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Chronopharmacology of Intrathecal Sufentanil for Labor Analgesia

Daily Variations in Duration of Action

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Background: **The pharmacokinetic and pharmacodynamic characteristics of opioids vary throughout the day, as demonstrated for oral morphine in chronic pain. However, little is known about the chronobiology of intrathecal lipid soluble opioids used for labor analgesia. The aim of this prospective study was to determine whether the duration of action of intrathecally administered sufentanil is influenced by the time of administration.**

Methods: **Ninety-one women in the first stage of labor were enrolled. Labor analgesia was first provided by 10 μg intrathecal sufentanil. The duration of action of intrathecal sufentanil was measured and analyzed by the cosinor method to determine periodic intraday variation.**

Results: **Pain assessed by a visual analog score was not different among patients (70 ± 17 mm) before the injection of intrathecal sufentanil. Rhythm analysis revealed a mean (± SD) duration of analgesia (mesor) of 93.0 ± 3.8 min. A highly significant 12-h rhythm was found, with two peaks: One was near midnight (0.78 ± 0.6 h), and the other was near noon (12.78 ± 0.6 min) ($P < 0.01$). The amplitude of this 12-h component was 16.1 ± 5.5 min.**

Conclusions: **The duration of intrathecal sufentanil analgesia exhibited a temporal pattern with 30% variations throughout the day period. The authors point out that the lack of consideration of chronobiological conditions in intrathecally administered analgesia studies can cause significant statistical bias. Further studies dealing with intrathecal opioids should consider the time of drug administration.**

INTRATHECAL opioids represent one of the most popular means to provide labor analgesia for more than ten years, and there has been a recent gain in interest.[1] The benefits of lipid-soluble opioids administered *via* combined spinal–epidural technique are the absence of motor block and their adaptation for analgesia in advanced labor.[1–5]

We have previously demonstrated major differences in the duration of action of ropivacaine by epidural route with respect to the time of administration (circadian rhythm) and discussed the consequences of this parameter on statistical analysis.[6] Surprisingly, nothing is known about influence of the time of the day on the effect of intrathecal opioids analgesic. Moreover, the consequences of unsuspected intraday variation on statistical results have not been investigated in the field of intrathecal opioids. Therefore, to test the hypothesis that the duration of action of sufentanil has a circadian rhythm when administered intrathecally, we enrolled laboring women who received intrathecal sufentanil for pain relief during the first stage of labor in a prospective design.

Materials and Methods

After obtaining written and informed consent from patients and agreement from the Ethical Committee of the University of Lyon (Lyon, France), we enrolled 104 women, from February 2001 to September 2001, who had American Society of Anesthesiologists physical status I, were nulliparous and multiparous (para 1 or 2), and had a singleton vertex pregnancy of at least 36 weeks' gestation. Each woman was in first stage of spontaneous labor, with a cervical dilation of 3–5 cm when requesting labor analgesia. Thirteen patients were secondarily excluded from the analysis because they received intravenous oxytocin before the injection of spinal sufentanil. Only patients with uncomplicated pregnancies and normal fetal heart rate tracings were enrolled. We excluded patients receiving antihypertensive drugs and patients who had already received opioids during this labor.

Each parturient received an intravenous infusion of 500 ml lactated Ringer's solution over 10 min before induction of intrathecal anesthesia. Each patient received 10 μg intrathecal sufentanil using a combined spinal–epidural technique. The combined spinal–epidural procedure was performed with the Braun Escopan® combination needle (Braun Medical SA, Boulogne, France). Patients were placed in the sitting position, and an 18-gauge Tuohy needle was inserted by using the loss of resistance to saline technique. After insertion of a 27-gauge pencil-point spinal needle and intrathecal sufentanil injection, a 20-gauge multiorifice catheter was inserted in the epidural space. The epidural catheter was left in position, without other drug administration until the end of the effect of sufentanil.

A prospective design was then applied. Blood pressure and heart rate were monitored using a noninvasive monitor before injection and at every 15 min after injection.

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Subsequent analgesia was maintained using the usual epidural design. Assessment of pain was made on a visual analog pain scale (VAS) 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 (12 ml ropivacaine, 0.1%, *via* the epidural catheter) if pain relief was unsatisfactory by 15 min after injection of the study drug; they were then excluded from data collection. When additional analgesia was requested (VAS score $>$ 40 mm), the study protocol and data collection were terminated, and analgesia duration was recorded. The time from study drug administration until a request for additional analgesia was 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 a 6-mg intravenous ephedrine bolus as necessary.

