Continuous extrapleural infusion of ropivacaine 0.2% after cardiovascular surgery via the lateral thoracotomy approach

Maurer, K ; Blumenthal, S ; Rentsch, K M ; Schmid, E R

DOI: https://doi.org/10.1053/j.jvca.2007.06.005

Continuous Extrapleural Infusion of Ropivacaine 0.2 % following Cardiovascular Surgery with Lateral Thoracotomy Approach

Konrad Maurer*; Stephan Blumenthal†; Katharina M. Rentsch ‡; Edith R. Schmid*¶

*Division of Cardiovascular Anesthesia, University Hospital of Zurich, Switzerland; †Department of Anesthesiology, Orthopedic University Clinic Balgrist, Zurich, Switzerland; ‡Institute of Clinical Chemistry, University Hospital, Zurich, Switzerland; ¶Head of Divison, University Hospital of Zurich, Switzerland

Acknowledgment:

Burkardt Seifert, PhD, Department of Biostatistics, ISPM, University Zurich

Address correspondence and reprint requests to Konrad Maurer, MD. *Present address:

Neural Plasticity Unit
Institute of Child Health
University College London
30, Guilford Street
London WC1N 1EH
United Kingdom
e-mail: konrad.maurer@googlemail.com
pone: +44 7843053363
fax. +44 2079052133

Support was provided solely from departmental sources and no conflict of interest exists.

Abstract

Objective: The pharmacokinetics of ropivacaine 0.2% were evaluated during a 48-h continuous extrapleural infusion with two different infusion rates, in patients undergoing cardiovascular surgery. We tested the hypotheses that no toxic plasma concentrations of ropivacaine would be reached and that proportionality exists between plasma concentrations and dosage used.

Design: The study had a prospective, randomized, non-blinded design.

Setting: The investigation was performed as a single-centre study in the Division of Cardiovascular Anesthesia, University Hospital of Zurich.

Participants: We enrolled 17 consenting adults scheduled for elective cardiovascular surgery, with or without extracorporeal bypass, with lateral thoracotomy approach.

Interventions: For postoperative pain relief, patients were randomly assigned to receive continuous extrapleural infusion of ropivacaine 0.2% at a rate of either 6 or 9ml/hr over 48 hours.

Measurements and Main Results: Plasma concentrations of ropivacaine reached toxic levels (>2.2 mg/L) in 25% of cases. No proportionality of plasma concentrations of ropivacaine existed when the two dosing regimens were compared.

Conclusions: Plasma concentrations of ropivacaine, administered at the given dose and rates during continuous extrapleural infusion, are unpredictable and may reach toxic levels in patients undergoing major cardiothoracic surgery.

Introduction

For patients selected for cardiovascular surgery, the left thoracotomy approach is a suitable alternative to the standard median sternotomy (1). However, pain after thoracic surgery has long been recognized as a cause of postoperative pulmonary morbidity (2), and is associated with inadequate ventilation, insufficient coughing, atelectasis, mucous plugging, hypoxia, and pulmonary infection (3,4). Parenteral opioids relieve acute postoperative pain in many patients at rest, but are associated with side effects such as respiratory depression, nausea, and bowel dysfunction.

The health of patients undergoing cardiovascular surgery is often compromised by cardiac performance and pulmonal function. This limits the postoperative administration of opioids. Epidural analgesia has been widely advocated as a means of controlling postthoracotomy pain (5,6), but its use is controversial when extracorporeal circulation is used (7).

The use of an extrapleural catheter, originally described by Sabanathan and associates (8), is a valid alternative to continuous epidural analgesia for relieving postthoracotomy pain (2,9,10). In contrast to bupivacaine, only one study provides information about the pharmacokinetics and efficacy of ropivacaine during long-term continuous extrapleural infusion (11). It is thought to possess a greater margin of safety than bupivacaine, however (12,13).

The aim of this study was to evaluate the pharmacokinetics of a 48-hour continuous extrapleural ropivacaine infusion following cardiovascular surgery with lateral thoracotomy. We assessed the pharmacokinetics of ropivacaine

0.2%, applied at a rate of 6 or 9ml/h. The primary endpoints were the plasma concentrations of total and unbound ropivacaine, and [alpha]$_1$-acid glycoprotein. Our hypotheses were that no toxic plasma concentrations of ropivacaine would be reached (12) and that proportionality exists between plasma concentrations and dosage used.

