ORIGINAL ARTICLE

The association of interpleural ropivacaine and epidural following major thoracic surgery: a randomised triple blind clinical trial investigating pharmacokinetics and benefits

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Contributions: This work was carried out in collaboration between all authors. Authors JPG, SMP, AA, and YK were involved in the design of the study. Authors JPG, SMP and AD were primarily involved in the subsequent conceptualization of the study protocol and drafting of this manuscript. Management and logistics were carried out by authors JPG and AD. SMP and AD were responsible for data analysis. All authors read the final version of the manuscript.
ABSTRACT

Background. Thoracic surgery is associated with high levels of postoperative pain. Interpleural blockades (IPB) can be effective in reducing this pain, but results after thoracotomy are controversial. The current study investigates the effects of the association of ropivacaine-based IPB and morphine epidurals after posterolateral thoracic surgery.

Method. In this prospective, randomised, triple blind, placebo-controlled trial, patients received either intermittent ropivacaine IPB (R-group), (30 mg every 6 hours over 48 hours) or a placebo containing saline serum (P-group). Both groups had a morphine lumbar epidural. Pain was evaluated via patients’ reports and total morphine requirements.

Results. 90 patients participated. There were no significant differences between levels of pain reported on activity or morphine consumption between the two groups. Patients in the R-group reported higher levels of pain at rest on day 2. The mean peak plasma concentrations of ropivacaine remained inferior to toxic plasma concentration levels.

Conclusion. Postoperative interpleural infusions of 30 mg of ropivacaine every 6 hours in association with morphine epidurals are safe and feasible but do not improve postoperative experience of pain.

Key words: Interpleural Analgesia; Injections, Epidural; thoracic surgery;

ABBREVIATIONS

Société Française d'Anesthésie et de Réanimation (SFAR)
Interpleural blockades (IPB).
Visual analog scale (VAS)
Intravenous (IV)
VAS on activity (VAS-A) and VAS at rest (VAS-R).
Relative Risk = RR
95% CI = 95% Confidence intervals

Intention to Treat – ITT

local analgesic (LA)
**Introduction**

Pulmonary surgery by posterolateral thoracotomy is one of the most painful types of surgery (1). Severe pain is experienced by 45 to 65% of patients at rest and up to 60 or 70% upon activity (1) and this plays a role in morbidity and mortality (2). Given these high levels of pain, the Société Française d'Anesthésie et de Réanimation (SFAR) recommends a multimodal analgesic approach including different locoregional techniques. As alternatives to standard intravenous (IV) analgesic techniques involving paracetamol, non-steroid based anti-inflammatories, and morphine, other techniques have been proposed as feasible and effective: epidurals with morphine (3, 4) and/or local anaesthesia, paravertebral or intercostal blockades (5), parietal infiltrations, and interpleural blockades (IPB).

The IPB procedure is simple (6) but controversial. Some studies have shown satisfactory analgesia, pre- or post-operative (7-9), after a thoracic trauma (10) or in chronic pain syndromes (11). Other studies are not conclusive when this method is used alone (12). However, adverse effects of this procedure are rare. In 703 cases, Stromskag et al.(13) found the main adverse effects to be pneumothorax (2%), systemic toxicity (1.3%) and pleural effusion (0.42%). This very low complication incidence, (which has been reduced by improvements in general technique and per operative catheter insertion and extremity fixation), offers relatively secure conditions.

Up until now, interpleural analgesia has been mostly performed with bupivacaine. Ropivacaine has been shown to have similar efficacy (14) and a higher therapeutic index (15). To our knowledge, this is this first time that the benefits of IPB using ropivacaine in conjunction with morphine-based epidurals have been evaluated and that interpleural absorption has been described. Up until now, most publications have focused on assessing
IPB as a stand alone treatment and do not provide details of the association of IPB with morphine epidurals.

The goal of this phase III, unicentric, randomised, triple-blind study was to evaluate the analgesic benefit of associating the interpleural blockade technique to multimodal analgesia including lumbar epidural morphine.

