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# A Comparison of Differences Between the Systemic Pharmacokinetics of Levobupivacaine and Ropivacaine During Continuous Epidural Infusion: A Prospective, Randomized, Multicenter, Double-Blind Controlled Trial

Luciano Perotti, MD,* Maria Cusato, Pharmacist,† Pablo Ingelmo, MD,‡ Thekla Larissa Niebel, MD, PhD,§ Marta Somaini, MD,‖ Francesca Riva, MD,¶# Carmine Tinelli, MD,** José De Andrés, MD, PhD, FIPP, EDRA,†† Guido Fanelli, MD,‡‡ Antonio Braschi, MD,§§ Mario Regazzi, PharmD,‖‖ and Massimo Allegri, MD¶¶##

**BACKGROUND:** Epidural infusion of levobupivacaine and ropivacaine provides adequate postoperative pain management by minimizing side effects related to IV opioids and improving patient outcome. The safety profile of different drugs can be better estimated by comparing their pharmacokinetic profiles than by considering their objective side effects. Because levobupivacaine and ropivacaine have different pharmacokinetic properties, our aim was to investigate whether there is a difference in the pharmacokinetic variability of the 2 drugs in a homogeneous population undergoing continuous epidural infusion. This double-blind, multicenter, randomized, controlled trial study was designed to compare the pharmacokinetics of continuous thoracic epidural infusion of levobupivacaine 0.125% or ropivacaine 0.2% for postoperative pain management in adult patients who had undergone major abdominal, urological, or gynecological surgery. This study is focused on the evaluation of the coefficient of variation (CV) to assess the equivalence in the systemic exposure and interindividual variability between levobupivacaine and ropivacaine and, therefore, the possible differences in the predictability of the plasmatic concentrations of the 2 drugs during thoracic epidural infusion.

**METHODS:** One hundred eighty-one adults undergoing major abdominal surgery were enrolled in the study. Patients were randomized to receive an epidural infusion of levobupivacaine 0.125% + sufentanil 0.75 μg/mL or of ropivacaine 0.2% + sufentanil 0.75 μg/mL at 5 mL/h for 48 hours. The primary end point of this study was to analyze the variability of plasma concentration of levobupivacaine and ropivacaine via an area under the curve within a range of 15% of the CV during 48 hours of continuous epidural infusion. The CV shows how the concentration values of local anesthetics are scattered around the median concentration value, thus indicating the extent to which plasma concentration is predictable during infusion. Secondary end points were to assess the pharmacologic profile of the local anesthetics used in the study, including an analysis of mean peak plasma concentrations, and also to assess plasma clearance, side effects, pain intensity (measured with a verbal numeric ranging score, i.e., static Numeric Rating Scale [NRS] and dynamic NRS]), and the need for rescue doses.

**RESULTS:** The comparison between the 2 CVs showed no statistical difference: the difference between area under the curve was within the range of 15%. The CV was 0.54 for levobupivacaine and 0.51 for ropivacaine ($P = 0.725$). The plasma concentrations of ropivacaine approached the $C_{max}$ significantly faster than those of levobupivacaine. Clearance of ropivacaine decreases with increasing patient age. There were no significant differences in NRS, dynamic NRS scores, the number of rescue doses, or in side effects between groups.

**CONCLUSIONS:** Considering the CV, the interindividual variability of plasma concentration for levobupivacaine and ropivacaine is equivalent after thoracic epidural infusion in adults. We found a reduction in clearance of ropivacaine depending on patient age, but this finding could be the result of some limitations of our study. The steady-state concentration was not reached during the 48-hour infusion and the behavior of plasma concentrations of ropivacaine and levobupivacaine during continuous infusions lasting more than 48 hours remains to be investigated, because they could reach toxic levels. Finally, no differences in the clinical efficacy or in the incidence of adverse effects between groups were found for either local anesthetic. (Anesth Analg 2015;121:348–56)

From the *Anesthesia and Intensive Care III, Cardiothoracic and Vascular Surgery Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; †Unit of Clinical Pharmacokinetics in Transplant and Autoimmune Diseases, Infectious Diseases Department, Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ‡Department of Anesthesia, Montreal Children's Hospital, Alan Edwards Research Center for Pain, McGill University, Montreal, Canada; §Anesthesia and Intensive Care I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ‖Anesthesia and Intensive Care I. Ca'Granda Niguarda Hospital, Milano, and Università degli Studi of Milan Bicocca, Milan, Italy; ¶Anesthesia and Intensive Care I. San Gerardo Hospital, Monza, Italy; #Department of Experimental Medicine. University of Milan Bicocca, Milan, Italy; **Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ††Department of Anesthesia, Critical Care and Pain Medicine, General University Hospital, Valencia, Spain; ‡‡Department of Anesthesiology, Critical Care and Pain Medicine, University of Parma, Parma, Italy; §§Department of Clinical, Surgical, Diagnostic and Pediatric Sciences, University of Pavia, Pavia, Italy; ‖‖Unit of Clinical Pharmacokinetics in Transplant and Autoimmune Diseases, Infectious Diseases Department, Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy; ¶¶Department of Surgical Sciences, University of Parma, Parma, Italy; and ##Anesthesia, Intensive Care and Pain Medicine Department, Azienda Ospedaliero-Universitaria di Parma, Parma, Italy; SIMPAR Group.



DOI: 10.1213/ANE.0000000000000775

Accepted for publication February 13, 2015.

Funding: This research was supported by a grant from the Scientific Direction of Fondazione IRCCS Policlinico San Matteo, Pavia, Italy.

