

of the putative phase advance is slight. Given then the small magnitude and the transient nature of the “circadian” response, it does not seem prudent to link postsurgical fatigue, drowsiness, sleep disorders, and mood alterations to anesthetic-induced changes in the circadian clock. In fact, the definitive studies to provide the necessary data to support this conclusion have not yet, to our knowledge, been performed.

Third, the authors conclude that the effects of propofol on melatonin injection “parallel the desynchronization of the circadian rhythms of locomotor activity previously observed after propofol.” However, the cited study⁴ was not performed in constant darkness, which is necessary to establish a direct linkage between anesthetic administration and circadian clock disruption. Interestingly, previous work in humans has shown that even 3 h of anesthetic exposure in humans does not affect the circadian phase of the body temperature rhythm.⁵ In summary, it must be stressed that the ability to distinguish between effects occurring directly on the circadian pacemaker and those occurring “downstream” from the pacemaker on other physiologic control systems requires extremely rigorous experimental conditions. These conditions have yet to be met, and so for now, it is more prudent to interpret the effects of propofol on the melatonin rhythm as “masking.” In other words, the data more strongly support the concept that the “hands” of the clock, rather than the “gears” of the clock, have been influenced by the propofol stimulus.

Matthias Eikermann, M.D., Ph.D.,* Nancy L. Chamberlin, Ph.D. *Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts. meikermann@partners.org

References

1. Dispersyn G, Pain L, Touitou Y: Propofol anesthesia significantly alters plasma blood levels of melatonin in rats. *ANESTHESIOLOGY* 2010; 112:333-7
2. Pain L, Oberling P, Sandner G, Di Scala G: Effect of propofol on affective state as assessed by place conditioning paradigm in rats. *ANESTHESIOLOGY* 1996; 85:121-8
3. Lewczuk B, Przybylska-Gornowicz B, Wyrzykowski Z: The effect of morphine on melatonin secretion in the domestic pig. *In vivo* and *in vitro* study. *Neuro Endocrinol Lett* 1999; 20:171-8
4. Dispersyn G, Pain L, Touitou Y: Circadian disruption of body core temperature and rest-activity rhythms after general (propofol) anesthesia in rats. *ANESTHESIOLOGY* 2009; 110: 1305-15
5. Sessler DI, Lee KA, McGuire J: Isoflurane anesthesia and circadian temperature cycles in humans. *ANESTHESIOLOGY* 1991; 75:985-9

(Accepted for publication May 26, 2010.)

In Reply:

We thank Drs. Eikermann and Chamberlin for their comments about our article.¹ We agree entirely that the key issue is whether anesthetics themselves can directly influence the functioning of the brain circadian clock. They contend that it is unacceptable for us to conclude that

propofol anesthesia acts directly on the circadian rhythm of circadian melatonin as well as the circadian rhythm of rest-activity and temperature in rodents.²

First, they make the point that the effects of intraperitoneal injection of propofol cannot be linked with propofol-induced anesthesia, arguing that the study design was not appropriate. We concur with them that we did not assess the depth of anesthesia; this was not the aim of our study. Because it is unclear in the first place from any clinical data available in the literature whether propofol injection could modify per se the plasma melatonin within the following 24 h, our study was designed to clarify this point. To the best of our knowledge, the loss of righting reflex in rats is an agreed upon method for assessing clinical anesthesia in rats in these circumstances.

Likewise, they use unusual logic to conclude that propofol has an opioid effect on melatonin secretion: (1) propofol has a pleasant effect that might be linked to an opioid effect; and (2) opiates indirectly affect melatonin secretion. As we know, the pleasant effect could be due to other factors, such as a dopaminergic effect.³ Such tautology does not permit us to concur with them on this point.

Second, we understand that the suggestion in the single sentence in the “what this article tells us that is new” may appear provocative. It is always challenging to summarize the innovative aspects of data in one brief sentence. However, as an in-depth reading of the results and discussion sections clearly show, there is an evident visual phase advance of melatonin secretion with significant differences between propofol injection and control at early (decrease) and late (increase) periods of melatonin collection. Cosinor analysis of the raw data supports this observation with a statistical trend ($P = 0.06$). Moreover, we have very clearly pointed out the limitations of our study and have stated that “from our data obtained in rats, we cannot demonstrate that the fatigue, drowsiness, and sleep disorders observed in patients are related to a disturbed circadian pattern of human melatonin.” We also suggest that our data provide an opportunity to open new lines of research to better understand these symptoms. Indeed, there is no clear explanation yet for these undesirable symptoms that could occur even after a short duration of anesthesia for small medical procedures.

