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

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Background: Although considered safe, no pharmacokinetic data of high dose, high volume local infiltration analgesia (LIA) with ropivacaine without the use of a surgical drain or intra-articular catheter have been described. The purpose of this study is to describe the maximum total and unbound ropivacaine concentrations (C_{max}, $C_{u\ max}$) and corresponding maximum times (T_{max}, $T_{u\ max}$) of a single-shot ropivacaine (200 ml 0.2%) and 0.75 mg epinephrine (1000 μg/ml) when used for LIA in patients for total knee arthroplasty.
Methods: In this prospective cohort study, 20 patients were treated with LIA of the knee for primary total knee arthroplasty. Plasma samples were taken at 20, 40, 60, 90, 120, 240, 360 min and at 24 h after tourniquet release, in which total and unbound ropivacaine concentrations were determined.
Results: Results are given as median [IQR]. Highest ropivacaine concentration (C_{max}) was 1.06 μg/ml [0.34]; highest unbound ropivacaine concentration ($C_{u\ max}$) was 0.09 μg/ml [0.05]. The corresponding time to reach the maximum concentration for total ropivacaine was 312 min [120] after tourniquet release, and for the unbound fraction 265 [110] min after tourniquet release.
Conclusion: Although great inter-individual variability was found between the maximum ropivacaine concentrations, both maximum total and unbound serum concentrations of ropivacaine remained well below the assumed systemic toxic thresholds of 4.3 and 0.56 μg/ml.

Editorial Comment
This study demonstrated, that a single local infiltration injection of 400 mg ropivacaine, with added epinephrine, appears to be safe after knee arthroplasty. Despite large individual variation in the absorption of local anesthetics, the maximum plasma concentrations of ropivacaine stayed far below the toxic threshold of 0.56 μg/ml free ropivacaine.

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Over the past few years enhanced rehabilitation protocols (fast-track surgery protocols) were introduced for numerous surgical procedures to improve short- and long-term functional recovery, reduce morbidity, decrease length of convalescence, and increase patient satisfaction – resulting in reduced hospital costs as a secondary gain.[1,2] To facilitate enhanced rehabilitation protocols, optimal analgesia with minimal side effects should be provided. Postoperative pain treatment is an integrated part of the fast-track protocol, usually including not only pre-emptive and multimodal analgesia but also locoregional and local infiltration.

In total knee arthroplasty (TKA), local infiltration analgesia (LIA) of the knee allows immediate post-operative mobilization without side effects such as drowsiness (opioids) or impaired motor function (femoral nerve block) that impedes rehabilitation.[3,4] The LIA technique is based on local infiltration of the soft tissues surrounding the knee with a long-acting local anesthetic (LA). LIA is a straightforward and effective technique, which provides effective analgesia in the initial postoperative period after TKA and is adopted by orthopedic surgeons around the globe.[5]

Local anesthetics exert their therapeutic effect directly at the site of injection. In a continuous manner, the LA is absorbed from tissue into the central compartment and is then eliminated from the plasma. Absorption speed and peak plasma concentration vary with the site of injection and type of LA used.[6]

The commonly used local anesthetic for LIA is ropivacaine, chosen for its long-acting profile, reduced cardiotoxicity in comparison to bupivacaine and its intrinsic vasoconstrictor properties. In plasma on average 95% of ropivacaine is bound to α1-glycoprotein and approximately 5% of the total plasma concentration of ropivacaine is in the free, unionized form. Only free, unbound ropivacaine is able to cross the cell membrane of the nerve cell, exerting its pharmacological effect by blocking voltage-gated sodium channels from inside the nerve cell and preventing depolarization.

The plasma levels of ropivacaine are determined by absorption from the injection site, distribution and metabolization by cytochrome P450 enzymes in the liver and subsequent primarily urinary excretion. Plasma levels of unbound ropivacaine are, instead of bound ropivacaïne, pharmacologically active and determine if, and to what extent, systemic effects of ropivacaine occur. When the plasma concentration of unionized ropivacaine exceeds the toxic threshold in the central nervous system (CNS) or heart, symptoms of systemic toxicity occur.