The authors declare no conflicts of interest.

Drs. Luciano Perotti and Maria Cusato are co-first authors.

Reprints will not be available from the authors.

Address correspondence to Luciano Perotti, MD, Anesthesia and Intensive Care III, Cardiothoracic and Vascular Surgery Department, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. Address e-mail to lucianoperotti@inwind.it.

Epidural infusion of levobupivacaine and ropivacaine provides adequate postoperative pain management, minimizing the side effects related to IV opioids and improving patient outcome.[1–5]

Systemic toxicity of local anesthetics can lead to a progressive range of neurologic and cardiac complications, resulting in disability or death.[6] The reported "toxic" plasma concentrations of levobupivacaine (1.74–2.7 μg/mL)[7,8] and ropivacaine (1.24–6.0 μg/mL)[9–21] only have been inferred from anecdotal data. Animal models of local anesthetic toxicity suggest that the systemic toxicity of levobupivacaine is midway between that of bupivacaine and ropivacaine.[22]

Clinical data in humans have suggested that ropivacaine 0.2% produces the same clinical effects as levobupivacaine 0.125%.[23,24] The drug safety profile of different drugs can be judged by the evaluation of side effects under controlled concentrations.

The differences in systemic absorption and disposition during epidural infusion between levobupivacaine and ropivacaine, however, have not yet been fully elucidated, even though these factors could be important in optimizing their clinical effectiveness, reducing the risk of systemic toxicity,[25] and estimating the therapeutic index for these drugs. Because they have different pharmacokinetic properties, our aim was to compare the possible difference in the pharmacokinetic variability of the 2 drugs in a homogeneous population undergoing continuous epidural infusion. Because these 2 drugs have a different lipophilicity, several confounding factors may affect their pharmacokinetics during epidural infusion (i.e., patient age, the distribution of the epidural fat, and the type of surgery). This study attempts to study the "in vivo" effect of these factors on the pharmacokinetic of levobupivacaine and ropivacaine.

This double-blind, multicenter, randomized, controlled trial study was designed to compare the pharmacokinetics of continuous thoracic epidural infusion of levobupivacaine 0.125% or ropivacaine 0.2% for postoperative pain management in adult patients who have undergone major abdominal, urological, or gynecologic surgery. This analysis allows us to assess the equivalence in systemic exposure and interindividual variability between levobupivacaine and ropivacaine, to verify the predictability of the concentration of these 2 drugs during continuous thoracic epidural infusion, and to investigate any difference in their pharmacokinetic variability in a homogeneous population who had undergone continuous epidural infusion.

## METHODS

This multicenter, randomized, double-blind, controlled study was approved by the ethical committees of the Fondazione IRCCS Policlinico San Matteo, Pavia and Azienda Ospedaliera San Gerardo Hospital di Monza (Ref. 272, N° 1732 of April 24, 2008), 2 academic institutions in Northern Italy, and registered at www.clinicaltrials.gov (NCT01229241) by the principal investigator. All patients provided written, informed consent. The CONSORT (i.e., Consolidated Standards of Reporting Trials) recommendations for reporting randomized controlled clinical trials were followed.[26]

### Participants

Eligible participants were adults of both sexes; ASA physical status I or II; undergoing major abdominal, urological, or gynecological surgery; and requiring an epidural catheter for postoperative pain management. Patients were excluded in case of emergency surgery; coagulation disorders (international normalized ratio > 1.2); renal, hepatic, neurologic, or psychiatric impairment; a preexisting central or peripheral neurologic deficit; pregnancy; or a history of opioid therapy.

Eligibility criteria and written, informed consent were collected during the preoperative anesthesia evaluation and confirmed on the day of surgery in the preoperative area of the operating room (OR) by a research assistant.

### Interventions

A standardized general anesthetic technique was used for all subjects. Premedication was not allowed. Before induction of anesthesia, patients received an epidural catheter between T6 and T9, depending on the type of surgery. The catheter was positioned by experienced staff with technique of air or liquid loss of resistance; the aspiration test and the bolus test, with lidocaine 2% 2 mL, were performed and only subsequently the catheter was fixed. To assess the correct positioning, before surgery and after bolus test, we evaluated the level of analgesia with the pinprick test and the cold test. The epidural catheter was not used during surgery to achieve blended anesthesia. The first use of the epidural catheter was the administration of the loading dose given at the start of closure of surgical incision. The catheter was then used 45 minutes after the loading dose at the beginning of continuous epidural infusion. Induction was performed with propofol 2 mg $kg^{-1}$ IV and fentanyl 2 μg $kg^{-1}$. Tracheal intubation was facilitated with cisatracurium 0.15 mg $kg^{-1}$ IV. Anesthesia was maintained with sevoflurane end-tidal concentration 1.5%–2.5% titrated according to clinical needs. Cisatracurium 0.03 mg $kg^{-1}$ was administered to maintain a train-of-four count response of 1–2, as well as according to clinical needs. Ventilation was controlled to maintain end-tidal $CO_2$ values between 35 and 40 mm Hg. After tracheal intubation, an orogastric tube and an esophageal temperature probe were inserted. The temperature of the OR was set at 20°C and patients were kept warm via a forced warm-air device and warmed IV solutions. At the end of the surgery, residual muscle paralysis was reversed with neostigmine 0.05 mg/kg and atropine 0.02 mg/kg, tracheal extubation was performed once clinically, and train-of-four count criteria were achieved.

After awakening, patients received a rescue dose of IV paracetamol 15 mg/kg up to 1 g (maximum dose: 4 g/d) in case of a dynamic Numeric Rating Scale (NRSd)—an 11-point scale for patient self-reporting of pain after deep breathing, coughing, or movement—score ≥3.

