Study to describe the processing of ropivacaine in the body when injected in the knee for pain treatment in total knee replacement surgery

Gepubliceerd: 07-08-2014 Laatst bijgewerkt: 13-12-2022

The objective of this study is to describe a pharmacokinetic profile of total and unbound plasma concentrations ropivacaine, when used for local infiltration analgesia in total knee arthroplasty

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON21012

Bron
NTR

Verkorte titel
LIAkin

Aandoening

patients requiring unilateral total knee replacement

Ondersteuning

Primaire sponsor: Sint Maartenskliniek Nijmegen
Overige ondersteuning: Sint Maartenskliniek Nijmegen

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

Mean total and unbound maximum serum concentration of ropivacaine (Cmax) and mean time to total and unbound maximum serum concentration of ropivacaine (Tmax)

Toelichting onderzoek

Achtergrond van het onderzoek

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 α1-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.

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.

Doel van het onderzoek

The objective of this study is to describe a pharmacokinetic profile of total and unbound plasma concentrations ropivacaine, when used for local infiltration analgesia in total knee arthroplasty

Onderzoeksopzet

A venous blood sample of 2-5 mL will be taken by the investigator before surgery from a PIVC before any i.v.fluid or i.v. medication is administered to the patient. During surgery a second PIVC will be placed in the contralateral arm and venous blood samples will be drawn from this catheter at 20, 40, 60, 90, 120, 240 and 360 minutes after release of the tourniquet. A last sample will be taken at 24 hours after release of the tourniquet.

Onderzoeksproduct en/of interventie

Patients will receive a total knee replacement under spinal anesthesia and Local Infiltration Analgesia (LIA) of the knee with 200 mL ropivacaine 0.2% and epinephrine.

Contactpersonen

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

- 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 under unilateral spinal anesthesia with 2 mL hyperbaric bupivacaine

- Scheduled for fast track protocol TKA

- Haemoglobin (Hb) concentration > 7.5 mMol/L

- Written informed consent

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

- 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

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Anders
Toewijzing:	N.v.t. / één studie arm
Blindering:	Open / niet geblindeerd
Controle:	N.v.t. / onbekend

Deelname

Nederland

Status:	Werving gestopt
(Verwachte) startdatum:	01-11-2014
Aantal proefpersonen:	20
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nee

Ethische beoordeling

Positief advies

Datum:	07-08-2014
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL4653
NTR-old	NTR4796
Ander register	NL50074.048.14 : 620

Resultaten

Samenvatting resultaten
Pharmacokinetics of 400 mg ropivacaine after periarticular local infiltration analgesia for total knee arthroplasty