Pharmacokinetics of high dose Ropivacaine with and without epinephrine for combined femoral and sciatic nerve block in lower extremity surgery. A pilot study.

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The purpose of the present study is to obtain a pharmacokinetic profile of ropivacaine in serum with epinephrine, and of ropivacaine in serum without epinephrine, used for high dosed combined femoral and sciatic nerve block in lower extremity...

Ethical review	Approved WMO
Status	Pending
Health condition type	Bone and joint therapeutic procedures
Study type	Observational invasive

Summary

ID

NL-OMON33042

Source
ToetsingOnline

Brief title
RopiPilot

Condition

- Bone and joint therapeutic procedures

Synonym
orthopaedic surgery of the lower extremity

Research involving
Human

Sponsors and support

Primary sponsor: Sint Maartenskliniek
Source(s) of monetary or material Support: Het onderzoek wordt intern gefinancierd

Intervention

Keyword: Combined femoral and sciatic nerve block, Epinephrine, Pharmacokinetics, Ropivacaine

Outcome measures

Primary outcome

1. Mean unbound and bound peak plasma concentration (Cmax) of ropivacaine with

and without

epinephrine

2. Mean time to unbound and bound peak plasma concentration (Tmax) of

ropivacaine with and

without epinephrine

3. Range of duration (width) of Cmax after single shot combined femoral and

sciatic nerve block with

and without epinephrine

4. Range of apparent half-life of ropivacaine with and without epinephrine in

combined femoral and

sciatic nerve block (T*).

5. Efficacy of the sensory blockade with and without epinephrine.

6. Duration of the sensory blockade with and without epinephrine.

Secondary outcome

age, length, weight and gender

possible complications or side effects

Study description

Background summary

Ropivacaine is a widely used long-acting amide local anesthetic. It was introduced into the market as a safer alternative to bupivacaine after reports of cardiac arrest with prolonged resuscitation after accidental intravascular injection of bupivacaine (1,2). Ropivacaine is structurally closely related to bupivacaine; however, unlike bupivacaine which is a racemate, ropivacaine is a pure S(-)-enantiomer of n-propivacaine (3). The S-enantiomer was chosen because it has a lower toxicity than the R-enantiomer (4).
Animal and volunteer studies indicate that ropivacaine is safer than bupivacaine in terms of its neurologic and cardiac toxicity profile (5). It has a higher convulsive threshold in different animal models, fewer CNS symptoms after intravenous administration in human volunteers, and fewer excitatory changes in the EEG than bupivacaine (2). In addition, ropivacaine has a lower cardiac toxicity as compared to both racemic and levobupivacaine (6-19).

Like other local anesthetics, ropivacaine elicits nerve block via reversible inhibition of sodium ion influx in nerve fibers. This action is potentiated by dose-dependent inhibition of potassium channels. Ropivacaine is less lipophilic than bupivacaine (3). Lipid solubility appears to be the primary determinant of intrinsic anesthetic potency (2).
Ropivacaine is extensively (94%) bound to plasma proteins, mainly α1-acid glycoprotein (AAG). Systemic toxicity is considered to be related to the unbound drug concentration (3). A threshold for CNS toxicity in healthy adult subjects is apparent at unbound ropivacaine plasma concentrations of 0.56 (0.34-0.85) mg/L (20). During prolonged postoperative epidural infusion of ropivacaine, unbound plasma drug concentrations plateaued or gradually declined despite a progressive increase in total concentrations (21-24). The total plasma concentration increase during continuous epidural infusion of ropivacaine is caused by an increase in the degree of protein binding and subsequent decrease in clearance of ropivacaine (3). Surgery stimulates the synthesis of AAG in the liver and, therefore, the local anesthetic binding capacity is enhanced and the risk of toxicity reduced post-operatively (25). Total ropivacaine plasma levels have a putative safe level for systemic toxicity of 2-4.5 mg/L (5).

Peripheral nerve block (PNB) as an anesthetic technique is rapidly gaining popularity among anesthesiologists and patients. Compared to general anesthesia or central neuraxis blockade, interference of PNB with vital functions is minimal and postoperative analgesia is excellent.

