

## Time to Maximum Effect Site Concentration

To the Editor:—We congratulate Dr. Minto *et al.*<sup>1</sup> for the introduction of the concept of  $t_{\text{peak}}$  and have several comments about its application.

1. The authors<sup>1</sup> use a polyexponential equation (equation 1) to describe the time course of the plasma concentrations of a drug in lieu of a compartmental interpretation suggested by Sheiner *et al.*<sup>2</sup> As a consequence, the effect compartment can now contain any amount of a drug and is not limited to being “negligibly small” as postulated by Sheiner *et al.*
2. Sheiner *et al.*<sup>2</sup> introduced  $k_{\text{e0}}$  as the first-order transport rate constant from the effect compartment to “outside” but did not define the transport rate constant from plasma into the effect compartment. It follows from theorem 1 (appendix) that the authors use  $k_{\text{e0}}$  as the rate constant for drug transport from plasma into the effect compartment as well as for the transport from the effect compartment into plasma. Hence, the transport of a drug into and out of the effect compartment is defined differently from that of Sheiner *et al.*, but the authors retain the label  $k_{\text{e0}}$ .
3. The definition of  $t_{\text{peak}}$  is given once (page 324) as “the time of maximum effect site concentration following an intravenous bolus dose when there is no drug initially in the system” and again as “a model independent parameter, as it can be directly observed following a submaximal bolus dose.” Which definition takes precedence? Because any dose of a drug may be injected as a bolus intravenously, all clinically used doses are presumably “submaximal.” It is the pharmacologic effect that is submaximal or maximal, as the case might be, and not the dose. Also, the time to peak pharmacologic effect represents a single time point among the observed points relating the magnitude of the effect to the time after injection. It is not a pharmacodynamic parameter. In our view, the time to the peak submaximal effect is observed during the collection of the data and, along with other data points, provides information necessary to simulate the time course of drug concentrations in the effect compartment and, in conjunction with the pharmacodynamic parameters ( $\gamma$  and  $IC_{50}$ ), the time course of the effect.
4. As evident from equation 3 on page 325,  $t_{\text{peak}}$  and  $k_{\text{e0}}$  are interrelated, but only if the pharmacologic effect is submaximal. A maximal pharmacologic effect may be associated with a given concentration in the effect compartment or with one many times higher. In theory and with extremely high doses, circulation time represents the lower limit for the time to the maximal effect for most drugs.
5. Are the authors satisfied that measuring an effect to an endpoint defines the peak, but submaximal, effect? The endpoint measurements were used in some of the cited studies.
6. Overlapping of the curve “Shanks PK/PD” with that labeled “Shanks PK with Stanski  $t_{\text{peak}}$ ” in figure 1 is only possible because the times to peak effect are nearly identical (Stanski and Maitre<sup>3</sup>  $\sim 1.75$  min and Shanks *et al.*<sup>4</sup>  $\sim 1.73$  min). The time course of the plasma concentrations described by Stanski and Maitre is markedly different from that described by Shanks *et al.*, and each description requires a separate  $k_{\text{e0}}$  (Stanski and Maitre =  $0.58 \text{ min}^{-1}$  and Shanks *et al.* =  $0.29 \text{ min}^{-1}$ ). In spite of these differences, the peak concentration in the effect compartment is simulated at approximately identical times. It is not “naïve” but mathematically and conceptually incorrect to substitute  $k_{\text{e0}}$  from one study into another. Therefore, this maneuver may be *a priori* excluded. Even if the value of

$k_{\text{e0}}$ , calculated from  $t_{\text{peak}}$  of Stanski and Maitre ( $k_{\text{e0}} = 0.284 \text{ min}^{-1}$ ), fits the concentration of Shanks *et al.* in the effect compartment well (fig. 1), so does the value of  $k_{\text{e0}}$ , calculated from  $t_{\text{peak}}$  of Shanks *et al.* ( $k_{\text{e0}} = 0.595 \text{ min}^{-1}$ ), produce concentrations in the effect compartment that overlap those simulated by Stanski and Maitre. However, the peak concentration of thiopental in the effect compartment simulated by Stanski and Maitre is higher than that simulated by Shanks *et al.* (0.0655 vs. 0.0438 relative units). Although the  $t_{\text{peak}}$  approach brings the two peak concentrations in the effect compartment to overlap in time, the approach does not reconcile the other aspects of the studies. The differences in the time course of the concentrations in plasma and the effect compartment, in the peak concentrations in the effect compartment, and, presumably, in the pharmacodynamic parameters ( $\gamma$  and  $IC_{50}$ ) remain. What can then be the purpose of the  $t_{\text{peak}}$  approach?

7. The authors compare different scenarios for the time course of the concentrations of remifentanyl in the effect compartment. However, no data for the time course of the pharmacologic effect are presented. In the absence of these data, no effect compartment can be postulated and, if one is postulated, it cannot be differentiated from any other peripheral compartment.
8. Concentrations of a drug in the effect compartment cannot be verified. Quality of simulations can be documented only by comparing the simulated with the observed time courses of (1) the plasma concentrations and (2) the effect. The goal of pharmacodynamic simulations is to reproduce the time course of the effect, but these simulations are missing in the article.

To conclude, we support the notion that the time to peak submaximal effect is important information to be obtained from the time course of the effect. It is important to stress that the peak effect must be submaximal. Simulation in a pharmacokinetic–pharmacodynamic model, if successful, produces a time course of the drug concentration in the effect compartment such that the peak concentration and the simulated peak effect occur at the time of the observed peak submaximal effect. Optimally, the whole simulated time course of the pharmacologic effect is close to the observed. The time to peak concentration in the effect compartment is a derived but unique function of  $k_{\text{e0}}$  and the parameters in the polyexponential description of the time course of plasma concentrations. The time to peak submaximal effect is an observed value.

Vladimir Nigrovic, M.D.,\* Anton Amann, Ph.D. \* Medical College of Ohio, Toledo, Ohio. vnigrovic@mco.edu

## References

1. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *ANESTHESIOLOGY* 2003; 99:324–33
2. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clin Pharmacol Ther* 1979; 25:358–71
3. Stanski DR, Maitre PO: Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited. *ANESTHESIOLOGY* 1999; 90:92–7
4. Shanks CA, Avram MJ, Krejcie TC, Henthorn TK, Gentry WB: A pharmacokinetic–pharmacodynamic model for quantal responses with thiopental. *J Pharmacokinetic Biopharm* 1993; 21:309–21

(Accepted for publication December 12, 2003.)

## Comments on Using the Time of Maximum Effect Site Concentration to Combine Pharmacokinetics and Pharmacodynamics

*To the Editor:*—We read with interest the article by Minto *et al.*,<sup>1</sup> which discusses a method for combining pharmacokinetic and pharmacodynamic parameter sets from different studies, in which the effect site equilibration constant  $k_{e0}$  is estimated based on the time of peak effect ( $t_{peak}$ ) after bolus injection. We have successfully used this approach for approximately a decade in pharmacokinetic-pharmacodynamic models for educational simulations and described it in detail in 1998.<sup>2</sup> We are grateful for the recommendation of Minto *et al.* for other investigators to acquire  $t_{peak}$ , because the availability of this parameter was cited as a limiting factor in establishing a complete parameter set in our article. Based on our study and experience, we would like to comment on the study presented by Minto *et al.*

Our first comment concerns caution regarding their statement: “As shown in the third remifentanyl example, a directly observed  $t_{peak}$  is a model-independent gold standard for describing with a single parameter the time course of concentration in the effect site.” We can relay a comment made by one of the reviewers of our article, which we elaborated on in the discussion section: “The time of peak effect is used to derive the equilibration time constant for the effector compartment. This is a one data point estimate for application in educational simulations. It does not allow for an estimation of the variability of the  $k_{e0}$  obtained in this manner. Therefore this method is not presented as an alternative for the estimation of  $k_{e0}$  based on multiple plasma concentration and effect measurements in a simultaneous study.”<sup>2</sup>

We also expect that an estimate for  $k_{e0}$  based on the pharmacokinetic parameter set for the considered experimental group and on the  $t_{peak}$  from a different experiment gives, in general, better results than simply combining the pharmacokinetic parameters with the  $k_{e0}$  of the second experiment, which does not contain any information regarding

the first group. Therefore, we do not contest the main conclusion that the  $t_{peak}$  method would yield better predictions of the time course of drug effect than the so-called naive method. However, we have some comments regarding the two simultaneous thiopental studies used to make this point by Minto *et al.* The unit disposition functions show that they have different pharmacokinetic parameter sets. The different  $k_{e0}$ s combined with the different pharmacokinetic parameter sets result in similar  $t_{peak}$ s, as can be seen in figures 1 and 2 of the article by Minto *et al.* Given the considerable differences in subject population, this similarity in  $t_{peak}$  could be serendipitous. Combining a pharmacokinetic parameter set with a  $t_{peak}$  from another experiment, which is almost identical to the  $t_{peak}$  of the first set, can be expected to lead to a better estimate for  $k_{e0}$ . Our article presents a detailed sensitivity analysis to evaluate how inconsistencies in parameter sets influence the derived parameters and model response.<sup>2</sup> In our opinion, more data and similar sensitivity studies applied to the specific situation proposed by Minto *et al.* are required to sustain the above conclusion.

**Willem L. van Meurs, Ph.D., Eric Nikkelen, M.S., Michael L. Good, M.D.\*** \*University of Florida College of Medicine, Gainesville, Florida. good@anest.ufl.edu

### References

1. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *ANESTHESIOLOGY* 2003; 99:324–33
2. Van Meurs WL, Nikkelen E, Good ML: Pharmacokinetic-pharmacodynamic model for educational simulations. *IEEE Trans Biomed Eng* 1998; 45:582–90

(Accepted for publication December 12, 2003.)

*In Reply:*—On behalf of our coauthors of the article “Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics,”<sup>1</sup> we welcome the comments and observations in the letter by Drs. Nigrovic and Amann and the letter by Dr. Van Meurs, Mr. Nikkelen, and Dr. Good. The letter by Drs. Nigrovic and Amann raises several points, which are addressed in the order presented:

1. Polyexponential equations are, of course, completely interchangeable with compartmental models mathematically. Although Sheiner *et al.*<sup>2</sup> postulated that the effect site was “negligibly small,” both the Sheiner model and our model readily permit drug to flow into the effect site simply by assigning an appreciable volume to the effect site. Of course, the amount is limited by the amount of drug in the plasma.
2. Our mathematical development of the effect site has some different nuances than that of Sheiner *et al.*,<sup>2</sup> but the definition of the effect site is identical:

$$\frac{dC_e}{dt} = k_{e0}(C_p - C_e).$$

\* STANPUMP program. Available at: <http://anesthesia.stanford.edu/pkpd>. Accessed January 28, 2004

† RUGLOOP program. Available at: <http://users.belgacombusiness.net/cd033704/index.html>. Accessed January 28, 2004

Sheiner *et al.* used the term  $k_{e0}$ , with *o* meaning “outside.” We have always believed that was a poor choice because it is anglo-centric. Compartment 0 is uniformly recognized in pharmacokinetic models as the external compartment. Hence is our preference for “ $k_{e0}$ .”