**Patients and Methods**

**Eligible patients**

Between November 2003 and February 2008, patients over 18 years, ASA 1 or 2, who had pulmonary carcinologic surgery by thoracotomy were included in the study. Exclusion criteria were: refusal of the protocol, hypersensitivity to ropivacaine, inability to use the visual analog scale (VAS) for pain measurement, major psychiatric disorders, contraindication to lumbar epidural, pneumonecetomy. Blind randomisation was performed to assign the patients to one of two groups: a P-group (placebo group) with interpleural injection of normal saline solution, and the R-group (ropivacaine group) with interpleural injection of ropivacaine.

This study excluded patients who could not receive one of the postoperative analgesic treatments, or those with possible medical or surgical complications. All patients gave informed consent and this study was approved by the local ethics committee.

**Anaesthesia protocol**

The basic anaesthesia protocol was standardised for both groups. Monitoring included 3 sensor monitors, cardiac frequency, Sp02, capnography, volume flow rate of halogenated ethers, temperature monitoring, and urinary drainage. The induction protocol used propofol 2-2.5 mg/kg, sufentanil 0.5 μg/kg, cisatracurium 0.15 mg/kg. Anaesthesia was maintained with sevoflurane (1 MAC), sufentanil (0.25 to 0.5 μg/kg per hour), and cisatracurium (0.08
mg/kg per hour) via a syringe pump. Differential lung ventilation was performed by selective intubation with 50% air/oxygen mix, possibly modified during the operation. One surgeon (AA) performed all operations per patient which consisted in a postero-lateral thoracotomy, followed by a lobectomy or a metastasectomy in the lateral decubitus position. Finally, the surgeon fitted an epidural-type catheter into the interpleural space, through the fourth intercostal space where the incision was performed. It was directed anteriorly and apically, away from the two pleural drains. The patient was monitored during the following 36 to 48 hours in a post intervention monitoring unit.

**Analgesia**

The base analgesic procedure was the same for all patients: we injected 0.075 mg/kg morphine via the lumbar epidural (which had been inserted before anaesthesia) following the anaesthesia induction (Day 0) and 24 hours later (Day 1). The intravenous (IV) analgesic standardised protocol was started around the end of the intervention, and continued for 48 hours. It comprised of 1g paracetamol via IV every 6 hours, 1mg/kg ketoprofen via IV every 6 to 8 hours depending on the patient’s age and renal function and morphine titration via IV. The protocol was then taken over by a morphine pump (PCA with 50 mg morphine and 2.5 mg droperidol), bolus doses of 1 mg, 10 minutes refractory period, and no continuous injection.

The patients in the IPB study group (R) then received injections of 8 mL of ropivacaine 3.75 mg/mL (30 mg). The pleural drains were not clamped, in order to avoid atelectasis. The first injection was made on awakening, and then injections followed every 6 hours during 48 hours. The patients in the placebo control group (P) received 8 mL of normal saline solution in the same process.
Criteria for evaluation

The main criterion was the appearance during the first 48 hours of at least one episode of acute pain during activity (nursing, active mobilisation, physiotherapy exercise, or other activity) as indicated by the patient on the Visual Analog Scale. Pain was defined as acute when VAS $\geq 70/100$.

Secondary criteria of pain experienced were recorded over Day 0, Day 1 and between Hour 0 and Hour 48. There were two subjective (patient-reported) measures of moderate to acute pain (at least one VAS$\geq$40/100): VAS on activity (VAS-A) and VAS at rest (VAS-R). These were first evaluated 15 minutes after the patient was extubated and then just before each injection of ropivacaine (every 6 hours). An objective measure of pain was recorded via the amount of morphine consumed (ie. cumulated number of boluses). Finally, the appearance of side effects that could be attributed to the interpleural injection of ropivacaine was noted.

Pharmacokinetic study

We took blood samples for the first 20 patients. On Day 0, they were taken before the first injection of ropivacaine then 10, 15, 20, 30 and 60 minutes after, and again just before the 6, 12, 18 and 24 hour injections; on Day 1 at 10, 15, 20 and 30 minutes after the 24th hour injection, then before the 30, 36 and 48 hour injections.