Doses of ropivacaine used for LIA or peripheral nerve blocks often exceed the recommended maximum dose of 3–4 mg/kg.[7,8] Concerns have been raised about the high doses of ropivacaine used for LIA with regard to LAST (local anesthetic systemic toxicity).[9] Since LIA has only recently gained popularity, its safety track record is relatively short and so far little is known about the pharmacokinetic profile of ropivacaine applied for single-shot LIA of the knee. Thousands of patients have received LIA for TKA and to our knowledge, only one case of LAST after LIA has been described,[10] suggesting that the technique is safe. Knowledge about plasma concentrations of ropivacaine and time to reach the highest plasma concentration will help determine safe doses of ropivacaine for LIA and provide a time frame for close monitoring of patients postoperatively.

The purpose of the present study is to describe the maximum total (C_{max}) and unbound ($C_{u\ max}$), ropivacaine concentration, corresponding maximum times (T_{max} resp. $T_{u\ max}$) and proximity to the toxic threshold, when a solution of 400 mg ropivacaine (200 ml, 0.2%) and 0.75 mg epinephrine (1000 μg/ml) is used as a single-shot LIA in TKA.

Methods

Patients

All patients who were scheduled for enhanced rehabilitation protocol for primary TKA under spinal anesthesia were assessed for eligibility. Eligible patients were those aged between 50–80 years with ASA physical health classification I-II, BMI < 40 and Hb ≥ 7.5 mmol/l. Exclusion criteria were placement of a surgical drain, known hypersensitivity to amide-type local anesthetics, known history of hepatic or renal

insufficiency, and use of any medications that affect the clearance of ropivacaine.[8]

Before onset of participant enrolment, this prospective cohort study was approved by the Medical Research Ethics Committee Slotervaart Hospital and Reade and registered at the Netherlands Trial Registry (http://www.trialregister.nl, NTR4796). All eligible patients were informed verbally and in writing about the study and written informed consent was obtained from all participating patients. The study was conducted at the Sint Maartensklinniek Nijmegen, the Netherlands between January and May 2015 according to the Declaration of Helsinki and later revisions thereof and in accordance with the ICH guidelines for Good Clinical Practice.

Anesthetic and surgical procedure

All patients were treated according to the standard hospital enhanced rehabilitation protocol. Basic oral pain treatment was started pre-operatively at the day of the surgery: paracetamol 1000 mg four times daily, etoricoxib 90 mg once daily, and gabapentin 300 mg and 600 mg both once daily (patients older than 70 years 300 mg twice daily). Pre-medication consisted of 10 mg oxazepam orally. Additional pain therapy was started when the postoperative pain score (Numerical rating scale, NRS) was ≥ 4.

Surgery was performed under spinal anesthesia and upon patient request supplemented with sedation using propofol. Before placement of spinal anesthesia, intravenous access and routine monitoring (ECG, non-invasive blood pressure and peripheral oxygen saturation) was established in all patients.

Spinal anesthesia was performed with the patient in the sitting position at the third or fourth lumbar interspace. After obtaining a free flow of cerebrospinal fluid, 10 mg hyperbaric bupivacaine was administered and the patient was placed in the lateral decubitus position with the operative side dependent. The lateral decubitus position was maintained for 20 min with the aim of obtaining a preferential sensory and motor block on the operative side.

A pneumatic tourniquet, inflated to 100 mmHg above normal systolic pressure, with a maximum of 300 mmHg, was used on the patient's thigh to diminish blood loss. Cemented posterior-stabilized total knee replacement with patella resurfacing, was performed according to standard hospital procedure. After cementing, the knee was infiltrated by the orthopedic surgeon. A total of 300 mg ropivacaine 0.2% (150 ml) was mixed with 0.75 ml epinephrine (1000 μg/ml). Two thirds of this solution was injected in the posterior and one-third in the anterior capsule. After closure of the parapatellar arthrotomy, another 100 mg of ropivacaine 0.2% (50 ml) without epinephrine was infiltrated in the subcutaneous tissues. Just before tourniquet release, patients received an i.v. bolus of 10 mg/kg tranexamic acid with a maximum of 1000 mg. All patients received a compression bandage before transfer to the recovery room.

