

# Chronobiology of Epidural Ropivacaine

## Variations in the Duration of Action Related to the Hour of Administration

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**Background:** A temporal pattern of the kinetics of local anesthetics is demonstrated in dental and skin anesthesia, with an important variation in the duration of action related to the hour of administration. The aim of this study is to determine whether the hour of injection influences the duration of epidurally administered ropivacaine during labor.

**Methods:** One hundred ninety-four women in the first stage of labor were assigned to one of four groups throughout the day period: group 1 (night: from 1:01 to 7:00 AM), group 2 (morning: from 7:01 AM to 1:00 PM), group 3 (afternoon: from 1:01 to 7:00 PM), and group 4 (evening: from 7:01 PM to 1:00 AM). Each patient received 14 ml ropivacaine, 0.17%, epidurally, and analgesia duration was measured.

**Results:** Pain assessed by a visual analog score was not different among groups before the first injection of local anesthetic. Analgesia duration was greater in the diurnal period (group 2:  $110 \pm 25$  min and group 3:  $117 \pm 23$  min) compared with the nocturnal period (group 1:  $94 \pm 23$  min and group 4:  $91 \pm 23$  min) ( $P < 0.01$ ). The largest intraday variation of analgesia duration among groups reached 28%.

**Conclusions:** Epidural analgesia duration exhibits a temporal pattern with important differences among diurnal and nocturnal phases. The authors emphasize that the lack of consideration of the chronobiologic conditions in epidural analgesia studies may create significant statistical bias. Future studies dealing with epidural local anesthetics should consider the time of drug administration.

THE efficacy of epidural local anesthetics for labor analgesia is established by numerous comparative, prospective, randomized, and double-blinded studies.<sup>1-3</sup> Relevance of such studies is increased when sample size is previously determined by power analysis and if patient demographic characteristics are strictly comparable.

However, temporal changes of drug kinetics have been reported in animals and humans for more than a hundred drugs, including local anesthetics.<sup>4</sup> Important differences in the duration of action of local anesthetic with respect to the hour of administration (circadian rhythm) have been demonstrated in several fields, including den-

tal surgery,<sup>5</sup> skin analgesia, and transcutaneous analgesia with eutectic mixture.<sup>6,7</sup> However, this important factor, which may strongly influence epidural analgesia duration and the results of comparative epidural analgesic studies comparing various analgesic mixtures, has never been taken into account.

Therefore, to test the hypothesis that ropivacaine duration of action has a circadian rhythm when injected epidurally, we enrolled laboring women who received epidural ropivacaine for pain relief during the first stage of labor in a prospective design.

## Methods

The study was approved by the local Clinical Research Ethics Committee (Lyon, France). Written and informed consent was obtained from all patients. From June 2000 to September 2000, we enrolled 194 women with American Society of Anesthesiologists physical status class I, nulliparous and multiparous (table 1), with a singleton vertex pregnancy of at least 36 weeks of gestation. Included patients were socially synchronized with diurnal activity from 7:00 AM to midnight and nocturnal rest, meaning that patients normally got up in the morning and slept at night.<sup>6</sup> To perform statistical analysis, the day period was divided into four groups of equal duration. The groups were built according to the hour of administration of epidural ropivacaine: group 1 (from 1:01 to 7:00 AM), group 2 (from 7:01 AM to 1:00 PM), group 3 (from 1:01 to 7:00 PM), and group 4 (from 7:01 PM to 1:00 AM). Each woman was in the first stage of labor and required epidural analgesia. Each of them received 14 ml ropivacaine, 0.17% (12 ml ropivacaine, 0.2%, added to 2 ml saline). Only patients with uncomplicated pregnancies, cervical dilatation less than 5 cm, and normal fetal heart rate tracings were enrolled. We excluded patients receiving antihypertensive drugs and patients who had already received opioid analgesia during this labor.

Each parturient received an intravenous infusion of 500 ml Ringer's lactate over 10 min before induction of epidural anesthesia and was positioned in the sitting position. The epidural space was cannulated at L2-L3 or L3-L4 using the loss of resistance to saline technique (3 ml), and 3 cm of catheter was left in place. The parturient was then repositioned to lie with a left lateral tilt.