The goals were to estimate the systemic passage of the ropivacaine, to determine the residual and peak seric concentrations and the exact time they occurred, and to look for any plasmatic accumulation. The pharmacists were in charge of unblinding and sending the 10 tubes of the R-group. Elevated levels of ropivacaine concentration ($> 2200$ ng/mL) was a criterion for ending the study. Pharmacokinetic data were processed on a computer with PK-Fit.
The main outcome evaluated was pain on activity. According to the literature, the ratio of patients with at least one acute pain episode (VAS $\geq 70$) during the first 48 hours after thoracotomy can reach 70%. Our null hypothesis was that the ropivacaine group would get half this score. With a type I error of 0.05, the estimated sampling size, for a bilateral test and a power of 90%, was 45 patients in each group of comparison. A 1:1 randomisation was performed with balanced blocks of 4 patients by the statistician (and kept secure in the pharmacy responsible for preparation and blinding of treatments). The unblinding of the first 20 patients was scheduled in the protocol solely upon pharmacokinetic criteria.

Group comparability was checked prior to surgery based on patient characteristics. Figure 1 shows the flow diagram of the trial population. We performed an intention to treat (ITT) analysis. Missing data at t=36h or 48h were replaced by the last available value (last observation carried forward strategy). When no value was available, any missing data were considered a treatment failure, whichever arm the patient belonged in. A maximum bias robustness analysis was performed.

We used a $\chi^2$ test or Fisher’s exact test for qualitative variables and two-tailed, $p<0.05$ t-tests or non parametric Wilcoxon tests for quantitative variables. After unblinding, the difference between the groups was expressed in terms of a relative risk (RR) and its 95% confidence interval (CI) for qualitative criteria (16). A RR less than 1 was in favour of ropivacaine efficacy. Some of the patients were included several times in the trial; these inclusions were maintained in the analysis and for our statistical tests we postulated the independence of the observations. The analyses were carried out using SAS 8.2.
Results

Results of the clinical trial

Table 1 shows the characteristics of the 85 randomised patients: 44 patients were included in the R-group and 41 in the P-group. Five patients were included several times (1 was included twice in each arm, 3 once in each arm, and 1 twice in the P-group). During the 48-hour recording of pain measurements, we obtained an average of 3 VAS-A for each patient in the R-group and 4 per patient in the P-group. The activity times were identical between the two groups. The lack of VAS evaluation at rest at H36 and H48 was due to patients returning to their rooms before the end of observation (11 patients in the R-group and 8 in the P-group).

There was no difference between the two groups for: VAS-A ≥ 70, VAS-A ≥ 40, at D0, at D1, or over the 2-days observation. Concerning VAS-R scores versus time there was no difference between the two groups at D0 (p = 0.76). But at D1 34.1% of patients in group R, versus 12.2% in group P had a VAS ≥ 40 at D1 (p = 0.02), that is a relative risk to experience acute pain of 2.8 for the R-group (95% CI = 1.1-7.0). These results are represented on Figures 2, 3 and 4.

Overall, the consumption level of morphine was low and the median dose was balanced across the 2 groups (Figure 5). Between D0 and D1, there was a diminution of the injected dose of morphine, with no difference of amplitude between the 2 groups (p = 0.99).

The robustness analysis concerning efficacy showed no major changes. Concerning the number of patients experiencing acute pain across groups (VAS ≥ 40/100) on D1, the RR for the study group compared to the placebo group varied between 3.5 (95% CI = 1.3-9.7 p = 0.01) with the hypothesis not supporting ropivacaine and 2.4 (95% CI = 0.9-6.2 p = 0.05) with the hypothesis in favour of ropivacaine against placebo.

We did not observe any complications that could be attributed directly to the interpleural injection of ropivacaine. One R patient suffered from an allergy to ketoprofen, and 9 (6 R
patients and 3 P patients, \( p = \text{ns} \) suffered from side effects due to morphine. Three patients in the R-group were given ondansetron.

**Results of the pharmacokinetic study of interpleural ropivacaine**

The study of residual serum concentrations showed a plasmatic accumulation of ropivacaine, with average minimal seric concentration of 88 ng/mL measured at H6, and maximal concentration of 329 ng/mL (135-757 ng/mL) at H30. Despite continuing injections, serum concentrations of ropivacaine appeared to decrease between H30 and H48. The peak serum concentration was reached 30 minutes after injection and plasmatic concentrations stayed below toxic doses for all patients despite some variation between individuals (Figure 6).