Statistical Methods

Data are presented as mean ± SD. Using the nonlinear fitting program WIN-ABPM-FIT,§ partial Fourier series were fitted to the data obtained on the duration of analgesia in the total number of patients.[7] The rhythm analysis calculates the mesor (rhythm-adjusted mean), the amplitude (half of the peak-to-trough of the fitted harmonic), and the acrophase (time of occurrence of maximum of a rhythmic component) according to the equation

$$y = \text{mesor} + \sum_{1}^{i}\{\text{amplitude}_i \times \cos[(x - \text{acrophase}_i) \times 2\pi/\text{period}_i]\},$$

where i is the number of harmonics.

The duration of analgesia between parity 1 and 2 women was analyzed using the Mann–Whitney test. Results were considered significant if P values were less than 0.05.

Results

Patient characteristics (n = 91) are provided in table 1. In the 91 patients, 31 received oxytocin at different times and different dosages. No technical problem was encountered, and no patient required additional epidural solution for inefficient analgesia. The mean VAS score before intrathecal injection was 70 ± 17 mm. Fifteen minutes after intrathecal sufentanil, the mean VAS score decreased to 0.3 ± 0.7 mm. The mean durations of analgesia were not statistically different between parity 1 and 2 women (97.5 ± 28.3 and 92.0 ± 45.9, respectively; $P < 0.09$).

Table 1. Demographic Data

Age, yr ± SD	Nulliparous	Height, cm ± SD	Weight, kg ± SD	Cervical dilation, cm ± SD
28 ± 5	67%	165.0 ± 5.7	72.2 ± 31.1	3.3 ± 0.7

The mean 24-h duration of analgesia (mesor) was 93.0 ± 3.8 min. Rhythm analysis revealed a highly significant 12-h rhythm with two peaks ($P < 0.01$; fig. 1): One was near midnight (0.78 ± 0.6 h), and the other was near noon (12.78 ± 0.6 min). The mean analgesia durations at acrophase and nadir were 109.1 ± 5 and 76.9 ± 5 min, respectively (fig. 1). Therefore, the difference between maximum and minimum fitted values (32.2 min) was approximately 30% of the mesor (fig. 1). A similar chronobiologic pattern was observed when cosinor analysis was restricted to parity 1 women (n = 61) (fig. 2).

Maternal heart rate and blood pressure changes were within the physiologic range throughout the study. No patient required ephedrine for transient hypotension. Four patients had transient uterine hyperactivity and nonreassuring fetal heart rate abnormalities, and more than 70% of the patients had pruritus.

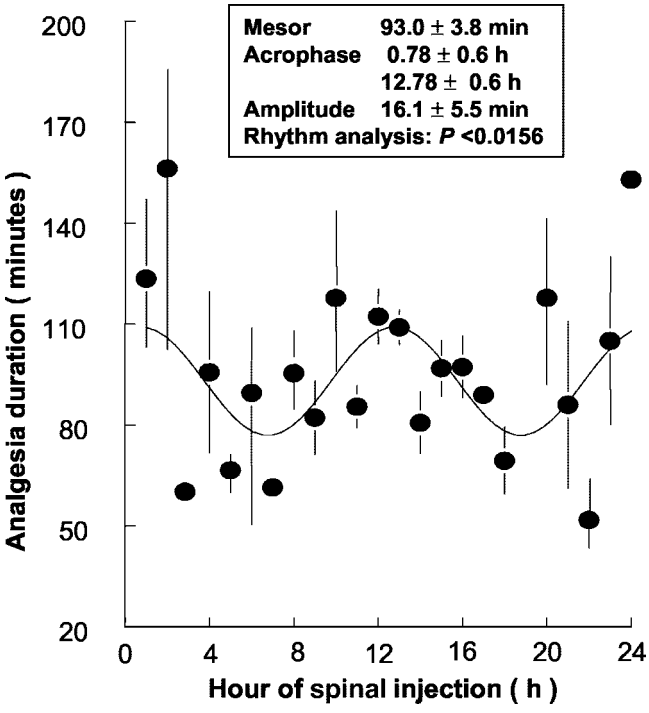

Fig. 1. Chronobiologic data of intrathecal duration of sufentanil for labor analgesia (parity 1 and 2 women, n = 91). Data are presented as mean ± SD.

§ P. Zuther and B. Lemmer, Chronos-Fit, http://www.ma.uni-heidelberg.de/inst/phar/forschungLemmer.html, 2004. Accessed August 2003.