A prospective design was then applied. Each parturient received a test dose of 2% lidocaine, 2 ml with 1:200,000 epinephrine. Five minutes later, they received a 14-ml epidural injection consisting of 12 ml ropiva-

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Table 1. Group Characteristics

	Group 1 (n = 41)	Group 2 (n = 69)	Group 3 (n = 46)	Group 4 (n = 38)
Age (yr)	28 ± 3	28 ± 4	29 ± 4	27 ± 4
Height (cm)	165 ± 4	166 ± 4	165 ± 4	165 ± 5
Weight (kg)	69 ± 10	71 ± 9	72 ± 11	70 ± 10
Primiparous (%)	46.3	50.7	47.8	52.6
Cervical dilatation (cm)	3 ± 1	3 ± 1	3 ± 1	3 ± 1

Values are mean ± SD. No significant differences among the groups.

caine, 0.2%, in which was added 0.9% saline (2 ml). The total volume (14 ml) was injected over 1 min. Blood pressure and heart rate were monitored using a noninvasive monitor before injection, every 5 min during the first 30 min, and every 15 min thereafter. Only some points are noted in this article, consisting of measurement before the first top-up injection, at 15 min, at 30 min, and at the time of additional analgesia requirement. When additional analgesia was requested, the study protocol and data collection were terminated, and analgesia duration was recorded according to the injection hour. Subsequent boluses were not standardized. Assessment of pain was made on a visual linear analog scale of pain intensity at the same time intervals. Each patient was presented with a line 100 mm long and was told that the left end represented no pain and the right end represented the worst pain imaginable. They were then asked to make a mark on the line to indicate the intensity of their pain at the peak of a contraction. Patients could request additional analgesia (0.2% ropivacaine, 10 ml, *via* the epidural catheter) if pain relief was unsatisfactory 15 min after injection of the study drug.

The time from study drug administration until a request for additional analgesia was recorded and assessed as duration of analgesia. Hypotension, defined as a decrease in systolic arterial pressure of at least 20% or systolic blood pressure less than 100 mmHg, was treated with intravenous ephedrine, 6-mg bolus, as necessary.

### Statistical Methods

For all calculations, the Statview computer software package was used (SAS Institute, Cary, NC). Intergroup comparisons of analgesia duration were performed by a one-way analysis of variance followed by a *post hoc* test (Bonferroni-adjusted comparisons). Consistent with a prospective and descriptive study, power analysis was subsequently calculated to determine relevance of the results. Then, with at least 38 patients per group (assuming  $\alpha = 0.05$ ) and with an SD of 24 min, the power of the analysis of variance reached 99%, with a goal of a 26-min difference in analgesia duration among the four groups. We also determined the effect of size (*f*) with SPSS software (SPSS Inc., Chicago, IL). Results are expressed as mean ± SD. A *P* value less than 0.05 was considered to be statistically significant.

## Results

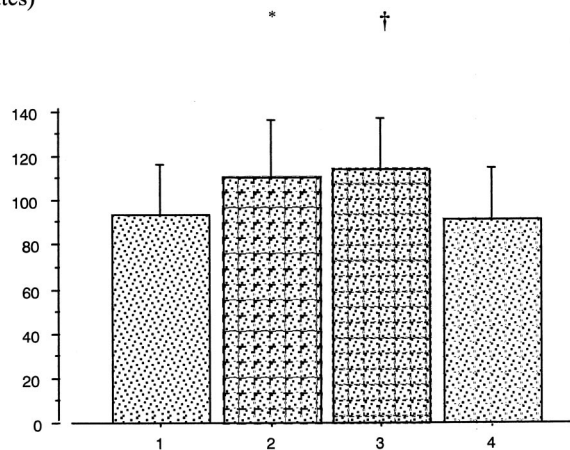
Patient demographic characteristics were comparable in all groups, as shown in table 1. No technical problems were encountered, and no patient needed an additional epidural solution because of inefficient analgesia.