**Discussion**

This study shows that associating an interpleural blockade with lumbar epidural after thoracotomy does not improve analgesia and paradoxically increases the percentage of patients with moderate pain. In fact, our results show that the usual multimodal analgesic technique without IPB efficiently reduced the ratio of patients experiencing pain at rest or during activity. We observed reduced morphine consumption on average of 10 mg, whereas many studies have reported consumptions as high as 50 to 100 mg at D0 when only epidural morphine was used (1). Lumbar morphine 0.075 mg/kg injected at D0 and D1 hence made it possible to use less morphine and decreased the incidence of systemic side effects (17). Further, the ratio of patients in acute pain on activity (VAS-A \( \geq 70 \)) was far below what was predicted by the hypothesis (12.2% observed vs. 35% hypothesised).

However, when interpreting the lack of analgesic differences in this study, potential technical limitations must be considered. We didn’t evaluate ropivacaine titration or the serosanguineous fluid volumes in the pleural drains and this may have had some consequences on the efficacy of the ropivacaine injections, such as the dilution of the local
analgesic (LA) into the pleural liquid (18), its chemical liaison to blood protides (19), its uneven distribution within the pleural cavity (12,20), or its rapid absorption in the operated lung (19). Ferrante has shown when bupivacaine is injected via the same route without clamping the thoracic drains, there as losses of between 30 and 40% of the injected dose (21). The antero-apical direction of the catheter (22), introduced through the anterior pleural drain, (23, 24), might have played a role in the lack of pain relief in the friction zone around the thoracic catheters, or even in the total lack of efficacy. Indeed, while Kambam reported some efficacy of bupivacaine injected in lateral and posterior thoracotomy, this technique did not relieve pain in anterior thoracotomy patients (19). He proposed a postero-basal direction for the catheter, directed towards the paravertebral gutter, to block the posterior spinal plexus that innervates the thoracic muscle-ligament structure (21). The anatomic variations of the intercostal space and the nerve routes (6, 21, 25, 26) and the partially understood action of LA injected in the interpleural space could explain the contradictory results of these studies (6, 7).

We must also consider the dosage or posology when interpreting the results of our study. Since the pharmacokinetic of ropivacaine remains unknown, we fixed a low maximum dose to avoid unacceptable levels of toxicity. This was set at 30 mg compared to 100mg of bupivacaine (20, 21) that usually appears to be efficient (3, 6) and can be associated with a “volume effect” (6). This amount may have been insufficient to alleviate acute pain and the frequency of the injection set was possibly unadapted to the duration of ropivacaine efficacy. That is, we consider that the rhythm of injections was probably under-estimated since the average analgesia duration obtained via this technique lasts between 3 (6, 22) and 6 hours (19, 21).

Some authors have recommended performing injections of 20 mL bupivacaine 0.25% every 4 hours or a continuous injection (20, 22, 24). This was prompted to us by the VAS scores at rest at D1 which were assessed only before each ropivacaine injection. The
patients might have felt some relief during 2 to 5 hours, and then might have experienced acute pain at the time of evaluation (27). This is reinforced by the diminution of morphine consumption between D0 and D1.

Other factors to take into account are the patient’s position during injection (7) and the time at which experiences of pain were measured. In terms of position, since the diffusion of LA is dependent on gravity (6, 19), it is recommended that the injection be done in the dorsal decubitus position, and that this position is kept for 20 to 30 minutes (6, 9, 19, 21, 28, 29). Our patients were semi-seated. In terms of the time at which pain was measured, we believe this may be a critical reason as to why we have observed no differences in self-reported pain. Our measurements were taken just prior to the injection of ropivacaine whereas the effects of the analgesic may have been wearing off and the subjective pain experienced for patients during this ‘wearing off’ phase was relatively high in comparison to the absence of pain after IPB compared to the more stable experience of pain experienced by patients in the placebo group. This effect of pain relief wearing off and subjective experience being greater when compared to previous pain alleviation may explain why we observed more cases of acute pain at D1 for patients in the R-group than in the P-group.