Patients were randomized to receive an epidural infusion of levobupivacaine 0.125% + sufentanil 0.75 μg/mL or ropivacaine 0.2% + sufentanil 0.75 μg/mL. At the beginning of closure of the surgical incision, the patients received a 10-mL loading dose of levobupivacaine 0.125% + sufentanil 10 μg or of ropivacaine 0.2% + sufentanil 10 μg within 15 minutes. At the end of the surgery—and/or 45 minutes after the loading dose—an epidural infusion of levobupivacaine

0.125% + sufentanil 0.75 μg/mL or ropivacaine 0.2% + sufentanil 0.75 μg/mL was started at 5 mL/h and maintained for the following 48 hours. However, regardless of the surgical time, the time between the loading dose and the beginning of the continuous epidural infusion was kept constant. No variation of the rate of infusion was allowed.

## Objectives and Outcomes

Our hypothesis was that there is equivalence in systemic exposure to levobupivacaine and ropivacaine. The primary end point of this equivalence study was the analysis of differences in the variability of plasma concentration of the 2 drugs attributable to the different lipophilicity of these 2 molecules. The variability of the 2 drugs was considered equivalent when the difference between the 2 area under the curve (AUC) was within a range of 15% of the coefficient of variation (CV) during 48 hours of continuous epidural infusion.

Secondary end points were (1) the assessment of the pharmacologic profile of the local anesthetics in the study, including the analysis of mean peak plasma concentration, and the assessment of the plasma clearance according with patients' age; (2) pain intensity measured with a verbal numeric ranging score (NRS 0–10) at rest (static NRS) and after deep breathing, coughing, or movement of the patient in the bed (dynamic NRS), where 0 represented no pain and 10 represented the worst possible pain NRS and a need for rescue doses; and (3) side effects.

## Randomization and Blinding

We used a computer-generated list of random numbers for the allocation of the participants. Patients were thus assigned randomly to 1 of the 2 treatment groups by a research assistant. The allocation sequence was concealed from the researcher assessing the participants by the use of sequentially numbered, opaque, sealed, and stapled envelopes. Later, the sealed envelopes were distributed equally between both institutions. Before the patients entered the OR, the anesthesia nurse received from the research assistant the sealed envelope containing the allocation number and instructions for the solution preparation. The anesthetic solutions were prepared in a dedicated area of the OR as in hospitals in which the study was performed the pharmacy does not prepare drugs for continuous epidural infusion. Corresponding envelopes were opened only after the enrolled participants had completed the identification checklist and after positioning the epidural catheter.

To maintain blinding, the researchers assessing the participants were not allowed to enter the OR until the study solutions were being prepared. The research assistants involved in data collection during or after surgery and the anesthesiologist of the case (not involved with the study) were unaware of the study group assignment. The blind was disclosed only after the statistical analysis. In case of medical emergency possibly correlated to drugs used in the study, the nurse was authorized to disclose the contents of the solutions to the research assistant.

## Blood Sampling and Pharmacokinetic Analysis

Blood samples were obtained through a dedicated venous catheter placed in the subject's arm contralateral to that used for drug infusion. The samples were obtained immediately before epidural bolus administration and at 3, 6, 12, 24, 48, 54, and 60 hours after starting the infusion. Plasma was separated by centrifugation, transferred to clean prelabeled tubes, and frozen at −20°C until analysis. The first blood sample was programmed at the third hour to avoid interferences as the result of surgery. We assumed that from the third hour the plasma concentration profiles were influenced mainly by the processes of absorption and elimination.

The individual plasma concentrations of total local anesthetics were evaluated by analyzing the drug disposition (median/range) during the 48-hour continuous infusion and at 54 and 60 hours, by means of the total area under the plasma concentration-time curve (AUC) and the apparent clearance (CL/F). The total area under the plasma concentration-time curve ($AUC_{0-\infty}$) was calculated by the linear trapezoidal rule up to the last data point ($AUC_{60h}$), and the residual area up to infinity ($AUC_{60h-\infty}$) was calculated by integration. The dose was the total dose of local anesthetic given (bolus dose + total dose infused). $C_{max}$ was defined as the greatest concentration achieved during drug accumulation toward the steady state; $T_{max}$ was the time corresponding to $C_{max}$. The terminal half-life ($t_{1/2}$) was obtained from the declining curve, considering the concentration data after the end of the infusion.

After the plasma was thawed at room temperature, an aliquot of each sample (250 μL) was pipetted into a glass tube, and 10 μL of I.S. working solution (10 μg/mg/mL) was added. After being vortexed briefly, 250 μL of distillated deionized water and 500 μL of dichloromethane were added to each sample. The samples were then shaken for 10 minutes and centrifuged for 10 minutes at 1200*g*. The organic phase was transferred into a clean conical tube and evaporated under a gentle nitrogen stream. The residue was dissolved in the mobile phase, and 50 μL was injected into the high-performance liquid chromatography instrument.

### *Standard Solution and Calibration*

A stock solution (1 mg/mL) of ropivacaine and levobupivacaine was prepared in methanol/water (50/50). Working solutions were prepared from the stock solution by serial methanol/water (50/50) dilutions. Plasma standards were prepared to achieve the final concentrations of 0.1, 0.2, 0.4, 1.0, 2.0, 4.0 μg/mL. Quality control samples of each compound were also prepared in 3 different concentrations—0.12, 0.8, and 1.6 μg/mL, respectively—by diluting appropriate aliquots of the stock solution with drug-free serum.