Materials and Methods

Patients

We performed a power analysis using previously published data (14) to determine the sample size where blood concentrations of total and unbound ropivacaine at the chosen infusion rates are expected to be different:. A two sided t-test with an error level of 0.05 and a power of 80% resulted in a sample size of total 16 patients. After obtaining institutional ethics committee approval (University Hospital of Zurich, Switzerland) and written informed consent, adult patients were prospectively enrolled when scheduled for elective cardiovascular surgery – with or without extracorporeal circulation - in which lateral thoracothomy was the chosen surgical approach. Exclusion criteria were any contraindications to extrapleural analgesia (such as pleural disease); known allergy to ropivacaine, propacetamol, and nicomorphine; administration of local anesthetics within 7 days prior to the present study; pregnancy and women without adequate contraception; concomitant medication with potent cytochrome P-450 1A2 inhibitors (such as fluvoxamine and ciprofloxacin); gamma-GT >100IU/l; creatinine >2.4mg/dl; neurologic disease and neuropsychiatric disorders.

Surgical procedures

Using computer-generated randomization, patients were allocated to receive a continuous extrapleural infusion of ropivacaine 0.2% postoperatively, at a rate of either 6 or 9 ml/h (12 or 18 mg/h). These infusion rates were chosen in order to compare the results directly with the study of Ekatodramis et al. (14). Intraoperative analgesia was performed with fentanyl (Fentanyl-Janssen®

Janssen-Cilag AG, Switzerland), max. 0.01mg/kg, given within the first two hours of surgery and then completed with remifentanil (Ultiva® GlaxoSmithKline AG, Switzerland) continuous infusion according to the patients needs. One-lung ventilation was introduced before thoracotomy was performed at the level of the 4^{th} to 5^{th} intercostal space, without fracturing a rib. The cannulation techniques for the extracorporeal perfusion – if needed - varied between cases according to the need of the procedure (full or partial cardiopulmonal bypass, selective cerebral perfusion). At the end of the operation and before closing the thoracic wall, the surgeon created an extrapleural pocket for two to three interspaces above and below the thoracotomy. A multiorifice catheter (20-gauge, SIMS Portex Ltd. Hythe, UK) was placed with the catheter in the inferior part of one pocket and the tip directed to the superior part as described by Watson et al. (15). 10mL sodium chloride 0.9% were injected to prevent occlusion of the catheter. Sedated and ventilated patients were then transferred to the intensive care unit. Sedation and analgesia continued with propofol (Disoprivan® 2%, AstraZeneca AG, Switzerland) and remifentanil until patients were hemodynamically stable and core temperature was at least 36°C. By the time the patients recovered from sedation and the visual analog scale (VAS; ranging from 0mm = 'no pain' to 100mm = 'worst pain imaginable') was >30mm (defined as time t_0), a bolus of 30ml ropivacaine 0.2 % (Naropin® 0.2%, AstraZeneca AG, Switzerland) was administered through the extrapleural catheter for an initial block. A continuous infusion of 6ml /h or 9ml/h ropivacaine 0.2% through the extrapleural catheter was administered immediately thereafter. 1g paracetamol (Perfalgan® 1g, UPSAMEDICA GmbH, Switzerland) was given every 6 hours and intravenous nicomorphine (Vilan®, SYNMEDIC AG, Switzerland) was scheduled for breakthrough pain. No specific study fluid

management was pursued. Replacement was guided by basal need, blood loss, blood pressure, coagulation and excretion. Extrapleural infusion of ropivacaine was maintained for 48h (t_{48}).

Pain was assessed by nurses or the investigator, who were not blinded to the infusion rate, every 20 minutes for the first hour after arriving on ICU and then hourly until t_{48}. Special attention was given to clinical signs and symptoms of local anesthetic toxicity such as light-headedness, tinnitus and seizures, noting that those signs could be tempered by paracetamol or nicomorphine.

