A randomized, controlled, parallel-group, double-blind trial of sugammadex or usual care (neostigmine or spontaneous recovery) for reversal of rocuronium- or vecuronium-induced neuromuscular blockade in patients receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip/knee) replacement.

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Primary Trial Objective:To assess the effect of reversal of neuromuscular blockade with sugammadex 4 mg.kg-1 compared with reversal according to usual care (neostigmine or spontaneous reversal) on the incidence of adjudicated postsurgical events of...

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

Summary

ID

NL-OMON35664

Source
ToetsingOnline

Brief title
P07038

Condition

- Other condition

Synonym
Reversal of muscle relaxant

Health condition

Opheffing van neuromusculaire blokkade bij heupfractuuroperatie of gewrichtsvervanging

Research involving
Human

Sponsors and support

Primary sponsor: Schering-Plough
Source(s) of monetary or material Support: Schering Plough Research Institute

Intervention

Keyword: hip/joint surgery, sugammadex, thromboprophylaxis

Outcome measures

Primary outcome

The primary analysis will assess the proportion of patients with at least one adjudicated event of bleeding (major or non-major) with an onset within 24 hours after administration of study medication. This assessment will use the stratified Cochran-Mantel-Haenszel method, stratifying for thromboprophylactic therapy (including LMWH, including UFH, or not including either LMWH or UFH) and renal function (estimated creatinine clearance < or >= 60 mL/min).

Secondary outcome

The key secondary analysis will assess aPTT measured at 10 and 60 minutes after administration of study medication. aPTT values will be analyzed using constrained longitudinal data analysis, adjusting for the following factors:

investigational center, thromboprophylactic therapy (including LMWH, including UFH, or not including either LMWH or UFH), renal function (estimated creatinine clearance < or >= 60 mL/min), usual care (neostigmine or spontaneous recovery), and surgical procedure (hip fracture surgery, hip replacement, knee replacement).

Study description

Background summary

In a clinical study of healthy subjects (Trial 19.4.115), doses of 4 mg.kg-1 and 16 mg.kg-1 of sugammadex resulted in mean prolongations of activated partial thromboplastin time (aPTT) and prothrombin time (PT) by up to 17-22% in a dose dependent manner. These limited, mean aPTT and PT prolongations resolved quickly (i.e., <= 30 minutes), and pooled analysis of the Phase II/III data from the sugammadex development program did not indicate an increase in clinically meaningful events of bleeding. However, to further investigate the potential clinical relevance of these findings, the current study will investigate the effects of (1) reversal of neuromuscular blockade using sugammadex at the clinical dose of 4 mg.kg-1 and (2) reversal of neuromuscular blockade according to usual care (neostigmine or spontaneous reversal) on adjudicated events of bleeding and coagulation parameters in surgical patients at increased risk for bleeding events due to concomitant administration of thromboprophylactic therapy.

Study objective

Primary Trial Objective:
To assess the effect of reversal of neuromuscular blockade with sugammadex 4 mg.kg-1 compared with reversal according to usual care (neostigmine or spontaneous reversal) on the incidence of adjudicated postsurgical events of bleeding over 24 hours, in patients receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip/knee) replacement with neuromuscular blockade induced by rocuronium or vecuronium.

Key Secondary Trial Objectives:
- To assess the effect of reversal of neuromuscular blockade with sugammadex 4 mg.kg-1 compared with reversal according to usual care (neostigmine or spontaneous reversal) on activated partial thromboplastin time (aPTT) (with values over a period of up to 2 hours in a subset of patients).

- To assess the safety of reversal of neuromuscular blockade with sugammadex 4 mg.kg-1 compared with reversal according to usual care (neostigmine or spontaneous reversal).

Study design

This is a randomized, controlled, parallel-group, multi-site, double-blind trial of sugammadex or usual care (neostigmine or spontaneous recovery) for reversal of rocuronium- or vecuronium-induced neuromuscular blockade in patients receiving thromboprophylaxis and undergoing hip fracture surgery or joint (hip/knee) replacement. Patients for whom active reversal would have been usual care will receive sugammadex or neostigmine (Usual Care Group 1). Patients for whom spontaneous recovery would have been usual care will receive sugammadex or placebo (Usual Care Group 2). Randomization to sugammadex or usual care (1:1) will be stratified according to thromboprophylaxis (including low molecular weight heparin [LMWH], including unfractionated heparin [UFH], or not including either LMWH or UFH) and renal function (estimated creatinine clearance < or >= 60 mL/min).

Duration of Participation:
Each patient will participate in the trial for approximately 56 days from the time the patient signs the Informed Consent Form (ICF) through the final contact. After a screening phase of up to 7 days, each patient will receive the assigned treatment. The primary period of observation will be 24 hours or until hospital discharge, whichever is sooner. A follow-up visit will occur 4 to 7 weeks after treatment.

Intervention

- Treatment with either sugammadex, combination of neostigmine and atropine, or placebo
- One follow-up visit 4-7 weeks after treatment

Study burden and risks

Sugammadex has been approved for use via the EU Centralised Procedure on 25 July 2008 and has been marketed since September 2008 as Bridion® in many EU countries. It is currently approved in over 64 countries around the world. Over 890,000 patients have been exposed to sugammadex based on marketing sales data [PSUR, 2009; PSUR, 2010 and PSUR, 2011].