3.  $t_{peak}$  is the time of maximum effect site concentration after a submaximal intravenous bolus dose when there is no drug initially in the system. By definition, the time of maximum effect is the same as the time of maximum effect site concentration for direct-acting monotonic pharmacodynamic models (as opposed to indirect effect models, or biphasic effect models, where none of this applies). Therefore,  $t_{peak}$  can be directly observed by observing the time of peak effect. Because no model is required to simply look at the raw data and identify the time of peak effect, this suggests that  $t_{peak}$  is model independent. We do not share the concern expressed by Drs. Nigrovic and Amann as to whether it is the dose or effect that is “submaximal” or “maximal.” We presume that Drs. Nigrovic and Amann would consider  $k_{e0}$  a pharmacodynamic parameter. Because  $t_{peak}$  is directly calculable from  $k_{e0}$  and *vice versa*, we do not understand their issue with labeling  $t_{peak}$  a pharmacodynamic parameter. Of course, the observed time of peak effect is limited by the resolution of the observations. Perhaps that is their point.
4. Drs. Nigrovic and Amann have correctly identified the reason that we focus on submaximal effect.

5. We interpret the question as saying that the “peak” effect should not be the last point observed in the study because it is not possible to know whether the effect has truly peaked if observations stop at or before the time of peak effect. We agree, which is why the period of observation extended well beyond the time of peak effect in all of the studies cited in our article.
6. We agree that the curves overlap because  $t_{\text{peak}}$  values predicted by the integrated pharmacokinetic–pharmacodynamic models were identical. In fact, that is exactly the point. As Drs. Nigrovic and Amann observe, the pharmacokinetic models are very different, and so the fact that the calculated  $t_{\text{peak}}$  values are nearly identical provides validation for the concept that  $t_{\text{peak}}$  is model independent. (As noted by Dr. Van Meurs, Mr. Nikkelen, and Dr. Good, this result could be serendipity, and so even though it provides validation, it is certainly not a proof). We agree that it is mathematically and conceptually incorrect to substitute  $k_{\text{e0}}$  from one study to another, but to the best of our knowledge, this is the current standard in every target-controlled anesthetic drug delivery system except for STANPUMP<sup>®</sup> and RUGLOOP.<sup>†</sup> Drs. Nigrovic and Amann observe that the magnitude of the time course of effect site concentrations predicted by Shanks *et al.*<sup>3</sup> is modestly different from that predicted by Stanski and Maitre.<sup>4</sup>  $k_{\text{e0}}$  (and  $t_{\text{peak}}$ ) only relates to the time delay between plasma and effect site and would not be expected to account for differences in the magnitude of the six parameter pharmacokinetic models. The purpose of the  $t_{\text{peak}}$  approach is to provide a means of building an integrated pharmacokinetic–pharmacodynamic model from a pharmacokinetic analysis that did not concurrently include estimation of  $k_{\text{e0}}$  (which is the majority of pharmacokinetic analyses).
7. The pharmacodynamics of remifentanyl are fully described by Minto *et al.*<sup>5</sup> (reference 9 of the article).
8. Simulated time courses of drug effect can be readily calculated from the simulated effect site concentrations using standard pharmacodynamic models.

In response to the letter from Dr. Van Meurs, Mr. Nikkelen, and Dr. Good, we acknowledge their excellent manuscript on  $k_{\text{e0}}$  and  $t_{\text{peak}}$  and appreciate their consistency with the definition of  $t_{\text{peak}}$  introduced by Shafer and Gregg<sup>6</sup> (reference 5 of their manuscript). Although we share many of the same conclusions, in particular, their observation on page 586 that “this result justifies the use of  $t_{\text{peak}}$  as a parameter to base a  $k_{\text{e0}}$  estimate on.” What particularly distinguishes their article is the thoughtful and novel sensitivity analysis. Their article describes development of their own software for this purpose. STANPUMP, which has been available over the Internet since 1989, provides a mean for nonprogrammers to perform the same simulations.

We do not know how the authors responded to their reviewer, but the reviewer is not quite correct. Assuming that effect has been continuously sampled (getting around the issue of discrete sample times that concerned Drs. Nigrovic and Amann), there is a one-to-one relation between  $k_{\text{e0}}$  and  $t_{\text{peak}}$ . When analyzing a population of pa-

tients, variability in  $k_{\text{e0}}$  can be determined directly from variability in  $t_{\text{peak}}$ . What the reviewer may have intended was that when analyzing an individual patient, the uncertainty (*e.g.*, SE) about the estimate of  $t_{\text{peak}}$  may be greater than the uncertainty about an estimate of  $k_{\text{e0}}$ , because  $t_{\text{peak}}$  is a single observation that may have considerable variability, whereas an estimate of  $k_{\text{e0}}$  is based on analysis of all points in the hysteresis curve and thus may be known with greater certainty. If one has access to multiple concentrations and measures of drug effect, the standard approach should be used to estimate  $k_{\text{e0}}$ . We would never advocate using  $t_{\text{peak}}$  to estimate  $k_{\text{e0}}$  when one has access to a full set of concentration and effect measures. Nevertheless, comparing the calculated  $t_{\text{peak}}$  from the resulting model with the observed time of peak effect provides a quick verification that the modeling was done correctly.

We certainly agree that the fact that different  $k_{\text{e0}}$ s, combined with different pharmacokinetic parameter sets, demonstrated nearly identical values for  $t_{\text{peak}}$  (figs. 1 and 2) in our article could be serendipitous. The purpose of our article was to present a theoretical concept and show some examples of the concept. It was not known before our analysis that the  $t_{\text{peak}}$  would be the same for figures 1 and 2. It is not clear how a sensitivity analysis could address the question of serendipity.

Again, on behalf of our coauthors, we appreciate the thoughtful letter of Drs. Nigrovic and Amann and that of Dr. Van Meurs, Mr. Nikkelen, and Dr. Good and hope that this discussion on a moderately arcane topic is of interest to the readers of ANESTHESIOLOGY.

**Steven L. Shafer, M.D.,<sup>‡</sup> Charles Minto, M.B., Ph.D., Thomas Schneider, M.D.** <sup>‡</sup> Palo Alto Veterans Affairs Health Care System, Palo Alto, California; Stanford University School of Medicine, Stanford, California; and University of California at San Francisco, San Francisco, California. steven.shafer@stanford.edu

## References

1. Minto CF, Schnider TW, Gregg KM, Henthorn TK, Shafer SL: Using the time of maximum effect site concentration to combine pharmacokinetics and pharmacodynamics. *ANESTHESIOLOGY* 2003; 99:324–33
2. Sheiner LB, Stanski DR, Vozeh S, Miller RD, Ham J: Simultaneous modeling of pharmacokinetics and pharmacodynamics: Application to d-tubocurarine. *Clin Pharmacol Ther* 1979; 25:358–71
3. Shanks CA, Avram MJ, Krejcie TC, Henthorn TK, Gentry WB: A pharmacokinetic–pharmacodynamic model for quantal responses with thiopental. *J Pharmacokinetic Biopharm* 1993; 21:309–21
4. Stanski DR, Maitre PO: Population pharmacokinetics and pharmacodynamics of thiopental: The effect of age revisited. *ANESTHESIOLOGY* 1999; 90:92–7
5. Minto CF, Schnider TW, Egan TD, Youngs E, Lemmens HJM, Gambús PL, Billard V, Hoke JF, Hermann DJ, Muir KT, Mandema JW, Shafer SL: The influence of age and gender on the pharmacokinetics and pharmacodynamics of remifentanyl: I. Model development. *ANESTHESIOLOGY* 1997; 86:10–23
6. Shafer SL, Gregg KM: Algorithms to rapidly achieve and maintain stable drug concentrations at the site of drug effect with a computer controlled infusion pump. *J Pharmacokinetic Biopharm* 1992; 20:147–69

(Accepted for publication December 12, 2003.)

## Moreno y Maíz: A Missed Rendezvous with Local Anesthesia

*To the Editor:*—We read with interest the history of cocaine as a local anesthetic published by Calatayud and Gonzales in the June issue of ANESTHESIOLOGY.<sup>1</sup> We would like to take the opportunity to add few comments to emphasize the role played by Thomas Moreno y Maíz in the understanding of the physiologic effects of cocaine and, even more, its ability to block nerve conduction. Dr. Moreno y Maíz was a Peruvian surgeon who spent at least 4 yr in Paris, where he completed his surgical education. He obtained the degree of doctor of medicine at the University of Paris in 1868.<sup>2</sup> Obviously, the nationality and the

culture of Moreno y Maíz led him to consider coca as a topic of study. His laboratory experiments, in continuation of physiologic experimentation in animals previously defined by Claude Bernard (1813–1878), may be considered a model of basic research in physiology. They were performed in a variety of animals, including rats, guinea pigs, and frogs. In the first experiments, he described the systemic effects of local anesthetics, including seizures and mydriasis related to the injection of high doses of cocaine. In addition, he observed that the spinal cord remained intact when systemic effects could alter sensibility. In an

experiment performed in guinea pigs, he observed paralysis on the side where cocaine was injected subcutaneously. In other studies, he noted the local effect of cocaine in frogs. To separate systemic and local effects, he applied the model used by Claude Bernard to study muscle relaxants, in which one leg was protected by vascular ligation. He demonstrated that the anesthetic effect of cocaine on peripheral nerve was independent of the systemic effects. Then, he injected cocaine into the left lower limb of a frog with isolated heart and isolated right lower limb to suppress the systemic diffusion and observed complete paralysis of the left limb 35 min after the injection. The frog did not remove this limb in response to painful stimulation applied locally or on the contralateral limb. Consequently, Moreno y Maíz wondered on page 77 of his medical thesis, "Could one utilize it [cocaine] as local anesthetic? We cannot state with so few experiments; the future must decide." More surprising is that these results and considerations remained futile, although the author was already a surgeon in Peru and members of the jury of his thesis were also academic surgeons in Paris. No attempt was made to repeat this first demonstration, at least in other animal models or in humans. Perhaps

Moreno y Maíz, more interested by the systemic effects of cocaine, was unable to perceive the treasure under his feet, or perhaps his professional neighborhood rejected his ideas. Moreno's life thereafter remains largely obscure. Nevertheless, as with von Anrep,<sup>3</sup> we should recognize the prime opus due to Thomas Moreno y Maíz.

**Emmanuel Marret, M.D., Marc Gentili, M.D.,\* Francis Bonnet, M.D.** \*Hôpital Tenon, Paris, France. Marc.Gentili@wanadoo.fr

## References

1. Calatayud J, Gonzales A: History of the development and evolution of local anesthesia since the coca leaf. *ANESTHESIOLOGY* 2003; 98:1503-8
2. Moreno y Maíz T: Recherches chimiques et physiologiques sur l'érythroxylym coca du Pérou et la cocaïne. Paris, Louis Leclerc Editeur, 1868, pp 65-78
3. Yentis SM, Vlassakov KV: Vassily von Anrep, forgotten pioneer of regional anesthesia. *ANESTHESIOLOGY* 1999; 90:890-5

(Accepted for publication January 6, 2004.)