Sample collection and analysis

Blood was collected from a central venous line which was used only for the administration of Ringer's lactate. Blood samples of 8ml were taken at the following timepoints: t= 1/6, 1/3, 1/2, 1, 3, 6, 18, 30, 48, 50, 52 and 54 hours. The samples were taken in heparinized tubes (Venoject®; Terumo, Leuven, Belgium), and plasma was separated by centrifugation at room temperature within 60min of collection. The plasma was stored at -20°C until drug assay. Total plasma concentrations of ropivacaine and unbound plasma concentrations of ropivacaine were determined. Levels of $[alpha]_1$-acid glycoprotein were also measured because it has the potential advantage to buffer the free concentration of ropivacaine, providing a protective mechanism against toxic reactions. The total ropivacaine plasma concentration was determined by liquid chromatography with mass spectrometry using electrospray ionization. Unbound plasma ropivacaine fraction was determined by the same method following ultrafiltration of the sample. Concentration of $[alpha]_1$-acid glycoprotein was measured by nephelometry.

Data analysis and statistics

The highest drug concentration after the start of the extrapleural infusion (C_{max}), the time to reach C_{max} (t_{max}), and the plasma concentration at the end of the infusion (C_{end}) were derived directly from the data for total and unbound ropivacaine. The unbound fraction (fu) of ropivacaine was calculated as unbound concentration (C_u) divided by total concentration in the same sample. Following the end of infusion, the terminal half-life ($t_{1/2}$) was determined for total ropivacaine by linear regression of the four last data points on the plasma concentration-*versus*-time curve. Plasma clearance of total (CL_{tot}) and unbound (CL_u) were estimated after 6 hours and at the end of the infusion, assuming steady state at those time points after extrapleural administration i.e., CL_{tot} = rate of infusion/C_{tot}. Using the linear trapezoidal rule, the area under the total (AUC_{total}) as well as the unbound ($AUC_{unbound}$) plasma concentration-time curve was calculated by numeric integration for the time during the continuous infusion ($t_0 - t_{48}$).

For data analysis *STATISTICA* software version 6 (StatSoft©) was used. To analyze demographic and surgical data, amount of fentanyl intraoperatively, time between end of surgery and injection of the first bolus of ropivacaine at t_0, amount of blood products during the study period ($t_0 - t_{54}$), postoperative consumption of intravenous nicomorphine and pharmacokinetic data (C_{max}, t_{max}, fu, $t_{1/2}$, CL_{tot}, $CL_{u,app}$, AUC) a Mann-Whitney test was used. Fisher's exact test was used to compare categorical data. ANOVA corrected for repeated measures was applied to compare plasma concentrations of total and unbound ropivacaine and of $[alpha]_1$-acid glycoprotein. The relationship between protein concentration, total dose per bodyweight or time and fraction of unbound

plasma concentration was studied by fitting a multiple regression line to the data. Simple linear regression was used to study the relationship between weight, height, blood loss, substituted blood products, liver function parameters, fluid balance and infusion rate for both total and unbound plasma concentration. All results are presented as mean ± SD or median/upper quartile/lower quartile. A *P* value <0.05 was considered to be statistically significant.

Results

Patients and surgical procedures

A total of 17 patients were enrolled in the study: 9 patients were randomized to receive ropivacaine 6ml/h and 8 patients to receive 9ml/h. One patient in the 9ml/h group was excluded from the study because the extrapleural catheter was removed during reexploration of the thorax. Data from 9 patients in the 6ml/h group and 7 patients in the 9ml/h group were analyzed. 11 patients received a thoracic aorta graft or a mitral valve repair, 1 patient underwent aortic isthmus stenosis graft repair, 1 closure of atrial septal defect and 3 patients had surgery for other problems.

Demographic data were statistically similar in both groups, as summarized in Table 1. Also, the surgery time, time between end of surgery and injection of the first bolus of ropivacaine (t_0), the amount of blood products needed during the study period, and the time of extracorporeal circulation did not differ between the two study groups (Table 2). However, there was an unexplained trend towards longer surgery time, longer time of extracorporeal circulation and higher need for fluid and blood product replacement in the higher dosage group.

Pharmacokinetic data

Plasma concentrations of total and unbound ropivacaine and of $[alpha]_1$-acid glycoprotein increased constantly during the continuous infusion in both groups, without reaching a clear steady state (Figure 1).

Table 3 shows measured and calculated pharmacokinetic data in the two groups. The only significant differences observed between the two groups were in the unbound fractions (fu_{30min} and fu_{end}, P <0.001). The unbound fractions decreased significantly over time within each group (fu_{30min} and fu_{end}, P <0.05).

