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Chronobiology and Anesthesia

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CHRONOBIOLOGY investigates biologic rhythms that are involved in the organization of living organisms.[1] Biologic rhythms consist of variations of biologic phenomena that are periodic and foreseeable in time.[2] They are genetically determined as indicated by their persistence during constant conditions such as continuous light or darkness.[3] Temporal variations in cycles of light–dark, rest–activity, fasting–eating, and other environmental conditions, defined as *synchronizers*, give the organism temporal markers and thus impose their period on these biologic rhythms.[4] These rhythms can therefore be characterized by different periods, leading to the division of circadian (a period of approximately 24 h), ultradian (a cycle that is shorter than 1 day), and infradian (a cycle that may last weeks, months, or seasons).[5] These clocks influence how our bodies change throughout the day, affecting blood pressure, activity of the immune system, blood coagulation, and gastric and renal functions.[2,6,7] Almost all hormones are regulated by circadian rhythms.[8] For example, cortisol naturally decreases to its lowest concentrations at bedtime and reaches its highest concentrations during the early waking hours.[9] This variation may be fit to a sinusoidal function by the cosinor method, a linear method of least squares (fig. 1). This function is characterized by parameters such as the midline-estimating statistic of rhythm (MESOR), *i.e.*, the mean level that is equal to the 24-h average), amplitude (half of the peak-to-trough difference of the fitted cosinus function), and acrophase (the crest time of rhythm given in degrees, where 360° corresponds to a 24-h cycle, or in hours and minutes).[10] Other methods, such as Fourier transformation, may be used to detect the periodicity of the rhythm.[11]

Biologic rhythms are influenced by socioecologic factors, such as jet lag and shiftwork, as well as by illness and drugs. Available clinical data have shown that signs and symptoms are not constant over time and often have cyclic patterns. More strokes and heart attacks occur in the morning compared with any other time of day, and people with osteoarthritis tend to feel less pain in the morning than at night.[12,13] Studies also suggest that chemotherapy and treatments for asthma and arthritis may be more effective and less toxic if drugs are administered at carefully selected times.[14,15] Taking into account the circadian rhythms for medical treatment by choosing the time of day for drug administration is called *chronotherapy*. Drug effects can be optimized and side effects can be reduced by basing drug administration on the circadian patterns of a disease.

Chronopharmacology is the study of the influence of the moment of administration of a drug (hour, month, and year) on its response according to the temporal structure of the organism receiving it.[16] Chronopharmacology also studies the drug-induced alterations of biologic rhythms. Two aspects of chronopharmacology must be distinguished: the time of administration of a drug may determine a different response from a qualitative or a quantitative point of view (chronopharmacodynamics) and/or a different effective drug concentration (chronopharmacokinetics).[17,18] Pharmacokinetic parameters are influenced by different physiologic functions displaying circadian rhythm.[19] Temporal changes of drug kinetics have been reported in animals and humans for more than a hundred drugs, including anesthetics.[20] It has been shown, for example, that despite a constant infusion rate of heparin, the risk of bleeding and the activated partial thromboplastin are higher at night.[21] Chronopharmacokinetic data may partly explain chronopharmacodynamic phenomena.[22] Knowledge of the influence of the time of administration on the drug kinetics could therefore have implications for its prescription by modulating the distribution of the total daily dose over a 24-h period.

The aim of this review is to provide an update on the chronobiologic and chronopharmacologic findings that could have an impact on the daily practice of anesthesiology and/or research in this area.

Anatomic Basis of Circadian Rhythms

The regulation of rhythmicity necessitates a central pacemaker, input pathways (synchronizers) connecting

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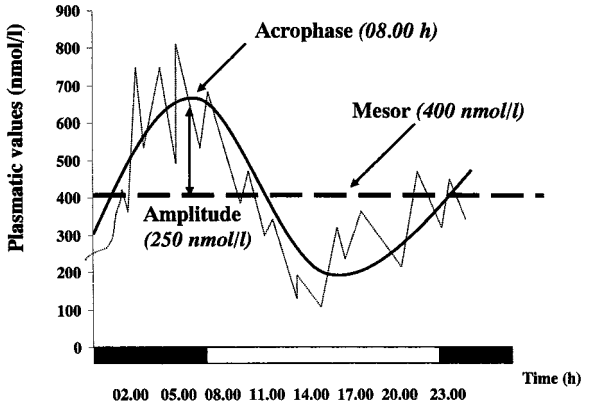

Fig. 1. Illustrative example of single cosinor analysis (*dotted line* = plasmatic concentrations measured in nmol/l; *solid line* = result of the cosinor analysis). Single cosinor analysis by least-square cosine regression is applied and allows detecting a circadian rhythm when $P < 0.05$. Different parameters of this rhythm may be determined. Acrophase = the peak time of rhythm given in degrees or hours and minutes; amplitude = half of the peak-to-trough difference of the fitted cosine function; MESOR = midline-estimating statistic of rhythm representing the mean level approximately equal to the 24-h average.

the clock to the external environment, and output pathways. In mammals, the central circadian pacemaker is located in the suprachiasmatic nucleus of the hypothalamus (fig. 2), and the main synchronizer is light.[23] The suprachiasmatic nucleus receives two photic projections. Photoreceptors located in the retina project directly to the suprachiasmatic nucleus through the retinohypothalamic tract. Glutamate is the main signaling molecule at this synaptic connection. Photic information can also indirectly reach the suprachiasmatic nucleus through the intergeniculate leaflet, then through the geniculohypothalamic tract. The γ-aminobutyric acid (GABA) type A and neuropeptide Y act as signaling molecules at this synaptic connection.[24] The circadian pacemaker can also be reset by nonphotic synchronizers such as locomotor activity, drugs, and feeding. Serotonergic afferent activity from the raphe nucleus and neuropeptide Y–GABA-mediated (GABAergic) input from the intergeniculate leaflet are involved in these pathways. Acetylcholine, histamine, and serotonin are involved in the control of the suprachiasmatic nucleus.

The suprachiasmatic nucleus contains several different peptidergic types of cells, including vasopressin, calretinin, substance P, GABAergic, gastrin-releasing peptide, and somatostatin.[25] Recording of electrical activity in the suprachiasmatic nucleus indicates that most of its neurons function as pacemakers. Previous studies have revealed that vasoactive intestinal peptide-expressing cells play a major role in its entrainment by light.[26]

The synthesis of melatonin in the pineal gland is one of the rhythms controlled by the suprachiasmatic nucleus. The neuronal input pathway regulating the pineal gland originates in the retina, which projects fibers to the suprachiasmatic nucleus *via* the retinohypothalamic tract. From the suprachiasmatic nucleus, the signal passes through the paraventricular nucleus, follows the medial forebrain bundle, and ends in the intermediolateral cell column of the upper thoracic spinal cord. From this, there is a projection to the superior cervical ganglion from which sympathetic neurons innervate the pineal gland.[27] The signal to the pineal gland is norepinephrine, which is inhibited by light. The synthesis and release of melatonin are therefore stimulated by darkness and inhibited by light. The daily rhythm of melatonin is also controlled by the suprachiasmatic nucleus *via* GABAergic projections to the paraventricular nucleus.

