■ CORRESPONDENCE

Ultrasound-guided Caudal Epidural Injection

To the Editor:—I read with interest the article "Ultrasound Guidance in Caudal Epidural Needle Placement" by Chen *et al.*[1] However, I have a couple of points to raise. The author's assertion that the application of ultrasonography to locate the sacral hiatus for caudal epidural injections has not been described is inaccurate.[2] The footprint property of the transducer is not mentioned in the article. The linear array transducer cannot be used in all patients. In obese patients, it is sometimes necessary to use a curvilinear array transducer with lower frequency ranges to achieve a sonographic image of reasonable quality. Similarly, in very thin individuals, a transducer with a smaller footprint is more appropriate.

I agree with the authors regarding the advantage of using ultrasonography for caudal epidural needle placement. The article mentions the fact that ultrasound cannot provide us with the image information as to the depth of the inserted needle as the only disadvantage. It makes no mention of the most important limitation of this method, *i.e.*, inadvertent intravascular injection. Inadvertent intravascular injection, which has been reported to occur in 5–9% of these procedures,[3] cannot be avoided with this technique. This is important because aspiration or return of blood is neither sensitive nor specific for intravascular positioning of the needle.[4] Toxic concentration of local anesthetic may occur on inadvertent injection into an epidural vein.

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Disadvantages of Ultrasound Guidance in Caudal Epidural Needle Placement

To the Editor:—I read with interest the article recently published by Chen *et al.*,[1] "Ultrasound Guidance in Caudal Epidural Needle Placement." The authors demonstrated that ultrasound can be used as an alternative tool to guide needle placement. The advantage of ultrasound is radiation free. The disadvantage is that ultrasound cannot monitor the depth of the inserted needle, as the authors indicated.[1] However, other disadvantages of ultrasound guiding caudal epidural needle placement should be discussed.

Complications of caudal epidural injection include intravascular placement or dural puncture. Aspirating the needle to check for blood or cerebrospinal fluid is helpful if positive, but the incidence of false-negative aspiration is too high to rely on this technique alone.[2] Fluoroscopic guidance and radiographic contrast administration can confirm needle position and rule out intravascular or subarachnoid placement immediately. The complication rate is significantly low when contrast is also used to verify the epidural needle placement. Johnson *et al.*[3] reported only 4 minor complications in 5,334 cases when epidural steroid injection was done using fluoroscopy and contrast at various spinal level.

Placement of epidural steroid injection close to the level of pathology can optimize patient response to treatment.[4,5] Fluoroscopic guidance and contrast administration are essential to assess spread of epidural injectate into the desired target level during caudal epidural steroid injection.

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In Reply:—We thank Dr. Edward for his comments. In this study,[1] we used the Philips S12 5–12 MHz real-time linear-array ultrasound transducer (Philips Medical Systems, Andover, MA). The contact surface area of the transducer head is 4.73 cm².

We tried both the linear-array and the curvilinear-array transducers. We found that the linear-array transducer was sufficient to depict the sacral cornua and the base of sacrum even in obese patients. The above-mentioned transducer is capable of penetrating to a depth of 8–10 cm. In patients weighing more than 100 kg, the distance from the skin to the base of the sacrum is far less than 8 cm. During the entire injection process, we adjusted the patient's posture (such as flexing the hip more) to obtain the most suitable position for placement of the

ultrasound probe and injection. The best sonogram can be obtained when full contact is made between the transducer head and the examined area. We found the curvilinear-array transducer inconvenient because full contact with the examined area cannot be achieved most of the time.

I agree with Dr. Huang that ultrasound has the limitation of not being able to observe the inadvertent placement of the needle intravascularly. During the initial draft of the manuscript, the Discussion section contained more content. I even mentioned the possible sonogram findings for patients without sacral hiatus. One of our authors wanted to include in the Discussion section the fact that ultrasound cannot be used to observe the inadvertent needle placement into the vessels. The reviewers suggested that we shorten the manuscript and focus mainly on the application of ultrasound in locating the sacral hiatus. Therefore, after revision, the entire article focused mainly on the sonograms of the sacral hiatus, and how ultrasound can be used as an adjuvant tool in caudal needle placement. Content about the drugs used and complications of caudal injections was not included in the article.