Anesthesiology 2004; 100:1322

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Coca Leaf and Local Anesthesia

*To the Editor:*—I enjoyed the fine article about the history of the coca leaf and local anesthesia<sup>1</sup> and would like to make a few comments, by way of addition and amendment.

Among the Spanish chronicles, no mention was made of the contribution of Inca Garcilaso de la Vega (1539-1616). Apart from his having a particular cultural insight, as the son of the Spanish captain Sebastián Garcilaso de la Vega and the Inca princess Chimpu Ocllo, he was himself a coca grower on the Beni. Of particular interest is his reference to the lost writings of the priest Blas Valera (1548-1598; Jesuit priest, writer, and linguist) on the medical uses of coca: "Coca [sic] protects the body from many ailments, and our doctors use it in powdered form to reduce the swelling from wounds; to strengthen broken bones, to expel cold from the body or prevent it from entering, and to cure rotten wounds or sores full of maggots."<sup>2</sup> It is interesting to note that cocaine is a natural insecticide because it blocks the recapture of octopamine, a neurotransmitter in insects.

Another episode that deserves mention is the role played by Jean Baptiste de Monet (physician and botanist, professor at the Musée National d'Histoire Naturelle after the French Revolution; 1744-1829), chevalier de Lamarck and better known by this name, who classified the shrub after receiving samples from Joseph de Jussieu (1704-1779), who had taken part in a French scientific expedition to South America, organized to settle an old argument between Sir Isaac Newton (1643-1727) and Jean Dominique Cassini (1627-1712; first of a family of famous astronomers, head of the Paris Observatory from 1671) over the shape of the earth, the dispute being if it was an oblate or a prolate sphere. As is generally known, Newton won the argument.

Perhaps the greatest coca connoisseur of the nineteenth century was Angelo Mariani (1838-1914), Corsican by birth, who invented a medicinal wine made with coca leaves, *vin Mariani*, and built an economic empire on it.<sup>3</sup> He was the greatest importer of coca of his time and grew several species, experimenting with them in his estate near Paris. His wine was the forerunner of many imitators, most notably John Pemberton's French Wine Coca that gave origin to Coca Cola. He wrote a monograph on coca in 1888, and authorities and celebrities all over the world endorsed his product, among them, to name but a few, Pope Leo XIII, Thomas Alva Edison, William Mackinley, Jules Verne, and Frederic Auguste Bartholdi, the sculptor of the Statue of Liberty who had finished his work in Paris just 3 months before Koller's discovery.

The contribution of Vassili Konstantinovich von Anrep (1852-1925;

Russian nobleman and physician who had done postgraduate research on cocaine at Professor Michael Rossbach's laboratory at Würzburg) would have been greater had he taken the trouble to publish his experiments with cocaine injections; in an article published in Russian<sup>4</sup> after Koller's discovery and prompted by it, he describes the use of cocaine to relieve the pain of a costal fracture, preceding Hall and Halsted's description of nerve blockade with cocaine. As mentioned in the current article,<sup>1</sup> Halsted became addicted to cocaine, but there is no evidence that Freud did, although he used cocaine at least until 1895.

Finally, the article gives the impression that Koller reached his discovery through methodic experimentation, but his own recall points to a serendipitous discovery. Serendipity, following Horace Walpole (1717-1797; English writer and antiquarian), who invented the word, requires a discovery made by accident and sagacity of a thing of which one is not in quest, and this is what happened to Koller. One day, he was taking some cocaine with Dr. Engel, who mentioned that it caused numbness of the tongue; Koller replied that this had been noted by all who had worked with cocaine and that "in the moment it flashed upon me that I was carrying in my pocket the local anesthetic for which I had searched some years earlier."<sup>5</sup> Koller's testimony and that of the direct witness of his first experiment, Gustav Gärtner (1855-1937; physician and researcher, Stricker's assistant), point to the fact that a "big and lively frog" from Professor Stricker's laboratory (1834-1898; head of the Institute for Experimental Pathology) was indeed that first subject of the experiment.

**Jorge Dagnino, M.D.** Pontificia Universidad Católica de Chile, Santiago, Chile. jdagnino@med.puc.cl

## References

1. Calatayud J, González A: History of the development and evolution of local anesthesia since the coca leaf. *ANESTHESIOLOGY* 2003; 98:1503-8
2. Inca Garcilaso de la Vega: Comentarios Reales de los Incas. Buenos Aires, Emecé, 1943, pp 186-7
3. Mortimer WG: History of Coca: The Divine Plant of the Incas [reprint of 1901 edition]. Honolulu, University Press of the Pacific, 2000
4. Yentis S, Vlassakov KV: Vassily von Anrep, forgotten pioneer of regional anesthesia. *ANESTHESIOLOGY* 1999; 90:890-5
5. Becker HK: "Coca Koller": Carl Koller's Discovery of Cocaine Anesthesia [reproduced in Byck R: Cocaine Papers by Sigmund Freud. New York, New American Library, 1975, p 283]. *Psychoanal Q* 1963; 32: 309-73

(Accepted for publication January 6, 2004.)

Anesthesiology 2004; 100:1323

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

*In Reply:*—We thank Drs. Marret, Gentili, Bonnet, and Dagnino for their interest in our article and the comments and annotations in their letters. We should perhaps clarify that our study was not intended to cover all the information on coca leaf and its ramifications, which are, nonetheless, fascinating, but to highlight the early history, which has always been a bit obscure. This is the reason that the first part of the article focuses on the sixteenth century and the rest on issues regarding local anesthesia.

We essentially agree with the comments contained of Drs. Marret, Gentili, and Bonnet about Thomas Moréno y Maíz, M.D., Ph.D. (more appropriately spelled, in Spanish, Tomás Moreno y Maíz; Paris, France).<sup>1</sup> He was, indeed, a pioneer, the first to conduct rigorous experimentation in animals to evaluate the effects of cocaine; we believe that this is reflected in the article we published in ANESTHESIOLOGY.<sup>2</sup>

With respect to the remarks in the above text on Basil (or Vassily) von Anrep, M.D., (Department of Pharmacology and Pharmacotherapy, University of Würzburg, Würzburg, Bavaria, Germany; 1852–1927),<sup>3</sup> we merely note that although he repeatedly cites the Moreno y Maíz article in his classic study published in 1880 (pages 39, 40, and 43),<sup>4</sup> the novelty of his contribution was that he experimented in human beings (*ibid.*, page 47), highlighting the anesthetic effect at the end of his 17 conclusions (page 73).

With further regard to von Anrep and in reply to Dr. Dagnino, we wish to thank the authors for this information,<sup>5</sup> of which we were unaware, and regret only that we have been subsequently unable to access the original publication. In any event, we point out that only 21/2 months elapsed between September 15, 1884,<sup>5</sup> when ophthalmologist Carl Koller (1857–1944) announced his discovery at the Heidelberg Congress (September 15–16, 1884; Heidelberg, Baden-

Württemberg, Germany), and December 6 of that year, when Richard John Hall (18??–1897) and Dr. William Stewart Halsted (1852–1922) reported blocking a nerve trunk<sup>6</sup>; moreover, because it was not until they read Dr. Henry D. Noyes' article<sup>7</sup> released on October 11 that they knew of Koller's work, the actual interim was no more than 11/2 months. Consequently, von Anrep's contribution in this regard is particularly relevant.

We agree, with respect to Koller, that his discovery may have been serendipitous, but as we noted in our article, he did go to the trouble of running experimental tests to verify his finding before reporting it to the Heidelberg Congress.<sup>2</sup>

**Jesús Calatayud, M.D., D.D.S., Ph.D.,\* Ángel González, M.D., D.D.S., Ph.D.** \*Universidad Complutense de Madrid, Madrid, Spain. calata@odon.ucm.es

## References

1. Moréno y Maíz T: Recherches chimiques et physiologiques sur l'érythroxylym coca du Perou et la cocaïne. Paris, Louis Leclerc Libraire-Editeur, 1868
2. Calatayud J, González A: History of the development and evolution of local anesthesia since the coca leaf. ANESTHESIOLOGY 2003; 98:1503–8
3. Yentis SM, and Vlassakov KV: Vassily von Anrep, forgotten pioneer of regional anesthesia. ANESTHESIOLOGY 1999; 90:890–5
4. von Anrep B: Ueber die physiologische Wirkung des Cocain. E Pfluger Arch Ges Physiol 1880; 21:38–77
5. Liljestrand G: Carl Koller and the development of local anesthesia. Acta Physiol Scand Suppl 1967; 299:3–30
6. Hall RJ: Hydrochlorate of cocaine. N Y Med J 1884; 40:643–4
7. Noyes HD: The ophthalmological congress in Heidelberg. Med Rec 1884; 26:417–8

(Accepted for publication January 6, 2004.)

Anesthesiology 2004; 100:1323–4

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams &amp; Wilkins, Inc.

## Cervical Transforaminal Blocks Should Not Be Attempted by Anyone without Extensive Documented Experience in Fluoroscopically Guided Injections

*To the Editor:*—We congratulate Dr. McMillan and Ms. Crumpton for their honest account of a serious complication that occurred in the course of a transforaminal cervical epidural injection (TFCEI).<sup>1</sup> However, we would like to point out some issues that, to the best of our knowledge, give rise to erroneous conclusions. The report describes a persistent neurologic injury (partial right homonymous hemianopsia) presumably caused by a combination of previous vertebral artery air embolism and subsequent radiocontrast cerebral toxicity. Although in their introduction the authors emphasized that TFCEI is technically demanding, they did not support this contention with needed information. They do not provide either enough information to ascertain how they actually performed the block or images of final needle placement. TFCEI has been associated with spinal cord infarction but the exact mechanisms for such catastrophic complication to occur are not known.<sup>2,3</sup> The cases published in the literature share that symptoms arose just after injecting the steroid solution, when contrast medium had been injected uneventfully. Apparently, the spinal cord blood supply was jeopardized because the particulate corticosteroid was inadvertently injected into one radicular feeder artery with resultant occlusion. As the authors themselves stated, it is difficult to detect intravascular injection during performance of lumbar transforaminal blocks. In fact, there is an overall higher incidence of intravascular injections with TFCEI as compared with lumbar ones. In a prospective observational study including 504 TFCEIs, the overall rate of fluoroscopically confirmed intravascular contrast injections was 19.4%. Fur-

thermore, the observed blood in the needle hub after aspiration was specific but lacked sensitivity, only 45.9%, and therefore is unreliable.<sup>4</sup> Accordingly, great care should be taken when performing those blocks, and close attention should be paid for any evidence of intra-arterial injection. Indeed, an almost certain disastrous outcome was recently avoided after noticing that the initial injection of contrast medium filled a radicular artery that passed to the spinal cord.<sup>5</sup> Therefore, a real-time fluoroscopy during contrast injection is mandatory for every TFCEI, and digital subtraction enhancement is recommended in case of misgiving about the resulting image. To strengthen safety, the International Spinal Injection Society (San Francisco, California) has developed guidelines to assist clinicians performing TFCEI and makes it clear that if an arterial puncture is suspected, the injection must be abandoned because any material subsequently injected could gain access to that vessel. Nevertheless, even though the authors aspirated "red blood near the opening of the foramen," suggesting "left vertebral artery puncture," they "retracted and repositioned" the needle afterward. Moreover, because the "epidurogram was judged to be technically unsatisfactory," they even tried to cannulate a new target, the C4–C5 foramen. Altogether, it seems to us that the authors were unable to accomplish a smooth and precise needle placement and should not have undertaken this intervention. In the final discussion, based on their technical misadventure, they questioned whether there would be any need to use radiocontrast in TFCEI. As previously stated, we consider its use of utmost importance and, in view of the potential

Anesthesiology, V 100, No 5, May 2004

complications associated with TFCEI, think that only skilled practitioners with extensive experience should perform these blocks.