The secretion of cortisol is controlled in the suprachiasmatic nucleus. Basal plasma adrenocorticotropic hormone is rhythmically driven by the suprachiasmatic nucleus, resulting in a peak cortisol concentration in the early hours of the morning, with a minimal concentration around midnight. At least two hypothalamic peptides, corticotropin-releasing hormone and vasopressin, modulate adrenocorticotropic hormone release from the anterior pituitary. The suprachiasmatic nucleus is also directly involved in regulating the sensitivity of the adrenal cortex to adrenocorticotropic hormone. It has been proposed that the suprachiasmatic nucleus uses autonomic neuronal pathways to spread the circadian message to the adrenal gland.[28] Clock genes are responsible for circadian rhythm.[24,29,30] Their expression is detected in many organs, and expression is not restricted to the central pacemaker. A transcriptional feedback loop is at the center of the clockwork mechanism. CLOCK, BMAL1 and Rev-erbα are transcription factors that drive the expression of two cryptochrome genes (cry1 and cry2) and three period genes (per 1–3). The per and cry proteins block their own synthesis by inhibiting CLOCK and BMAL1.[29,30] This feedback is delayed, generating oscillations. The genes that encode this feedback loop respond to synchronizers, of which light is

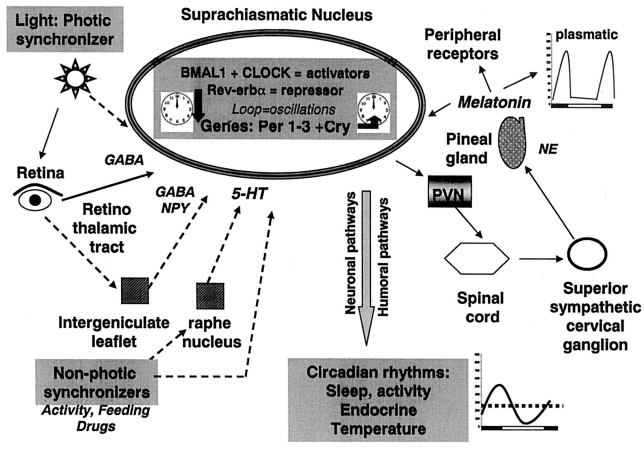

Fig. 2. Schematic illustration of the mammalian circadian system. GABA = γ-aminobutyric acid. 5-HT = 5-hydroxytryptamine; NE = norepinephrine; NPY = neuropeptide Y; PVN = paraventricular nucleus.

Table 1. Clinical Chronopharmacology of Local Anesthetics

Drug	Measured Parameter	Main Observed Change	Reference
Articaine	Sensitivity threshold (area-under-curve effect) (n = 55 patients)	Maximum local anesthetic effect at 14:00 h (approximately 37% change)	Lemmer and Wiemers,[104] (1989)
Betoxycaine	Local anesthetic duration (cutaneous) (n = 35 patients)	Maximum local anesthetic effect at 15:00 h (approximately 50% change)	Reinberg and Reinberg,[36] (1977)
Lidocaine	Local anesthetic duration (dental, n = 5 patients; cutaneous, n = 35 patients)	Maximum local anesthetic effect at 15:00 h (approximately 40% and 60% change for cutaneous and dental, respectively)	Reinberg and Reinberg[36] (1977)
Mepivacaine	Local anaesthetic duration (dental) (n = 67 patients)	Maximum local anesthetic effect at 15:00 h (approximately 69% change)	Pollmann,[88] (1984)
Ropivacaine	Epidural ropivacaine, women in labor, duration of analgesia (n = 194 patients)	Analgesia duration greater at 13:00 h and 19:00 h (approximately 17% change)	Debon *et al.*,[38] (2002)

one of the most important. Rhythms are not restricted to the central clock because circadian rhythms have been identified in peripheral organs, such as the heart and the liver, and also in isolated cells. Circadian rhythm persists in cultured suprachiasmatic nucleus neurons, and transplanted suprachiasmatic nucleus cells can restore circadian function after destruction of the host suprachiasmatic nucleus. Peripheral tissue clocks have been shown to be directly regulated by light–dark cycles in culture.[31] Glucocorticoids can also change per gene expression in peripheral tissues without affecting the suprachiasmatic nucleus.[32] In conclusion, current understanding of mammalian circadian rhythms suggests that they are regulated by synchronizers that target signaling pathways in the hypothalamic suprachiasmatic nuclei. The genetic basis of circadian rhythms has been established, and almost every biologic process in cells or in organs seems to be affected at some level by a circadian clock.

Circadian Rhythms for Local Anesthetics

Chronopharmacology for Local Anesthetics

Anesthesiologists choose a particular local anesthetic in part because of the differences in onset and duration of effect. As for many other drugs, the efficacy and toxicity of local anesthetics depend on the time of administration.

Time Dependency in Toxicity. Many studies have shown circadian time-dependent changes in acute or chronic toxicity, and data indicating that the circadian susceptibility of mice to local anesthetics is highest during the dark phase (*i.e.*, the activity period for mice) and lowest during the light phase (*i.e.*, the resting period for mice).[33] A single dose of 65 mg/kg lidocaine given intraperitoneally in mice induces convulsant activity, with a maximal percentage of convulsions (83%) occurring at 21:00 h.[33] The lowest concentrations of bupivacaine and mepivacaine inducing 50% of mortality in rodents (LD_{50}, in mg/kg) occurred during the dark period, at 22:00 and 19:00 h, respectively. Mepivacaine values of LD_{50} varied within a 30% range over a 24-h period (100 mg/kg during the day compared with 130 mg/kg at night).[34] Latency for lidocaine-induced convulsions was the shortest at the beginning of the night (128 ± 11 s at 23:00 h *vs.* 177 ± 14 s at 10:00 h), corresponding to the time of maximal mortality.[35] In addition, flumazenil influenced lidocaine-induced toxicity in a circadian time-dependent manner

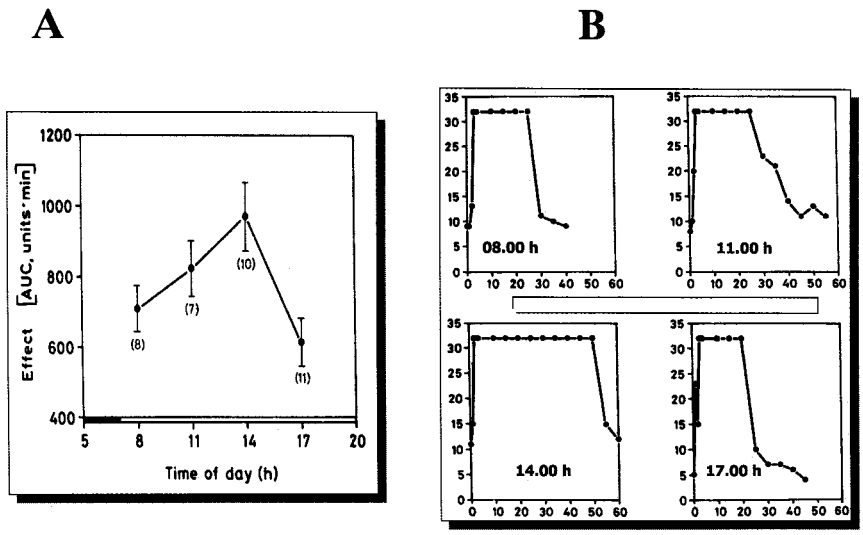

Fig. 3. Circadian changes in the local anesthetic effect of carticaine in dental surgery measured with an electronic pulptester. (*A*) Effect calculated as area under the curve (AUC): units in pain sensitivity · min. (*B*) Effect on pain sensitivity at a frontal tooth of four representative patients who were injected at 08:00, 11:00, 14:00, or 17:00 h. Effect is shown as relative units of the pulptester. From Lemmer and Wiemers[104]; used with permission.