The total plasma clearance (CL_{tot}) and the calculated unbound ropivacaine clearance (CL_u) were independent of the infusion dose, but decreased significantly between 6 hours and the end of treatment: Cl_{tot} in the 6ml/h group decreased by 33% (range -6 to –46%); Cl_{tot} in the 9ml/h group decreased by 48% (range -15 to –74%); Cl_u in the 6ml/h group decreased by 52% (range -20 to –110%); Cl_u in the 9ml/h group decreased by 70% (range -13 to –190%) (*P* <0.05 for all values).

In order to measure the average total and unbound ropivacaine concentrations during the infusion period, the area under the curve (AUC) was calculated. AUC^{total} was equal for both groups (6ml/h: 18.9 ± 10.9mg*s*l^{-1}; 9ml/h vs. 22.0 ± 15.5mg*s*l^{-1}, *P*=0.64). $AUC^{unbound}$ was significantly different between the groups (6ml/h: 0.35 ± 0.17mcg*s*l^{-1} vs. 9ml/h: 0.83 ± 0.55mcg*s*l^{-1}, *P*=0.02) (Figure 2). A significant postoperative increase in $[alpha]_1$-acid glycoprotein levels was observed between the start and end of the extrapleural infusion in both groups (6ml/h: 0.77 ± 0.43mg/ml vs. 1.47 ± 0.50mg/ml, *P* <0.05; 9ml/h: 0.79 ± 0.42mg/ml vs. 1.60 ± 0.57mg/ml, *P*<0.05). However, $[alpha]_1$-acid glycoprotein levels were similar in both goups.

The terminal half-life after the end of the infusion was 4.9 ± 3.2h in the 6ml/h group and 6.9 ± 4.8 h in the 9ml/h group (*P*>0.05) (Table 3). No linear correlation could be established between the highest concentration of total or unbound plasma concentration of ropivacaine and weight, height, blood loss, substituted blood products, liver function parameters, infusion rate of ropivacaine or fluid balance. Also, plasma concentrations of ropivacaine and $[alpha]_1$-acid glycoprotein did not correlate with presence of extracorporeal circulation. Multiple linear regression revealed that the level of $[alpha]_1$-acid glycoprotein was significantly correlated with levels of unbound ropivacaine in

plasma (r=0.95, *P* <0.001, n=12). Total ropivacaine plasma concentration, total dose per body weight and time had no correlation.

During the investigation, no symptoms of local anasthetic toxicity or clinical signs of local inflammation at the catheter insertion site were observed.

The 6ml/h group required a higher amount of nicomorphine for breakthrough pain (6ml/h: 1.5 ± 1.3mg/kg vs. 9ml/h: 0.4 ± 0.3 mg, *P*<0.01), measured 48 hours after starting the infusion. There was a trend for higher VAS values in the 6ml/h group (Figure 3).

Discussion

The main conclusion of this study is that, during continuous extrapleural infusion of ropivacaine 0.2% for postthoracotomy pain, plasma concentrations of total and unbound ropivacaine are unpredictable. In addition, toxic ropivacaine levels were reached in 25 % of patients in the study population (1 case in the low dosage group and 3 cases in the high dosage group).

Several aspects of our results were not in accordance with previous investigations. In contrast with previous studies, we did not observe significant dose-proportional increases in plasma concentrations of total or unbound ropivacaine following infusion (14,16,17). Furthermore, we did not observe any correlations between maximum concentrations of total or unbound ropivacaine and factors (such as body weight, height, blood loss, substituted blood products, fluid balance, liver function parameters, use of extracorporeal circulation or dose per bodyweight) that may influence ropivacaine concentrations.

In four patients, total ropivacaine concentrations exceeded 2.2mg/L, a level previously determined toxic in healthy subjects after intravenous infusion of ropivacaine (12). Three of those patients were in the high dosage group, suggesting that 9ml/h of ropivacaine 0.2% is too a high dosage for extrapleural analgesia. In contrast to a continuous interscalene infusion (14), the dynamics of drug dispersal into tissues varies more because distribution can be into vessel rich zones within the intercostal space or into the slowly absorbent tissue over the vertebral bodies (18). However, with a steady infusion rate, the

differences in the kinetics of absorption should not influence the variability of plasma concentrations of the local anasthetic.

