have to have a causal relationship with treatment. An AE can be:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of study medication, whether or not considered related to the study medication.
- Any new disease or exacerbation of an existing disease.
- Any deterioration in protocol-required or non-protocol-required measurements of laboratory value or other clinical tests (e.g. ECG or X-ray) that results in symptoms, a change in treatment, or discontinuation from study medication.
- Recurrence of an intermittent medical condition (e.g. headache) not present at baseline.

Subjects with AEs that are ongoing at the subject's completion/discontinuation visit (last treatment visit) will be followed up for *7* days and the follow up information will be recorded in the CRF. New AEs that are reported in the *7* days following the subject's completion/discontinuation visit will be recorded in the AE section of the CRF. Any AE that is still ongoing 7 days after the completion/discontinuation visit will have an end date of 'ongoing' in the CRF, however the investigator will continue to follow up ongoing AEs and record information in the source documents. SAEs will be followed until the event resolves or the event or sequels stabilize and this information will be reported to the Sponsor, local and central ethics committees using the SAE Data Form.

10.2 Reporting of Adverse Events

For subjects who receive study medication, all AEs (learned through spontaneous reports, subject interview) starting from providing informed consent for study participation through the period beyond study completion will be collected on the AE pages of the CRF. In addition, a note should be made in the source documentation of the subject. For each AE on the AE pages of CRF, the following information will be recorded: AE (e.g. headache), start date, start time, stop time, severity, study medication action taken, other action taken, relationship to study medication, outcome, seriousness. A cluster of signs and symptoms that results from a single cause should be reported as a single AE (e.g. fever, elevated WBC, cough, abnormal chest x-ray, etc. can all be reported as "pneumonia.").

10.3 Criteria for Assessing Severity

The Investigator will evaluate the comments of the subject and the response to treatment in order that he/she may judge the true nature and severity of the AE.

Severity refers to the accumulated intensity of discomfort/impairment of health since the last recording of AEs and will be assessed according to the following criteria:

Mild: Awareness of sign, symptom, or event, but easily tolerated.

Moderate: Discomfort enough to cause interference with usual activity and may warrant intervention.

Severe: Incapacitating with inability to do usual activities or significantly affects clinical status and warrants intervention.

The criteria for assessing severity are different to those used for seriousness (see below for the definition of an SAE).

10.4 Criteria for Assessing Causality

The question of the relationship of an AE to study medication should be determined by the Investigator after thorough consideration of all facts that are available. Assessment of causality is based on considering associative connections (time or place), pharmacological explanations, previous knowledge of the drug, presence of characteristic clinical or pathological phenomena, exclusion of other causes, and/or absence of alternative explanations.

The causal relationship of an AE to study medication will be assessed according to the following criteria (based on World Health Organization definitions):

Not related: Temporal relationship to study medication administration is missing or implausible, or there is an evident other cause.

Related

Unlikely to be related: Temporal relationship to study medication administration makes a causal relationship improbable; and other drugs, chemicals, or underlying disease provide plausible explanations.

Possibly related: Reasonable time sequence to administration of study drug, but event could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

Probably related: Reasonable time sequence to administration of study drug, but unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required.

Definitely related: Plausible time relationship to study medication administration; event cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary.

10.5 Serious Adverse Events

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death;

- Is life-threatening (i.e. the subject was at immediate risk of death from the AE as it occurred. This does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death);
- Requires inpatient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study medication);
- Is a medically important event or reaction (see below).

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but may, based on appropriate medical judgment, jeopardize the subject or require intervention to prevent one of the outcomes in the definition of SAE listed above should also be considered SAEs. Examples of such events are intensive treatments in an emergency room or at home for allergic bronchospasm, blood dyscrasias or seizures that do not result in hospitalization, or development of drug dependency or drug abuse. These events may be considered to need rapid reporting by the Sponsor to competent authorities.

All SAEs, including those occurring up to 7 days following the subject's completion/ discontinuation visit (subject's last treatment visit), will be recorded on the AE pages of the CRF. In addition, SAEs must be reported to the Sponsor, local and central ethics committees using the SAE Data Form (Sponsor), letter (local ethics committee) and CCMO website (central ethics committee). Subjects with SAEs must be followed until the event resolves or the event or sequels stabilize.

10.6 Reporting of SAEs

All SAEs must be reported to the Sponsor within one business day of first knowledge of the SAE using the SAE Data Form. In the initial report, all of the information requested that is available should be provided. The SAE Data Form must be signed by the Investigator prior to submission to the Sponsor. Follow-up information, or new information available after the initial report, should be actively sought and reported to the Sponsor as it becomes available using the SAE Data Form. SAE Data Forms must contain the following information, at a minimum: the reportable event, the study medication (if known), the protocol number, the subject number, and the Investigator name. Additionally, SAEs will be reported to the local ethics committee (through a letter to the committee at LUMC) and central ethics committee (through the CCMO website). Additionally the manufacturer of the product (tapentadol) will be informed of an AE.

10.7 Expedited Reporting

Adverse Reaction. Any untoward and unintended responses to an investigational medicinal product related to any dose administered. All AEs judged by either the reporting Investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression "reasonable causal

relationship" means to convey in general that there is evidence or argument to suggest a causal relationship (i.e. causality is at least "unlikely").
Unexpected Adverse Reaction. An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator' Brochure for an unregistered investigational product or summary of product characteristics for a registered product). When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.
Suspected Unexpected Serious Adverse Reaction (SUSAR). A SUSAR is an adverse drug reaction, which is both serious and unexpected. If an SAE was assessed to be a SUSAR by the Sponsor, the Competent Authorities, ECs and Investigators must be informed as soon as possible but no later than 15 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. If the SUSAR was immediately life threatening or fatal, it must be reported as soon as possible but no later than 7 calendar days after the sponsor has first knowledge of the minimum criteria for expedited reporting. Relevant follow-up information should be communicated to the competent authority and the Ethics Committee within an additional 8 calendar days.

The Sponsor is responsible for expedited reporting of SUSARs and other reportable events and safety issues to the Competent Authorities, according to local legislations. Investigators will be informed by the Sponsor. The Investigator or Sponsor, depending on local regulations, must inform the EC/IRB about SUSARs and other reportable events and safety issues in accordance with ICH guidelines and the practices of the governing ECs.

10.8 Data Safety Committee (DSC)
The data safety committee of the Department of Anesthesiology at LUMC will assess the data collected in the CRF in case of occurrence of serious adverse events (SAE) or more frequently if required for any reason. In case a SAE occurs, the DSC will advice the research team on the measures that are required to enable a successful completion of the study. The independent physician is part of the DSC (dr. Elise Sarton). The primary concern of the DMC is patient safety. If AEs or SAEs do occur they will advise the Investigator on the continuation of the study. Reporting to the DMC is independent of the reporting to sponsor, local and central ethics committees.

11. References

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