**Jose L. De Córdoba, M.D.,\* José Bernal, M.D.** \* Hospital Mútua de Terrassa, Barcelona, Spain. 20807jdb@comb.es

## References

1. McMillan MR, Crumpton C: Cortical blindness and neurologic injury complicating cervical transforaminal injection for cervical radiculopathy. *ANESTHESIOLOGY* 2003; 99:509-11

*Anesthesiology* 2004; 100:1324

*In Reply:*—We appreciate the effort of Drs. De Córdoba and Bernal to reaffirm that transforaminal cervical epidural injections should be performed only by skilled spinal injectionists with documented training and experience in advanced fluoroscopic techniques. We agree. These authors suggest that the description of the technical details of the transforaminal cervical injection procedure are insufficient. We maintain that the information presented is not intended to serve as a tutorial on the procedure under discussion, but is meant to provide a knowledgeable reader with adequate technical details to visualize what was done.<sup>1</sup> Second, when blood was initially aspirated at C5-C6, no further injections were performed until the needle was repositioned in the foramen and aspiration was negative. Only then was 1 ml air, followed by 2 ml appropriate radiocontrast, injected. The use of air to identify the epidural space is well established in anesthetic practice, and no admonitions against its use in transforaminal cervical or lumbar procedures have been published previously. Radiocontrast was subsequently injected, with the resultant appearance of the epidurogram judged to be unacceptable based on previous experience, and the procedure was aborted at that level. We believe that anatomic abnormalities resulting from extensive previous spinal surgery likely contributed to these findings and that a second attempt to enter the epidural space at another level was justified. Foraminal entry at C4-C5 was accomplished smoothly and precisely without technical difficulty. The procedure was aborted at this level because the patient became restless, agitated, and uncooperative, making safe performance of injection impossible, presumably related to the developing neurologic injury that forms the basis for this report.

Our report emphasizes the previously unreported risk of cortical blindness associated with cervical transforaminal injections, including the relatively obscure risk of this complication reported in association with radiocontrast agents.<sup>2</sup> The potential for direct neurotoxicity caused by these agents when placed in the vertebral intracranial circulation is obviously relevant to spinal injectionists who use them as a means of avoiding complications resulting from unrecognized intravascular puncture. This additional potential risk of radiocontrast agents has not been widely recognized in the interventional pain management community. In addition, the additional potential risks of cervical transforaminal injections in patients with anatomic alterations resulting from previous cervical spinal surgery have not been previously addressed. We believe that appreciation and discussion of these risks will facilitate greater informed consent by patients and allow recognition, modification, and avoidance of risk factors associated with specific complications. Although “technical misadventure” may be associated with adverse outcomes, it is naive to overlook the fact that complications also result from patient-specific factors as well as the adverse

2. Brouwers PJAM, Kottink EJBL, Simon MAM, Prevo RL: A cervical anterior spinal artery syndrome after diagnostic blockade of the right C6-nerve root. *Pain* 2001; 91:397-9

3. Houten JK, Errico TJ: Paraplegia after lumbosacral nerve root block: Report of three cases. *Spine J* 2002; 2:70-5

4. Furman MB, Giovanniello MT, O'Brien EM: Incidence of intravascular penetration in transforaminal cervical epidural steroid injection. *Spine* 2003; 28:21-5

5. Baker R, Dreyfuss P, Mercer S, Bogduk N: Cervical transforaminal injection into a radicular artery: A possible mechanism for spinal cord injury. *Pain* 2003; 103:211-5

(Accepted for publication January 6, 2004.)

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

effects of therapeutic agents and established techniques, known and unknown. Because we now know that radiocontrast agents themselves are not necessarily benign, it is important to know that cervical transforaminal injections have been safely performed without their use and reported in the literature.<sup>3</sup> Although the imaging findings and clinical course of our patient are not specific for ischemic brain injury, the use of air to identify the periradicular cervical epidural space likely increases the risk of this complication and adds little to the successful performance of cervical transforaminal injections. Given the increased recognition of the significant risks associated with epidural steroid injections, a procedure that does not change the natural history of cervical radiculopathy or any other disorder associated with chronic spinal pain, perhaps the risk:benefit ratio of cervical transforaminal and all therapeutic epidural injections of corticosteroids should be reexamined. In their recent analysis of closed liability claims for chronic pain management, Fitzgibbon *et al.*<sup>4</sup> reported that fully 40% of all chronic pain claims were associated with epidural steroid injection procedures. Newer, minimally invasive procedures, such as coblation nucleoplasty<sup>5</sup> and percutaneous laser disc decompression,<sup>6</sup> may offer greater potential for long-term remission of spinal pain symptoms as well as an enhanced safety profile compared with existing palliative therapies, such as epidural corticosteroid injections.<sup>7</sup>

**Marion R. McMillan, M.D.,\* Cynthia Crumpton, R.N.** \* Foothills Regional Pain Center, Seneca, South Carolina. marionmc@att.net

## References

1. McMillan MR, Crumpton C: Cortical blindness and neurologic injury complicating cervical transforaminal injection for cervical radiculopathy. *ANESTHESIOLOGY* 2003; 99:509-11

2. Lantos G: Cortical blindness due to osmotic disruption of the blood-brain barrier by angiographic contrast material: CT and MRI studies. *Neurology* 1989; 39:567-71

3. Vallee J, Feydy A, Carlier RY, Mutschler C, Mompont D, Vallee C: Chronic cervical radiculopathy: Lateral approach periradicular corticosteroid injection. *Radiology* 2001; 218:886-92

4. Fitzgibbon DR, Posner KL, Domino KB, Caplan RA, Lee LA, Cheney FW: Chronic pain management: American Society of Anesthesiologists closed claims project. *ANESTHESIOLOGY* 2004; 100:98-105

5. Chen YC, Lee SH, Chen D: Intradiscal pressure study of percutaneous disc decompression with nucleoplasty in human cadavers. *Spine* 2003; 28:661-5

6. Hellinger J: Technical aspects of the percutaneous cervical and lumbar laser disc decompression and nucleotomy. *Neurol Res* 1999; 21:99-102

7. Carette S, Leclaire R, Marcoux S, Morin F, Blaise GA, St. Pierre A, Truchon R, Parent F, Levesque J, Bergeron V, Montminy P, Blanchette C: Epidural corticosteroid injections for sciatica due to herniated nucleus pulposus. *N Engl J Med* 1997; 336:1634-40

(Accepted for publication January 6, 2004.)

## A Concerning Direction

*To the Editor:*—The recent article of Perlas *et al.*<sup>1</sup> attests to the capability of ultrasound to image neural structures. These authors elegantly demonstrate, as previously reported, that spatial compounding of ultrasound beams allows excellent definition of nerves<sup>2,3</sup> and tissue planes,<sup>4</sup> both critical to the success of peripheral nerve block procedures. Their landmark study also identifies fundamental limitations of the commonly practiced nerve stimulation techniques.

The authors' own approach, however, is not without risk. Perlas *et al.* propose to advance the needle in a lateral to medial direction above the clavicle to the brachial plexus, a mesial direction first proscribed by Winnie.<sup>5</sup> With this approach, the needle heads toward the spinal cord, lung, and major vessels, thereby risking injury to these vital structures. This small volunteer study is underpowered to address these safety concerns at a statistical level.

Other technical issues in the article also deserve comment. When scanned perpendicular to the long axis with a linear-array transducer, tendons seem more echogenic than nerves.<sup>6</sup> However, the echogenicity of nerves and tendons varies with the angle of the scan head, a phenomenon known as *anisotropy*.<sup>7,8</sup> Tendons, which have few non-specular reflectors, are much more highly anisotropic than nerves.<sup>9</sup> Therefore, whether a tendon is more echogenic than a nerve depends on the angle of the scan head. Although compound imaging reduces these anisotropic effects,<sup>4</sup> the same principles apply.

Another important issue is what constitutes contact of nerve and needle (lack of ability to detect separation). Resolution of ultrasound images is limited, with lateral resolution typically worse than axial resolution. This gives rise to the needle blur pattern, the extent of which also depends on the acoustic background and image quality controls.<sup>10</sup> Even with optimal alignment of the ultrasound beam and needle to identify the needle tip, the "contact" thus depends on the angle of approach and the complexity of the surrounding tissues. To complicate matters further, small structures may be interposed between nerve and needle but unresolvable from background with ultrasound imaging. The study therefore begs the question of single-injection block success rates with sonographic evidence of contact in the absence of nerve-stimulated muscle contraction.

Ultrasound-guided procedures are not without complications. Although compound imaging improves needle tip visibility,<sup>11</sup> even in skilled hands it is difficult to keep the needle tip within the plane of

imaging during an entire procedure. Needle visibility issues are especially important with thin flexible needles, such as the 22-gauge, 2-inch needles used by these investigators, which may bend partially out of the plane of imaging. The lateral to medial approach to brachial plexus blocks above the clavicle invokes potential risks to vital structures in the event of poor needle tip visibility. We are therefore concerned that the approach of Perlas *et al.* may be a step in the wrong direction.