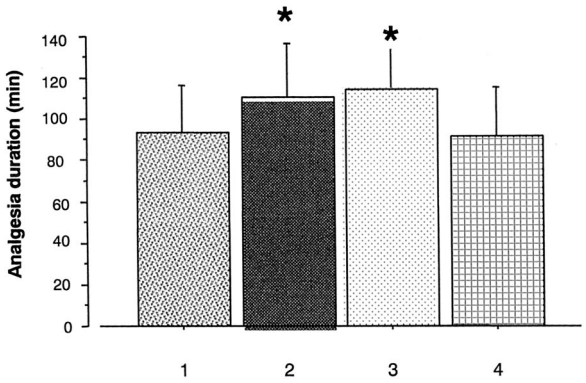

Fig. 4. Influence of the hour of injection on the duration (mean ± SD) of epidurally administered ropivacaine during labor. Group 1 (01:00–07:00 h), group 2 (07:00–13:00 h), group 3 (13:00–19:00 h), group 4 (19:00–01:00 h). * $P < 0.01$ *versus* groups 1 and 4. From Debon *et al*[38]; used with permission.

because the antagonist activity of flumazenil was only significantly detected during the day and not at night.[35]

Time Dependency in Local Anesthetic Activity. Overall, the results show that the longest duration of anesthesia is at approximately at 15:00 h, whatever the local anesthetic agent (table 1). The longest duration of lidocaine skin anesthesia was found at 15:00 h, with a large peak–trough difference amounting to more than 100% of the 24-h mean.[36] Under the conditions of daily dental practice, the duration of mepivacaine or articaine anesthesia was found to be the longest at approximately 15:00 h, and both the onset of pain and the disappearance of numbness followed a similar circadian rhythm[37] (fig. 3). The duration of epidural analgesia with ropivacaine during labor was longer in the diurnal period (117 ± 23 min between 13:00 and 19:00 h) than at night (91 ± 23 min between 19:00 and 01:00 h)[38] (fig. 4).

Time Dependency in Pharmacokinetics in Animals and Humans. When intramuscular lidocaine was administered to mice at 16:00 h, its elimination half-life was shorter than when given at 10:00, 22:00, or 04:00 h. The peak drug concentration (C_{max}) was the highest (6 μg/ml) at 16:00 h and the lowest (3 μg/ml) at 10:00, 22:00, or 04:00 h.[39] These findings could explain, at least in part, that the highest susceptibility of mice to lidocaine was observed in the dark period.[33,35] In rats, after a single dose of 20 mg/kg intraperitoneal bupivacaine at 10:00, 16:00, 22:00, or 04:00 h, toxicity was highest at 22:00 h, coinciding with its peak plasma concentration.[40] Similar data have been reported on the plasma chronokinetics of etidocaine and mepivacaine in mice.[41] A significant circadian variation in the penetration of local anesthetics to heart and brain tissues was also demonstrated, with peak values at 10:00 h in cardiac tissue for bupivacaine, etidocaine and mepivacaine. The maximum penetrations in brain tissue were at 10:00, 16:00, and 22:00 h for bupivacaine, etidocaine and mepivacaine, respectively.[41,42] A time dependency in the transcutaneous passage of lidocaine has also been investigated in rats, resulting in significantly higher plasma concentrations after morning application.[43]

Several human studies have been devoted to chronokinetics of local anesthetics. In one study, four groups of men were injected at 09:30, 12:30, 15:30, and 18:30 h with a single dose of 0.65 mg/kg lidocaine during dental surgical interventions.[44] A significant variation of the area under the plasma concentration curves (as much as a 30% difference in plasma concentration) was demonstrated according to the hour of injection, with the area under the curve at its greatest at 15:30 h (table 2).

The chronokinetics of bupivacaine were also investigated for postoperative pain relief in patients receiving a constant-rate epidural infusion (0.25 mg · kg^{-1} · h^{-1} for 36 h).[45] Bupivacaine plasma concentrations were not constant and in addition never reached toxic plasma concentrations. In spite of the continuous (36 h) and constant infusion rate, the plasma clearance of bupivacaine varied during the 24-h period, with a maximum clearance at 06:30 h (approximately 60% change).

The kinetics of the cutaneous application of lidocaine had significantly higher lidocaine plasma concentrations in the evening, with an inverse correlation with pain scores.[43] The plasma concentrations of local anesthetics

Table 2. Chronopharmacokinetic Changes of Some Local Anesthetics in Humans

Local Anesthetic	Subjects	Route and Hours of Administration	Major Findings	Reference
Bupivacaine	Elderly subjects (n = 13)	Epidural constant rate infusion during 36 h; 0.25 mg · kg^{-1} · h^{-1}	Daily variations of bupivacaine plasma concentrations in spite of a constant rate infusion; maximum clearance at 06:30 h (approximately 60% change)	Bruguerolle *et al.*,[45] (1988)
Lidocaine	Adult subjects (n = 24)	09:30, 12:30, 15:30, 18:30 h; 0.65 mg/kg acute intravenous administration	Area under plasma concentration curve greatest at 15:30 h (approximately 30% change)	Bruguerolle and Isnardon,[44] (1985)
Lidocaine + prilocaine (EMLA®)	Children (n = 29)	07:30 h, 16:30 h; cutaneous application of EMLA®	Cmax higher after evening administration *vs.* morning (approximately 44% change)	Bruguerolle *et al.*,[43] (1991)

Cmax = maximum plasma concentration.

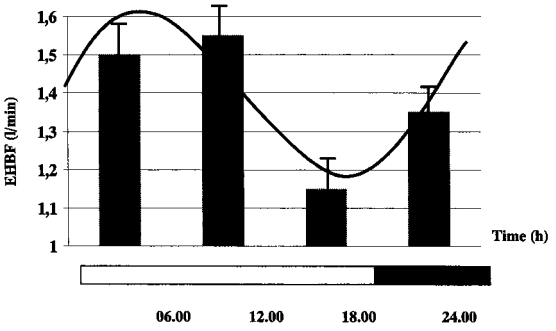

Fig. 5. Circadian changes in estimated hepatic blood flow (EHBF) in healthy subjects. From Lemmer and Nold[50]; used with permission.

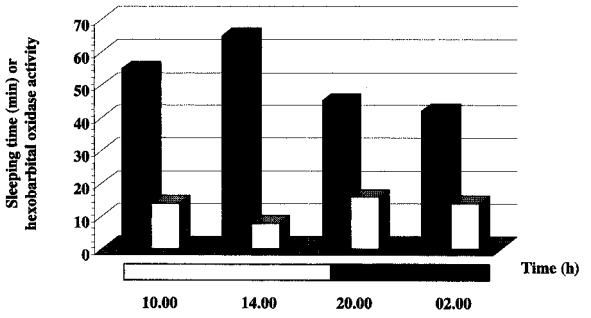

Fig. 6. Time-dependent variations in the hexobarbital sleeping time (*solid bars*) and the hepatic hexobarbital oxidase activity (*open bars*) in rats. Redrawing from Nair and Casper[60]; used with permission.

could be affected by the degree of elimination and could therefore be inversely correlated to the amount of the drug applied to the skin. These data obtained in rodents and humans had opposite synchronization, according to phase.

Possible Mechanisms Involved. Circadian changes in membrane permeability and access to channels may partially explain temporal changes in local anesthetic efficacy and kinetics. Penetration of lidocaine into rat erythrocytes showed circadian variations independently of the circadian variations of total plasma concentrations of lidocaine.[39,42] A circadian variation of erythrocyte penetration was also demonstrated for bupivacaine, etidocaine, and mepivacaine, with the maximum occurring at 04:00 h for bupivacaine and at 10:00 h for etidocaine and mepivacaine.[42,46] The highest amplitude in the circadian rhythm in local anesthetic penetration into erythrocytes was observed with the most lipophilic compound, bupivacaine.