In accordance with previous studies, concentrations of unbound ropivacaine - primarily responsible for systemic toxic effects - did not exceed 0.08 in the low infusion group and 0.2 in the high infusion group. Threshold levels for central nervous system toxicity reported by Knudsen et al. were 0.34 – 0.85 mg/l. In this study, the range between concentrations of unbound ropivacaine was considerably wider and the course over time more dispersed, especially in the 9ml/h group. This finding is best illustrated by the difference in $AUC^{unbound}$ between the two groups, whereas AUC^{total} was not different (Figure 2).

Plasma levels of [alpha]$_1$-acid glycoprotein increase as a cytokine-triggered response to inflammation following major surgery. The availability of [alpha]$_1$-acid glycoprotein as a binding partner is a key factor determining plasma concentrations of unbound ropivacaine. Our results confirm a strong relationship between [alpha]$_1$-acid glycoprotein and unbound ropivacaine. This finding was consistent between groups and independent of other factors such as extracorporeal circulation with its possible role of disturbed hepatic perfusion. We therefore can assume that the increase in [alpha]$_1$-acid glycoprotein enhances protein binding of unbound ropivacaine and therefore decreases the unbound fraction, confirming the results of earlier trials (14). However, a recent investigation highlighted the inter-individual variability of [alpha]$_1$-acid glycoprotein and its impact on the plasma concentration of unbound ropivacaine (19). According to this report, the binding capacity of unbound ropivacaine was variable due to different individual variants of [alpha]$_1$-acid glycoprotein.

The significant decrease in the estimated clearance of ropivacaine between 6 hours and the end of the infusion suggests that a steady state was not reached after 48 hours. Although only an estimate of the actual value, these observations strongly contrast with previous studies that reported stable unbound concentrations during continuous infusion (11,14,20). A possible explanation is variability in the intrinsic metabolic clearance of ropivacaine (CL_{int}), assuming that the hepatic extraction ratio of ropivacaine is low and the intrinsic clearance corresponds to the unbound clearance (CL_u). This is supported by our results, in which the plasma clearance of ropivacaine also showed a marked and consistent decrease in the unbound fraction. We assume that steady state would have been reached later and therefore, a longer study period (>48 hours) would provide more information, although at an increased risk of toxicity.

It is unlikely that a single factor alone led to the unpredictable plasma ropivacaine concentrations observed in the current study. We propose, rather, that a combination of factors such as patient co-morbidities (average ASA score 3.4), and surgeries associated with mayor fluid shifts were reflected in our findings.

Previous studies agree on the safety of higher doses of a continuous infusion of ropivacaine. However, our results point out a possible, important caveat, that concentrations of total and unbound ropivacaine may be extremely variable in patients with a high ASA class undergoing cardiovascular surgery. As we have

previously suggested, a sound evaluation of the indications and concentrations used for such procedures is urgently needed (21).

The first priority is, of course, the efficacy of the method. This technique has been shown to be as effective as epidural analgesia for postoperative thoracotomy pain relief (10,15,22,23). Our results indicate a greater need for pain medication in the 6ml/h group than in the 9ml/h group, although we cannot draw conclusions from this observation because the study was not designed to measure the efficacy of pain relief. For this purpose, the study would require a greater sample size to overcome the intersubject variability seen in our trial, and include a control group.

In summary, our study showed that in patients undergoing major cardiothoracic surgery, plasma concentrations of total and unbound ropivacaine are unpredictable during continuous extrapleural infusion. Furthermore, we identified a high risk of reaching toxic concentrations of ropivacaine using this methodology. We therefore advise a cautious use of continuous extrapleural infusion of ropivacaine in this population.

References

1. Pratt JW, Williams TE, Michler RE, Brown DA. Current indications for left thoracotomy in coronary revascularization and valvular procedures. The Annals of Thoracic Surgery 2000;70:1366-70.

2. Sabanathan S, Eng J, Mearns AJ. Alterations in respiratory mechanics following thoracotomy. J R Coll Surg Edinb 1990;35:144-50.

3. Ballantyne JC, Carr DB, deFerranti S, et al. The comparative effects of postoperative analgesic therapies on pulmonary outcome: cumulative meta-analyses of randomized, controlled trials. Anesth Analg 1998;86:598-612.