We were fortunate that the Christmas tree–like appearance (fig. 4 in the article) was observed under fluoroscope in all of our patients after locating the sacral hiatus accurately first by ultrasound. This symbolizes the fact that intravascular injection did not occur. Fluoroscopic guidance and contrast dye administration is still the standard in the assessment of the spread of the injected drugs into the desired target levels during caudal epidural injection.

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Anesthesia for Outpatient Surgery: How Fast Is Fast?

To the Editor:—I read with interest the recent article by Hadzic *et al.*[1] and its accompanying editorial by Williams[2] regarding the role of regional anesthesia in ambulatory surgery. Hadzic *et al.* reported that the use of infraclavicular block was associated with a significant decrease in discharge time (121 *vs.* 218 min) compared with "fast-track" general anesthesia among patients undergoing hand or wrist surgery. Williams called for more randomized trials to determine the relative merits of regional anesthesia and "emerging pharmacology and technology" in the ambulatory setting. Although these results are encouraging to believers in regional anesthesia, I have to ask: Does it really take 2–3 h to recover from regional or general "fast-track" anesthesia?

I work with a group of anesthesiologists who provide services to a freestanding orthopedic surgery center. The center has two operating rooms and performs 120–160 cases/month. Patients undergoing hand or wrist surgery may receive monitored anesthesia care with local infiltration by the surgeon, peripheral nerve block (digital, wrist, elbow, or brachial plexus) by the anesthesiologist, intravenous regional anesthesia with additional local infiltration by the surgeon, or general anesthesia with local infiltration by the surgeon. Patients may receive midazolam, fentanyl, and propofol for anxiolysis, analgesia, and sedation. The general anesthetic technique includes propofol induction and nitrous oxide and isoflurane *via* laryngeal mask airway maintenance. Muscle relaxants are rarely used, and antiemetics are given at the discretion of the anesthetist.

Between April 1 and June 31, 2004, 138 patients had hand or wrist surgery using the above anesthetics. Operative (time from skin incision to completed dressing) and discharge (time from arrival in the postanesthesia care unit until discharge from the facility) times are presented in table 1. Patients were discharged from the facility when they met standardized criteria (Aldrete score[3] of 10, no significant surgical bleeding, controlled nausea and pain).

The striking differences in discharge times between our facility and that of Hadzic *et al.* probably have nothing to do with anesthetic technique. Instead, institutional inefficiencies related to size, staffing, and processes serve to prolong patient stay and increase the cost of providing ambulatory surgery in a hospital setting. Among these inefficiencies, I believe one of the most important to be the two-stage recovery process. Instead of having to be admitted and discharged from two separate recovery units, our patients can awaken, recover, and prepare for discharge at a single site, cared for by a single nurse.

Table 1. Surgical and Recovery Times for Patients Undergoing Hand or Wrist Surgery in a Freestanding, Single-specialty Surgery Center

Anesthetic	Surgical Time, min	Recovery Time, min
MAC (n = 53)	34 ± 8	40 ± 15
Intravenous regional anesthesia (n = 22)	17 ± 9	31 ± 17
Peripheral nerve block (n = 35)	27 ± 21	32 ± 16
General anesthesia (n = 28)	37 ± 24	45 ± 17
All hand or wrist cases (n = 138)	22 ± 19	32 ± 17

Data are presented as mean ± SD.

With this approach, we also can achieve rapid discharge times with more extensive surgeries. During the above-mentioned time, 46 patients underwent open or arthroscopic shoulder surgery lasting 55 ± 25 min. Discharge times ranged from 25 to 165 min (mean, 59 ± 24 min).