**Andrew T. Gray, M.D., Ph.D., \* Ingeborg Schafhalter-Zoppoth, M.D.** \* University of California, San Francisco, San Francisco General Hospital, San Francisco, California. [graya@anesthesia.ucsf.edu](mailto:graya@anesthesia.ucsf.edu)

## References

1. Perlas A, Chan VWS, Simons M: Brachial plexus examination and localization using ultrasound and electrical stimulation: A volunteer study. *ANESTHESIOLOGY* 2003; 99:429-35
2. Peer S, Kovacs P, Harpf C, Bodner G: High-resolution sonography of lower extremity peripheral nerves: Anatomic correlation and spectrum of disease. *J Ultrasound Med* 2002; 21:315-22
3. Peer S, Bodner G: High Resolution Sonography of the Peripheral Nervous System. Berlin, Springer Verlag, 2003, pp 6-7
4. Lin DC, Nazarian LN, O'Kane PL, McShane JM, Parker L, Merritt CR: Advantages of real-time spatial compound sonography of the musculoskeletal system versus conventional sonography. *AJR Am J Roentgenol* 2002; 179:1629-31
5. Winnie AP: Interscalene brachial plexus block. *Anesth Analg* 1970; 49:455-66
6. Silvestri E, Martinoli C, Derchi LE, Bertolotto M, Chiaramondia M, Rosenberg I: Echotexture of peripheral nerves: correlation between US and histologic findings and criteria to differentiate tendons. *Radiology* 1995; 197:291-6
7. Crass JR, van de Vegte GL, Harkavy LA: Tendon echogenicity: Ex vivo study. *Radiology* 1988; 167:499-501
8. Greher M, Kapral S: Is regional anesthesia simply an exercise in applied sonoanatomy? Aiming at higher frequencies of ultrasonographic imaging. *ANESTHESIOLOGY* 2003; 99:250-1
9. Van Holsbeeck MT, Introcaso JH: *Musculoskeletal Ultrasound*, 2nd edition. Philadelphia, Mosby, 2001, p 17
10. Goldstein A, Yudelev M, Sharma RK, Arterbery E: Design of quality assurance for sonographic prostate brachytherapy needle guides. *J Ultrasound Med* 2002; 21:947-54
11. Cohnen M, Saleh A, Luthen R, Bode J, Modder U: Improvement of sonographic needle visibility in cirrhotic livers during transjugular intrahepatic portosystemic stent-shunt procedures with use of real-time compound imaging. *J Vasc Interv Radiol* 2003; 14:103-6

(Accepted for publication January 7, 2004.)

## Ultrasound Imaging of Brachial Plexus

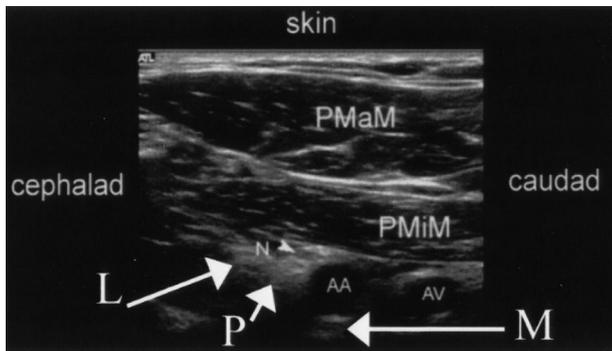
*To the Editor:*—Perlas, Chan, and Simons should be congratulated for their interesting article on imaging of the brachial plexus.<sup>1</sup> However, because they failed to image the infraclavicular plexus in 73% of the small number of cases in their study, they create the false impression that the plexus is very difficult to image in the infraclavicular area.

I have been able to visualize all three cords of the plexus with low-resolution, 2.5-MHz-frequency probes and to inject anesthetic around each nerve cord separately. This may not give publication-quality images, but is good enough for administering a block.<sup>2</sup> Currently, I use a 4- to 7-MHz variable frequency probe, obtaining a good quality image in every patient, and the cords seem to be slightly hyperechoic in most adults. I have administered nearly 3,000 successful blocks with sonography alone, without using a nerve stimulator. The image of the nerve depends on the architecture of the nerve, the frequency of the transducer, the distance of the nerve from the probe,

the angle between the nerve and the ultrasound beam, and the nature of the surrounding tissues.

The cords seem hyperechoic in the infraclavicular area and, being closer to the probe, seem hypoechoic in the axilla and the interscalene area. Perlas *et al.* were possibly looking for hypoechoic cords in the infraclavicular area. What they have labeled in the infraclavicular area is not likely to be a nerve because of its extremely small size; all the cords in the figure seem to be hyperechoic. This can be confirmed by obtaining a longitudinal image of the structure in question. It is not clear why they did not electrically stimulate the cords in the infraclavicular area. I have relabeled their figure 5, which is more like a medially placed sagittal section of the cords. By keeping the arm adducted and pronated, one can rotate the cords (fig. 1).

I disagree with their statement that earlier studies using a frequency less than 10 MHz have not seen nerves. The cords of the plexus can be clearly seen with 4-7 MHz (fig. 2). Ting and Sivagratnam<sup>3</sup> showed



**Fig. 1.** Relabeled figure 5 of Perlas *et al.*<sup>1</sup> AA = axillary artery; AV = axillary vein; L = lateral cord; M = medial cord; N = nerve; P = posterior cord; PMaM = pectoralis major muscle; PMiM = pectoralis minor muscle.

images of different regions of the plexus with lower-resolution probes. Kapral *et al.*<sup>4</sup> and others also obtained images of trunks and nerve branches in the supraclavicular and axillary areas, respectively.

As Greher and Kapral<sup>5</sup> have rightly pointed out in their editorial, simply using a 12-MHz probe may not improve images in all areas. However, their criticism of Perlas *et al.* for keeping the needle under the ultrasound beam at all the times seems unfair. In Kapral's technique, the needle and the ultrasound beam cross each other at only one point, and the needle will be seen as a speck, which may not necessarily be its tip. This, as well as a single injection, might be responsible for the prolonged onset time of 40 min in the study of Kapral *et al.*<sup>4</sup> Keeping the needle under the beam allows visualization of the entire needle, the nerve, and the spread of the local anesthetic. The approach of Perlas *et al.* allows the needle to be seen at all times, adds safety, and allows multiple injections without moving the transducer or completely removing the needle. On the other hand, their use of a large-size probe requires a longer course by the needle through the soft tissues, which is a minor disadvantage as long as one can recognize images of important structures and avoid them, which can be accomplished by simply using a smaller probe.

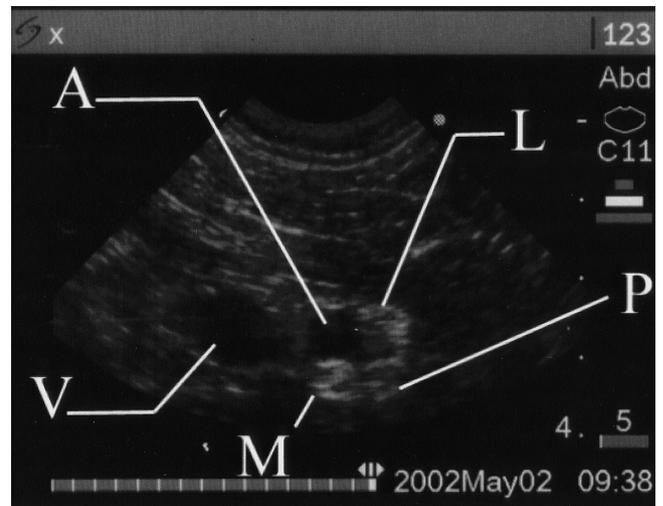
**NavParkash S. Sandhu, M.D.** New York University School of Medicine, New York New York. navparkashsandhu@hotmail.com

Anesthesiology 2004; 100:1326-7

*In Reply:*—We thank Drs. Gray and Schafhalter-Zoppoth for their interest in our article<sup>1</sup> and confirming the usefulness of ultrasound imaging for nerve localization based on their own experience. The value of ultrasound technology is obvious when the technical skill is acquired.

Drs. Gray and Schafhalter-Zoppoth raised concerns about potential danger of the technique we proposed for advancing the needle in the lateral to medial direction in the supraclavicular location. As stated in the text, this approach makes anatomic sense because the plexus is located lateral to the subclavian vessels; thus, needle will reach neural structures before the vessels. Ultrasound-guided nerve localization in this manner is safe, as demonstrated in our recent study.<sup>2</sup>

Ultrasound imaging clearly defines the target nerves we wish to block and vital structures we wish to avoid, *e.g.*, pleura and vessels. We agree with Drs. Gray and Schafhalter-Zoppoth that "ultrasound-guided procedures are not without complications." It is important to emphasize that the safety of ultrasound techniques relies on real-time observation of needle movement at the time of advancement. Without keeping the needle shaft and tip in constant view, needle penetration may be deeper than what is perceived on the monitor. With increased practice and technical experience over the past years, we are now



**Fig. 2.** Image of plexus in infraclavicular area taken with 4- to 7-MHz probe with abdominal mode setting (mid range, approximately 5–6 mHz). A = axillary artery; L = lateral cord; M = medial cord; P = posterior cord; V = axillary vein. The top and right side of the image represent the anterior and cephalad aspects, respectively.

## References

1. Perlas A, Chan VWS, Simons M: Brachial plexus examination and localization using ultrasound and electrical stimulation: A volunteer study. *ANESTHESIOLOGY* 2003; 99:429-35
2. Sandhu NS, Capan LM: Ultrasound guided infraclavicular brachial plexus block. *Br J Anaesth* 2002; 89:256-9
3. Ting RL, Sivagratham V: Ultrasonographic study of spread of local anaesthetic during axillary brachial plexus block. *Br J Anaesth* 1989; 63:326-9
4. Kapral S, Kraft P, Eibenberger K, Fitzgerald R, Gosch M, Weinstabl C: Ultrasonographic guided supraclavicular approach for regional of brachial plexus. *Anesth Analg* 1994; 78:507-13
5. Greher M, Kapral S: Is regional anaesthesia simply an exercise in applied sonoanatomy? *ANESTHESIOLOGY* 2003; 99:250-1

(Accepted for publication January 7, 2004.)

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

confident in maintaining constant and proper needle-probe alignment to optimize needle visibility throughout the procedure. We have learned to make only purposeful needle movement and resist any advancement whenever needle tip visualization is in question. Another practical maneuver that helps to highlight needle tip position is injection of a small saline or air bolus through the needle so that an alert echo signal is generated in the tissue immediately adjacent to the needle tip. In our opinion, taking these cautionary steps during ultrasound-guided nerve localization is clearly a step in the right direction to combine accuracy with safety.

We also appreciate the comments from Dr. Sandhu, who expressed concern about our high failure rate of imaging the brachial plexus with the L12-L5 MHz probe in the infraclavicular region, creating a false impression that the plexus is very difficult to image in this area. This is not true. We have clearly pointed out in the Discussion that one must find the optimal balance between image quality and the depth of penetration when selecting a probe for brachial plexus scanning. Although the high-frequency L12-L5 MHz probe generates brachial plexus images with superb resolution in superficial locations (*e.g.*, interscalene, supraclavicular, axillary, and midhumeral), it has limited tissue penetration capability, precluding its usefulness at the deeper infraclavicular coracoid location.

To scan deep-seated structures, probes of lower frequency (*e.g.*, in the 4- to 7-MHz range) are necessary.