Analgesia duration was 94 ± 23 min in group 1, 110 ± 25 min in group 2, 117 ± 23 min in group 3, and 91 ± 23 min in group 4. Statistically significant intergroup differences were observed as shown in figure 1. The most important difference in analgesia duration among the groups reached 26 min, representing a 28% longer analgesia duration in group 3 compared with group 4. Statistically significant differences in analgesia duration among other groups were 19 min between groups 2 and 4, 23 min between groups 1 and 3, and 16 min between groups 1 and 2. The effect of size *f* was 0.471.

The mean visual analog scale scores before epidural injection were comparable in all groups (table 2). No statistically significant difference was observed after epidural injection at either 15 or 30 min.

Maternal heart rate and blood pressure were comparable among groups both before administration of the epidural mixture and throughout the study. No patient required ephedrine for transient hypotension.

Analgesia duration  
(minutes)



\* *P* < 0.01 versus group 1 and group 4

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Fig. 1. Differences among groups in terms of analgesia duration. Statistically significant differences in duration of analgesia are observed in group 2 versus groups 1 and 4 (*P* < 0.01) and in group 3 versus groups 1 and 4 (*P* < 0.01).

**Table 2. Hemodynamic Characteristics and Pain Scores throughout the Day-period**

	Group 1 1:01 AM to 7:00 AM (n = 41)	Group 2 7:01 AM to 1:00 PM (n = 69)	Group 3 1:01 PM to 7:00 PM (n = 46)	Group 4 7:01 PM to 1:00 AM (n = 38)
SBP (mmHg)				
Baseline	128 ± 11	125 ± 11	122 ± 13	125 ± 9
15 min	115 ± 12	113 ± 12	115 ± 13	116 ± 12
30 min	115 ± 10	112 ± 11	114 ± 14	115 ± 11
Reinjection	123 ± 14	120 ± 11	121 ± 13	123 ± 11
HR (beats/min)				
Baseline	89 ± 15	85 ± 14	85 ± 14	84 ± 12
15 min	82 ± 13	80 ± 13	83 ± 16	85 ± 12
30 min	85 ± 14	79 ± 12	83 ± 19	83 ± 13
VAPS (mm)				
Baseline	69 ± 15	70 ± 18	71 ± 15	77 ± 16
15 min	5 ± 10	5 ± 10	8 ± 17	7 ± 14
30 min	3 ± 8	2 ± 6	3 ± 4	4 ± 10
Reinjection	38 ± 16	46 ± 22	40 ± 17	46 ± 22

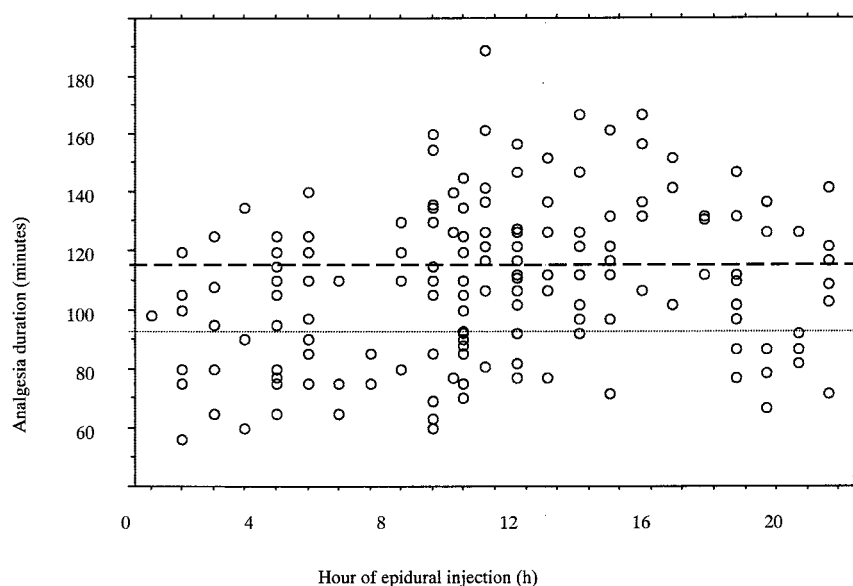
Values are mean ± SD. No significant differences among the groups.