### *Chromatography*

The high-performance liquid chromatography equipment consisted of a Varian Prostar Model 430 pump with a variable-wavelength Varian Prostar Model 330-UV detector. The separation was performed with a Hypersyl BDS-$C_{18}$ (250 × 4.6 mm I.D., particle size 5 μm) reverse phase column (CPS Analitica, Italy).

The mobile phase used for analysis consisted of a mixture of acetonitrile, methanol, and $KH_2PO_4$ 50 mM 180:160:660, v/v/v). The mobile phase was adjusted to pH 6 with phosphoric acid and delivered at a flow rate of 1.3 mL/min. Chromatographic separation was performed at laboratory room temperature and monitored at 210 nm.

A 1-compartment model with sequential bolus and infusion input was fitted to the total plasma concentration-time data during the infusion period to give estimates of apparent total clearance (CL/F). Bioavailability, F, was assumed to be 1. The plasma kinetics of drugs in our study has been described by the 1-compartment model, as the distribution phase was easily masked by the absorption phase.

Pain, sedation (0- to 3-point scale), vital signs, $O_2$ saturation, motor block (Bromage Scale), and complications (nausea, vomiting, itching, local anesthetic toxicity, etc.) were measured in the postaesthesia care unit and at 3, 6, 12, 24, 36, 48, 54, and 60 hours after surgery.

### Statistical Analysis

The sample size was calculated according to Zanen and Lammers.[27] Between 55 and 79 patients per group would be needed to find a difference between mean AUC of zero, lower equivalence interval of 10%, and CV of 50 ± 15% (35% or 65%) with an 80% power and an alpha error of 5%. Ninety patients were enrolled in each group to allow for protocol violations.

Quantitative data are reported as median and range values because they are not normally distributed, (Shapiro's test), and differences between groups were analyzed by use of the nonparametric Mann-Whitney *U* test. Qualitative data are reported as counts and frequencies, and differences between groups were analyzed with the $\chi^2$ test or Fisher exact test, as appropriate. Linear regression models for repeated measures were used to analyze differences over time and between different protocols for NRS, after log transformation. The Pearson's *r* coefficient was used to evaluate the correlation between parameters. Concentrations were analyzed with Innaphase Kinetica pharmacokinetic software. For each subject, we obtained an AUC, and then the CVs of the AUC were compared between groups by a Shafer and Sullivan[28] correction of the method of Bennett[29] based on the approximation by McKay.[30] Confidence intervals (CIs) of 95% also were calculated with a pivotal method by McKay,[30] modified by Vangel.[31] Data analysis was performed with the STATA statistical package (version 11; Stata Corporation, College Station, TX).

## RESULTS

### Patient Characteristics

Two hundred thirty-seven patients were assessed for eligibility; 181 were enrolled and 166 (81 in the levobupivacaine group and 85 in the ropivacaine group) were analyzed for the primary end point (Fig. 1). There were no significant differences between groups or within hospitals in their clinical or surgical characteristics (Table 1).

### Plasma Concentration and Area Under the Curve

Plasma concentrations and pharmacokinetic parameters of levobupivacaine and ropivacaine are summarized in Figure 2 and in Table 2. The plasma concentration-time curves for levobupivacaine and ropivacaine differed during the study. The plasma concentrations of both local anesthetics increased markedly throughout the infusion time, with the greatest concentrations noted at the end of the infusion ($C_{48h}$). The median peak plasma concentration ($C_{max}$) in the levobupivacaine group was 0.95 μg/mL (range: 0.23–2.13