4. Craig DB. Postoperative recovery of pulmonary function. Anesth Analg 1981;60:46-52.

5. Kaplan JA, Miller ED, Jr., Gallagher EG, Jr. Postoperative analgesia for thoracotomy patients. Anesth Analg 1975;54:773-7.

6. Logas WG, el-Baz N, el-Ganzouri A, et al. Continuous thoracic epidural analgesia for postoperative pain relief following thoracotomy: a randomized prospective study. Anesthesiology 1987;67:787-91.

7. Smith BE. Epidural Anesthesia/Analgesia and Coronary Artery Bypass Surgery Utilizing Extracorporeal Circulation. Chest 2005;128:1097-9.

8. Sabanathan S, Smith PJ, Pradhan GN, et al. Continuous intercostal nerve block for pain relief after thoracotomy. Ann Thorac Surg 1988;46:425-6.

9. Deneuville M, Bisserier A, Regnard JF, et al. Continuous intercostal analgesia with 0.5% bupivacaine after thoracotomy: a randomized study. Ann Thorac Surg 1993;55:381-5.

10. Kaiser AM, Zollinger A, De Lorenzi D, et al. Prospective, randomized comparison of extrapleural versus epidural analgesia for postthoracotomy pain 67. The Annals of Thoracic Surgery 1998;66:367-72.

11. Meyer M, Siauw PT, Scholz G, Frey DJM. Plasma Concentrations and Analgesic Effects of Ropivacaine 3.75 mg/mL During Long-Term Extrapleural Analgesia After Thoracotomy. Regional Anesthesia and Pain Medicine 2005;30:356-62.

12. Knudsen K, Beckman Suurkula M, Blomberg S, et al. Central nervous and cardiovascular effects of i.v. infusions of ropivacaine, bupivacaine and placebo in volunteers. Br J Anaesth 1997;78:507-14.

13. Scott DB, Lee A, Fagan D, et al. Acute toxicity of ropivacaine compared with that of bupivacaine. Anesth Analg 1989;69:563-9.

14. Ekatodramis G, Borgeat A, Huledal G, et al. Continuous interscalene analgesia with ropivacaine 2 mg/ml after major shoulder surgery. Anesthesiology 2003;98:143-50.

15. Watson DS, Panian S, Kendall V, et al. Pain control after thoracotomy: bupivacaine versus lidocaine in continuous extrapleural intercostal nerve blockade. Ann Thorac Surg 1999;67:825-8.

16. Burm AG, Stienstra R, Brouwer RP, et al. Epidural infusion of ropivacaine for postoperative analgesia after major orthopedic surgery: pharmacokinetic evaluation. Anesthesiology 2000;93:395-403.

17. Blumenthal S, Dullenkopf A, Rentsch K, Borgeat A. Continuous infusion of ropivacaine for pain relief after iliac crest bone grafting for shoulder surgery. Anesthesiology 2005;102:392-7.

18. Karmakar MK, Ho AM, Law BK, et al. Arterial and venous pharmacokinetics of ropivacaine with and without epinephrine after thoracic paravertebral block. Anesthesiology 2005;103:704-11.

19. Yokogawa K, Shimomura S, Ishizaki J, et al. Involvement of alpha1-acid glycoprotein in inter-individual variation of disposition kinetics of ropivacaine following epidural infusion in off-pump coronary artery bypass grafting. J Pharm Pharmacol 2007;59:67-73.

20. Erichsen CJ, Sjovall J, Kehlet H, et al. Pharmacokinetics and analgesic effect of ropivacaine during continuous epidural infusion for postoperative pain relief. Anesthesiology 1996;84:834-42.

21. Maurer K, Rentsch KM, Dullenkopf A, et al. Continuous extrapleural infusion of ropivacaine in children: is it safe? Can J Anaesth 2005;52:112-3.

22. Richardson J, Sabanathan S, Jones J, et al. A prospective, randomized comparison of preoperative and continuous balanced epidural or paravertebral bupivacaine on post-thoracotomy pain, pulmonary function and stress responses 84. Br J Anaesth 1999;83:387-92.

23. Sabanathan S, Mearns AJ, Bickford Smith PJ, et al. Efficacy of continuous extrapleural intercostal nerve block on post-thoracotomy pain and pulmonary mechanics. Br J Surg 1990;77:221-5.

