Farmacokinetiek van ropivacaïne met en zonder adrenaline bij hoge doseringen voor n. femoralis en ischiadicus blok bij orthopedische chirurgie van de onderste extremiteit.

No registrations found.

Ethical review	Positive opinion
Status	Recruitment stopped
Health condition type	-
Study type	Observational non invasive

Summary

ID

NL-OMON21564

Source
NTR

Brief title
RopiPilot

Health condition

combined femoral and sciatic nerve block for lower extremity orthopedic surgery

Sponsors and support

Primary sponsor: Sint Maartenskliniek Nijmegen, The Netherlands
Source(s) of monetary or material Support: Internal financing, no funding source

Intervention

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 (T½);

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

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

Secondary outcome

N/A

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. Animal and volunteer studies indicate that ropivacaine is safer than bupivacaine in terms of its neurologic and cardiac toxicity profile.

Ropivacaine is extensively (94%) bound to plasma proteins, mainly á1-acid glycoprotein (AAG). Systemic toxicity is considered to be related to the unbound drug concentration. 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.
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. 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. 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 ìg/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 á2 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. The literature is mixed about the advantages of adding epinephrine. Some studies found an advantage compared to ropivacaine alone, whereas others did not.

To confirm the 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.

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.

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.

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

Venous blood samples of 2 -5 mL will be taken by the investigator (KS) before the first injection, and at times 15, 30, 45, 60, 75, 90, 120, 150, 180, 210 and 240 minutes, (to determine the epinephrine effect) and at 6, 12, 18 (end of block), 24, 36 and 48 hours (to determine elimination until there is no ropivacaine left traceable in the blood) following the end of the sciatic nerve block. Fifteen and thirty minutes after the last injection of local anesthetic solution, a blinded observer (KS) will assess the sensory and motor block.

Intervention

Using a sealed envelope technique, patients will be randomly allocated to receive combined femoral sciatic nerve block with 60 mL of either ropivacaine 0.75% alone or ropivacaine 0.75% plus 5 mcg/mL (1:200.000) epinephrine.

18 venous blood samples of 2 -5 mL will be taken by the investigator (KS) during the 48h study period. Before the first injection, to determine the epinephrine effect, at the end of block and to determine elimination until there is no ropivacaine left traceable in the blood. We will take samples until 6 times the estimated half-life of 8h to be sure all ropivacaine has been cleared.

Samples will be placed on ice and centrifuged within one hour of collection. Plasma samples will be stored at -18 degrees Celcius until assay, using high performance liquid chromatography.
Total bound plasma ropivacaine levels will be determined. Later on total unbound plasma ropivacaine levels will be determined in the samples with the highest total bound concentration per patient.

The duration of sensory block is considered as the time interval between the administration of the local anesthetic and the first request for postoperative pain treatment.
The efficacy of the block will be assessed as successful (no additional intraoperative medication), partial (intraoperative sedation) or unsuccessful (general anesthesia).

Contacts

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Eligibility criteria

Inclusion criteria

1. Patients over 18 years, under 60 years of age;

2. Body Weight over 70 kg;

3. ASA classification I-III;

4. Patients undergoing combined femoral and sciatic nerve block for lower extremity orthopaedic surgery;

5. Who will be admitted for at least 48 hours;

6. Written informed consent.

Exclusion criteria

1. Contra-indications for regional anesthesia (infection at the injection site, coagulopathy);

2. Known hypersensitivity to amide-type local anesthetics;

3. Known history of peripheral neuropathy;

4. Hepatic or renal insufficiency;

5. Use of fluvoxamine, ciprofloxacin, ketoconazole, erythromycin, clarithromycin, itraconazole, or rifampicin because of their effect on ropivacaine clearance.

Study design

Design

Study type:	Observational non invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2009
Enrollment:	12
Type:	Actual

Ethics review

Positive opinion

Date:	28-08-2009
Application type:	First submission

Study registrations

Followed up by the following (possibly more current) registration

ID: 33042
Bron: ToetsingOnline
Titel:

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

No registrations found.

In other registers

Register	ID
NTR-new	NL1861
NTR-old	NTR1973
CCMO	NL28616.072.09
ISRCTN	ISRCTN wordt niet meer aangevraagd.
OMON	NL-OMON33042

Study results

Summary results
N/A