Having worked in tertiary care centers, community hospitals, and freestanding facilities, I think that the challenges presented by the latter to the former two are formidable. Although good pain control and absence of adverse effects clearly can facilitate the ambulatory surgical process, the potential for shortening discharge times by altering anesthetic techniques pales in comparison to the savings that could be achieved by more systematic improvements such as eliminating stage 2 recovery. Pilot studies have shown that tertiary care centers can overcome some of these obstacles and achieve results close to ours.[4] I suggest that it is time for more centers to do the same.

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In Reply:—We commend Dr. Norris for his thoughtful comments. Indeed, if an institution can overcome care-process bottlenecks by creating fast-track paths from existing time points (*e.g.*, by eliminating phase 2 instead of bypassing phase 1 recovery), congratulations to such institutions for reengineering such costly and complex processes!

When using published criteria to determine discharge eligibility from any phase of recovery, a modified Aldrete score[1] of 10 is typically recommended. However, it should be noted that it is difficult to achieve such a score in nerve block patients because of (1) residual block and (2) patients' inability to move the blocked extremity. Discharge eligibility scores relating to limb mobility are relevant, but the modified Aldrete score threshold of 10 technically forbids same-day discharge eligibility when nerve blocks are in place. As a result, the modified Aldrete score may not be the most well-suited home-discharge criterion in the practice of peripheral nerve block anesthesia in ambulatory surgery.

As Dr. Norris alludes, duration of the surgical procedure is an independent risk factor both for a higher rate of unplanned hospital admissions[2] and for increased risk of postoperative nausea and vomiting.[3] As anesthesiologists, however, we can only control anesthesia selection, not the duration of the surgical procedure.

Therefore, this reply seeks not to explain or rationalize the importance of teaching in teaching hospitals and the likely effect that teaching has on increasing surgical case durations. Rather, with the referenced report[4] and accompanying editorial,[5] we have attempted to raise awareness that routine use of much-improved nerve blocks in outpatient orthopedic surgery (1) offers multiple, independent recovery advantages over routine use of general anesthesia with volatile agents and (2) calls for a revision of recovery scoring parameters when peripheral nerve blocks are used and extremities are rendered temporarily immobile or insensate in otherwise stable patients.

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In Clinical Practice, Coadministration of Sevoflurane or Propofol Could Antagonize Remifentanil Stimulation of *N*-methyl-D-aspartate Receptors

To the Editor:—In an important, exhaustive study, Hahnenkamp *et al.*[1] found that remifentanil, in clinically relevant concentrations, directly activates recombinantly expressed human *N*-methyl-D-aspartate (NMDA) receptors. As evidenced by Hahnenkamp *et al.*,[1] NMDA receptors are thought to play a critical role in the development of opioid tolerance and secondary hyperalgesia and also in neuroprotection, because antagonists of NMDA glutamate receptors can protect the brain against some injuries (such as stroke and trauma).[2] The NR1/2B subunit is the focus of increasing interest as a therapeutic target in a wide range of central nervous system pathologies, including acute and chronic pain, ischemic brain injury, and head trauma.[3,4] It could be concluded that administration of remifentanil is disadvantageous.

Nevertheless, it should be considered that in modern clinical practice, remifentanil-based anesthesia is performed administering either propofol or sevoflurane as adjuvants. Propofol inhibits the NMDA glutamate receptor subtype, possibly through an allosteric modulation of channel gating.[5] Nagels *et al.*[4] could not demonstrate that ketamine, an NMDA antagonist, resulted in greater neuroprotective effects compared with remifentanil during cardiopulmonary bypass procedures when both were combined with propofol, and Luginbuhl *et al.*[6] reported that adding a small dose of ketamine to opioids may prevent acute tolerance to opioids. It is thought that the NR1/2A complex in particular displays a higher affinity for competitive NMDA antagonists than for agonists. Sevoflurane also exerts an NMDA receptor antagonism effect in a dose-dependent manner, producing an inhibition of NMDA-gated currents and partially inhibiting NMDA-induced mitochondrial membrane depolarization.[7,8]

These data, taken together, support the hypothesis that propofol or sevoflurane, coadministered with remifentanil during anesthesia, produced an inhibiting effect at NMDA receptors antagonizing remifentanil-related stimulation.