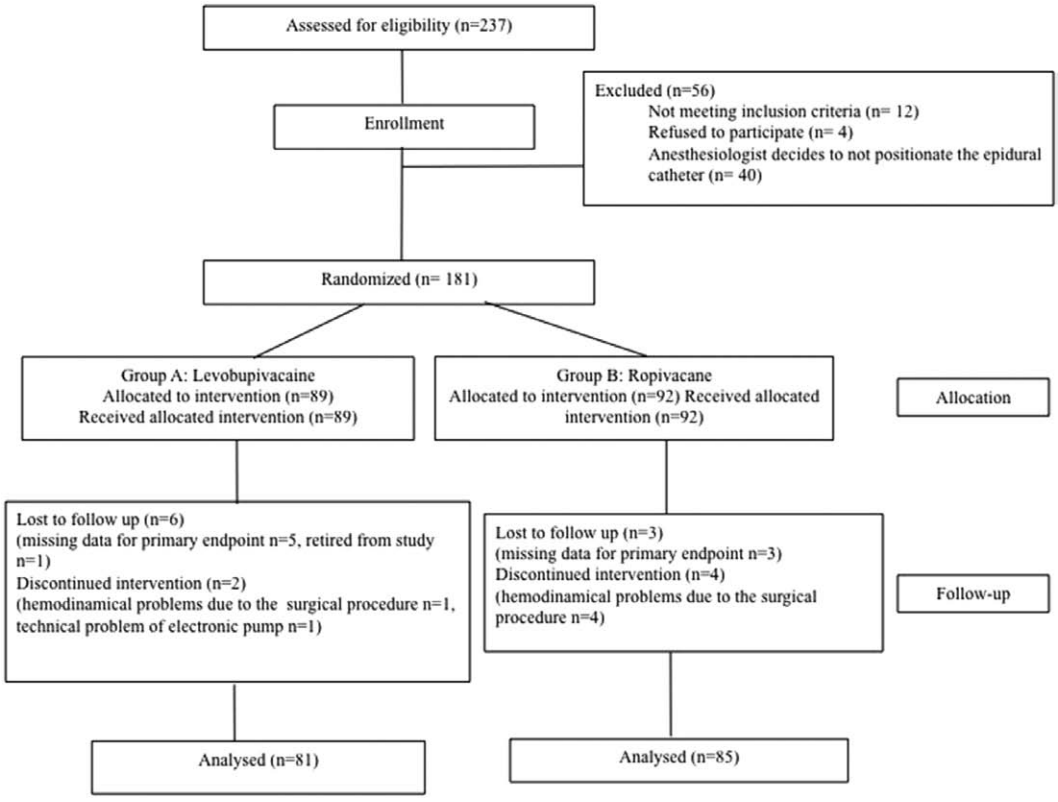


**Figure 1.** Consort diagram: flow of patients through the study.

**Table 1. Group Characteristics, Demographic Data, and *P* Values for All Patients**

| | Group A Levobupivacaine (*n* = 89) | Group B Ropivacaine (*n* = 92) | Total (*n* = 181) | *P* value |
|---|---|---|---|---|
| Age (years) | 64 (55–72) | 66 (57,5-72) | 65 (56–72) | 0.667 |
| Sex (M/F) | 62/27 | 56/36 | 118/63 | 0.214 |
| Body mass index | 24.6 (22.5–27.4) | 25.2 (23.1–27.7) | 24.8 (22.9–27.7) | 0.352 |
| Intraoperative fentanyl (μg/kg) | 2.98 (2.3–3.6) | 2.73 (2.1–3.5) | 2.86 (2.2–3.5) | 0.686 |
| Center (P/M) | 69/20 | 76/16 | 145/36 | 0.392 |
| Type of surgery | | | | |
| Urological surgery | 18 | 18 | 36 | 0.784 |
| General surgery | 64 | 68 | 132 | |
| Gynecological surgery | 6 | 6 | 12 | |
| Vascular surgery | 1 | 0 | 1 | |

P = IRCCS Policlinico San Matteo, Pavia, Italy; M = Azienda Ospedaliera San Gerardo, Monza, Italy.

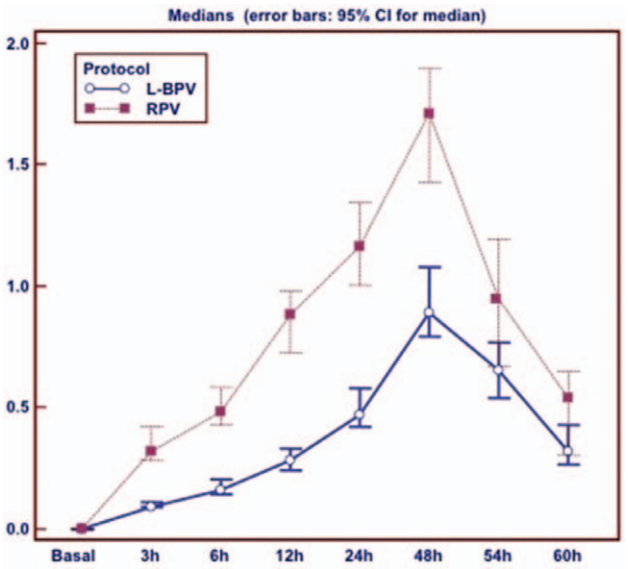


**Figure 2.** Total plasma drug concentration versus time curves during and after epidural continuous infusion preceded by 2 sequential boluses. L-BPV = levobupivacaine; RPV = ropivacaine.

**Table 2. Median Pharmacokinetic Data for the 2 Groups of Patients**

| | Group A Levobupivacaine (*n* = 81) | Group B Ropivacaine (*n* = 85) |
|---|---|---|
| $C_{max}$ (μg/mL) | 0.95 (0.23–2.13) | 1.71 (0.22–4.85) |
| $T_{max}$ (hours) | 48 (12–60) | 48 (12–60) |
| $AUC_{0\text{-}60}$ (μg × h × $mL^{-1}$) | 30.0 (4.85–66.6) | 60.9 (0.87–202.2) |
| $AUC_{0\text{-}48}$ (μg × h × $mL^{-1}$) | 23.6 (0.40–64.82) | 53.4 (5.09–157.74) |
| CL/F (L/h/kg) | 0.13 (0.1–1.28) | 0.10 (0.06–0.71) |
| $t_{1/2}$ (hours) | 7.5 (1.74–43.4) | 6.2 (1.5–54.6) |

Values in parentheses indicate range.
$C_{max}$ = peak plasma concentration; $T_{max}$ = time to obtain the greatest plasma concentration; AUC = area under the plasma concentration-time curve; CL/F = apparent plasma clearance (CL); here, F is the bioavailability (fraction of dose entering systemic circulation); $t_{1/2}$ = terminal half-life.

μg/mL), whereas in the ropivacaine group it was 1.71 μg/mL (range: 0.22–4.85 μg/mL) at 48 hours ($T_{max}$) (range: 12–60 hours). After the end of the infusion, the total plasma concentrations decreased from 0.66 μg/mL at 54 hours (<0.1–2.02 μg/mL) to 0.32 μg/mL at 60 hours (<0.1–1.48 μg/mL) in the levobupivacaine group and from 0.95 μg/mL at 54 hours (<0.1–4.04 μg/mL) to 0.54 μg/mL at 60 hours (<0.1–3.48 μg/mL) in the ropivacaine group.