We agree with Dr. Sandhu that the brachial plexus seems hyperechoic in the infraclavicular region, whereas it is hypoechoic in the other four superficial locations examined. With clinical experience, we can now visualize the brachial plexus in the infraclavicular location using a linear 4- to 7-MHz probe and achieve consistent block success. It is important to point out that probe frequency (high *vs.* low) is only one of several important determinants of image clarity on ultrasound. Technological advance such as real time compound imaging with the Philips HDI 5000 unit (ATL Ultrasound, Bethell, WA) also adds to the image quality we observed,<sup>1</sup> significantly superior to that seen in earlier studies.<sup>3,4</sup>

**Anahi Perlas, M.D., F.R.C.P.C., Vincent W. S. Chan, M.D., F.R.C.P.C.\*** \* Toronto Western Hospital, University Health Network, Toronto, Ontario, Canada. vincent.chan@uhn.on.ca

Anesthesiology 2004; 100:1327-8

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

## Anesthetic Preconditioning Versus Anesthetic Treatment: Effects on Ischemic Injury in Isolated Hearts

*To the Editor:*—We read with interest the article recently published by Kevin *et al.*,<sup>1</sup> “Anesthetic preconditioning: Effects on latency to ischemic injury in isolated hearts.” The recent observation that anesthetic preconditioning (APC) by volatile anesthetics may possess therapeutic benefit on postischemic myocardial injury is of intense interest. The study of Kevin *et al.*<sup>1</sup> shows that, in ischemic-reperfused isolated guinea pig hearts, the therapeutic time frame for APC against postischemic contractile dysfunction and infarction is approximately 25–40 min. The protection is maximal when ischemic duration is between 30 and 35 min.<sup>1</sup> The authors suggested that APC may be useful therapy if the typical duration of ischemia during coronary artery bypass falls within this range. By contrast, APC is unlikely to be of benefit in patients who undergo more prolonged ischemia. This study provides a strong message reminding us of the potential clinical limitations to APC.

Mechanistically, studies by the same group have shown that brief exposure of the heart to volatile anesthetics before ischemia may lead to decreased formation of reactive oxygen species (ROS) during ischemia and subsequent reperfusion.<sup>2,3</sup> This would seem to be a promising approach. It is well known that increased ROS formation during ischemia and reperfusion may contribute significantly to myocardial ischemia-reperfusion injury. It should be noted, however, that volatile anesthetic-mediated APC primarily requires the generation of ROS in advance (*i.e.*, before ischemia) as a trigger of myocardial preconditioning.<sup>2,3</sup> Theoretically, the additional generation of ROS in a population with preexisting high degrees of oxidative stress, *e.g.*, chronic heart failure and diabetes, may stimulate increased mitochondrial permeability transition, releasing large amounts of ROS (involving radical-induced radical release).<sup>4</sup> This would overwhelm endogenous antioxidant defenses, resulting in extensive lipid peroxidation and cellular destruction.<sup>4</sup> It is reasonable to postulate that APC is unlikely to be of benefit or even to be detrimental in high-risk patients whose endogenous antioxidant capacity is reduced. Hence, the clinical utility of APC may be further limited, and alternative approaches to APC are required.

We have focused our efforts on the development of a therapeutic regimen using propofol as antioxidant supplementation during global myocardial ischemia-reperfusion injury. We found that propofol, when applied before ischemia, during ischemia, and during the early phase of reperfusion at clinically achievable high doses, can enhance myocardial tissue antioxidant capacity after prolonged (40 min) global ischemia and subsequent reperfusion in the isolated rat heart.<sup>5,6</sup> The enhancement in tissue antioxidant capacity is associated with better postischemic functional recovery. Propofol increased the latency to the onset of ischemic contracture and decreased the magnitude of

## References

1. Perlas A, Chan VWS, Simons M: Brachial plexus examination and localization using ultrasound and electrical stimulation: A volunteer study. *ANESTHESIOLOGY* 2003; 99:429–35
2. Chan VW, Perlas A, Rawson R, Odukoya O: Ultrasound-guided supraclavicular brachial plexus block. *Anesth Analg* 2003; 97:1514–7
3. Ting PL, Sivagnanaratnam V: Ultrasonographic study of the spread of local anaesthetic during axillary brachial plexus block. *Br J Anaesth* 1989; 63:326–9
4. Kapral S, Krafft P, Eibenberger K, Fitzgerald R, Gosch M, Weinstabl C: Ultrasound-guided supraclavicular approach for regional anesthesia of the brachial plexus. *Anesth Analg* 1994; 78:507–13

(Accepted for publication January 3, 2004.)

contracture development during ischemia in a dose-dependent manner.<sup>5</sup> When the ischemia duration is shorter than 25 min, propofol applied in concentrations of 5 or 12  $\mu\text{g/ml}$  attenuates the magnitude of ischemic contracture to a similar degree.<sup>5</sup> However, propofol at 5  $\mu\text{g/ml}$  essentially has no effect in attenuating the magnitude of ischemic contracture, as compared with untreated control, when the ischemic duration reaches 35 min. Significant reduction in the magnitude of ischemic contracture is seen with propofol at 12  $\mu\text{g/ml}$  when the ischemic duration is prolonged to 40 min. Postischemic contracture, represented as the increase in left ventricular end-diastolic pressure (LVEDP), reflects diastolic functional impairment. Propofol at 12  $\mu\text{g/ml}$  completely prevents the increase in LVEDP during 90 min of reperfusion after 40 min of global ischemia in isolated rat hearts.<sup>5</sup> In contrast, a significant increase in LVEDP during reperfusion ( $12 \pm 6$  mmHg at reperfusion 60 min *vs.*  $0 \pm 0$  at baseline) was observed after 40 min of global ischemia in the APC group studied by Kevin *et al.*<sup>1</sup> LVEDP also significantly increased during reperfusion in the APC group when the ischemic interval was between 30 and 35 min, the time frame thought to demonstrate maximal therapeutic potential.<sup>1</sup> We suspect that anesthetic treatment with high-dose propofol could be superior to APC with volatile anesthetics in protecting myocardial ischemic injury, in particular when the duration of aortic cross clamp may be prolonged, when patients with abnormally high levels of oxidant stress present for cardiac surgery, or both. Because the postischemic contracture and subsequent myocardial injury are generally attributable to cytosolic free  $\text{Ca}^{2+}$  overload, the property of propofol in inhibiting myocyte  $\text{Ca}^{2+}$  influx may also contribute to its cardiac protection.

In conclusion, despite laboratory evidence supporting cardiac protection by APC, the traditional administration of volatile anesthetics throughout the course of cardiac surgery has not been associated with a decrease in morbidity or mortality.<sup>7</sup> Large prospective clinical trials comparing volatile anesthetic preconditioning and intravenous “anesthetic treatment” or trials comparing a combination of the two are merited.

**David M. Ansley, M.D.,\* Zhengyuan Xia, M.D.** \* University of British Columbia, Vancouver, British Columbia, Canada. dansley@vanhosp.bc.ca

## References

1. Kevin LG, Katz P, Camara AKS, Novalija E, Riess ML, Stowe DF: Anesthetic preconditioning: Effects on latency to ischemic injury in isolated hearts. *ANESTHESIOLOGY* 2003; 99:385–91
2. Kevin LG, Novalija E, Riess ML, Camara AK, Rhodes SS, Stowe DF: Sevoflu-

rane exposure generates superoxide but leads to decreased superoxide during ischemia and reperfusion in isolated hearts. *Anesth Analg* 2003; 96:949–55

3. Novalija E, Kevin LG, Camara AK, Bosnjak ZJ, Kampine JP, Stowe DF: Reactive oxygen species precede the epsilon isoform of protein kinase C in the anesthetic preconditioning signaling cascade. *ANESTHESIOLOGY* 2003; 99:421–8

4. Zorov DB, Filburn CR, Klotz LO, Zweier JL, Sollott SJ: Reactive oxygen species (ROS)-induced ROS release: A new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. *J Exp Med* 2000; 192:1001–14

5. Xia Z, Godin DV, Chang TK, Ansley DM: Dose-dependent protection of

cardiac function by propofol during ischemia and early reperfusion in rats: Effects on 15-F2t-isoprostane formation. *Can J Physiol Pharmacol* 2003; 81:14–21

6. Xia Z, Godin DV, Ansley DM: Propofol enhances ischemic tolerance of middle-aged rat hearts: Effects on 15-F(2t)-isoprostane formation and tissue antioxidant capacity. *Cardiovasc Res* 2003; 59:113–21

7. Slogoff S, Keats AS: Randomized trial of primary anesthetic agents on outcome of coronary artery bypass operations. *ANESTHESIOLOGY* 1989; 70:179–88

(Accepted for publication January 7, 2004.)

*Anesthesiology* 2004; 100:1328

**In Reply:**—We thank Drs. Ansley and Xia for their interest in our recent article<sup>1</sup> and for reviewing their results regarding cardioprotective effects of propofol.<sup>2,3</sup> They proffered that volatile anesthetic-induced reactive oxygen species (ROS) formation (required for the triggering of anesthetic preconditioning [APC]) might be deleterious in patients with a preexisting high degree of oxidative stress and, furthermore, that APC is unlikely to be of benefit in high-risk patients whose antioxidant capacity is reduced.

Our isolated heart experiments do not support such a postulate. First, the amount of ROS generated in the heart during exposure to a volatile anesthetic is miniscule compared with that generated during ischemia-reperfusion.<sup>4</sup> This seems to make sense because we know that patients, even high-risk patients, can receive volatile anesthetic agents for many hours without evidence of myocardial injury, and these agents have a record of safety stretching back 50 yr. This would probably not be the case if ROS generation in response to volatile anesthetics were inherently deleterious. Second, APC, although triggered by a small pulse of ROS during exposure to the volatile anesthetic, is characterized by a great reduction in the amount of ROS subsequently released during ischemia-reperfusion.<sup>4,5</sup> Therefore, actual exposure of the heart to ROS is greatly reduced after APC, and patients with reduced antioxidant defenses might be precisely those who stand to benefit most from APC.

Ansley and Xia comment that inhibition of myocyte Ca<sup>2+</sup> influx may contribute to the cardioprotective effect of propofol. This may be true, but a similar effect has been described for volatile anesthetic agents.<sup>6</sup> Furthermore, we have recently reported attenuated ischemic and post-ischemic mitochondrial Ca<sup>2+</sup> loading in hearts previously treated with sevoflurane.<sup>7</sup> Given the known deleterious effects of mitochondrial Ca<sup>2+</sup> overload and the key role played by the mitochondrion in post-ischemic cellular integrity and function, this effect is likely to underlie, at least in part, the cardioprotective effect of APC.