It is also in accord with a number of recent clinical studies suggesting that administration of remifentanil is also safe in neurosurgery, neuro–intensive care unit sedation, and postoperative analgesia after craniotomy.[9–11] Based on the cerebral effects of remifentanil and the evidence currently available, Hancock and Nathanson[2] argue that remifentanil should replace nitrous oxide in the "at-risk" brain. As stated by Hahnenkamp *et al.*,[1] the clinical use of remifentanil has gained wide clinical acceptance by anesthesiologists.[1]

The clinical relevance is that during anesthesia, the coadministered anesthetics, especially the NMDA antagonists propofol and sevoflurane, should antagonize the remifentanil stimulation of NMDA receptors. We would like to ask for the authors' thoughts on this possibility.

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In Reply:—We thank Drs. Fodale and Santamaria for their kind comments and thoughts on our study.[1] They note that possible disadvantages of the use of remifentanil-based analgesia resulting from N-methyl-D-aspartate receptor activation might be prevented clinically, when given in combination with sevoflurane or propofol. These substances have indeed been shown to produce an inhibiting effect on glutamate-evoked (N-methyl-D-aspartate) receptor currents in electrophysiologic experiments,[2,3] and volatile anesthetics in addition have been shown to reduce cell damage in cultured neurons.[4]

This is certainly a potentially valid train of thought. In no way did we intend to imply that remifentanil would not be an appropriate compound to be used in the clinical setting. The suggestion by Drs. Fodale and Santamaria provides additional reassurance that clinical use of the drugs should not necessarily be associated with detrimental N-methyl-D-aspartate–related effects. Also, their observation might explain some of the disagreements in the literature regarding the increased analgesic required observed postoperatively after remifentanil-based anesthesia.

At the same time, this provides a testable hypothesis that could be explored in a clinical setting (although it seems there are not many clinically applicable anesthetics left that do not induce N-methyl-D-aspartate receptor antagonism).

We thank the authors for this insightful suggestion.

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CobraPLA™ Is the Perilaryngeal Airway

To the Editor:—The recent letter proposing a classification system for what until now have been termed *supraglottic* airway devices represents another contribution to the field of airway management by its author, Dr. Joseph Brimacombe.[1] With the many products now available to practitioners wishing to use these more properly termed *extraglottic* devices, the criteria described for the system are both useful and logical. However, I would like to clarify that the cuffed, orally inserted hypopharyngeal airway CobraPLA™ (Engineered Medical Systems, Indianapolis, IN) is an abbreviated name for Cobra *perilaryngeal airway* and not *pharyngeal lumen airway* as listed in table 1. The device is termed *perilaryngeal* because the distal end of the airway (the snake-like appearing "cobra head") abuts the aryepiglottic folds and thus seats itself directly along the entrance of the glottis.

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Reference

1. Brimacombe J: A proposed classification system for extraglottic airway devices (letter). ANESTHESIOLOGY 2004; 101:559

In Reply:—I would like to thank Dr. Alfrey for his positive feedback about my proposed classification system[1] and for correctly pointing out that the *PLA* in *CobraPLA*™(Engineered Medical Systems, Indianapolis, IN) stands for *perilaryngeal airway* rather than *pharyngeal lumen airway*. Dr. Alfrey states that the rationale behind the term *perilaryngeal* is that the CobraPLA™ head abuts against the aryepiglottic folds near the laryngeal inlet. Perhaps *periaryepiglottic* would have been a more accurate term, making it the CobraPAA. Interestingly, the use of the prefix *peri-* in this instance is used to mean "near" rather than "around," because the CobraPLA™ does not form a seal around the larynx, unlike the Laryngeal Mask Airway® (Laryngeal Mask Company Limited, San Diego, CA).