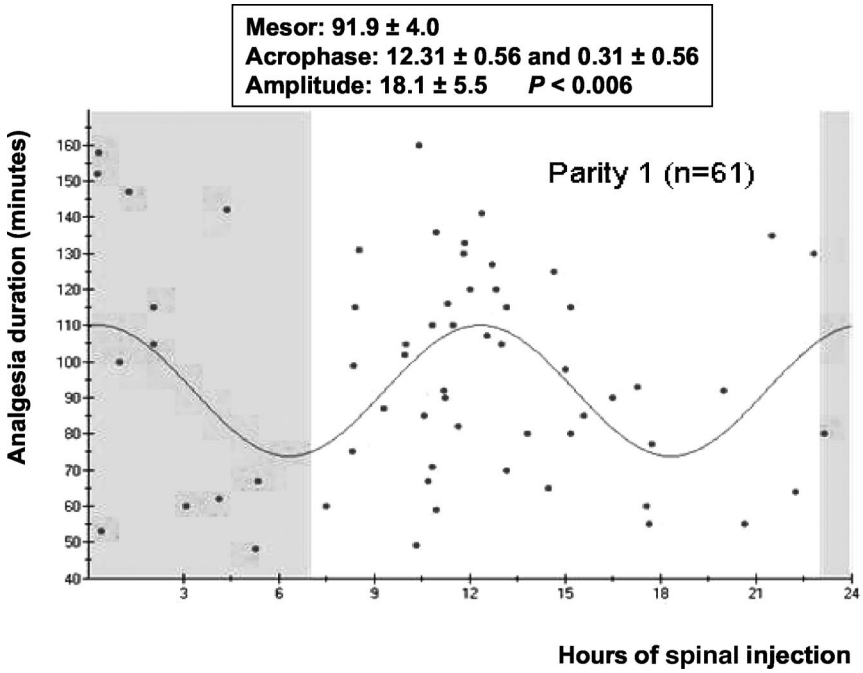

Fig. 2. Chronobiologic data of intrathecal duration of sufentanil for labor analgesia in parity 1 women (n = 61). Data are presented as mean ± SD.

Discussion

We demonstrated that duration of analgesia obtained after administration of the same dose of intrathecal sufentanil varied significantly according to the time of drug administration. We observed a rhythmic variation of analgesia duration of intrathecal sufentanil throughout the day period with a 12-h component. The mean durations of analgesia were 109.1 ± 5 and 76.9 ± 5 min at acrophase and nadir, respectively, demonstrating that the daily variation was approximately 30% of the 24-h mean.

Intrathecally administered sufentanil had a peak effect near midnight and a second peak effect near noon. Interestingly, the peak effect obtained after paraapical administration of articaine and of epidural ropivacaine was near noon similar to the secondary peak of sufentanil observed in our study.[6,8]

The sufentanil dose chosen (10 μg intrathecal sufentanil) has been used and validated in many clinical studies interested in the combined spinal–epidural technique.[9–11] It represents the total volume of a 2-ml sufentanil ampoule, making the manipulation easy for clinical practice and avoiding sampling errors. Ten micrograms also represents the clinical dosage closest to the ED_{95} defined by Herman *et al.*[12] These authors found that the ED_{95} for intrathecal sufentanil in laboring women was 8.9 μg (95% confidence interval, 7.5–11.5 μg). However, high intrathecal sufentanil doses used to relieve labor pain have been associated with uterine hyperactivity and nonreassuring fetal heart rate abnormalities. Although no severe complications were observed in our study, lower intrathecal sufentanil doses are recommended in clinical practice.

The duration of action of intrathecal sufentanil 10 μg reported in our study is close to that previously reported by Nelson *et al.*,[10] with 8 μg (104 ± 34 min). Conversely, D'Angelo *et al.*[11] reported a longer duration of action with 10 μg (123 min), whereas Camann *et al.*[10] demonstrated, in a small sample, a much shorter duration of action of the same dose (84 min) in comparable patients. In laboring women requiring analgesia in the first stage of labor, the mean analgesia duration of 10 μg intrathecal sufentanil should vary from 84 min (70–92 min) to 123 min.

These major discrepancies could at least in part be related to chronopharmacologic conditions. However, results could have also been influenced by several factors other that the time of the day. We did not note any circadian variation in VAS score when patients were in the active phase of the first part of labor. Major differences in duration of spinal sufentanil have been observed when comparing early labor (cervical dilation of 3–5 cm) with more advanced labor (7–10 cm).[13] The standardization of our parturients (cervical dilation of at least 4 cm) could have excluded this bias. Another factor that could influence the results of obstetric studies is parity. Parity was not standardized because parities 1 and 2 were both included in our study. However, analysis of data restricted to parity 1 women has shown that the chronobiologic profile in parity 1 women is similar that of to the total population.