Differences in chronokinetics can also be explained by circadian variations of distribution, protein binding, and metabolism. Temporal variations in plasma protein binding and drug distribution have been documented for lidocaine in rats and bupivacaine, etidocaine, and mepivacaine in mice.[47] However, a temporal relation between the respective free plasma concentrations and the tissue concentrations was not demonstrated. Therefore, the temporal variations of free drug in plasma, brain, and heart do not explain the temporal changes of local anesthetic–induced mortality as previously demonstrated.[48,49] Hepatic drug metabolism is generally assumed to depend on liver enzyme activity and/or hepatic blood flow. Metabolism mainly depends on hepatic blood flow for drugs with a high extraction ratio, such as local anesthetics. Circadian variations in hepatic blood flow could therefore explain temporal variations in the clearance of local anesthetic drugs. A clinical study on hepatic clearance of indocyanine green in human volunteers documented daily variations of hepatic blood flow, with higher values occurring in the morning (fig. 5).[50]

Chronobiology has a greater impact on pharmacokinetic studies than on clinical practice. The duration of effect of local anesthetics is often circumvented by the use of a pump that is controlled by the patient or physician. The circadian variations of the speed of onset of the effects of local anesthetics have not been the object of many studies and could be of practical interest, particularly in obstetric anesthesia.

Circadian Rhythms for General Anesthetics

Numerous studies have reported temporal changes among general anesthetic agents. However, these studies were performed before the discovery of the newer anesthetic agents propofol, desflurane, and sevoflurane. Furthermore, some of the older agents, such as ether and althesin, are not currently in use. However, the results of initial chronopharmacokinetic studies performed with older agents have remained of interest because of the possible applicability to newer drugs. Initial studies evaluated circadian changes in the toxicity and efficacy of these drugs. It seems that in mice and rats, barbiturates are more toxic in the early morning, and althesin is more toxic at 10:00 h.[51,52] Althesin-induced duration of anesthesia in the rat was also 120% higher at 12:00 h than at 06:00 h. The toxicity of halothane (3.5%) varies throughout the day, with mortality ranging from 5% during the day to 76% at night.[53]

Barbiturates

The duration of sleep produced by 60 mg/kg pentobarbital has been found to be longer during the resting period of mice.[54] In rats, the mean duration of anesthesia induced by 35 mg/kg pentobarbital varied from 53 min at 09:00 h to 90 min when the same dose was given at 19:00 h, and the efficacy of pentobarbital was maximal from 17:00 to 20:00 h.[55,56] Oral administration of hexobarbital to volunteers was more effective in the evening than in the morning.[57] Initial pharmacologic studies showed higher brain pentobarbital or hexobarbital concentrations when mice were injected during the dark phase.[58,59] These investigations also showed that endogenous variation in hepatic drug metabolism is correlated

to the circadian changes in drug efficacy. Sleeping time for hexobarbital was maximal when activity hexobarbital of the hepatic oxydase was minimal (fig. 6).[60] Another explanation for the temporal changes in clinical efficacy could be the existence of diurnal changes in the target receptor for barbiturates. Type A GABAergic and *N*-methyl-D-aspartate receptors are now considered as important sites for general anesthetic action.[61,62] Several studies have produced evidence that postsynaptic type A GABAergic activity is increased during nocturnal hours,[63] corresponding to the duration of the maximal efficacy of barbiturates.

Benzodiazepines

The influence of the time of day on the sedative or anesthetic properties of benzodiazepines has yet to be well explored. In mice, intraperitoneal diazepam is more toxic during the light phase of the cycle than during the dark phase.[64] Pharmacokinetic studies have reported that plasma concentrations of the total diazepam and its metabolite, N-desmethyldiazepam, are lower than predicted between 23:00 and 08:00 h and higher by 09:00 h.[65] In contrast, the free fraction of diazepam is at its highest between 23:00 and 08:00 h and lower by 09:00 h. More recently, the elimination half-life of midazolam was found to be at its shortest at 14:00 h and at its longest at 02:00 h (1.26 ± 0.47 *vs.* 1.57 ± 0.44 h [mean ± SD]).[66] A temporal pattern in the sensitivity of the central nervous system to midazolam, as reflected in α wave activity, occurred after short infusion, whereas a circadian fluctuation in the sedative properties of long-term infusion of midazolam (26 h) was not considered to be of clinical significance.[66,67]

The mechanisms of these circadian variations are probably multifactorial. In the rat, circadian variation in the number and activity of benzodiazepine receptors has been reported, with a higher number during the resting period.[68] A peak during the nocturnal hours in postsynaptic type A GABAergic activity has been demonstrated in the cerebral cortex of hamsters.[69]

Enzyme induction, enzyme inhibition by metabolic products, and altered kinetics have been postulated in the circadian disposition processes of benzodiazepines.[70] With lorazepam and nitrazepam, no changes in metabolic activity have been reported, whereas reduced metabolic activity during periods of physical inactivity increased circadian fluctuations in steady state concentrations of clonazepam. Furthermore, the systemic and intrinsic clearances of midazolam were found to be higher after an intravenous dose in the late afternoon than after a morning dose. The protein binding of diazepam is also subject to diurnal variations. The rate of absorption of several benzodiazepines (including diazepam, clobazam, clorazepate, and lorazepam) probably also varies over a 24-h period.[71] No significant circadian changes in absorption and distribution processes or the elimination half-lifes of midazolam were observed in volunteers while total plasma clearance was lower during morning activity (317 ml/min) than during evening activity (463 ml/min) or morning rest (616 ml/min).[72]

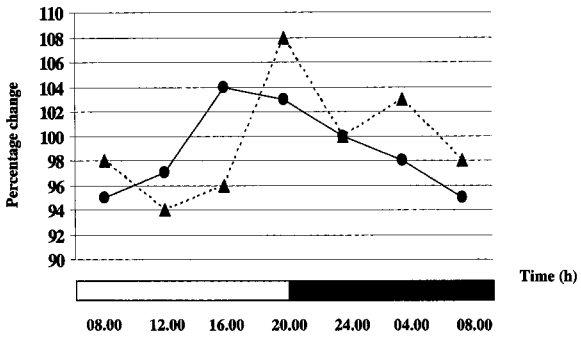

Fig. 7. Circadian variations in anesthetic requirement (expressed as a percentage of the mean minimum alveolar concentration [MAC]) in rats. *Triangles* = halothane; *circles* = cyclopropane. Redrawing from Munson *et al*[76]; used with permission.

Ketamine, Etomidate, Propofol, and Halogenated Agents

In chicken, the duration of catatonia after 600 mg/kg gamma hydroxybutyrate or 60 mg/kg ketamine was longer during the night than during the day.[73] This circadian rhythm also followed a seasonal pattern between 115% in January to 54% in May–June. This could be related to melatonin secretion because these variations were not observed after pinealectomy.[74] No human study has been performed to demonstrate a circadian rhythm for ketamine effects. Nevertheless, numerous animal studies have shown the existence of a circadian dynamic in the expression of *N*-methyl-D-aspartate receptors in the brain.[75] No data are currently available regarding circadian changes for propofol or etomidate. The diurnal changes in the efficacy or toxicity of halogenated agents are also poorly explored. The minimum alveolar concentration of halothane in the rat was 1.26% at 12:00 h and increased to 1.45% at 20:00 h (fig. 7).[76] One human study reported that the greatest efficacy of halothane (as measured by the consumption of the agent) occurred between 24:00 and 06:00 h.[77] The mechanisms of these circadian changes have not been studied. Like other general anesthetics, circadian rhythmicity in receptor number activity as well in distribution and metabolism could be involved.