Figure 1. Plasma concentrations of total ropivacaine, unbound ropivacaine and [alpha]1-acid glycoprotein (AAG). Plasma concentrations were measured during a 48-h extrapleural infusion of 6 and 9ml/h ropivacaine 0.2%, started after an initial bolus with 30ml ropivacaine 0.2%, and for 6 hours after stopping the infusion. Each line represents one patient. Mean concentrations (grey band) with 95% confidence intervals (dashed band) are indicated. Thick dashed line marks the total ropivacaine limit considered non-toxic (2.2mg/L, Knudsen et al.). Filled symbols indicate extracorporeal circulation during the operation, empty symbols indicate no extracorporeal circulation. Concentrations of unbound ropivacaine never reached toxic levels (0.34 – 0.85mg/l, Knudsen et al.).

Figure 2: Area under the concentration-time curve of total and unbound ropivacaine during the time of the extrapleural infusion (t0 – t48). No difference between the two chosen infusion rates was found for total ropivacaine (* $P < 0.05$).

Figure 3: Average pain scores with standard deviation over the investigation period. 0mm = no pain, 100mm = worst pain imaginable.

Table 2. Surgical data

	6 ml/h (n=9)	9 ml/h (n=7)	
Type of surgery (n)			
Thoracic aorta graft	4	4	
Mitral valve repair	1	2	
Aorta isthmus stenosis repair	1	0	
Closure of atrial septum defect	1	0	
others	2	1	
Numbers of patients with extarcorporeal bypass during surgery (complete/partial)	2/2	5/1	
Time of surgery (min)	200/155/310	295/230/390	*(P = 0.17)*
Time of extracorporeal bypass	0/0/60	70/45/130	*(P = 0.07)*
Time between end of surgery and t_0 (min)	50/40/245	630/110/710	*(P = 0.07)*
Total blood products during study period (ml/kg)	5.2/3/15.8	23/4/36	*(P = 0.18)*
Total consumption of nicomorphine postoperatively (mg/kg)	92/36/109	24/14/34	*(P = 0.01)*

Table 2. Surgical data. Values are presented as number (n) or as median/lower quartile/upper quartile; $P < 0.05$ is considered statistically significant.

Fig. 1. Plasma concentrations of total and unbound ropivacaine and [alpha]1-acid glycoprotein