Another limitation of this study is that approximately 50% of women received oxytocin infusion during the study period. Oxytocin infusions are generally believed to increase the pain of labor and epidural analgesic requirement. However, Panni and Segal[14] showed that the minimum local analgesic concentration values for

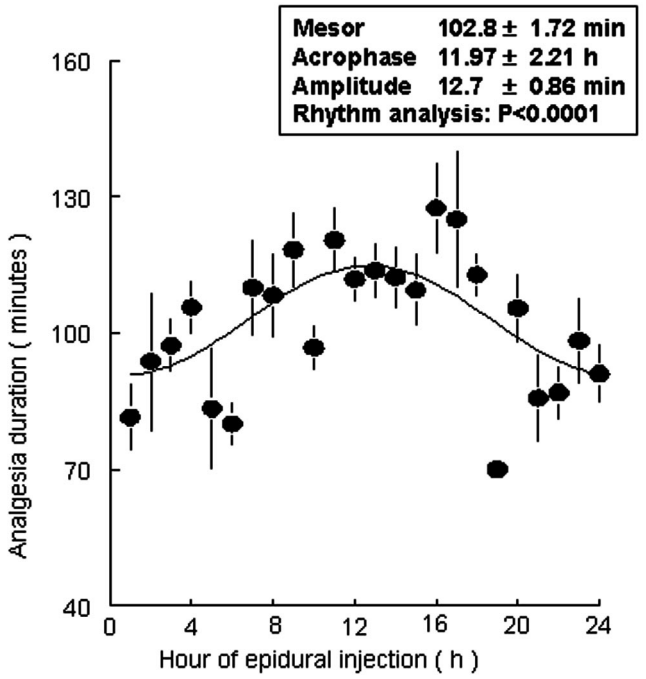

Fig. 3. Rhythm in analgesia after epidural injection of ropivacaine during labor. Results are expressed as mean ± SD. These data were analysis by the cosinor method of those published in Debon *et al.*[19]

bupivacaine were similar in women receiving oxytocin or not. Acute uterine cervical distension, the source of labor pain during the first stage of labor, like bladder, esophageal and colorectal distension, induce visceral pain.[15] In the field of gastroenterology, oxytocin significantly increases thresholds for visceral pain but only at doses of 20 mU/min or greater.[16] Dawood[17] reported that approximately 90% of laboring women achieve adequate uterine activity with rarely more than 6 mU/min. The 6 mU/min during labor is far from the 20 mU/min that increases thresholds for visceral pain. We agree that this could be different during labor. At this time, no previous study has clearly established, in laboring women, the relations among oxytocin infusion rhythms, intensity of pain, and the requirements for analgesics. Finally, it is also impossible to exclude that the perceived degree of pain labor in our patients was affected by the care provided by our doctors and nurses.

In our previous study regarding chronobiology of epidural ropivacaine duration of action, the statistical analysis consisted of an analysis of variance.[6] This method did not allow the characterization of the rhythmic variation observed—it only described the phenomenon. In the current study, we used the cosinor analysis, a statistical method that is the accepted standard in the field of chronopharmacology.[18] We subsequently applied the cosinor method to our previous study and demonstrated a strong cyclic variation of epidural ropivacaine duration of action (fig. 3).[19]

Our study reported the cyclic circadian variations in sufentanil analgesia duration but was not designed to provide mechanistic explanations. Several phenomena should be investigated to explain our results: First, opioid receptor affinity or number or both should vary throughout the day period, as speculated about circadian variations of pupillary response to naloxone and morphine in mice.[20] Second, the implication of oxytocin pattern or circadian variation and its analgesic effect on circadian variation during labor should be investigated. Third, the circadian variation of β-endorphin secretion and activity should be investigated.[21–23]

These results are relevant for two reasons: First, there is a clinical relevance consisting of a 30% difference of duration of analgesia between acrophase and nadir. Second, our results have major statistical implications related to the bias created by ignoring chronopharmacologic parameters. We demonstrated major differences in effectiveness of intrathecal sufentanil related to the time of administration that may cause statistically significant differences in themselves. This implies that ignorance of circadian parameters in design of comparative studies may lead to a statistical bias called type I error as demonstrated in our previous study.[6] As a conclusion, we demonstrated cyclic circadian variations in intrathecal sufentanil duration of action, but further studies are needed to reveal the mechanisms involved.

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