Circadian Rhythm for Muscle Relaxants

The circadian changes for newer neuromuscular blocking agents, such as atracurium, cisatracurium, rocuronium, and mivacurium, have not been explored. In rats, the curarizing activity of pancuronium was lower during the activity period.[78] Neuromuscular blockade measured by the area under the curve of curarization within 10 min was lowered by 27% at night (fig. 8). This

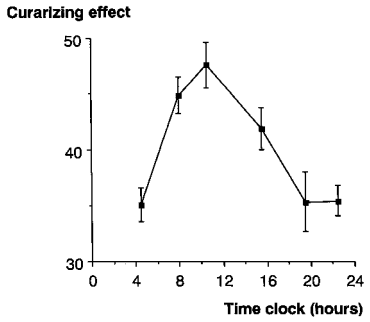

Fig. 8. Circadian variations of the effects of pancuronium in rats anesthetized with althesin. From Bruguerolle B: General concepts and new trends in chronopharmacology, Biologic Clocks: Mechanisms and Applications. Proceedings of the International Congress on Chronobiology. Paris, 1977. Edited by Touitou Y. Amsterdam, Elsevier, 1998, pp 7–11. Used with permission.

nocturnal decrease was also observed with other drugs, inducing decreases of 25%, 20%, and 19% in neuromuscular blockade with gallamine, D-tubocurarine, and fazadinium, respectively.[79] The requirements for pancuronium were higher at 09:00 h than at 11:00 h during cholecystectomy performed in man.[80] Time-dependent changes in renal elimination and cholinesterase activity could be involved in the circadian changes observed.[81] The impact of chronobiology on the clinical practice of anesthesiology remains to be determined. However, chronobiology should be considered as any other variable in pharmacokinetic studies of drugs used in the practice of anesthesia. It would be of interest to verify the impact of biorhythms on the pharmacokinetic models currently proposed in anesthesia for agents such as propofol or opioids.

Circadian Rhythm in Pain

Biologic Rhythms in Pain

The response to noxious stimuli is not constant over the entire 24-h period. Morris and Lutsch[82] were the first to study the circadian variation in morphine-induced analgesia using the hot plate test. They showed that the maximal analgesic effect of morphine occurred at 21:00 h (activity period), whereas the minimal analgesic effect was obtained at 15:00 h (resting period) in mice. Further studies in rodents also showed that the latent period before a response to a noxious stimulus was shorter during the activity period (fig. 9).[83,84] In horses, painful stimuli were best tolerated at 09:00 and 15:00 h.[85] Visceral sensitivity assessed by the abdominal wall electromyogram in response to colorectal distension in the rat was higher at midnight and early in the morning.[86] It has also been shown that the interaction of morphine, naloxone, and N^G-nitro-L-arginine methylester on pain sensitivity is dependent on this circadian rhythm of pain (as much as a 60% change for morphine-induced analgesia).[87]

In accordance with these animal studies, circadian rhythms in sensory pain thresholds have been experimentally demonstrated in humans. The sensitivity threshold of the gingiva to a cold stimulus was maximal at 18:00 h and reached a peak at 03:00 h (35% difference). Tooth sensitivity was lowest between 15:00 and 18:00 h, with a peak in pain intensity at 08:00 h (160% increase).[88] However, pain threshold does not follow the same pattern in all tissues. Skin sensitivity to radiant heat is minimal at 18:00 h and maximal at 06:00 h.[89] The electrical threshold that induced a nociceptive flexion reflex was least at 01:00 h and reached a peak at 17:00 h (25% higher). In the same study, the intensity of pain secondary to the electrical stimulus was 70% higher during the night.[90]

Circadian rhythms in acute pain have been also recorded, such as in dental surgery, with a morning peak during the first postoperative day.[91] Diurnal variation in pain perception has also been reported after abdominal

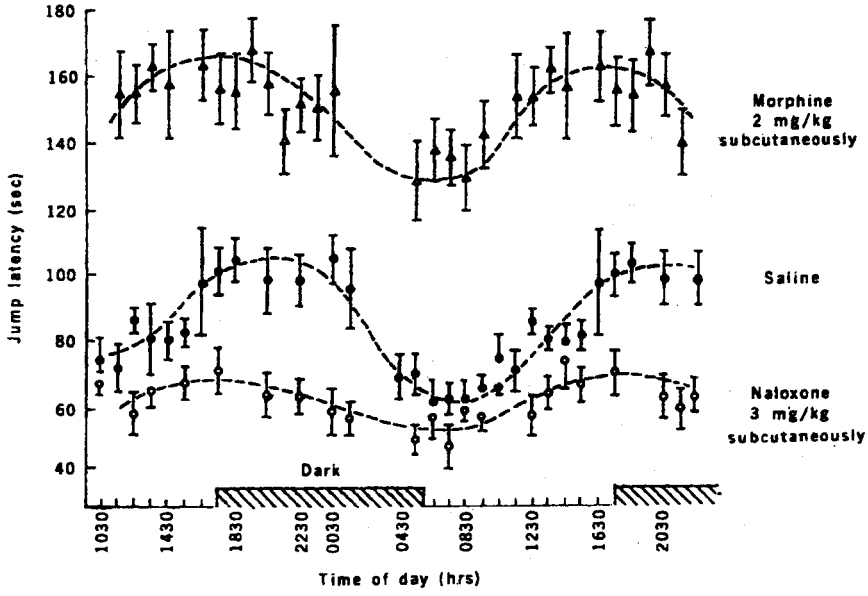

Fig. 9. Example of diurnal rhythm observed in the responsiveness of mice (jump latencies on the mouse hot plate) to nociceptive stimuli (mean ± SEM). A period of increased irritability is observed during morning hours. The effects of naloxone are small during the morning and early afternoon. From Frederickson *et al*[83]; used with permission.

surgery using a patient-controlled analgesia device. The peak of morphine use occurred at 09:00 h and was the least at 15:00 h in patients undergoing elective surgery.[92] In this study, the daytime dosing rate of morphine was 1.86 ± 1.21 mg/h compared with 1.62 ± 1.18 mg/h at night (mean ± SD). The peak demand for morphine or hydromorphone occurred in the early morning and was lowest during the night in postoperative gynecologic patients.[93] In patients undergoing exploratory laparotomy for gynecologic malignancies, the peak morphine delivery achieved by a patient-controlled analgesia pump was obtained between 08:00 and 12:00 h (60% difference with the night period).[94] Such a pattern was also found in chest and abdominal surgery, although a second peak of morphine consumption was identified between 16:00 and 20:00 h.[95] In surgical patients, the need for fentanyl was less in a group of patients undergoing elective cholecystectomy performed earlier in the morning (08:00–10:00 h: 3.03 mg · kg^{-1} · h^{-1} · 10^{-3}) as compared with a late group (11:00–15:00 h: 4.32 mg · kg^{-1} · h^{-1} · 10^{-3}).[96]

Chronic pain has also been shown to display a circadian pattern. The greatest pain intensity for rheumatoid arthritis has been reported to occur early in the morning.[97] Pain is most severe at night for migraine and biliary colic (30% increase at 20:00 h as compared with pain intensity at 08:00 h).[98,99] Little research has been performed on chronic cancer pain despite the large patient population. Most patients showed an evening peak for additional morphine treatment.[100]

In contrast to experimental animal research, experimental studies in humans have shown apparent contradictory or divergent findings between reports, with peak pain occurring either in the morning and/or the evening. Some human studies could not show any temporal pattern in pain intensity.[101–104]

It is important to note that many factors influence circadian variation. The sleep–activity pattern, which is the main synchronizer of human biologic rhythm, has been poorly taken into account in studies. Some investigations involved fewer than four volunteers, and not all conclusions have been confirmed by appropriate statistics.[103] Elsewhere, the type of pain stimuli varied throughout studies (chemical, electrical, thermal), and the intensity of the stimuli was not standardized. However, the results depend on either the threshold or the response to the suprathreshold stimuli that are used. In addition, a repetitive electrical stimulus applied to mimic pain cannot reproduce the pathophysiology of pain that includes stimulation, transmission, inflammation, and the release of algogenic mediators. Temporal changes to painful stimuli in healthy volunteers and animals can be different than pain measured in patients with chronic diseases. Variations in the locations of the body where stimuli are applied may produce differences in study results. Finally, anxiety to a nociceptive stimulus may influence circadian variations in experimental pain results.