Finally, to the list of modern extraglottic airway devices given in my original proposal[1] must be added several new products: the Elisha airway device (Elisha Medical Technologies, Katzrin, Israel); disposable versions of the flexible and intubating laryngeal mask airway (Laryngeal Mask Company, San Diego, CA); several disposable laryngeal mask airway–like devices; a modified esophageal tracheal Combitube (Kendall Sheridan Catheter Corporation, Argyle, NY); and the C-Trach® (Laryngeal Mask Company, San Diego, CA), an intubating laryngeal mask airway with built-in fiberoptics and a viewing screen. Many new extraglottic airway devices will make their debuts in the near future; few will stand the test of time. There is no doubt that none will have a name quite as troublesome as the CobraPLA™, at least for those among us with snake phobias.

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1. Brimacombe J: A proposed classification system for extraglottic airway devices (letter). ANESTHESIOLOGY 2004; 101:559

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Metabolic Acidosis due to Propofol Infusion

To the Editor:—We read with great interest the reports by Burow *et al.*[1] and Salengros *et al.*[2] of the development of metabolic acidosis during propofol infusion in the operating room and intensive care unit. It has been proposed in these articles that the patients' symptoms were the result of excessive doses of propofol that inhibited mitochondrial respiration resulting in a metabolic acidosis. Because hundreds of thousands of adult patients have received propofol without experiencing this complication, what is different about these reported patients? We propose that these patients may have subclinical forms of mitochondrial diseases affecting either the respiratory chain complex or fatty acid oxidation,[3,4] which were uncovered by the infusion of propofol. The spectrum of mitochondrial disorders varies greatly and includes both primary disorders (presumably genetic) and secondary disorders that may affect mitochondrial function (such as untreated hyperthyroidism or hypothyroidism, diabetes mellitus, or drugs that would include the agents used to treat human immunodeficiency virus infections, statins, aspirin, and others).[5–7] The patient described by Salengros *et al.*[2] had a history of adult-onset diabetes mellitus. Primary mitochondrial disorders can present in adults with a huge variety of signs and symptoms, including cardiac conduction defects in apparently otherwise healthy persons.[8,9]

As a referral center for mitochondrial diseases, we use the muscle biopsy as one tool for assisting in the diagnosis of mitochondrial disorders. We avoid the use of propofol for anesthetizing patients undergoing this procedure. In the past, we have used short-term (15–30 min) and low-dose infusions of propofol for noninvasive diagnostic procedures in known mitochondrial patients. However, we have found in the more symptomatic patients that the use of propofol has been associated with prolonged anesthesia recovery and at times required intensive care unit admission. It seems that the duration of the infusion and the total dose of propofol may be the critical factors in these cases. In addition to propofol inhibiting mitochondrial metabolism, the lipid component of the formulation may play a role in toxicity for those patients with fatty acid oxidation disorders.

Mitochondrial diseases represent hundreds of known and theorized disorders, so there are probably some specific disorders that are more susceptible to the toxic effects of propofol and other mitochondrial poisons. The guidelines for anesthetizing these patients are to maintain normoglycemia and normothermia and to avoid any period of hypoxia so as not to stress the already diseased mitochondria.[10,11] Furthermore, the metabolic energy required to clear any drug must be considered before its administration. During anesthesia, the blood glucose and lactate concentrations should be carefully monitored because these patients may need glucose supplementation during these periods of stress and metabolic acidosis. This is especially important for infants because glucose is the major energy supply to the myocardium, and hypoglycemia may contribute to myocardial depression. The hypoglycemia is due to the inability of the diseased mitochondria to sustain their energy requirements from fatty acid oxidation during periods of stress, thus leading to the depletion of carbohydrate stores and the development of hypoglycemia.

We think it would be appropriate for the patients mentioned in the reports by Burow *et al.* and Salengros *et al.* to be evaluated a by neurologist and investigated for a mitochondrial disorder.

Ehab Farag, M.D., F.R.C.A., Glenn DeBoer, M.D.,* Bruce H. Cohen, M.D., Julie Niezgoda, M.D., * The Cleveland Clinic Foundation, Cleveland, Ohio. deboerg@ccf.org

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In Reply:—I appreciate the interest of Dr. Farag *et al.* in the recent case report of asymptomatic metabolic acidosis in a patient receiving prolonged propofol infusion in the absence of any likely cause of the acidosis except propofol.[1] I agree that an occult mitochondrial disease is a possible etiology. The anecdotal reports of Dr. Farag *et al.* on the effects of propofol in patients with mitochondrial disease are interesting, and I encourage them to publish details in a more systematized form.