In the Sint Maartenskliniek in Nijmegen, The Netherlands, the combined femoral and sciatic nerve block is commonly used for lower extremity orthopedic surgery. Obtaining adequate anesthesia and long lasting analgesia requires the use of large volumes of ropivacaine in high concentration. As a consequence, doses up to 60 mL of ropivacaine 0,75% (450 mg) are no exception. A potential problem with high doses of local anesthetics is that they exceed the recommendations for maximum doses that are, in large part, not (yet) evidence based and published by the manufacturer as a necessary step in the registration process (25). As a consequence, these recommended maximum doses (200-300 mg) are conservative and, especially in case of PNB, widely disregarded in clinical practice.
In the Sint Maartenskliniek, the vast majority of surgery is performed under regional anesthesia. In the past years, the safety of high doses ropivacaine in combined sciatic femoral nerve block has been established in more than 10,000 patients, with symptoms of systemic toxicity being both rare and mild. Differences in absorption of local anesthetic from different injection sites support block-specific and site-specific dose recommendations (26). I.e., in the absence of evidence-based recommended maximum doses, there is a need to support the clinically experienced safety of high doses of local anesthetics with pharmacokinetic data.

It is not clear whether the addition of epinephrine 5 µg/mL (1:200.000) offers pharmacokinetic advantages over ropivacaine alone. The primary action of epinephrine is probably local vasoconstriction that reduces systemic absorption from the site of injection and by a direct agonist effect on spinal α2 receptors. This reduces the risk of local anesthetic toxicity when large doses are given. Because ropivacaine has intrinsic vasoconstrictor properties in concentrations <1%, the addition of epinephrine has been considered unnecessary by some (27).
The literature is mixed about the advantages of adding epinephrine. Some studies found an advantage compared to ropivacaine alone (2,27,28), whereas others did not (29-31).

To confirm safety of using high doses of ropivacaine, large scale investigation of mean peak plasma concentration (Cmax) and mean time to peak plasma concentration (Tmax) is necessary. Thereafter we can determine block specific maximum doses of ropivacaine with or without epinephrine. To investigate Cmax and Tmax, we first need a complete pharmacokinetic profile of ropivacaine.

(For references, we refer to the study protocol)

Study objective

The purpose of the present study is to obtain a pharmacokinetic profile of ropivacaine in serum with epinephrine, and of ropivacaine in serum without epinephrine, used for high dosed combined femoral and sciatic nerve block in lower extremity orthopedic surgery. Results of this pilot study will be used in

a follow-up study to determine block specific maximum doses using the determined width of Cmax¬ found in this study.

Study design

The design of this pilot study is parallel, prospective, double blind and explorative. Twelve patients scheduled for combined femoral and sciatic nerve block in lower extremity orthopedic surgery will be studied. The study will be conducted at the Sint Maartenskliniek Nijmegen, The Netherlands according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice. No patients will be recruited before written approval has been obtained from the local Medical Ethics Review Committee as well as from the board of Directors of the Sint Maartenskliniek Nijmegen.

Study burden and risks

We are aware of the burden of taking bloodsamples during the night. By determining the range and duration of Cmax in a pilot study, we can limit the inconvenience for future patients in a larger follow up study designed to establish block specific recommendations considering maximum dosage of ropivacaine.

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 >= 18 years, <= 60 years
- Body Weight >= 70 kg
- ASA classification I - III
- Patients undergoing combined femoral and sciatic nerve block for lower extremity orthopaedic surgery
- Who will be admitted for at least 48 hours
- Written informed consent

Exclusion criteria

- Contra-indications for regional anesthesia (infection at the injection site, coagulopathy)
- Known hypersensitivity to amide-type local anesthetics
- Known history of peripheral neuropathy
- Known hepatic or renal insufficiency
- Use of fluvoxamine, ciprofloxacin, ketoconazole, erythromycin, clarithromycin, itraconazole, or rifampicin because of their effect on ropivacaine clearance.

Study design

Design

Study phase:	4
Study type:	Observational invasive
Intervention model:	Parallel
Masking:	Double blinded (masking used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2009
Enrollment:	12
Type:	Anticipated

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Epinephrine
Generic name:	Epinephrine
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Naropin
Generic name:	Ropivacaine
Registration:	Yes - NL intended use

Ethics review

Approved WMO

Date:	16-09-2009
Application type:	First submission
Review commission:	IRB Nijmegen: Independent Review Board Nijmegen (Wijchen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 21564
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2009-013481-10-NL
CCMO	NL28616.072.09
OMON	NL-OMON21564