The area under the plasma concentration curve, $AUC_{(0\text{–}60)}$, was 30.0 (4.85–66.6) μg × h × $mL^{-1}$ in the levobupivacaine group and 60.9 (0.87–202.2) μg × h × $mL^{-1}$ in the ropivacaine group. The comparison between the 2 CVs showed no statistical difference, with a difference between AUC within the range of maximum variation of 15%: the CV was 0.54 (95% CI: 0.45–0.67) for levobupivacaine and 0.51 (95% CI: 0.42–0.64) for ropivacaine ($P = 0.725$).

To determine differences in the accumulation rate of the 2 drugs, the fragmented AUCs from T0 to 3, 6, 12, and 24 hours were calculated for the 2 curves, and then the ratio with $AUC_{0\text{-}48}$ (AUC ratio) for each drug was calculated. The plasma concentrations of ropivacaine approached the $C_{max}$ significantly faster than those of levobupivacaine (Table 3).

## Clearance

A 1 - compartment open model with an infusion input was fitted to the data obtained during the epidural infusion for all patients enrolled. The median apparent plasma clearance values (CL/F) were estimated to be 0.13 L/h/kg (range: 0.1–1.28 L/h/kg) in the levobupivacaine group and 0.10 L/h/kg (range: 0.06–0.71 L/h/kg) in the ropivacaine group. The terminal half-life was 7.5 hours (1.74–43.4 hours) in the levobupivacaine group and 6.2 hours (1.5–54.6 hours) in the ropivacaine group.

In the study, the value of the clearance of ropivacaine decreases with increasing patient age, whereas the values of clearance of levobupivacaine show a distribution with no correlation with the age of the patient (Fig. 3). The data collected in the study show the aforementioned relationships, but we cannot rule out that these are not related to the large variability in plasma concentrations, the slightly different range of age, and to the size of the study. Therefore, we are not able to exclude that, with a larger sample, the results would be similar to the data already reported in the literature.

Total ropivacaine concentrations were comparable with those reported in previous studies to be tolerated by adult patients: 1.0 to 3.0 μg/mL.[32] The maximum value of total ropivacaine concentrations in our study was 4.9 μg/mL. The mean peak value was 1.75 μg/mL (95% CI: 1.541–1.951 μg/mL).

Total levobupivacaine concentrations were lower than the reported toxic systemic threshold of 2.4 to 2.7 μg/mL[7,33]

**Table 3. AUC Ratios at 3, 6, 12, and 24 Hours for Both Curves**

| AUC ratio | Group A Levobupivacaine (%) | Group B Ropivacaine (%) | *P* value |
|---|---|---|---|
| AUC (0-3 h)/AUC (0-48 h) | 0.74 (0.55–1.2) | 1.3 (0.70–1.8) | 0.001 |
| AUC (0-6 h)/AUC (0-48 h) | 2.7 (2.0–3.7) | 4.0 (2.5–5.7) | 0.0005 |
| AUC (0-12 h)/AUC (0-48 h) | 8.3 (6.57–10.2) | 11.1 (8.5–15.3) | <0.00001 |
| AUC (0-24 h)/AUC (0-48 h) | 27.7 (23.5–31.9) | 31.7 (26.85–40.6) | 0.0019 |

P values were calculated with the nonparametric Mann-Whitney *U* test.
AUC = area under the plasma concentration-time curve.

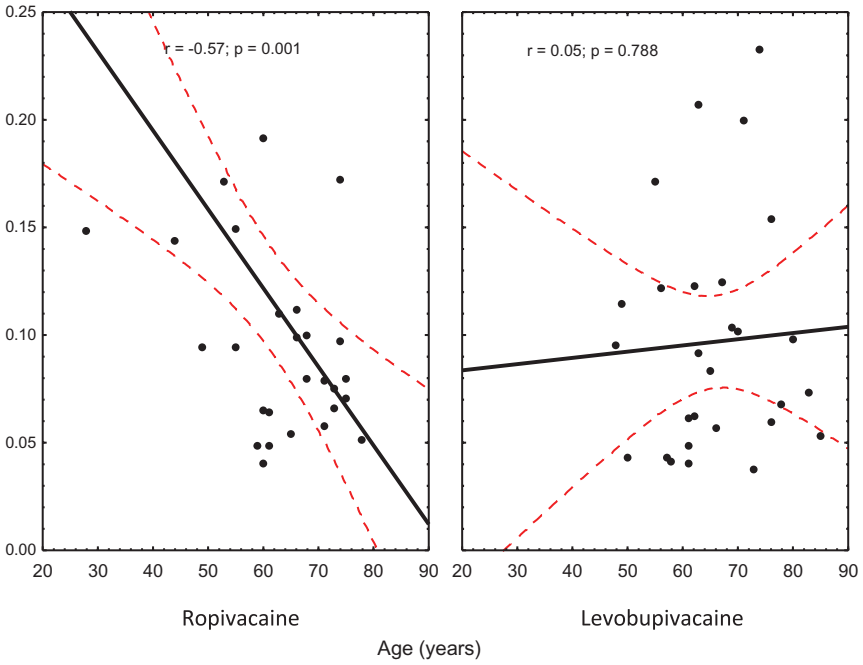


**Figure 3.** Correlation between clearance and patients' age for levobupivacaine and ropivacaine (Dashed lines are 95% confidence interval of regression line).

except in 1 case, which had a maximum concentration of 3.27 μg/mL. The mean peak value was 1.03 μg/mL (95% CI: 0.908–1.160 μg/mL). We did not find a relationship between the value of the plasma concentration and the onset or type of side effects.