However, their letter makes unsupported assumptions about propofol infusion syndrome that might adversely affect the level of vigilance for and detection of this complication. It is not true that "hundreds of thousands of adult patients have received propofol without experiencing this complication." To the best of my knowledge, no large-scale study of acid–base balance on thousands of patients receiving high-dose, prolonged propofol infusion has been reported. The subject of the case report by me and my colleagues was completely asymptomatic and was detected only because concern about respiratory depression under deep sedation caused arterial blood gases to be checked.[1] It is possible that mild forms of propofol-induced acidosis are much more common than appreciated, and it is also possible that they are as rare as suggested by Farag *et al.* We simply do not have the data at this time. A large-scale study is needed to answer the question.

It is also important to note that propofol infusion syndrome is so far defined only clinically, with metabolic acidosis being the invariant common factor, usually accompanied by circulatory collapse.[1] Although propofol can have adverse effects on mitochondria *in vitro*,[2] there are multiple potential pathways to the clinically defined syndrome besides mitochondrial disease. Pharmacogenomic variability in propofol metabolism and nonmitochondrial sites of propofol action could cause accumulation of propofol or unusual propofol metabolites,[3,4] or loss of the cytoprotective effects of propofol,[5–8] which might otherwise mask harmful effects of propofol. The recommendations of Farag *et al.* for anesthetizing patients with mitochondrial disease are reasonable and appropriate. However, anesthesiologists should still be vigilant for propofol infusion syndrome in patients without mitochondrial disease.

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In Reply:—We read with great interest the comments of Farag *et al.* on our case report.[1] We also think that our patient could have a subclinical form of mitochondrial disease (whether genetic or acquired by drug or disease) that was uncovered, in this case, by the intravenous infusion of propofol.

What is interesting and special in the case we presented is the fact that it is what can be called a "pure" case. In every case reported in the adult literature, the patient was already stressed by an acute illness. In the case described by Marinella,[2] the patient had asthma exacerbation complicated with acute respiratory failure necessitating mechanical ventilation and sedation. In the case described by Perrier *et al.*,[3] the patient had been in an automobile accident requiring sedation. These two patients were already in a condition consistent with mitochondrial stress and received significant amounts of propofol for a long period of time.

Our patient had an American Society of Anesthesiologists physical status of II (mature-onset diabetes and gastric ulcer). A large proportion of our surgical patients meet those two criteria. Nothing preoperatively suggested that our patient had any mitochondrial disease. Furthermore, the amount and duration of propofol infusion (approximately 7.8 mg · $kg^{-1} \cdot h^{-1}$ for 4.5 h) are not uncommon during surgical anesthesia.

We assume that some patients could be more sensitive to the effects of propofol on mitochondrial free fatty acid oxidation or on the mitochondrial respiratory chain complex. Whether this is due to primary or secondary mitochondrial disorders is of minor interest for the "everyday" clinician. What might be more important is the fact that the patient seemed to be representative of many of our surgical patients. Furthermore, he was not very, if at all, symptomatic; he was anesthetized for a short period of time with a very commonly used general anesthetic; and he was nevertheless subject to a potentially life-threatening perioperative event. How can we distinguish between these patients and "normal" ones? Could there be a potential biochemical marker that is available before administration of propofol that could help us to diagnose such a patient?

This could only be based on a more precise knowledge of the exact biochemical mechanisms involved. Interesting work has been done for the past 10–12 yr in the pediatric literature.[4] Among these studies, Wolf *et al.*[5] have studied the biochemical mechanisms and proposed to

measure blood acyl-carnitines frequently to allow early identification of a possible propofol infusion syndrome in pediatric intensive care units. Currently, such a test cannot be performed at the bedside or even in a routine laboratory, but such a test could prove invaluable in the future. What still remains unknown is which population of patients would benefit from screening before or during surgery.