Regarding prospective clinical trials comparing volatile anesthetic agents and propofol, two interesting studies were recently published in *ANESTHESIOLOGY*.<sup>8,9</sup> In the first of these,<sup>8</sup> 45 high-risk coronary surgery patients were randomly assigned to a primary anesthetic of propofol, sevoflurane, or desflurane. After cardiopulmonary bypass, cardiac index was found to be significantly higher in the sevoflurane and desflurane groups compared with the propofol group, and postoperative troponin I concentrations were lower, indicating less severe myocardial injury. In the second study,<sup>9</sup> 20 patients undergoing off-pump coronary artery bypass surgery were randomized to receive propofol or sevoflurane as their primary anesthetic. In the sevoflurane group, postoperative troponin I concentrations were found to be significantly lower compared with the propofol group. Although these trials do not provide conclusive evidence of a preconditioning effect of volatile anesthetics, they do provide an enticing basis for further study. Other “direct” protective effects of the volatile anesthetics or a possible deleterious effect of propofol could have been responsible for the observed outcome differences. Although propofol is thought to have antioxidant effects, it should also be noted that many animal studies do not support a role for propofol as a preconditioning agent.<sup>10–14</sup>

Much work remains to be done in elucidating mechanisms and

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

characteristics of cardioprotective effects of both types of anesthetics. The direct antioxidant effects of propofol may prove to be most advantageous during the reperfusion phase, when ROS generation by the heart is great and unquestionably injurious. The preconditioning effect of volatile agents suggests that their protective effect is maximal when administered before ischemia. The future challenge for investigators is to find an optimal regimen for patients that fully exploits the cardioprotective effects identified in the laboratory.

**Leo G. Kevin, F.C.A.R.C.S.I., Peter Katz, B.Sc., Amadou K. S. Camara, Ph.D., Enis Novalija, M.D., Matthias L. Riess, M.D., David F. Stowe, M.D., Ph.D.\*** \*The Medical College of Wisconsin, Milwaukee, Wisconsin. [dfstowe@mcw.edu](mailto:dfstowe@mcw.edu)

## References

- Kevin LG, Katz P, Camara AKS, Novalija E, Riess ML, Stowe DF: Anesthetic preconditioning: Effects on latency to ischemic injury in isolated hearts. *ANESTHESIOLOGY* 2003; 99:385–91
- Zorov DB, Filburn CR, Klotz LO, Zweier JL, Sollott SJ: Reactive oxygen species (ROS)-induced ROS release: A new phenomenon accompanying induction of the mitochondrial permeability transition in cardiac myocytes. *J Exp Med* 2000; 192:1001–14
- Xia Z, Godin DV, Ansley DM: Propofol enhances ischemic tolerance of middle-aged rat hearts: Effects on 15-F(2t)-isoprostane formation and tissue antioxidant capacity. *Cardiovasc Res* 2003; 59:113–21
- Kevin LG, Novalija E, Riess ML, Camara AK, Rhodes SS, Stowe DF: Sevoflurane exposure generates superoxide but leads to decreased superoxide during ischemia and reperfusion in isolated hearts. *Anesth Analg* 2003; 96:949–55
- Novalija E, Varadarajan SG, Camara AK, An J, Chen Q, Riess ML, Hogg N, Stowe DF: Anesthetic preconditioning: Triggering role of reactive oxygen and nitrogen species in isolated hearts. *Am J Physiol Heart Circ Physiol* 2002; 283: H44–52
- An J, Varadarajan SG, Novalija E, Stowe DF: Ischemic and anesthetic preconditioning reduces cytosolic [Ca<sup>2+</sup>] and improves Ca<sup>2+</sup> responses in intact hearts. *Am J Physiol Heart Circ Physiol* 2001; 281:H1508–23
- Riess ML, Camara AK, Novalija E, Chen Q, Rhodes SS, Stowe DF: Anesthetic preconditioning attenuates mitochondrial Ca<sup>2+</sup> overload during ischemia in guinea pig intact hearts: Reversal by 5-hydroxydecanoic acid. *Anesth Analg* 2002; 95:1540–6
- De Hert SG, Cromheecke S, ten Broecke PW, Mertens E, De Blier IG, Stockman BA, Rodrigus IE, Van der Linden PJ: Effects of propofol, desflurane, and sevoflurane on recovery of myocardial function after coronary surgery in elderly high-risk patients. *ANESTHESIOLOGY* 2003; 99:314–23
- Conzen PF, Fischer S, Detter C, Peter K: Sevoflurane provides greater protection of the myocardium than propofol in patients undergoing off-pump coronary artery bypass surgery. *ANESTHESIOLOGY* 2003; 99:826–33
- Ebel D, Schlack W, Comfere T, Preckel B, Thamer V: Effect of propofol on reperfusion injury after regional ischaemia in the isolated rat heart. *Br J Anaesth* 1999; 83:903–8
- Zaugg M, Lucchinetti E, Spahn DR, Pasch T, Garcia C, Schaub MC: Differential effects of anesthetics on mitochondrial K<sub>ATP</sub> channel activity and cardiomyocyte protection. *ANESTHESIOLOGY* 2002; 97:15–23
- Kohro S, Hogan QH, Nakae Y, Yamakage M, Bosnjak ZJ: Anesthetic effects on mitochondrial ATP-sensitive K channel. *ANESTHESIOLOGY* 2001; 95:1435–340
- Cope DK, Impastato WK, Cohen MV, Downey JM: Volatile anesthetics protect the ischemic rabbit myocardium from infarction. *ANESTHESIOLOGY* 1997; 86:699–709
- Kato R, Foex P: Myocardial protection by anesthetic agents against ischemia-reperfusion injury: An update for anesthesiologists. *Can J Anaesth* 2002; 49:777–91

(Accepted for publication January 7, 2004.)

## Near-miss Accident during Magnetic Resonance Imaging by a “Flying Sevoflurane Vaporizer” due to Ferromagnetism Undetectable by Handheld Magnet

*To the Editor:*—Since the first report of anesthesia for magnetic resonance imaging (MRI) in 1984,<sup>1</sup> anesthesiologists increasingly cover MRI procedures, mostly in children and infants. We report a near-miss accident during MRI in a child due to a sevoflurane vaporizer brought into the MRI suite.

A 2-yr-old boy with retroperitoneal rhabdomyosarcoma was scheduled to undergo abdominal MRI. Anesthesia was provided by an anesthesiologist/nurse team with experience in anesthesia for MRI. After a check for removal of all ferromagnetic materials and of the MRI compatible ventilator (Titus MRI; Dräger, Lübeck, Germany), anesthesia was induced and maintained *via* a closely fitting facemask in the spontaneously breathing child using sevoflurane-nitrous oxide in 50% oxygen, and vital signs were monitored using MRI-safe equipment (graphite electrocardiogram leads, fiberoptic pulse oximetry, end-expiratory carbon dioxide, noninvasive blood pressure).

When a low level of sevoflurane was noted in the vaporizer (model 19.3; Dräger), the nurse was asked to refill it. However, because a refill bottle of sevoflurane was not immediately found, the nurse instead carried a portable sevoflurane vaporizer from the induction room into the MRI suite. Neither she nor the anesthesiologist considered that the almost empty sevoflurane vaporizer in the MRI suite was unremovably fixed to the ventilator and hence could not be replaced at all.

When the nurse put the vaporizer on the examination table (approximately 150 cm from the bore of the magnet, just beyond the 40-mT line), it was rapidly attracted toward the 1.5-T magnet. It was only by the force of four hands that the vaporizer could be directed to strike against the gantry instead of flying directly into the magnet, where it might have hit the child. However, a strong attraction toward the bore of the magnet was still felt, and the vaporizer could hardly be maintained at the side of the gantry.

The table with the sleeping child was rapidly moved out of the gantry, avoiding further danger. “Quenching,” *i.e.*, emergency release of liquid helium from the superconducting magnet coils with collapse of the magnetic field, was initially considered, but the vaporizer could be removed from the gantry with the help of a third person. Fortunately, neither the child nor the MRI machine were harmed, and the examination went on without further complications after excluding MRI damage and refilling the fixed vaporizer.

Furthermore, immediately after the accident the portable vaporizer was tested for magnetism with a handheld horseshoe magnet (RS Electronic, Mörfelden-Waldorf, Germany; length, 8 cm; width, 1 cm). However, no attraction was seen.

This is the first report, to our knowledge, of a near-miss accident in an MRI involving a portable vaporizer considered MRI-safe when fixed to a rack. Furthermore, the hazard was undetectable by using a powerful handheld magnet.

Contact with the manufacturer (Dräger Medical) revealed that this vaporizer contains ferromagnetic material in the temperature compensation module. An exchange of this material by nonmagnetic materials is impossible. The user manual of this vaporizer also contains a warning to change vaporizers only outside an MRI suite and to not put the vaporizer down in the MRI suite because it contains ferromagnetic

parts and can be attracted by the MRI magnet. It also states that its use is safe for magnetic fields up to 70 mT, when the vaporizer is fixed to an MRI-safe ventilator.

Mainly, this near-miss accident was evoked by human error and communication lapse, which is by far the most important hazard in the MRI suite. First, neither the anesthesiologist nor the nurse was aware of the unremovable fixation of the vaporizer to the ventilator rack. In fact, this was specifically done to avoid an accident evoked by changing a vaporizer inside the MRI suite. Second, both were unaware of the warning in the user manual of this vaporizer regarding its use in the MRI suite.

The greatest hazard results from “projectile” or “missile” effects of ferromagnetic materials brought into the magnetic field. Of five reported accidents, two happened while inexperienced personal brought metal oxygen cylinders into an MRI suite, resulting in a serious facial fracture in one patient.<sup>2</sup> In the other three cases, anesthesia or radiology personnel confused aluminum oxygen cylinders (MRI compatible) with metal oxygen cylinders, causing remarkable damage to the MRI machine.<sup>2</sup>

Inattentiveness to hazards even caused by MRI-compatible anesthetic equipment has been also reported,<sup>3</sup> as evidenced by an “MRI-compatible” anesthetic monitor (weight, 25 kg) rapidly attracted into the opening of the magnet when crossing the 40-mT line. The (small print) recommendations of the user manual had not been read before use.

Even MRI-compatible machines may contain ferromagnetic materials and bear risks when violating safety rules. Of note, even a test with a small handheld magnet likely would not have prevented the accident because of the heavy weight of the vaporizer and its small, hidden ferromagnetic parts. In another case, a pillow containing metal springs not detectable by a handheld magnet flew into the magnet during positioning of a patient, fortunately without causing injury.<sup>4</sup>

Different concepts may increase patient safety during MRI, including completing an MRI safety form in a four-step process from ward to patient transport, MRI coordinator, and technologists. Furthermore, personnel with MRI access can be educated with safety videos demonstrating dangers. In addition, all equipment allowed in the MRI can be marked with fluorescent stickers as “MRI safe.”<sup>5</sup>

Our case altered departmental safety rules for MRI procedures. First, it was reinforced that only educated and instructed personnel are allowed to provide anesthesia for MRI, and additional safety courses are offered monthly by the radiology department. Second, all anesthesia nurses now work in the MRI suite for rotations of at least 3 months.

In summary, the attracted “flying vaporizer” highlights the dangers of weak ferromagnetic objects, undetectable by routine testing, when brought into the magnetic field as well as the dangers of deviating from the established protocol. The death of a child caused by a missile oxygen cylinder<sup>6</sup> has focused both public and professional attention on MRI safety. In an American Society of Anesthesiologists newsletter after that accident, the authors’ message is that because “we have known for decades about MRI magnets being able to violently suck in heavy metal objects, this accident tells us about a challenge that goes beyond requiring physicians to understand basic MRI safety principles. That challenge is to inculcate everyone with safety habits and protocols that are always followed, with no exceptions.”<sup>7</sup> Human error can only be minimized by consequent and repetitive teaching of all personnel with MRI access.