SBA = systolic blood pressure; HR = heart rate; VAPS = visual analog score for pain.

## Discussion

In this study, analgesia duration recorded after administration of the same dose of epidural ropivacaine (14 ml ropivacaine, 0.17%) varied significantly according to the time of drug administration (fig. 2). We observed a significantly longer effect of epidural ropivacaine during the first stage of labor in the diurnal period (morning and afternoon) when compared with the nocturnal period (evening and night). The analgesia duration was 20–28% longer in the diurnal period. Our results are in accordance with previous studies, which exhibited a circadian rhythm of the duration of local anesthesia induced by lidocaine in both human teeth and skin,<sup>6</sup> with the longest anesthesia duration in the afternoon, at 3:00 PM. However, these previous chronopharmacologic studies dealing with local anesthetics' duration of action in the fields of cutaneous or dental analgesia had different de-

signs. These studies consisted of injection of local anesthetic at four or six precise time points throughout the day period, followed by measurement of analgesia duration.<sup>5–7</sup> This type of design is adopted when local anesthetics are administered at precise and predictable time points, but not in the field of obstetric analgesia during labor. During labor, epidural analgesia is administered according to a physiologic variable (cervical dilatation) rather than a previously determined time point. After epidural ropivacaine administration, patients were divided into the different groups according to the hour of epidural analgesia administration. This design led to four groups throughout the day period, in accordance with social markers (morning, afternoon, evening, and night) because synchronization on social markers represents a major basis in chronobiologic studies.<sup>6</sup> This division is necessary to examine the results from a statistical point



**Fig. 2.** Descriptive representation of analgesia duration throughout the 24-h period. The two dotted lines represent the shortest and the longest mean analgesia durations.

of view, consisting of mean analgesia duration comparisons using analysis of variance. Moreover, comparison of analgesia duration between morning, afternoon, evening, and night has more clinical meaning than hourly comparison.

Our results imply two points of relevance. First, there is clinical relevance consisting of a 28% difference in analgesia duration between afternoon and night periods. Second, our results imply that bias may be created by ignoring chronobiologic parameters. We show that differences in analgesia duration are partially related to circadian conditions. The ignoring of circadian parameters in the design of comparative studies may introduce a statistical bias of type I error.

The design of previous studies regarding epidural local anesthetic duration of action during labor did not take chronobiologic parameters into account. The purpose of these studies usually consisted of the comparison of drugs,<sup>8,9</sup> in addition of opioids to local anesthetics, in comparing different methods of administration and in evaluating the consequences of these procedures on epidural labor analgesia.<sup>10-12</sup> In these previous studies, patients' assignment in the different groups was established without regard to the hour of drug administration, subjecting the analysis of the results to bias.

Bruguerolle and Prat<sup>4,13,14</sup> suggested that the time of administration and its pharmacologic consequences are involved in toxicity and efficacy of local anesthetics. Regarding epidural analgesia, our study is the first to investigate the influence of the hour of administration of epidural local anesthetics on the duration of analgesia. We exhibited less important but statistically significant differences (25-30%) when compared with dental or skin analgesia.

Several mechanisms are thought to be involved. First, circadian changes in membrane nerve cell permeability to ions was reported by Njus *et al.*<sup>15</sup> In the same way, Ede *et al.*<sup>16</sup> showed that the cell potassium concentration and the K<sup>+</sup> efflux from cells is lowest around 3:00 PM. The possible effect of a circadian rhythm of catecholamine release has also been reported.<sup>17</sup> A hormonal path implicating progesterone has also been discussed, although no circadian pathway has been demonstrated.<sup>18</sup>

We demonstrate a circadian variation of analgesia duration, with lowest duration in the evening and night and maximal duration in the diurnal period. The variation throughout the day period is consistent with a maximum

difference of 28% using the same dose during the night or in the afternoon. On the contrary, visual analog scale pain scores did not differ at any time of day, excluding nyctohemeral variation in pain.

We conclude that the hour of drug injection contributes to analgesia duration when local anesthetics are administered epidurally during labor. Further studies in the field of epidural obstetrical anesthesia should include this parameter.

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