Pupillary Reflex Dilation to Predict Movement

A Step Forward Toward Real-time Individualized Intravenous Anesthetics

Merlin D. Larson, M.D., Dhanesh K. Gupta, M.D.

Surgeons often ask if the patient is ready for the case to begin. An affirmative answer might require an awkward retraction if the patient then moves or coughs. When using total intravenous anesthesia (TIVA), we are never truly certain how to answer the surgeon’s query, unless the patients are paralyzed. By contrast, with volatile anesthetics, we can confidently answer that the patient will not remember or move based on the limited interindividual variability in the concentration–effect relationships. In this issue of Anesthesiology, Guglielminotti et al have proposed a simple pupillary test that might provide the anesthesia provider with a more precise answer for TIVA. These authors suggest that depression of pupillary reflex dilation in response to a standardized noxious stimulus will predict nonmovement to a surgical stimulus. The pupillary test predicted nonmovement with an accuracy that was equivalent to pharmacokinetic–pharmacodynamic (PK/PD) model predictions for propofol–remifentanil anesthetics in healthy young females.

There are similarities between the movement reflex and reflex dilation of the pupil during anesthesia. Both reflexes are subcortically mediated, initiated by nociceptors, and suppressed by opioids. Opioids are known to essentially obliterate pupillary reflex dilation at concentrations equivalent to 5 ng/ml of remifentanil in the presence of propofol. As reported by these authors, failure of pupillary reflex dilation essentially guaranteed absence of movement to a surgical stimulus.

Intermittent testing of patient responsiveness with a standardized noxious stimulus during anesthesia is an idea that has been slow to develop, but is overdue because it has the potential to add precision to the management of our TIVA and combined regional–general anesthetics. If we decide to use intermittent testing to detect nociception, then it becomes important to know how to provide the stimulus and what parameters to measure after the stimulus.

The stimulus parameters of the “standardized noxious test” are slightly different for each reference cited by Guglielminotti et al., so the stimulus is only standardized for each specific study. Some of the factors that can affect the response to the stimulus include the intensity of the stimulating current, the type of stimulating electrodes, the duration of the stimulus, and the frequency of the stimulus train. There is a trend toward the use of skin surface electrocardiographic electrodes, 60 mA current intensity, and 100 Hz frequency of stimulation, and Guglielminotti et al. used these stimulating parameters. If placed over the ulnar nerve, the same stimulator might be used to evaluate the neuromuscular junction.

The responses to measure after the stimulus also differ. Despite the fact that it has been known for over 50 yr that the sympathetic nervous system is relatively slow to respond during anesthesia compared to reflex dilation of the pupil (fig. 1), hemodynamic changes in response to nociception are a common parameter used to titrate hypnotics and opioids.
because they are developed in healthy surgical patients who demonstrate stationary physiologic conditions. The predictive ability of PK/PD models has not been tested in other physiologic conditions. In common clinical situations where there are alterations in cardiac output or its distribution, such as obesity, hemorrhage, pneumoperitoneum, or extremes of age, these PK/PD models may perform poorly. One might expect that the pupillary measurement would outperform the targeted infusions as a predictor of nonmovement in situations where PK/PD model predictions might be inaccurate. The relative advantage of using reflex dilation compared to targeted infusions as predictors of nonmovement in these common subgroups will require additional studies.

The authors targeted the propofol concentration in these healthy volunteers to 4 ng/ml and then used varying concentrations of remifentanil to provide additional analgesia. However, propofol given with nitrous oxide without opioids does not block pupillary reflex dilation even though the subjects do not move in response to the same stimulus. Guglielminotti et al. recognize that they are essentially evaluating the effect of remifentanil on movement and that the use of pupillary reflex dilation to predict nonmovement might vary at different targeted propofol concentrations. In addition, other IV adjuvants such as ketamine, dexmedetomidine, and lidocaine might alter the relationship between pupillary reflex dilation and movement.

In spite of these issues, the observations of Guglielminotti et al. are valuable and add insight to how we might succeed in determining the opposing factors of nociception and antinociception during surgical anesthesia. Patients have widely differing responses to opioids, and this technique might allow us to deliver these drugs during general anesthesia in a more precise fashion. Meanwhile, we look forward to additional studies examining this pupillary test to predict nonmovement in a more diverse population.

**Competing Interests**

The authors are not supported by, nor maintain any financial interest in, any commercial activity that may be associated with the topic of this article.

**Correspondence**

Address correspondence to Dr. Larson: larsonmm@anesthesia.ucsf.edu

**References**

3. Larson MD, Kurz A, Sessler DI, Dechert M, Bjorksten AR, Tayefeh F: Alfentanil blocks reflex pupillary dilation in
response to noxious stimulation but does not diminish the light reflex. Anesthesiology 1997; 87:849–55


ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Sulphuric Ether as “Salvation Oil”: A 2% Solution “In Place of a Physician”

With labels in English and German, a 2% solution of “SULPH[uric] ETHER” was peddled to rural American families as “Salvation Oil.” Used as an external liniment, this panacea was truly a family affair—it could be applied or rubbed onto the skin of family members or onto the hide of horses, cattle, or other family livestock. In December of 1898, Nebraska’s Cherry County Independent newspaper advertised the use of “Salvation Oil for what it is recommended in place of a physician. It never fails.” (Copyright © the American Society of Anesthesiologists, Inc.)

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

Anesthesiology 2015; 122:961-3