### Pain Control and Side Effects

There were no significant differences in NRS, NRSd scores, or in the number of rescue doses between groups ($P = 0.209$). Adverse effects were mild, with no significant differences between groups.

## DISCUSSION

In this trial, we investigated the pharmacokinetic patterns of levobupivacaine and ropivacaine in adult patients receiving a continuous, 48-hour thoracic epidural infusion for pain management after major abdominal surgery with epidural infusion in the same level (T6–T9) in all patients. There were no differences in the CV of the 2 AUC. The values of ropivacaine clearance decreased as the patient's age increased; this result could be related to some limitations of our study. During the 48 hours of infusion, plasma concentration did not reach the steady state. Finally, the clinical efficacy and the incidence of adverse effects between groups were equivalent.

The interindividual variability of plasma concentration for levobupivacaine and ropivacaine during thoracic epidural infusions in adults are equivalent; however, the plasma concentration of ropivacaine increased more rapidly than that of levobupivacaine.

Only the clearance of ropivacaine decreased with the increase in patient age. This finding contrasts with previous observations that showed a reduction in the clearance of both ropivacaine and levobupivacaine with correspondence to a patient's increasing age.[34–36] Our data may be related to the large variability in drug plasma concentrations, the slight differences in the age range, and to the size of the study; therefore, we are not able to exclude that with a larger sample, the results would be similar to the data already reported in the literature.

A steady-state concentration was not reached during the 48-hour infusion. This is consistent with previous studies and is presumably attributable to the increase in plasma proteins in the immediate postoperative period. This finding also raises a question about the behavior of ropivacaine and levobupivacaine plasma concentrations during continuous infusions lasting more than 48 hours, especially regarding side effects and local anesthetics systemic toxicity. Finally, equipotent concentrations of levobupivacaine and ropivacaine produced no differences in clinical efficacy, as expected, or in the incidence of adverse effects between groups.

The analysis of the CV (which represents the dispersion of plasma concentration from the median value) revealed

that interindividual variability was the same for both drugs. Thus, the manageability of ropivacaine and levobupivacaine in terms of interindividual variability in systemic exposure can be considered equivalent.

In both groups, we observed a continuous, progressive increase in plasma concentration during the infusion, without a steady state being reached. The clearance (CL/F) of ropivacaine was slightly lower than that of levobupivacaine, as would be expected from ropivacaine's shorter half-life. Previous studies also report that the clearance of local anesthetics can decrease in relation to patient age.[34–36] Our results showed that only the clearance of ropivacaine decreases with the increasing age of the patients, but we are not able to exclude that this result may be related to some limitations of our study; for example, the large variability in plasma concentrations, the slightly different range of age inadequate study size for detecting differences the clearance of local anesthetic.

Analysis of the AUC ratio indicated that ropivacaine tended to approach the $C_{max}$ faster than levobupivacaine (Table 3). Total ropivacaine peak concentrations were comparable to those reported in previous studies to be tolerated by adult patients; total levobupivacaine peak concentrations were lower than the reported toxic systemic threshold, except in 1 case. Given the reduced number of side effects observed and the absence of correlation with the value of peak plasma concentration of local anesthetic, it has not been possible to perform a detailed analysis of the toxicity of the 2 molecules.

It is important to emphasize that, given the lack of clear indications about the toxic plasma drug concentration in the literature, the calculation of a therapeutic index for each of the drugs under study is fraught with problems. From this it follows that, at present, it is not possible to obtain precise indications of the greater or lesser manageability (ratio between concentration related to toxic effect and concentration related to efficacy) of drugs relative to each other in term of side effects. Plasma concentrations reported in the literature from case reports and case series have no standard temporal relation to the onset of symptoms. However, to our knowledge, in no randomized trials have authors compared whether one or the other of these 2 drugs more frequently presents concentrations above those for which there are case reports of systemic toxicity.

This information does not allow us to draw definitive conclusions regarding the safety of the analyzed drugs; in fact, we did not find any statistical difference in clinical side effects related to the 2 local anesthetics. Hence, our data confirm the conclusions of the review by Di Gregorio et al.[37] in which the authors, who analyzed published cases of toxicity from 1979 to 2009, stated that clinical manifestations of toxicity can be extremely heterogeneous and that there is a real need to establish a clear plasma concentration threshold related to systemic toxicity to allow an exhaustive analysis of the safety profile of local anesthetics. The determination of a plasma concentration threshold with regard to the toxic effects also raises many ethical problems that limit the possibility of performing randomized controlled trials. For this reason, it is important to use alternative methods for evaluating the safety of a local anesthetic, such as the assessment of the variability of its plasma concentrations.

From a clinical point of view, the NRS and NRSd scores remained under 4 and without statistical differences throughout the entire follow-up period. No statistical difference was found between the 2 groups regarding the need for rescue doses, showing the optimal effectiveness of both protocols. Likewise, no statistical difference was found in the onset of side effects between the 2 groups, whether considering the total number or single manifestations.

Some shortcomings of our study should be acknowledged. First, there could be differences in local anesthetic absorption as the result of differences in the distribution of epidural fat. In fact, there are some reports indicating that the absorption of local anesthetics is probably affected by the amount of epidural fat. This fat, in turn, is not equally represented along the epidural space and changes with age.[38–40] We tried to reduce this variability by comparing data from a sample without statistical differences in age, and in whom the tip of the epidural catheter was in the same position, but we cannot be sure that there were no differences in epidural fat between the groups receiving the different treatments. It would be interesting to investigate the exact correlation of absorption of local anesthetics in relation to epidural fat.