Another possible explanation is that the type of pain might have changed between D0 and D1: Pain at D0 is mainly localised around the incision site, about the catheter, whereas at D1 it comes from irritation due to the pleural drain. An irritation of the pleura due to ropivacaine, or acute tolerance phenomena, rarely studied in this context, is also possible (30, 31). The addition of adrenaline, often associated with bupivacaine (19, 21, 25), was not considered as likely to have an effect (32) so was not administered. Further, some of the pain experienced after thoracotomy is due to some other causes such as diaphragmatic irritation and scapular retraction (25), which are poorly relieved by IV opioids and loco-regional analgesia, including thoracic epidural (18, 33).
The lack of efficacy of the IPB noted here matches what has been reported in many other thoracic surgery studies. Most of the studies report analgesia that is equivalent to IV opiates (3), and less efficient than epidural analgesia (24). Whether this technique should be used during thoracotomy needs more evaluation since analgesic efficacy (24, 27, 28) and benefits for respiratory function remain controversial (6, 33) and there are few publications examining the efficacy of the association of IPB with a lumbar morphine epidural and pharmacokinetic of ropivacaine injected via this route. Given that lumbar morphine epidural is of similar efficacy to thoracic epidural (1) and shows theoretically lower risk of neurologic lesion and less insertion difficulties, this technique may provide an useful alternative to thoracic epidurals as it is easy to learn and to reproduce, there are few contraindications (3, 6, 33) and few complications. Another alternative technique to thoracic epidural may consist of a paravertebral blockade (1, 3, 28).

The pharmacokinetic study demonstrated that the peak ropivacaine serum concentrations always remained far below the toxic dose, despite large inter-individual variations. The peak of systemic absorption at 30 minutes was close to the level observed with bupivacaine (19). The vasoconstrictive properties of ropivacaine did not delay the passage of LA into blood. However, several studies have shown that the risk of adverse effects is essentially linked to the kinetic augmentation of seric concentration rather than to the absolute value of the concentration (25, 33). Moreover, like bupivacaine, peak concentrations of ropivacaine increase with repeated injections, and seem to be linked to the dose and concentration injected (25). Serum samples after 48 hours could have given the elimination half-life of ropivacaine, and samples from the pleural drains the loss in LA. Moreover, we did not measure the free fraction of ropivacaine, nor the $\alpha_1$-glycoprotein acid concentrations (20).

Finally, the risk of neurologic and cardiovascular toxicity after IPB must also be considered. The incidence is low (1.3%) but should not be neglected (33), especially as
seric bupivacaine concentrations are often beyond the toxicity limit and show some important inter-individual variations. Ropivacaine has a higher therapeutic index (1, 15) but the lack of initial studies concerning its systemic absorption explains why we chose such a dosage. Finally, the 20% variation between arterial and venous concentrations of LA injected into the interpleural space led to analyse the arterial concentrations (19, 36).

**Conclusion**

Intermittent interpleural blockades with 30 mg ropivacaine every 6 hours seem to be a safe and feasible technique. The pharmacokinetic study showed a fast resorption and plasmatic concentrations far under the toxic dose. However, we did not observe any analgesia benefit neither on activity, nor at rest, and the proportion of patients in acute pain at D1 was greater in the group receiving the treatment. We believe that the lack of differences observed in our results may be explained by two major methodological limitations that warrant further investigation. Firstly, perhaps the posology was insufficient and given the low levels of toxicity observed, it should be possible in the future to evaluate analgesic effects of higher doses of ripovacaine in association with morphine epidurals. Secondly, patients’ experience of pain should be evaluated more regularly so as to investigate whether there are shorter term benefits for the use of IPB and epidurals, or trials should be designed so that patients’ own experiences of pain are compared across time with and without IPB, instead of across patients.

Overall, our results feed the ongoing controversy about the IPB’s role in thoracic surgery and indicate that future research must take into account these two important methodological considerations. We believe that this is an important area of research for the future to assess whether the use of interpleural blockades should be continued in clinical practice.
Ethical Approval

This study was approved by the Internal Review Board of Institut Bergonié, regional ethics committee (Comité des Protection des Personnes, Aquitaine) and National French Agency for Security of Drugs and Health Products. It was registered with clinicaltrials.gov as NCT00210132. All patients gave informed consent.