Safety data of sugammadex has been collected from more than 32 trials conducted in more than 2,500 surgical patients. In addition 664 healthy subjects have been administered sugammadex in doses ranging from 0.5-96 mg/kg. The safety profile has shown that sugammadex is generally safe and well tolerated. The CCDS [2011] indicates that the undesirable effects of sugammadex include drug

hypersensitivity [Uncommon (>= 1/1000 to <1/100], anesthetic complication [Common (>= 1/100 to <1/10)] which includes movements indicative of the restoration of neuromuscular function (movement of a limb or the body or coughing during the anaesthetic procedure or during surgery, grimacing, or suckling on the endotracheal tube) and slow recovery from neuromuscular blockade [Common (>= 1/100 to <1/10)] which were common when sub-optimal doses of sugammadex were administered below the recommended doses.

Hypersensitivity reactions, including anaphylaxis, have been observed with sugammadex. In a study in healthy conscious volunteers (Trial P06042; placebo, n=150; 4 mg/kg, n=148; and 16 mg/kg, n=150), hypersensitivity reactions were reported commonly with sugammadex 16 mg/kg (n=7, 4.7%) and uncommonly with sugammadex 4 mg/kg (n=1, 0.7%) and none with placebo (n=0, 0%). Moreover, in clinical trials of surgical patients hypersensitivity reactions were reported uncommonly and for post-marketing reports, which include nonserious cases of hypersensitivity reactions and rare serious cases describing anaphylactic reactions, the frequency is unknown.

With respect to the effect of sugammadex on hemostasis, in a clinical study of healthy subjects (Trial 19.4.115), doses of 4 mg.kg-1 and 16 mg.kg-1 of sugammadex resulted in maximum mean prolongations of activated partial thromboplastin time (aPTT) by 17 and 22% respectively and of prothrombin time (PT) by 11 and 22% respectively. These limited, mean aPTT and PT prolongations resolved quickly (i.e., <= 30 minutes), and pooled analysis of the Phase II/III data from the sugammadex development program did not indicate an increase in clinically meaningful events of bleeding. However, to further investigate the potential clinical relevance of the observed effects on aPTT and PT, the current study will investigate the effects of (1) reversal of neuromuscular blockade using sugammadex at the clinical dose of 4 mg.kg-1 and (2) reversal of neuromuscular blockade according to usual care (neostigmine or spontaneous reversal) on adjudicated events of bleeding and coagulation parameters in surgical patients at increased risk for bleeding events due to concomitant administration of thromboprophylactic therapy.

The background risk associated with events of unanticipated post-surgical bleeding varies depending on factors such as surgical procedure and concomitant medication as well as intrinsic factors/underlying medical conditions (eg, hemophilia, congenital platelet disorder, von Willebrand disease, advanced hepatic insufficiency, or severe renal insufficiency). In order to better understand the risk for bleeding in the context of previously defined incidences of bleeding events in surgical patients, this study will assess adult surgical patients of ASA Class 1-3 undergoing hip fracture surgery or joint (hip/knee) replacement surgery and receiving pre- or intra-operative thromboprophylaxis. Key features of the population of patients undergoing hip fracture surgery or joint (hip/knee) replacement surgery and the rationale supporting focused study of this population are listed below.

This is an appropriate population to study for a number of reasons. First, thromboprophylactic therapies are routinely indicated in such patients because of the high risk (40-60% without prophylaxis) of venous thromboembolism associated with major orthopedic surgery of the lower limb. Second, focusing on this particular set of procedures which has an increased incidence of bleeding/blood loss may decrease the observed variability of bleeding risk related to surgical procedure or technique while regarding the incidences of bleeding events in patients whose neuromuscular blockade is reversed with sugammadex versus according to usual care (neostigmine or spontaneous reversal). Third, these procedures have well-studied risks for bleeding that can provide historical context for incidences of bleeding events; indeed, the best-studied paradigms assessing risk for postoperative bleeding are the double-blind, randomized controlled thromboprophylaxis studies of hip and knee surgeries.

An analysis of the clinical data from the pooled Phase II/III development program for events of bleeding in patients taking antithrombotic therapy did not demonstrate an increased risk for clinically meaningful events of bleeding. The current study is designed to gather additional data in a prospective manner to evaluate possible interactions manifested as clinical events in a surgical population. To that end, this study will enrich for this population, specifically assessing the potential of sugammadex to increase bleeding risk in patients receiving prophylactic antithrombotic therapy.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Patients must be: aged >=*18 years; ASA (American Society of Anesthesiologists) Class 1, 2, or 3; scheduled for hip fracture surgery or joint (hip or knee) replacement surgery under general anesthesia including the use of rocuronium or vecuronium for neuromuscular blockade; and appropriate candidates for rapid reversal of neuromuscular blockade.
At screening, patients must be: currently receiving ongoing thromboprophylactic therapy with low molecular weight heparins (LMWH) or unfractionated heparins (UFH); planned to initiate thromboprophylactic therapy with LMWH or UFH prior to or during surgery (ie, prior to administration of study medication); currently receiving thromboprophylactic therapy with a vitamin K antagonist which will be temporarily substituted with peri-operative LMWH or UFH; and/or currently receiving ongoing thromboprophylaxis with low-dose aspirin or other antiplatelet therapy (eg, clopidogrel, ticlopidine, dipyridamole). Platelet count must be above the lower limit of the normal range.

Exclusion criteria

Patients with severe renal impairment (eg, creatinine clearance < 30 mL/min) are excluded from participation.

Study design

Design

Study phase:	3
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):	12-09-2011
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Bridion
Generic name:	sugammadex
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n.v.t (volgens ziekenhuis standaardzorg)
Generic name:	atropine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	n.v.t (volgens ziekenhuis standaardzorg)
Generic name:	neostigmine
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	19-08-2011
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-01-2012
Application type:	First submission

Review commission: CMO regio Arnhem-Nijmegen (Nijmegen)

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	EUCTR2011-001201-27-NL
CCMO	NL37824.091.11
Other	nog niet bekend