Second, levobupivacaine and ropivacaine are highly bound to α1 acid glycoprotein (AAG) after surgical stress.[41–43] Unfortunately, as the result of difficulties related to laboratory, we did not measure the levels of AAG in our trial. Surgery is known to have an important influence on plasma proteins, especially on the concentrations of albumin and AAG.[44] Measurements of AAG concentrations after major surgical procedures have shown that these increase gradually within few hours after the surgical procedures.[45] We also find in literature that levels of AAG decrease immediately after surgical procedures before recovery and may not reach concentrations comparable to basal until the second postoperative day.[46] Because our period of observation was between 24 and 48 hours postoperatively, we can assume that the changes in AAG values during that period were relatively marginal. Nevertheless, the dosage of AAG would have allowed a more accurate analysis of the pharmacokinetic data than emerged from this study.

Finally, the question of pharmacodynamics effects of local anesthetics administrated was not addressed. This is because the low number of side effects recorded during the study did not allow us to evaluate a correlation between pharmacokinetics and pharmacodynamics.

## CONCLUSIONS

The interindividual variability of plasma concentration of levobupivacaine and ropivacaine were equivalent during 48 hours thoracic epidural infusions in adults. As the difference between coefficients of variation is within the 15%, this indicates that the 2 molecules have the same manageability. Only the clearance of ropivacaine decreased in accordance with the patient's age. These data could be related to some limitations of the study. For both drugs, it was not possible to reach the steady-state concentration during 48 hours of epidural infusion; the behavior of the plasma concentrations of local anesthetics for infusions longer than 48 hours remains subject of debate and would require dedicated studies. Finally, we found no differences in the clinical efficacy or in the incidence of adverse effects between groups.

## APPENDIX 1

### SIMPAR Group

Manuela De Gregori, Biologist, Pain Therapy Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: manuela.degregori@unipv.it; Simona De Gregori, Unit of Clinical Pharmacokinetics in Transplant and Autoimmune Diseases, Infectious Diseases Department, Clinical Epidemiology and Biometric Unit, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: degregor@unipv.it; Cristina Ermanna Minella, MD, Pain Therapy Service, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: cristina.minella@gmail.com; Dario Bugada, MD, Anesthesia and Intensive Care I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: dariobugada@gmail.com; Silvia Bettinelli, MD, Anesthesia and Intensive Care I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: bettinellisilvia@yahoo.it; Chiara Baldi, MD, Anesthesia and Intensive Care I, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy. E-mail: cc.baldi@gmail.com; Valeria Rossini, Anesthesia and Intensive Care I. San Gerardo Hospital, Monza, and Department of Experimental Medicine. University of Milan Bicocca, Italy. E-mail: valeria.rossini84@gmail.com; and Luca Ghislanzoni, Anesthesia and Intensive Care I. San Gerardo Hospital, Monza, and Department of Experimental Medicine. University of Milan Bicocca, Italy. E-mail: lucaghislanzoni@me.com.

### ACKNOWLEDGEMENTS

The manuscript was corrected by the professional proofreading service Anchor English.

### DISCLOSURES

**Name:** Luciano Perotti, MD.
**Contribution:** This author helped analyze the data and prepare the manuscript.
**Attestation:** Luciano Perotti approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
**Name:** Maria Cusato, Pharmacist.
**Contribution:** This author helped design the study, conducted laboratory tests and data analysis, and helped in prepare the pharmacokinetic analysis.
**Attestation:** Maria Cusato approved the final manuscript.
**Name:** Pablo Ingelmo, MD.
**Contribution:** This author helped review the manuscript.
**Attestation:** Pablo Ingelmo approved the final manuscript.
**Name:** Thekla Larissa Niebel, MD, PhD.
**Contribution:** This author helped design the study, collect data, analyze the data, and prepare the manuscript.
**Attestation:** Thekla Larissa Niebel approved the final manuscript.
**Name:** Marta Somaini, MD.
**Contribution:** This author helped collect data.
**Attestation:** Marta Somaini approved the final manuscript.
**Name:** Francesca Riva, MD.
**Contribution:** This author helped collect data.
**Attestation:** Francesca Riva approved the final manuscript.
**Name:** Carmine Tinelli, MD.
**Contribution:** This author helped design the study, and analyze the data and statistics.
**Attestation:** Carmine Tinelli approved the final manuscript.
**Name:** José De Andrés, MD, PhD, FIPP, EDRA.
**Contribution:** This author helped review the manuscript.
**Attestation:** José De Andrés approved the final manuscript.
**Name:** Guido Fanelli, MD.
**Contribution:** This author helped review the manuscript.
**Attestation:** Guido Fanelli approved the final manuscript.
**Name:** Antonio Braschi, MD.
**Contribution:** This author helped review the manuscript.
**Attestation:** Antonio Braschi approved the final manuscript.
**Name:** Mario Regazzi, PharmD.
**Contribution:** This author helped design the study, analyze the data, and prepared the pharmacokinetic analysis.
**Attestation:** Mario Regazzi approved the final manuscript.
**Name:** Massimo Allegri, MD.
**Contribution:** This author helped design the study, collect data, analyze data, and prepare and review the manuscript.
**Attestation:** Massimo Allegri approved the final manuscript and attests to the integrity of the original data and the analysis reported in this manuscript.
**Name:** SIMPAR Group.
**Contribution:** These authors helped design the study, collect data, analyze data, and prepare the manuscript.
**Attestation:** These authors approved the final manuscript.
**This manuscript was handled by:** Tony Gin, MD, FRCA, FANZCA.

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