To summarize, many animal and human studies have indicated a temporal pattern in pain. The results of studies in humans have identified rhythms of a particular period for specific conditions, different types of pain, and different diseases.

Circadian Variations in the Neurochemistry of Pain

Variation in the production of pain mediators during a 24-h period could participate in circadian alterations in pain observed in experimental and clinical studies. Brain concentrations of Met-enkephalin were lower at the end of the activity period (07:30 h: 1,099 ± 120 pmol/g tissue) as compared with brain concentrations measured at the beginning of the rest period (15:30 h: 2,173 ± 119 pmol/g tissue).[105,106] A circadian rhythm in the production of opioid peptides and time-dependent changes in the concentration of β-endorphin and substance P in different brain areas of the rat have been described, indicating a peak during the activity period.[107] Circadian variations of plasma concentrations of β-endorphin have been demonstrated in neonates and adult humans, with higher values in the morning compared with the evening.[108] Higher morning values of methionine enkephalin-like, substance P–like, and β-endorphin-like immunoreactivity in human parotid saliva have been shown in humans.[109]

Finally, the analgesic effect of melatonin is more pronounced at night.[110] These data must be reconciled with those showing that acute pain stimuli produced decreases in salivary melatonin and increases in melatonin secretion in healthy subjects.[111]

Implications of Chronopharmacology for Pain Treatment

Nonsteroidal antiinflammatory drugs (NSAIDs), opioids, and α_2 agonists are widely prescribed to treat postoperative pain. However, many reports have shown that these drugs may have a circadian component.

Chronopharmacokinetics for NSAIDs. Since the demonstration that NSAIDs reduce opioid use and prevent opioid-associated side effects, these drugs are often used during the postoperative period. Clinical studies have shown that the pharmacokinetics of NSAIDs are not constant throughout the day. Higher plasma peaks were obtained at 07:00 h for ketoprofen (approximately 50% change for the peak concentration and 58% change for the area under the curve), and earlier and higher concentrations (approximately 50% change for the peak concentration) were observed for indomethacin when given at 07:00 and 11:00 h *versus* at other times of the day or night (fig. 10).[112,113] Higher and faster morning absorption has also been observed with controlled-release indomethacin and ketoprofen formulations.[114] The

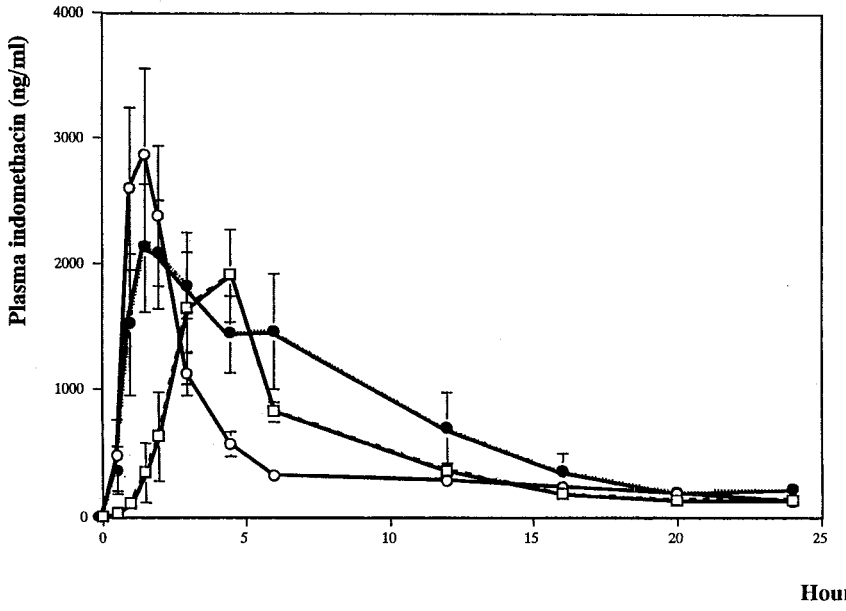

Fig. 10. Example of chronopharmacokinetic study. Plasma concentrations of indomethacin (ng/ml) were measured in volunteers after 75 mg oral administration at 08:00 (*open squares*), 12:00 (*solid circles*), and 20:00 h (*open circles*). From Bruguerolle B: A propos de la chronopharmacologie (in French). Act Pharmacol 2001; 398:17–21. Used with permission.

rate and extent of bioavailability of time-controlled release formulation of ibuprofen in healthy volunteers were lower when dosing took place at 08:00 h than when dosing took place at 22:00 h (6 *vs.* 4 h time to peak concentration, respectively).[115] On the contrary, chronopharmacokinetic behavior for immediate-release ibuprofen tablets was not observed.[115] Recently, it has been shown that half-life, volume of distribution, and area under the curve of intravenous indomethacin followed chronobiologic variations in sheep.[116] No chronobiologic data are available regarding the new cyclooxygenase-2 inhibitors.

The circadian changes in the pharmacokinetics of NSAIDs are mainly related to alterations in drug distribution. In the rat, initial plasma concentrations and area under the curve were significantly lower at rest, whereas distribution volume and total metabolic clearance were higher than those observed during activity.[117] Morning absorption for NSAIDs is better than that at night.[118] Greater blood flow to the gastrointestinal tract in the morning, renal function, and plasma binding could also explain circadian changes in NSAID pharmacokinetics.[119]

Opioid Chronopharmacokinetics. Numerous studies have focused on temporal changes in pain sensitivity, but limited data are available regarding the chronopharmacokinetics of opioids. In dogs, a chronopharmacokinetic variability for oral sustained-release morphine sulfate when administered every 12 h has been reported. Maximum concentration and area under the curve were higher at 07:30 h *versus* dosing at 19:30 h.[120] However, these temporal changes were not observed in an 8-h treatment group. In two groups of patients with sickle cell anemia, intramuscular meperidine showed circadian changes in drug disposition with an elimination half-life that was 46% shorter and total serum clearance that was 70% greater during the night. According to the time of oral morphine administration, clear differences in maximum concentration (30% change) and area under the curve values (12% change) for morphine and its morphine-6-glucuronide metabolite were shown in a cancer patient population.[121] Higher values were measured at 18:00 h, whereas lower values were measured at 10:00 and 14:00 h. Stronger analgesic effects were observed when tramadol and dihydrocodeine were applied in the evening to relieve painful stimuli in volunteers, but this difference was unlikely to be related to changes in drug plasma concentrations (fig. 11).[122] Little information is available regarding the chronopharmacokinetic variability for opioids used during general anesthesia. With fen-