Blood sampling and assays

Pre-operatively, before any intravenous fluids were administered to the patient, a baseline blood sample was taken. Before start of the surgery, all patients received two peripheral intravenous catheters (PIVC). One of the PIVCs, at least 16G in size, was placed in the antecubital vein or great saphenous vein and was only used for blood sampling. No intravenous fluids were administered through this PIVC. Venous blood samples were taken at 20, 40, 60, 90, 120, 240, and 360 min and at 24 h by one of the investigators (MF/SB) after release of the tourniquet.

At each collection moment, two samples of 5 ml blood were drawn. The first sample was drawn and discarded, as this sample was diluted with NaCl 0.9%. The second (undiluted) 5 ml was kept in an EDTA tube, centrifuged within 1 h after collection and stored at −80°C until assay of the whole batch. Total ropivacaine concentrations were determined in all serum samples. After determining the sample with the highest total concentration per patient, the unbound ropivacaine levels were determined in ultra filtrates of these samples as well as in the samples taken immediately before and after this time point. Ropivacaine levels were detected by a validated liquid chromatography – tandem mass spectrometry (LCMSMS) method as previously described.[11]

Sample size and statistics

The study was designed to describe the pharmacokinetic profile of 400 mg ropivacaine with epinephrine, when used for LIA of the knee. Because a sample size calculation is not possible in a descriptive study, we based the chosen sample size on experience and common sense. In case of small inter-individual variation and a homogenous study group, a sample size of six subjects is well accepted for pharmacokinetic studies. Since the study subjects in our study are heterogeneic and more than one variable is measured, a larger sample size is required. We assumed that a sample size of 18 subjects would be appropriate, allowing for subjects to withdraw during the study period we chose to include 20 subjects. Analysis was conducted using GraphPad Prism 6 software (GraphPad Software Inc, San Diego, CA, USA). Frequency distribution was tested using Kolmogorov–Smirnov test for normality. Normally distributed data are presented as mean (SD) and non-normal distributed data are presented as median [IQR]. Primary end points were peak serum concentration of total ropivacaine in plasma (C_{max}) and unbound ropivacaine in ultra-filtrate ($C_{u\ max}$) and the corresponding times to reach peak concentrations in serum (T_{max} and $T_{u\ max}$, respectively).

Results

All patients completed the study protocol. None of the patients showed any sign of LAST. Patient characteristics are shown in Table 1.

Pharmacokinetic data

A summary of the pharmacokinetic data is given in Table 2. In eight samples the unbound ropivacaine concentration was below the lower limit of quantitation (< 0.05 μg/ml). For further calculations these samples were classified as 0.05 μg/ml to prevent underestimation of mean $C_{u\ max}$.

Table 1 Patient characteristics.

Sex (M/F)	12/8
Age (year)	58.5 ± 6.7
Weight (kg)	89 ± 14
Height (m)	1.73 ± 0.10
BMI (kg/m^2)	30 ± 4

Values are proportions or mean ± SD.

Table 2 Pharmacokinetic parameters.

	Median [IQR]
C_{max} (μg/ml)	1.00 [0.34]
T_{max} (min)	240 [120]
$C_{u\ max}$ (μg/ml)	0.09 [0.05]
$T_{u\ max}$ (min)	300 [110]

C_{max}, maximum total ropivacaine concentration; T_{max}, time to C_{max}; $C_{u\ max}$, maximum free ropivacaine concentration.;$T_{u\ max}$, time to $C_{u\ max}$.

Median peak plasma concentration of total ropivacaine (C_{max}) was 1.06 μg/ml [0.34], median time to reach maximum plasma concentration (T_{max}) was 240 min [120]. Figure 1 shows the pharmacokinetic data; Fig. 2 shows total ropivacaine plasma concentrations for all individual patients. Median peak plasma concentration of unbound ropivacaine ($C_{u\ max}$) was 0.09 μg/ml [0.05], median $T_{u\ max}$ was 300 min [110].

