Pharmacokinetic Profile of Ropivacaïne after Periarticular Local Infiltration Analgesia for Primary Total Knee Arthroplasty

Published: 09-10-2014
Last updated: 22-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Joint disorders
Study type	Observational invasive

Summary

ID

NL-OMON40725

Source
ToetsingOnline

Brief title
LIAkin

Condition

- Joint disorders

Synonym
knee arthrosis, total knee arthroplasty

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek

Source(s) of monetary or material Support: Sint Maartenskliniek

Intervention

Keyword: Local Infiltration Analgesia, Pharmacokinetics, Ropivacaine, Total Knee Arthroplasty

Outcome measures

Primary outcome

- Mean total and unbound maximum serum concentration of ropivacaine (Cmax)

- Mean time to total and unbound maximum serum concentration of ropivacaine

(Tmax)

Secondary outcome

-

Study description

Background summary

Knee osteoarthritis is a leading cause of disability in our ageing society.
Total knee arthroplasty (TKA) has been shown to be an effective treatment in reducing pain and improving function and quality of life in individuals suffering from severe knee osteoarthritis. For an optimal and fast recovery after TKA, a fast track rehabilitation protocol has been developed. Fast track surgery results in quicker functional recovery, reduced morbidity, decreased length of convalescence, increased satisfaction and * as a secondary gain * reduced hospital costs.
Finding the most appropriate analgesic technique for fast track TKA is challenging: the patient needs to be pain free to mobilize for physical therapy, while side effects of the pain treatment like drowsiness (opioids) and impaired motor function (femoral nerve block) impede the fast track protocol. Therefore, a technique for the control of pain following knee and hip surgery, to allow virtually immediate mobilization and earlier discharge from the hospital called *local infiltration analgesia* (LIA) has been developed.
For the LIA a relatively high dose long acting local anesthestic, ropivacaine, is injected in the soft tissue surrounding the knee and the subcutis around the incision. Ropivacaine is slowly absorbed into the circulation from the injection site. Epinephrine is added to the ropivacaïne injected in the soft

tissue to decrease absorption speed and lower peak plasma concentrations by inducing vasoconstriction.
A potential hazard of the LIA technique is the relatively high dose of local anesthetic used, increasing the risk of LAST (local anesthestic systemic toxicity). Usually a dose of 400 mg ropivacaïne is used for LIA, which is in most cases above the recommended maximum dose of 3-4 mg/kg. Nevertheless, in the past few years thousands of patients have been undergoing LIA for knee surgery with high doses of ropivacaïne, and only one case of LAST after LIA has been described.
In the plasma, approximately 95% of the ropivacaïne is bound to *1-glycoprotein [ref]. approximately 5% of the total plasma concentration of ropivacaïne is the free, unionized form. The unbound ropivacaïne interacts with receptors inducing its pharmacological properties. When the free, unbound ropivacaïne concentration exceeds the toxic threshold in the central nervous system (CNS) or heart, symptoms of toxicity (LAST) occur. Typical CNS toxicity symptoms are perioral numbness, tinnitus and visual disturbances. More severe LAST symptoms of CNS toxicity are convulsions, coma and respiratory arrest. In ropivacaine induced LAST, cardiac toxicity symptoms may be mild or even absent, but when present they range from rhythm disturbances to circulatory arrest due to cardiac arrest.
Although LIA with ropivacaine is frequently applied, little is known about the pharmacokinetic profile of ropivacaïne applied for LIA of the knee. Knowledge of the pharmacokinetic parameters will give more insight in the onset (Tmax), duration (halve live) and extent (Cmax) of ropivacaine concentrations. Knowledge of the Tmax (time when highest plasma concentration is reached) can provide more insight to the time frame in which the patient is at risk of LAST and should be monitored. Cmax of ropivacaïne for LIA gives insight in the range to toxic concentrations. Knudsen et al. administered ropivacaïne intravenously in healthy volunteers and found that symptoms of toxicity occurred at arterial plasma concentrations of 4.3 mg/L for total and 0.56 mg/L for unbound ropivacaïne concentrations. It is unclear whether this *toxic concentration* of ropivacaïne can also be applied to a situation where ropivacaïne is injected in soft tissue (LIA) instead of injected intravenously. Serum concentrations of ropivacaïne rise much slower in LIA, than when injected intravenously as did Knudsen et al., because of the slow drug uptake from the tissue site into the blood stream. Even so, the study of Knudsen et al. is the only study investigating toxic concentrations of ropivacaïne in humans and therefore, it is generally accepted that serum concentrations of ropivacaïne should remain below 4.3 mg/L for total and 0.56 mg/L for unbound ropivacaïne.

Study objective

The primary objective of this study is to describe a pharmacokinetic profile of bound and unbound plasma concentrations of ropivacaïne, when used in the LIA technique for the knee. Especially describing the Cmax and Tmax gives arguments for dosage of ropivacaïne when used for LIA and for monitoring time of patients

after surgery in everyday medical practice.

Study design

Cohort study

Study burden and risks

In this study, patients will receive standard anesthesia according to the hospital protocol. Blood samples will be drawn from an indwelling peripheral intravenous catheter (PIVC), placed on the contralateral side of the PIVC that is used for routine monitoring. If the catheter fails, another will be placed, or the remaining sample(s) can be drawn by venipuncture if the PIVC is not necessary for the patient*s medical care (if the patient receives no intravenous antiemetics or intravenous pain medicine, the PIVC will be discontinued by hospital protocol the day after surgery).
Per patient 45 mL of blood will be drawn in total, i.e. 9 times 3-5 mL. The patient will not experience any consequences from this minimal blood loss. For comparison: total blood volume of an average adult person is 5L and for voluntary blood donation 0.5L is drawn. The much smaller amount of blood drawn for this study won*t induce health concerns.
Because of the sampling schedule, which does not include sampling between t=6 hours and t=24 hours, no blood will be drawn during night hours, guaranteeing no nightly disturbances for the patient for study purposes.
By participation in this study the patient is subjected to a small risk of hematoma at the puncture site and a very small risk of infection at the puncture site.

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

- age 50-80 years
- ASA physical health classification I * II
- Body Mass Index (BMI) < 40
- patient planned for a primary unilateral posterior-stabilized tri-compartmental cemented total knee replacement (Genesis II - PS) under unilateral spinal anesthesia with 2 mL hyperbaric bupivacaine 0.5%
- scheduled for fast-track protocol TKA
- haemoglobin (Hb) concentration * 7.5 mMol/L
- written informed consent

Exclusion criteria

- Placement of a surgical drain
- Contra-indications for spinal anesthesia
- Known hypersensitivity to amide-type local anesthetics
- Hepatic or renal insufficiency
- Use of fluvoxamine, ciprofloxacin, ketoconazole, erythromycin, clarithromycin, itraconazole, or rifampicin because of their effect on ropivacaine clearance.
- Any other reason which in the opinion of the investigator makes the patient unsuitable for participation in the study

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Other
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	05-01-2015
Enrollment:	20
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	09-10-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)
Approved WMO Date:	15-10-2014
Application type:	First submission
Review commission:	METC Slotervaartziekenhuis en Reade (Amsterdam)

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	EUCTR2014-003010-93-NL
CCMO	NL50074.048.14

Study results

Date completed:	06-05-2016
Results posted:	04-10-2016
Actual enrolment:	20

First publication
04-10-2016