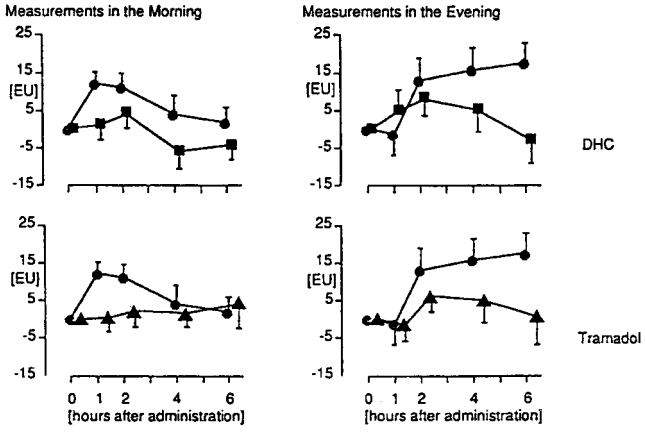

Fig. 11. Analgesic effects of placebo (*circles*), 90 mg dihydrocodeine (DHC; *squares*), and 50 mg tramadol (*triangles*) when administered either in the morning or in the evening. Painful chemical stimuli were applied to nasal mucosa. Subjects estimated the perceived intensity (estimation units [EU]) in relation to a standard stimulus (60% volume/volume CO_2). Painful intensity of the stimuli increased during evening periods, and analgesic effects were most pronounced after drug administration in the evening. From Hummel *et al*[122]; used with permission.

tanyl infusion over 2 days, fentanyl clearance did not display any circadian change in six volunteers receiving a constant 50 μg/h.[123] No data has been published regarding fentanyl or sufentanil in surgical patients. Interestingly, a prospective study reported the existence of circadian variation in the distribution of lethal opiate overdoses in drug abusers, with a high death risk in the evening hours (03:00–09:00 h).[124]

Circadian Rhythms for Other Drugs Used for Analgesia. In rats, chronobiologic dependence of the effect of clonidine on arterial pressure has been demonstrated, with a more pronounced hypotensive effect at night in comparison with day.[125] However, no chronobiologic data are available at this time for other drugs used as coanalgesic agents, such as α_2-adrenergic agonists, ketamine, and neostigmine.

Together, these data showed that circadian effects in experimentation on pain have different patterns that are sometimes complex. There is no doubt that the time of day acts on the intensity of pain and that the hour of pain-drug delivery contributes to the duration of analgesia. Future research on experimental pain, the pharmacologic aspects of opioids, and studies comparing different pain strategies should include the time of day.

Circadian Rhythms during the Perioperative Period

Melatonin is produced by the pineal gland almost exclusively at night or in a light-free environment.[126] Like an anesthetic, melatonin affects sleep, and melatonin supplements have been used to treat sleep-related problems, such as insomnia, sleep apnea, and jet lag.[127] Moreover, physicians have noted since antiquity that their patients reported less pain and needed fewer analgesics at night. The maximal analgesic effects of melatonin occur at night and are abolished by pinealectomy. Opioid receptor blockade inhibits the circadian rhythm in nociception.[128] In mice, melatonin may reverse morphine tolerance and dependence.[129]

Melatonin also affects cell-mediated immunity and the production and subsequent action of several hormones.[130,131] Melatonin works concomitant with serotonin, a powerful neurotransmitter involved in several central physiologic processes, including blood pressure and temperature regulation and several neuropsychologic functions, such as appetite, memory, and mood.[132,133] These alterations, as well as cognitive impairment, are usually observed in the postoperative period. Some stress-induced responses in postoperative and critically ill patients may be due either to the loss of the circadian secretion of melatonin or to a drug-induced phase shift in circadian rhythm.[134,135]

In patients undergoing coronary artery bypass grafting, postoperative circadian melatonin secretion has been found to decrease during the first 24 h.[136] These findings are in agreement with those reported after orthopedic surgery where the loss of the circadian pattern of melatonin secretion did not depend on the type of anesthesia, *i.e.*, general or epidural anesthesia.[137] In contrast, changes in postoperative melatonin secretion were not found in patients undergoing gynecologic surgery.[138] Persisting increased plasma melatonin concentrations were observed after isoflurane anesthesia, whereas a decrease in plasma melatonin concentrations was found in patients anesthetized with propofol. Animal studies have shown that halothane decreased whereas pentobarbital had no effect on and ketamine increased nocturnal concentrations of melatonin.[139] On the other hand, a low dose of melatonin increased the duration of narcosis induced by thiopental in rats.[140] Finally, a potential clinical use of melatonin as a sedative has been reported in one study showing that gynecologic patients premedicated either with melatonin (5 g) or with midazolam (15 mg) had a significant decrease in anxiety and an increase in sedation before surgery.[141]

A variety of nonphotic stimuli, including anesthetic agents, can shift the phase of the circadian pacemaker. GABA is a major inhibitory neurotransmitter in the brain, and pharmacologic manipulations of GABA receptors have been shown to shift circadian rhythms in rodents.[142] δ-Opioid agonists significantly shifted activity (wheel running) in hamsters by approximately 45 min.[143] Morphine injections advanced phase shifts and also induced hyperactivity. Restriction of activity prevented these phase shifts. The results indicated that morphine shifts circadian rhythms by its effects on behavior, rather than by a direct action on the circadian pacemaker.[143] Ether shifted the phases of several circadian rhythms, including temperature and heart rate, in rodents.[144] In contrast, isoflurane anesthesia did not impair circadian temperature rhythm in volunteers.[145]

To summarize, melatonin affects the duration and quality of sleep and has hypnotic effects. Melatonin also has a role in the regulation of circadian rhythms, which are often disturbed in postoperative and intensive care patients. Melatonin has been proposed as a premedicant agent. The use of melatonin as an anesthetic agent in humans must be studied further.

Implications

The principles of chronobiology have practical applications for treatment. Chronotherapy for peptic ulcer disease and asthma with evening doses of ranitidine and theophylline and morning administration of methylprednisolone has proven to be beneficial.[146,147] It is important to consider the possible role of chronobiology in anesthesia and intensive care.

Chronopharmacokinetic–Chronopharmacodynamic Studies

One of the goals of clinical pharmacology is to understand interindividual differences in responses to drugs. Pharmacokinetic–pharmacodynamic (PK/PD) modeling concepts make it possible to describe and predict the time course of drug effects under physiologic and pathologic conditions, including the perioperative period. The effects of covariates on the PK/PD parameters of muscle relaxants, opioids, and hypnotics are often analyzed by using the NONMEM software.[148] The important determinants of intersubject variability that are frequently identified are demographic (age, weight, sex), genetic, disease state, and physiologic characteristics.

In anesthesia, chronobiology is apparently not often taken into account because the times that pharmacokinetic studies are performed are still rarely available. Most of the steps involved in the disposition of drugs are subject to circadian variations. Significant circadian variations in absorption, degree of plasma protein binding, rate of metabolism, liver content of cytochrome P-450, and hydrolysis have been demonstrated. Hepatic clearance is dependent on liver blood flow, which has been shown to vary by up to 40% during a 24-h period.[50] Therefore, differences in blood concentrations of drugs with a high hepatic extraction ratio, such as propofol and sufentanil, could be related to a reduction in hepatic clearance. Many drugs used in anesthesia (opioids, local anesthetics, halogenated agents, granisetron, midazolam) are metabolized by the hepatic enzyme cytochrome P-450. A growing body of data suggests that pharmacologic studies should be carefully interpreted when performed at different times of day. An illustrative example is given by the chronopharmacology of amikacin. Bleyzac *et al.*[149] reported AM values for amikacin elimination constant of 0.18 ± 0.05. However, they also reported in the same study an AM + PM value of 0.16 ± 0.06 and a PM value of only 0.11 ± 0.01.

If these findings are similar for anesthetics, pharmacokinetic studies restricted to morning data could lead to an overestimate or underestimate of PK/PD values compared with PM and PK/PD values for the entire day. A chronopharmacologic approach would provide better precision in pharmacologic studies of anesthetics than the conventional approach, which does not use time-related data. The influence of time of administration on the incidence of drug-related side effects is also of interest for intensive care medicine.