Raw data of total and unbound ropivacaine are presented in Table 3.

Discussion

This is the first study that describes the pharmacokinetic profile of ropivacaine after high dose, high volume, single-shot LIA of the knee with

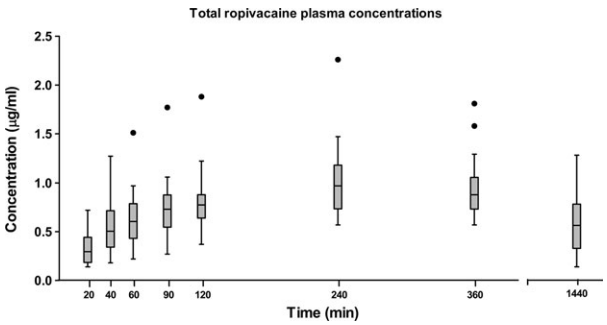

Fig. 1. Median total ropivacaine concentrations. Data are presented as median with first and third quartiles, whiskers represent data in 1.5 interquartile range with outliers plotted as individual points (Tukey boxplot).

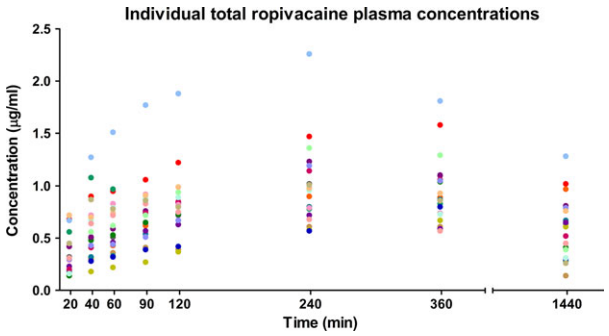

Fig. 2. Individual datapoints of total ropivacaine plasma concentrations.

epinephrine, without the use of a periarticular catheter or surgical drain. We found a great inter-individual variation in the plasma concentration of ropivacaine, but even the highest measured C_{max} (2.26 µg/ml) and $C_{u\ max}$ (0.13 µg/ml) are well below the toxic threshold described by Knudsen et al. in 1997, which were 4.3 and 0.56 µg/ml, respectively.[12]

In the literature, many different procedures of LIA for knee surgery are described with varying doses of ropivacaine and additives such as epinephrine or analgesics. Some authors use an intra- or periarticular catheter for continuous postoperative ropivacaine infusion, and sometimes a surgical drain is left at the operative site. These variations in technique may influence the efficacy of the LIA in terms of pain relief, but they may affect ropivacaine plasma concentrations as well.

The first to describe the pharmacokinetic profile of ropivacaine LIA after TKA was Affas et al. in 2012.[13] They studied pharmacokinetics of 300 mg ropivacaine, epinephrine and additional ketorolac by taking blood samples at 40 and 60 min, and at 2, 4, 6, 12, 24 h after tourniquet release. Slightly lower mean maximum ropivacaine concentrations (mean: 0.813 µg/ml, range: 0.435–1.735 µg/ml) were found compared to our study. They found the T_{max} between 4–6 h after tourniquet release and, also similar to our study, some of the patients showed the highest plasma concentrations at 24 h after tourniquet release. They slightly lower peak plasma concentrations they found can be explained by the 25% lower dose compared to our study.

The cause of the great inter-individual variety of plasma concentrations and time to peak plasma concentrations is unclear. Patient characteristics such as protein-binding capacity and speed of elimination through cytochrome P450 enzymes may be a factor. Also, the adding of epinephrine to the ropivacaine could be of influence, slowing the uptake of ropivacaine by its vasoconstrictive properties, and possibly the injection technique may also contribute to plasma absorption of ropivacaine.