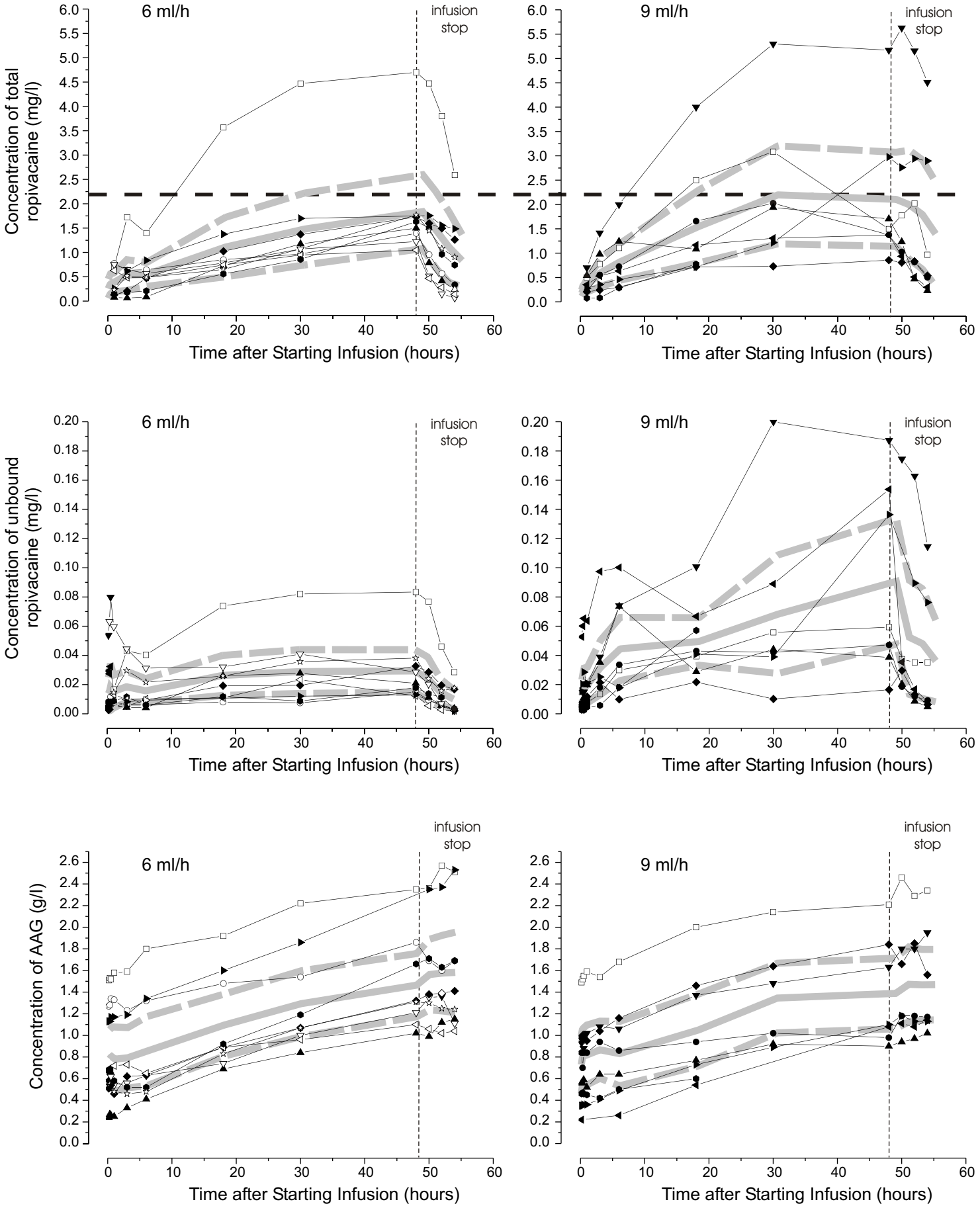

Figure 2. Area under the total and unbound plasma concentration-time curve (AUC).

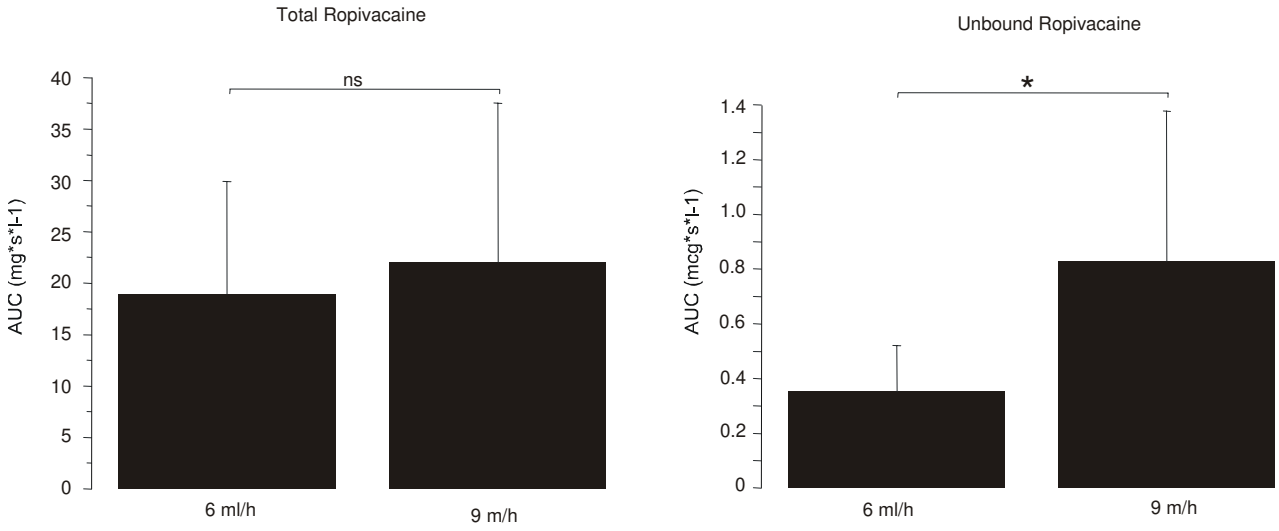

Fig. 3. Average pain scores