Anesthesiology 2010; 113:271–2

Disentangling Hypnos from His Poppies

USUALLY a combination of opioid and hypnotic drugs are used to achieve a state of balanced general anesthesia in the surgical patient. As evidenced by the great variation in practice, a fundamental but unanswered question is "How much opioid should be given intraoperatively?" In Greek mythology, Hypnos was the god of sleep. He lived on the island of Lemnos in a dark cave surrounded by poppies. One of his sons was Morpheus, who gave form to the dreams of kings and heroes. The article by Liley *et al.*[1] in this issue of ANESTHESIOLOGY proposes an electroencephalographic index of opioid effect. Perhaps, this study has given us a tool to dissect out the influence of the poppies on Hypnos?

Previous work on the electroencephalographic effects of opioids is somewhat contradictory. When given alone, in very high doses, opioids induce δ waves.[2] However, at normal clinical analgesic doses, the electroencephalographic effects are less obvious. When remifentanil is given in combination with hypnotic drugs (in this case propofol), there seem to be somewhat complex and subtle asymmetric interactions. Various electroencephalographic indices (including the median frequency, bispectral index, approximate entropy, and spectral entropy) are acceptable indicators of hypnotic drug effects but comparatively poor indicators of opioid drug effects.[3–6] Using the prediction probability statistic as a comparator, the results of Liley *et al.* are essentially similar to (or perhaps slightly better than) these previous studies. Increasing propofol concentration caused a progressive decrease in consciousness and a corresponding change in electroencephalographic activity, which they quantified using their autoregressive moving average-derived "Cortical State" (CS) Index. The autoregressive moving-average model is a method of quantifying the frequency structure of the electroencephalographic signal. Remifentanil seems to have no direct effect on the Cortical State index, but it does act indirectly to shift the propofol–cortical state dose-response curve to the left—in a fashion similar to that in the model proposed by Bouillon *et al.*[3]

However, what is new in the study by Liley *et al.* is that they also estimated an index of "cortical input" (CI). This quantity is effectively a multiplier of the autoregressive moving-average filter to scale the autoregressive moving-average model correctly to the size of the raw electroencephalographic signal. In the context of the background cortical theory, the CI can be interpreted as an indicator of the intensity of sub-cortical input. They found that increasing concentrations of remifentanil caused a profound decrease in this parameter that was most marked in the presence of high propofol concentrations. The CI index correlates well with the absolute amplitude of the electroencephalograph. The propofol-induced increase in electroencephalographic amplitude is, therefore, suppressed by the concomitant administration of remifentanil. In this respect, the CI index is markedly different from almost all the other electroencephalographic monitors in common use (such as the bispectral index and various entropies), the algorithms of which are designed to ignore the information contained in absolute amplitude of the electroencephalographic signal. It is unclear exactly how remifentanil acts to decrease the electroencephalographic amplitude and whether the concept of input blockade is too simplistic. There are also questions as to how these results can be reconciled with the opioid effects to increase δ power, which should increase electroencephalographic amplitude. Perhaps this is because the alteration in electroencephalographic frequency structure has been captured already in the CS parameter.

There is clearly much work to be done before these observations could be translated into clinical practice. This study was performed in patients without a surgical stimulus. Does a skin incision increase the CI index? Does increased dose of opioid (or hypnotic) protect against this? What are the effects of paradoxical electroencephalographic arousal? Will it be robust to the interindividual variation in electroencephalographic power across large number of patients? These are some of the questions that need to be answered first.

The other novel concept in this work is that it was derived, "bottom-up," from a quantitative model of cortical neuronal population interactions. Variations of this complex model have been published in journals that are not often read by anesthesiologists,[7,8] but the theory has been simplified and its core used to derive a practical instrument for the measurement of drug effects in real patients. This is the first generation of indices to be derived from a theory of brain function. There will be blind alleys and disappointments. The current form of the model does not include many factors that are probably essential for brain function—such as the

◆ This Editorial View accompanies the following article: Liley DTJ, Sinclair NC, Lipping T, Heyse B, Vereecke HEM, Struys MMRF: Propofol and remifentanil differentially modulate frontal electroencephalographic activity. ANESTHESIOLOGY 2010; 113:292–304.

Accepted for publication February 8, 2010. The author is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this article.

effect of intrinsic currents and intracellular modulation of neuronal excitability. But in the end, a clear scientific understanding of the causal mechanistic links among drug effect and electroencephalographic and neurobiologic function must be superior to the existing heuristically derived black-box electroencephalographic monitors.

Jamie Sleigh, M.D., Department of Anaesthesia, Waikato Clinical School, University of Auckland, Hamilton, New Zealand. sleighj@waikatodhb.govt.nz

References

1. Liley DTJ, Sinclair NC, Lipping T, Heyse B, Vereecke HEM, Struys MMRF: Propofol and remifentanil differentially modulate frontal electroencephalographic activity. ANESTHESIOLOGY 2010; 113:292–304
2. Sebel PS, Bovill JG, Wauquier A, Rog P: Effects of high-dose fentanyl anesthesia on the electroencephalogram. ANESTHESIOLOGY 1981; 55:203–11
3. Bouillon TW, Bruhn J, Radulescu L, Andresen C, Shafer TJ, Cohane C, Shafer SL: Pharmacodynamic interaction between propofol and remifentanil regarding hypnosis, tolerance of laryngoscopy, bispectral index, and electroencephalographic approximate entropy. ANESTHESIOLOGY 2004; 100:1353–72
4. Ferenets R, Vanluchene A, Lipping T, Heyse B, Struys MM: Behavior of entropy/complexity measures of the electroencephalogram during propofol-induced sedation: Dose-dependent effects of remifentanil. ANESTHESIOLOGY 2007; 106: 696–706
5. Vanluchene AL, Struys MM, Heyse BE, Mortier EP: Spectral entropy measurement of patient responsiveness during propofol and remifentanil. A comparison with the bispectral index. Br J Anaesth 2004; 93:645–54
6. Fechner J, Hering W, Ihmsen H, Palmaers T, Schuttler J, Albrecht S: Modelling the pharmacodynamic interaction between remifentanil and propofol by EEG-controlled dosing. Eur J Anaesthesiol 2003; 20:373–9
7. Bojak I, Liley DT: Modeling the effects of anesthesia on the electroencephalogram. Phys Rev E Stat Nonlin Soft Matter Phys 2005; 71:041902
8. Foster BL, Bojak I, Liley DT: Population based models of cortical drug response: Insights from anaesthesia. Cogn Neurodyn 2008; 2:283–96

ANESTHESIOLOGY REFLECTIONS

McMunn's Elixir of Opium

By 1837 New York's John B. McMunn, M.D. (ca. 1803–1867), had devised a laudanum alternative by using ether to deodorize opium before combining it with alcohol. "McMunn's Elixir of Opium" became a leading American analgesic and "cure" for the "nervous irritability" of hysteria, epilepsy, tic douloureux, pertussis, rabies, and even tetanus. The elixir's New York proprietors, Abraham B. and David Sands, were both dead by 1862, yet their legacy firm would die-stamp their initials (*see above*) on labels until 1876, the year after reports surfaced of a toddler's death by elixir overdose "for worms." (Copyright © the American Society of Anesthesiologists, Inc. This image appears in color in the *Anesthesiology Reflections* online collection available at www.anesthesiology.org.)

George S. Bause, M.D., M.P.H., Honorary Curator, ASA's Wood Library-Museum of Anesthesiology, Park Ridge, Illinois, and Clinical Associate Professor, Case Western Reserve University, Cleveland, Ohio. UJYC@aol.com.