Brydone et al.[14] used 400 mg ropivacaine for LIA, a similar dose as in our study, without added epinephrine and they found a more rapid rise in plasma concentration, with a peak concentration at 20 min after tourniquet release. A maximum peak concentration of 3.093 µg/ml was found, 37% higher than our maximum. In contrast to our protocol, an intra-articular catheter was placed infusing 20 mg ropivacaine per hour, therefore making it unclear whether the rapid rise in plasma concentration and higher peak plasma concentration is due to the intra-articular catheter or to the absence of epinephrine.

In their study, potential toxic concentrations of total ropivacaine were reached in two patients. However, their highest mean free ropivacaine concentration was 0.041 µg/ml (SD 0.023) at $t = 20$ min, overall sample concentrations varied from 0.001 µg/ml to 0.104 µg/ml and thus stayed far below the toxic threshold.

Another study combined 375 mg ropivacaine with epinephrine as LIA with two infusion catheters, both infusing 40 mg/h.[15] Patients reached the maximum unbound ropivacaine concentration 6 h after ropivacaine injection, however, maximum total plasma concentrations were reached 24 h after the end of surgery. Despite the additional 192 mg administrated via both catheters, maximum total and unbound ropivacaine concentrations were slightly lower (0.888 µg/ml (0.539–1689) and 0.050 µg/ml (0.025–0.105), respectively) as compared to our study, which could be explained by the surgical drain. An average volume of 600 ml shed blood with high ropivacaine concentrations was collected via the surgical drain in the first 6 h after surgery. Like in our study, free fractions were here highly variable; with a range of 2.7–12.6% and an average free fraction of 4.8%.

Table 3 Peak total and unbound ropivacaine plasma concentrations.

	Peak concentration				Measurement just before peak concentration				Measurement just after peak concentration			
Patient	Time (min)	Total conc. (μg/ml)	Free conc. (μg/ml)	% free	Time (min)	Total conc. (μg/ml)	Free conc. (μg/ml)	% free	Time (min)	Total conc. (μg/ml)	Free conc. (μg/ml)	% free
1	360	1.05	0.11	10.5	240	1.02	0.07	6.9	1440	0.64	0.05	7.8
2	90	0.92	0.07	7.6	60	0.83	0.07	8.4	120	0.82	0.06	7.3
3	40	1.08	0.06	5.6	20	0.56	0.05	8.9	60	0.97	0.07	7.2
4	360	0.89	0.10	11.2	240	0.90	0.07	7.8	1440	0.97	0.08	8.2
5	360	1.04	0.09	8.7	240	1.01	0.10	9.9	1440	0.41	<0.05	Na
6	240	1.19	0.08	6.7	120	0.67	<0.05	Na	360	1.05	0.09	8.6
7	360	0.67	0.11	16.4	240	0.58	0.08	11.8	1440	0.61	0.07	11.5
8	250*	0.61	<0.05	Na	120	0.39	<0.05	Na	370*	0.61	0.06	9.8
9	240	0.72	0.05	6.9	120	0.63	<0.05	Na	360	0.59	0.05	8.4
10	360	1.58	0.13	8.2	240	1.47	0.12	8.1	1440	1.02	0.06	5.9
11	250*	0.96	0.05	5.2	120	0.89	0.06	6.7	360	0.73	0.05	6.8
12	360	0.80	<0.05	Na	240	0.57	<0.05	Na	1440	0.30	<0.05	Na
13	240	1.14	0.08	7.0	120	0.85	0.06	7.1	360	1.06	0.09	8.5
14	360	0.87	0.05	5.7	240	0.80	0.06	7.5	1440	0.67	0.05	7.5
15	240	1.23	0.08	6.5	120	0.84	0.08	9.5	360	1.10	0.10	9.1
16	120	0.99	0.08	8.1	90	0.91	0.08	8.8	240	0.98	0.08	8.2
17	240	2.26	0.12	5.3	120	1.88	0.10	5.3	360	1.81	0.13	7.2
18	90	0.83	0.09	10.8	60	0.72	0.07	9.7	120	0.75	0.08	10.7
19	240	1.36	0.11	8.1	120	0.94	0.06	6.4	360	1.29	0.11	8.5
20	240	1.01	0.09	8.9	120	0.80	0.09	11.3	360	0.86	0.06	7.0

Total ropivacaine serum concentrations (μg/ml) and corresponding unbound ropivacaine ultra-filtrate concentrations (μg/ml). Na, not applicable. *Samples drawn 10 min later than scheduled due to logistic reasons.