Support was provided solely from institutional and/or departmental sources.

After numerous unsuccessful attempts to acquire a Reply to this Letter, it is being published without a response. —Michael M. Todd, Editor-in-Chief.

**Christian Zimmer, M.D.,\* Markus Norbert Janssen, M.D., Tanja Astrid Treschan, M.D., Jürgen Peters M.D.** \* Klinik für Anästhesiologie und Intensivmedizin, Universitätsklinikum Essen, Essen, Germany. christian.zimmer@uni-essen.de

## References

1. Geiger RS, Cascorbi HF: Anesthesia in an NMR scanner. *Anesth Analg* 1984; 63:622-3
2. Chaljub G, Kramer LA, Johnson RF, Johnson RF Jr, Singh H, Crow, WN:

*Anesthesiology* 2004; 100:1330

## Safety of Indocyanine Green as a Vital Stain

*To the Editor:*—Indocyanine green (ICG) has been identified as a potential alternative to epinephrine as a means of detecting inadvertent intravascular injection of local anesthetic during epidural anesthesia. Dietz and Jaffe<sup>1</sup> have shown apparent neurotoxicity with this agent and cautioned against its use. They noted that neurotoxicity had not been reported previously. However, there are a series of reports of possible retinal neurotoxicity that may support the authors' claim. ICG is commonly used as an intraoperative vital stain to identify and remove the internal limiting membrane during macular surgery.<sup>2</sup> Concerns have been expressed regarding its safety.<sup>3</sup> Some experimental reports have shown ICG mediated neororetinal<sup>4</sup> and retinal pigment epithelial cell damage.<sup>5</sup> There are also clinical studies showing functional visual loss after ICG-assisted macular surgery.<sup>6</sup> ICG is usually mixed in distilled water and then saline, resulting in a hypotonic solution. Some reports suggest that it is the combined exposure to low osmolarity and ICG that produces cell damage.<sup>7</sup> Authors have suggested alternative means of preparing ICG, and other agents, such as infracyanine green and trypan blue, have been advocated.<sup>8</sup> Other vital stains, such as sodium fluorescein, are widely available and well tested. Many of these and other related articles may be of interest to readers concerned about the safety of ICG.

Dr. Jackson has received funding from the Allerton Trust, London, United Kingdom, and The Special Trustees of Guys and St. Thomas' Hospital, London, United Kingdom, within 3 yr of preparing this letter.

*Anesthesiology* 2004; 100:1330-1

## Unanticipated Vomiting and Pulmonary Aspiration at Anesthesia Induction in a Formula-fed 4-Month-old Infant

*To the Editor:*—Anesthesiologists have been focusing their attention on preanesthetic fasting time to prevent pulmonary aspiration. To establish a standard for preanesthetic fasting time, large surveys have been conducted in the United Kingdom and Ireland<sup>1</sup> and the United States.<sup>2</sup> By these efforts, a consensus was reached and was presented in the form of practice guidelines.<sup>3</sup> However, some disagreement about fasting time for formula-fed infants remains, and the topic is still controversial. We experienced unanticipated vomiting and pulmonary aspiration at the time of anesthesia induction in a formula-fed infant with 4 h of preanesthetic fasting.

A female patient was born at full term; cheiloschisis was diagnosed without any other anomaly. An elective cheiloplasty was planned at

Projectile cylinder accidents resulting from the presence of ferromagnetic nitrous oxide or oxygen tanks in the MR suite. *Am J Roentgenol* 2001; 177:27-30

3. McBrien ME, Winder RJ: Magnetic resonance compatible equipment: Read the small print. *Anaesthesia* 2003; 58:86-7
4. Condon B, Hadley DM, Hodgson R: The ferromagnetic pillow: A potential MR hazard not detectable by hand-held magnet. *Br J Radiol* 2001; 74:847-51
5. Kerr JD: MRI safety: Everyone's job. *Radiol Manage* 2001; 23:36-9
6. Chen DW: Boy, 6, dies of skull injury during M. R. I. *The New York Times*. July 31, 2001; sect B:1, 5
7. Litt L, Cauldwell CB: Being extra safe when providing anesthesia for MRI examinations. *ASA Newsletter* 2002; 66:17-8

(Accepted for publication December 8, 2003.)

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

**Timothy L. Jackson, F.R.C.Ophth., Ph.D.** The Rayne Institute, St. Thomas' Hospital, London, United Kingdom. TimLJackson@hotmail.com

## References

1. Dietz FB, Jaffe RA: Indocyanine green: Evidence of neurotoxicity in spinal root axons. *ANESTHESIOLOGY* 2003; 98:516-20
2. Burk SE, Da-Mata AP, Snyder ME, Rosa R-HJ, Foster RE: Indocyanine green-assisted peeling of the retinal internal limiting membrane. *Ophthalmology* 2000; 107:2010-4
3. Kampik A, Sternberg P: Indocyanine green in vitreomacular surgery (why is it a problem?) *Am J Ophthalmol* 2003; 136:527-9
4. Gandorfer A, Haritoglou C, Gandorfer A, Kampik A: Retinal damage from indocyanine green in experimental macular surgery. *Invest Ophthalmol Vis Sci* 2003; 44:316-23
5. Sippy BD, Engelbrecht NE, Hubbard GB, Moriarty SE, Jiang S, Aaberg TM Jr, Aaberg Sr TM, Grossniklaus HE, Sternberg P Jr: Indocyanine green effect on cultured human epithelial cells: Implications for macular hole surgery. *Am J Ophthalmol* 2001; 132:433-5
6. Haritoglou C, Gandorfer A, Gass CA, Schaumberger M, Ulbig MW, Kampik A: The effect of indocyanine-green on functional outcome of macular pucker surgery. *Am J Ophthalmol* 2003; 135:328-37
7. Stalmans P, Van Aken EH, Veckeneer M, Feron EJ, Stalmans I: Toxic effect of indocyanine green on retinal pigment epithelium related to osmotic effects of the solvent. *Am J Ophthalmol* 2002; 134:282-5
8. Stalmans P, Feron EJ, Parys-Van Ginderdeuren R, Van Lommel A, Melles GR, Veckeneer M: Double vital staining using trypan blue and infracyanine green in macular pucker surgery. *Br J Ophthalmol* 2003; 87:713-6

(Accepted for publication November 24, 2003.)

© 2004 American Society of Anesthesiologists, Inc. Lippincott Williams & Wilkins, Inc.

4 months of age. The patient's body weight and height were 6,260 g and 60 cm, respectively.

Infant formula was allowed up to 4 h before anesthesia, and clear liquids were permitted up to 2 h before. However, the patient actually drank 160 ml formula 5.5 h before anesthesia and an additional 100 ml 4.5 h before anesthesia. This formula was a product of cow milk that contained 9.7 g whey protein, 6.4 g casein protein, 34 g fat, and 76 g carbohydrates per liter. No premedication was administered.

Anesthesia was induced by inhalation of sevoflurane and nitrous oxide with 33% oxygen. During the induction, the anesthesiologist in charge tried to maintain the patient's spontaneous respiration. However, abruptly, mask ventilation could not be performed, and then arterial oxygen saturation decreased to 28%. Immediately, the anesthesiologist checked the patient's mouth and found infant formula in it. It was excluded with suction of the oral cavity, and tracheal intubation was performed. Arterial oxygen saturation recovered to 100%. A coarse

Support was provided solely from institutional and/or departmental sources.

*Anesthesiology*, V 100, No 5, May 2004

crackle on chest auscultation and a shadow on the chest radiograph suggested atelectasis at the right upper lung field. Transendotracheal suction and physiotherapy for 1 h improved the atelectasis; finally, the patient was extubated.

The recommended preoperative fasting time for formula-fed infants varies from 4 to 8 h. The American Society of Anesthesiologists (ASA) recommends 6 h for formula-fed infants in their guidelines.<sup>3</sup> However, the ASA recommends 4 h for formula-fed infants younger than 6 months in their ASA refresher course lecture.<sup>4</sup> Therefore, disagreement is present in this matter. Our institution adopted the latter fasting time.

Some reports have suggested that the half-life of formula is 1 h;<sup>5-7</sup> therefore, the gastric residue of formula for a 4-h fasting time and that for 6 h are expected to be 6 and 1.5%, respectively. Furthermore, it has been reported that 9% of formula-fed infants who fasted for 4 h had undigested traces of formula in their gastric content.<sup>8</sup>

In our case, the patient vomited undigested formula and aspirated it under the condition of a 4.5-h fasting time. We think that our case should be considered an extreme case, but the importance is that the risk of vomiting still remained following the ASA refresher course's recommendation. Therefore, more studies and discussions are needed for a consensus on fasting time for infant formula.

**Tetsuya Kawabata, M.D.,\* Joho Tokumine, M.D., Ph.D., Seiya Nakamura, M.D., Ph.D., Kazuhiro Sugahara, M.D., Ph.D.**

\* University of the Ryukyus, Okinawa, Japan. higeekawa@ybb.ne.jp

## References

1. Emerson BM, Wrigley R, Newton M: Pre-operative fasting for paediatric anaesthesia: A survey of current practice. *Anaesthesia* 1998; 53:326-30
2. Ferrari LR, Rooney FM, Rockoff MA: Preoperative fasting practices in pediatrics. *ANESTHESIOLOGY* 1999; 90:978-80
3. Practice guidelines for preoperative fasting and the use of pharmacologic agents to reduce the risk of pulmonary aspiration: application to healthy patients undergoing elective procedures: A report by the American Society of Anesthesiologist Task Force on Preoperative Fasting. *ANESTHESIOLOGY* 1999; 90:896-905
4. Coté CJ: Preparation, premedication and induction of anesthesia, 54th Annual Refresher Course Lectures, Clinical Updates and Basic Science Reviews 2003. Park Ridge, Illinois, American Society of Anesthesiologists, 2003, p 164
5. Cavell B: Gastric emptying in preterm infants. *Acta Paediatr Scand* 1979; 68:725-30
6. Cavell B: Gastric emptying in infants fed human milk or infant formula. *Acta Paediatr Scand* 1981; 70:639-41
7. Van Den Driessche M, Peeters K, Marien P, Ghooys Y, Devlieger H, Veerman-Wauters G: Gastric emptying in formula-fed and breast-fed infants measured with the <sup>13</sup>C-octanoic acid breath test. *J Pediatr Gastroenterol Nutr* 1999; 29:46-51
8. Cook-Sather SD, Harris KA, Chiavacci R, Gallagher PR, Schreiner MS: A liberalized fasting guideline for formula-fed infants does not increase average gastric fluid volume before elective surgery. *Anesth Analg* 2003; 96: 965-9

(Accepted for publication January 12, 2004.)