Design of Clinical and Experimental Studies

Many investigations of anesthetics on physiologic variables, such as blood pressure, cardiac output, and pulmonary function, may be influenced by significant spontaneous circadian changes. At the cellular level, cell division, enzyme activity, and gene expression are also timed by oscillators.

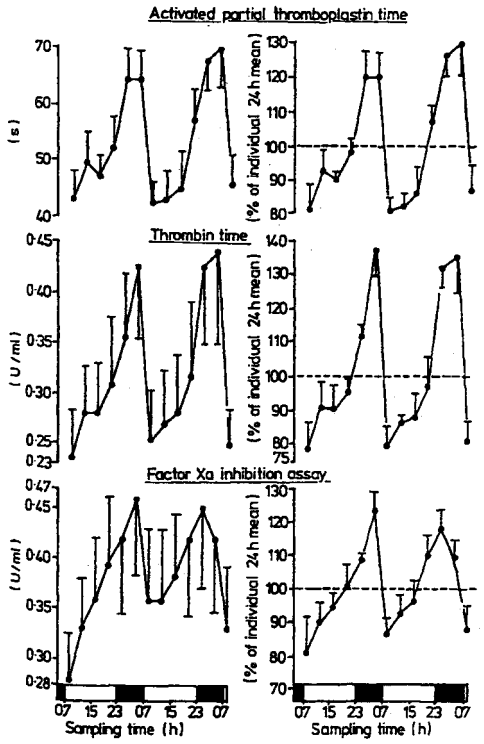

Fig. 12. Circadian changes in anticoagulant effect of heparin infused at a constant rate. From Decousus *et al*[21]; used with permission.

The 24-h low-to-high variability in blood pressure, heart rate, and cardiac output usually amounts to 10–20%. In humans, renal function, as measured by inulin clearance, is greater during the day (122 ± 22 ml/min) than at night (86 ± 12 ml/min).[150] Almost all noninvasive cardiac electrophysiologic phenomena, such as cardiac refractoriness and conduction, pacing and defibrillation threshold, and heart rate variability, show diurnal variability. A 24-h rhythm of the ventricular fibrillation threshold in female rats showed a significant circadian rhythm, with a MESOR at 2.59 ± 0.53 mA, an amplitude of 0.33 ± 0.11 mA, and acrophase at 22:53 h.[151] Circadian variation in defibrillation energy requirements has been reported, with a morning defibrillation energy requirement at 15.1 ± 1.2 J compared with 13.1 ± 0.9 J in the midafternoon and 13.0 ± 0.7 J in the late afternoon.[152] Peak expiratory flow, airway resistance, and pulmonary diffusion present circadian rhythms in healthy people and in asthmatic subjects.[153] Airway hyperactivity to provocative agents is more profound and prolonged after evening and overnight tests as compared with tests conducted at noon and in the afternoon. Immunologic and inflammatory processes exhibit circadian patterns.[154] Thus, when the same dose of histamine was injected at different times of the day, large differences in redness and swelling were noted: 30% higher at 22:00 h and 25% lower at 11:00 h (percent of the 24-h mean).[155] Circadian changes in the anticoagulant effect of heparin are depicted in figure 12.[21] The morning

hours of the day are associated with higher blood concentrations of clotting factors, decreased fibrinolytic activity, and an increase in platelet stickiness. The successful thrombolysis rates between noon and 18:00 h and 06:00 h and noon are 75% and 33%, respectively.[156] Plasma concentrations of activated factor FVII, prothrombin fragment F1 + 2, and plasminogen activator inhibitor 1 measured at 20:00 h decreased as compared with plasma concentrations measured at 08:00 h (40%, 16%, and 80%, respectively). On the contrary, plasma concentrations of plasmin–plasmin inhibitor complex were 91% higher at 20:00 h than the values measured at 08:00 h.[157] Peak vitamin K concentrations were at a maximum at 22:00 h and a minimum (32% of the maximum) at 10:00 h.[158]

Previous studies have shown that the effects of contractile or relaxant agents on experimental smooth muscle preparations depends on the time when the animal was killed. The sensitivity of deendothelized rat aorta to phenylephrine or KCl is not the same throughout the day.[159] The median effective concentrations ($EC_{50} \times 10^{-9}$ M for phenylephrine) were 13.2 ± 3.5, 4.1 ± 1.0, and 13.9 ± 4.1 at 09:00, 13:00, and 17:00 h, respectively. The EC_{50} for KCl also displayed a significant temporal variation, with a twofold increase at 17:00 h compared with 13:00 h (13.1 ± 0.9 *vs.* 7:00 ± 0.4).

In conclusion, many of these circadian changes are significant and may affect the results of clinical or experimental studies. Both *in vivo* and *in vitro* study designs should include the time of the day in the general protocol. The characteristics of any system studied necessitate that time of the day be considered as a factor that could have an impact on the results.

Prevention of Perioperative Vascular Complications

The impact of chronobiology may be of interest when studying physiologic ranges where early alterations can be detected in terms of changes in rhythm parameters. It may be possible to diagnose predisease states before symptoms become overt and before there is target organ damage. Blood pressure and heart rate in normotensive and (primary) hypertensive patients display their highest values during the day, followed by a nightly decrease and an early morning increase. In secondary hypertension, this rhythmic pattern is abolished or even reversed, exhibiting nightly peaks in blood pressure. Two new disease risk syndromes associated with large increases in the risk of vascular disease are circadian hyper-amplitude-tension, a condition characterized by an excessive circadian amplitude of blood pressure, and alterations in heart rate variability.[160] These interpretations of blood pressure and heart rate variability provide information *vis-à-vis* the risk of morbid events in subjects without obvious heart disease.

Careful preoperative evaluation must be undertaken to identify patients who are at the highest risk of perioperative stroke or myocardial infarction. Reduced heart rate variability is associated with an increase in the risk of coronary artery disease, whereas an excessive circadian blood pressure amplitude is associated with an increase in the risk of cerebral ischemic events.[161,162] The application of such a technique to detect patients at risk for vascular complications during the perioperative period is promising but remains to be proven.

Treatment of Postoperative Pain

Treatment of pain has been extensively studied over the past decade. Most work has focused on the development of new analgesic drugs and on the development of optimal modes of administration. Numerous studies have also focused on circadian changes in nociception. The results have failed to produce a consistent picture with peaks in the morning or in the evening. Measurement of cyclic variations in pain perception may predict rhythmic changes in analgesic requirements for individuals undergoing a particular type of surgery. Pain relief could be increased by manipulation of the timing of drug administration. This is supported by studies resulting from the development and use of patient-controlled analgesia. Administration of analgesic or local anesthetics at a constant and continuous dosage ignore temporal variation in the perception of pain and ignore a great number of chronobiologic studies showing the influence of biologic rhythms on the PK/PD of analgesics.

Conclusions

Considerable information is currently available on the origins of circadian rhythm and the influence of such rhythms on the pharmacodynamics and pharmacokinetics of drugs. Chronobiology clearly influences the pharmacologic sensitivity of many drugs, and time-dependent variations in pain are highly relevant to the daily practice of pain management. Except for local anesthetics, information regarding circadian rhythms for general anesthetics and newer analgesic agents remains fragmentary. Introduction of chronobiology in the field of anesthesia has become necessary for the quality of future clinical or experimental research. Ignoring temporal patterns of anesthetic drug action or the severity of disease states in the design of research protocols could have a profound impact on the results and should be controlled whenever possible. The potential impact of chronobiology on the clinical practice of anesthesia is less obvious or unknown. Research on the influence of circadian rhythms on general and regional anesthesia is warranted.

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