Third, using a similar approach, Drs. Eikermann and Chamberlin do not accept our statements of a previously described desynchronization of the rest-activity rhythm induced by propofol because, as they claim, the data were not obtained in constant darkness. To support their statements, they cite one of our previous articles where experiments were performed in dark/light conditions.² However, we are fully aware that it is necessary to have data in constant darkness to establish a direct linkage between anesthetic administration and circadian clock disruption. To that end, we published a study⁴ in *Neuropsychopharmacology* in 2007 (cited in the article) in which the same experiments were performed in constant darkness. This

study was unfortunately overlooked by Drs. Eikermann and Chamberlin. Indeed, we provided evidence that propofol anesthesia desynchronized the circadian rhythms of rest-activity and body temperature in rodents in the experimental condition of either alternation of light/dark² or constant darkness.⁴

By citing the study of Sessler *et al.* of 1991,⁵ they create the impression that anesthetic exposure does not affect the circadian rhythms in humans. It must be pointed out that this first study was unable to demonstrate any effect in five human volunteers. Sessler *et al.*⁵ acknowledged that such data did not exclude an effect that could be missed. Indeed, the shifts in acrophase were +1.2, +2.1, -0.7, -1.6, and -0.7 h in the five subjects. Drs. Eikermann and Chamberlin have once again overlooked our previous study (cited in the article) that demonstrated a desynchronization of the circadian rest-activity rhythm after propofol anesthesia in patients.⁶ When dealing with clinical studies, as we clearly state in the discussion of our article, one has to be cautious in drawing conclusion from merely one or two studies. Further studies are necessary to specify the magnitude of anesthetic effects on human circadian rhythms.

In contrast to the concerns of Drs. Eikermann and Chamberlin, we find that data in this field support the concept that either the “gears” and/or the “hands” of the clock might be influenced by propofol administration. It is premature to eliminate the importance of the concept of gears or hands at this early stage, as they suggest. However, we agree with them that a more profound understanding of the mechanism is an important question. Future studies should rigorously examine the effects of anesthesia on the complex pathways involved in the regulation of the clock. To this end, we are currently pursuing further experiments on the effect of anesthesia on some of these pathways (*i.e.*, the expression of clock genes within the suprachiasmatic nucleus, the melatonin release by the pineal gland).

Garance Dispersyn, Ph.D., Laure Pain, M.D., Yvan Touitou, Ph.D.* *Fondation A. de Rothschild, Paris, France. yvan.touitou@chronobiology.fr

References

1. Dispersyn G, Pain L, Touitou Y: Propofol anesthesia significantly alters plasma blood levels of melatonin in rats. *ANESTHESIOLOGY* 2010; 112:333-7
2. Dispersyn G, Pain L, Touitou Y: Circadian disruption of body core temperature and rest-activity rhythms after general (propofol) anesthesia in rats. *ANESTHESIOLOGY* 2009; 110: 1305-15
3. Pain L, Gobaille S, Schlee C, Aunis D, Oberling P: *In vivo* dopamine measurements in the nucleus accumbens after nonanesthetic and anesthetic doses of propofol in rats. *Anesth Analg* 2002; 95:915-9
4. Challet E, Gourmelen S, Pevet P, Oberling P, Pain L: Reciprocal relationships between general (Propofol) anesthesia and circadian time in rats. *Neuropsychopharmacology* 2007; 32:728-35
5. Sessler DI, Lee KA, McGuire J: Isoflurane anesthesia and circadian temperature cycles in humans. *ANESTHESIOLOGY* 1991; 75:985-9
6. Dispersyn G, Touitou Y, Coste O, Jouffroy L, Llleu JC, Challet E, Pain L: Desynchronization of daily rest-activity rhythm in the days following light propofol anesthesia for colonoscopy. *Clin Pharmacol Ther* 2009; 85:51-5

(Accepted for publication May 26, 2010.)

Clinical Usefulness of the Muscle Contracture Test: Time to Reevaluate?

To the Editor:

In a recent article, Tautz *et al.*¹ discussed the use of a muscle contracture test for diagnosis of malignant hyperthermia (MH) susceptibility. They correctly noted that there is a 2% chance that contracture testing will incorrectly mislabel an MH-susceptible individual as normal. It is difficult to believe that any of my colleagues will expose a patient to a 2% risk of severe complications by giving triggering anesthetics. In my opinion, the fact that a patient has been evaluated for MH will be a strong indication for using nontriggering anesthesia management. Tautz *et al.* stated that there is a consensus among experts that a person who has had contracture testing and who is labeled not susceptible can safely receive triggering anesthetics. Unfortunately, they did not provide references to any written guidelines or consensus statements on that issue.

Tautz *et al.* mentioned another reason for using the contractility test: the fact that for certain patients (children, severe asthmatics, and patients with difficult airways) potent inhaled anesthetics are useful. Yes, they are useful. But how safe are they? Is 98% safe enough when we have 100% safe nontriggering alternatives available? Most biopsy centers do not perform these tests for children under 5 yr old.* In the very few situations in which inhalation induction is the safest approach (*e.g.*, acute epiglottitis or a difficult pediatric airway), the anesthesiologist should be prepared to monitor and treat a possible MH crisis regardless of the patient's test results.

I recall consulting one of my own patients regarding contracture testing after an MH crisis.² According to the clinical grading scale, this patient's likelihood of MH was “almost certain.”³ The patient and family were informed, and the patient was advised to wear a Medic Alert bracelet. However, I felt uneasy recommending a procedure that was very expensive (\$6,000 USD), invasive (need for another anesthesia, relative disability for 3–4 days), and burdensome (3-h flight to nearest biopsy center), with no clear benefits for the patient. In their article, Tautz *et al.* wrote: “We cannot fault a clinician who wishes to give a nontriggering anesthetic to a person who has had contracture testing and who is not susceptible to MH.” Thank you for not blaming me for playing

* www.mhaus.org. Accessed March 19, 2010.