Acknowledgements

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Competing Interests

The authors report no conflicting interests.
References


Table 1. Patient characteristics

Data given in terms of means ± σ (age, weight), median (1st and 3rd quartile) for morphine or ketoprofen doses or total value (ratio). ED: epidural dose

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<tr>
<th>Variables</th>
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<th>PLACEBO (n=41)</th>
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<td>Gender (M/F)</td>
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<td>31 (70.5%)</td>
<td>23 (56.1%)</td>
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Figures legends

**Figure 1.** Flow Diagram of the randomised and analysed population.

**Figure 2.** Comparison of the proportion (95% CI) of patients with VAS-A ≥ 70 between Placebo group (P, 41 patients) and Ropivacaine group (R, 44 patients) over day 0 and day 1, p=0.62.

**Figure 3.** Comparison of the proportion (95% CI) of patients with VAS-A ≥ 40 between group Placebo group (P, 41 patients) and Ropivacaine group (R, 44 patients) at day 0 (D0, p=0.16) and day 1 (D1, p=0.55).

**Figure 4.** Comparison of the proportion (95% CI) of patients with VAS-R ≥ 40 between Placebo group (P) and Ropivacaine group (R) at day 0 (D0, p=0.67) and day 1 (D1, p=0.02).

**Figure 5.** Evolution of morphine consumption (median; 25th-75th percentiles; minimum and maximum) versus time (of evaluation) in the two groups.

**Figure 6.** Median serum concentrations of ropivacaine (ng/mL) versus time (vertical lines represent the 10th and 90th percentiles).

*R = ropivacaine, P = placebo.

ITT = Intention to Treat analysis
Randomised
N = 90

Exclusion due to non respect of peroperative eligibility criteria (no treatment administrated) N = 5
- Preoperative hyperthermia (n = 1)
- Pneumonectomy (n = 1)
- Bilateral surgery (n = 1)
- Major anaesthesia problem (n = 1)
- Impossibility to perform the epidural (n = 1)

Treated patients: N = 85
Population analysed in ITT
R-group: N = 44 / P-group: N = 41

Patients evaluated: N = 82
R-group: N = 42 / P-group: N = 40

VAS criterion/mobilisation:
- “at least one VAS ≥ 40 (or at least one VAS ≥ 70) on mobilisation during the 0-48h period”:
  (n = 80 patients with at least one evaluation at mobilisation)
- “at least one VAS ≥ 70 (or at least one VAS ≥ 40) on mobilisation during the 0-48h period” (n = 76 patients with at least one evaluation at mobilisation)

VAS criterion/rest:
- “at least one VAS ≥ 40 at rest during the 0-48h period”:
  (n = 63 patients evaluated each time)
- “at least one VAS ≥ 40 at rest during the 0-24h period”:
  (n = 82 patients evaluated each time)

Morphine consumption:
- # of cumulated boli of morphine during the 0-48h period:
  (n = 62 patients evaluated each time)
- # of cumulated boli of morphine during the 0-24h period:
  (n = 82 patients evaluated each time)

Non-evaluated patients: N = 3
R group: n=2 / P group: n=1
- Patient transferred due to fire during peroperatory period (n = 1)
- Anaphylactoid reaction to Ketoprofen (n = 1)
- Loss of data (n = 1)
Figure 2. Comparison of the proportion (95% CI) of patients with VAS-A $\geq 70$ between Placebo group (P, 41 patients) and Ropivacaine group (R, 44 patients) over day 0 and day 1, $p=0.62$
Figure 3. Comparison of the proportion (95% CI) of patients with VAS-M ≥ 40 between group Placebo group (P, 41 patients) and Ropivacaine group (R, 44 patients) at day 0 (D0, p=0.16) and day 1 (D1, p=0.55)
Figure 4. Comparison of the proportion (95% CI) of patients with VAS-R ≥ 40 between Placebo group (P) and Ropivacaine group (R) at day 0 (D0, p=0.67) and day 1 (D1, p=0.02)
Figure 5. Evolution of morphine consumption (median; 25th-75th percentiles; minimum and maximum) versus time (of evaluation) in the two groups

Morphine (mg)

The boxes represent the median, the 25th and 75th percentiles; extremities of the vertical lines reflect the minima and maxima.
Figure 6. Median serum concentrations of ropivacaine (ng/mL) versus time (vertical lines represent the 10th and 90th percentiles).