A limitation of our study is the scarcity of samples between 6 and 24 h, just after the peak concentration. Based on the literature available when we designed the study, we had expected a much faster uptake of ropivacaine. Brydone et al. and Ng et al.[16] found a T_{max} of 30 min after LIA resp. intra-articular administration of ropivacaine without epinephrine, while Thomassen et al.[15] and Affas et al.[13] found the T_{max} 4–6 h after the administration of LIA with added epinephrine. These two latter studies encountered the same problem of 'missing' peak plasma concentrations in the sampling scheme. Unfortunately both these studies were yet to be published when we designed our study and we used the sampling scheme of the two first studies, expecting an earlier rise in plasma concentrations.

One of our patients had unexpected early peak plasma concentrations. Peak concentrations were found in the first hour after tourniquet release, while C_{max} was comparable with other

patients (Table 3, patient 3). In this patient, the analgesia was already insufficient from 1.5 h after tourniquet release. This patient was successfully titrated with intravenous morphine and clonidine. The early rise of plasma ropivacaine and insufficient analgesia may be explained by rapid intravenous absorption of ropivacaïne, the cause of which is unknown.

In our study, we used 150 ml ropivacaine 0.2% with-, and without epinephrine. The ropivacaine with epinephrine was injected in the periarticular tissue. After closure of the knee capsule, the subcutaneous tissue of the knee was infiltrated with 50 ml of ropivacaine without epinephrine in order to prevent blistering of the skin. Compared with ropivacaine with epinephrine, the portion of ropivacaine without epinephrine will be absorbed more rapidly with an expected C_{max} of 20 min after tourniquet release.[14] From a theoretical perspective, this portion may be expected to contribute to the rise in the plasma concentration of ropivacaine especially during the first 20–40 min. However, since the plasma concentration continued to rise well beyond 40 min, we do not believe that the portion of ropivacaine without epinephrine affected the C_{max} an T_{max} found in our study.

We cannot exclude the possibility that the true maximum plasma concentration lies between 4 and 6 or even 6 and 24 h in some patients. This T_{max}, which appears to be at least later than 4 h after tourniquet release, makes monitoring the patients, until beyond this point, logistically and financially challenging. In addition, prolonged monitoring would also interfere with the principles of fast track recovery. Although actual maximum plasma concentrations may be missed in our study, maximum plasma levels of unbound ropivacaine remain so far below toxic concentrations that LIA with high-dose ropivacaine and added epinephrine can be considered safe. Prolonged monitoring is in our opinion therefore not necessary.

This pharmacokinetic study was not powered to investigate the incidence of LAST, however, based on current data there are no indications that the use of 400 mg ropivacaine combined with epinephrine in TKA yields a high risk of LAST. Knudsen et al.[12] defined the unbound ropivacaine toxic threshold in arterial samples to be 0.56 (range: 0.34–0.85) μg/ml. With a maximum unbound ropivacaine concentration of 0.13 μg/ml when ropivacaine is used for LIA, the peak concentration remains far below the toxic threshold.

In conclusion, a single shot of 400 mg ropivacaine with added epinephrine for LIA after TKA appears to be safe, the maximum plasma concentrations of ropivacaine stay far below the toxic threshold of 0.56 μg/ml free ropivacaine. However, because of great inter-individual variety in the absorption of local anesthetics and in the threshold of local anesthetic toxicity, sporadic cases of LAST may still occur. The time to reach C_{max} might be several hours after tourniquet release, this slow absorption is contributing to the safety profile of high-dose ropivacaine for LIA.

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