Currently, neurologic and genetic evaluations are under way to refine the diagnosis in our particular patient. Nevertheless, we would be interested to know what clinical and biochemical picture was witnessed by the authors of the correspondence in those patients with known mitochondrial disorders who were anesthetized for a short period of time with propofol and admitted subsequently to the intensive care unit.

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Cardioprotective Properties of Sevoflurane in Patients Undergoing Coronary Surgery with Cardiopulmonary Bypass Are Related to the Modalities of Its Administration

To the Editor:—We read with interest the article by De Hert *et al.*[1] in which the cardioprotective properties of sevoflurane were investigated. A well-designed study by Conzen *et al.*,[2] published in 2003, investigating off-pump procedures, came to similar conclusions. Troponin I was the marker of myocardial damage in this study. It is well established that troponin is a specific marker of myocardial injury and a risk predictor, especially in patients with acute coronary disease without ST-segment elevation.[3] However, there are other causes of troponin increases, such as acute pericarditis, myocarditis, renal failure, acute pulmonary emboli, sepsis, congestive heart failure, tachycardia, heavy exercise, and heterophilic antibodies.[4,5] Measurable troponin concentrations may also occur after procedures such as coronary angioplasty, electrophysiologic ablation, and cardioversion. Furthermore, the relevance of troponin and its correlation to the magnitude of myocardial injury after cardiac surgery has not been validated. Only in an animal model has such a correlation been established.[6] Although some studies, such as that of Fellahi *et al.*,[7] have demonstrated that patients with a high concentration of troponin I have an increased risk of death postoperatively, it is not clear that the troponin concentration differences in this study correlate with clinical outcome. It is also not clear that these differences in the context of a multidrug regimen are due to sevoflurane alone. Propofol was used in all groups for induction of anesthesia and continued postoperatively, weakening the cause-and-effect relation.

Substantial efforts were made by the investigators to demonstrate the effect of sevoflurane as a function of the duration of its use. Unfortunately, sevoflurane concentrations varied between 0.5 and 2.5% (not mentioned if related to minimum alveolar concentration, vapor setting, or expiratory concentration) according to the Bispectral Index. Because other medications, temperature, ventilation, and age have effects on the Bispectral Index, a large variation in the partial pressure of sevoflurane among the subjects might have resulted, making an estimate of dose dependency impossible. In addition, as acknowledged by the investigators, troponin differences among the sevoflurane groups were not significant; therefore, a conclusion that effects of sevoflurane were most clinically apparent in the "SEVO all" group is not statistically supported because the sevoflurane groups are not different from one another.

With a half-life of 7–9 days, troponin remains in the circulation for a long time. Consequently, one would assume that when the concentrations have reached a peak, they would remain high, making the repeated sampling unnecessary and even confusing.

Troponin measurements are a sensitive and expensive marker whose utility is to establish whether myocardial injury is present. The value of multiple sampling used in this study is unclear and needs validation.

In this study, troponin concentrations may have been influenced by the extent of the surgical manipulation. Distribution of the individual surgeons among the patient groups would be valuable for the interpretation of the results. Furthermore, localization of the bypassed vessels would give useful insight into whether the procedures were comparable.[2] The significance of troponin increases in patients with abnormal renal function is an important and still-debated issue.[8,9] Although the study excluded patients with a baseline creatinine concentration of greater than 1.5 mg/dl, it is well known that renal injury can occur during cardiopulmonary bypass; no information is presented on the patients' postoperative renal function, which, if impaired, could further cloud the meaning of troponin increases.

Another interesting question could have been answered if the study design had included a group in which sevoflurane was used only during the cardiopulmonary bypass to assess its effect on myocardium when administered only during the most traumatic phase of the operation.

In other studies, isoflurane has been shown to exert protective properties on the heart.[10] Isoflurane is considerably less expensive than sevoflurane. We look forward to studies including an isoflurane arm in the experimental design.

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In Reply:—We thank Drs. Djalali and Sadovnikoff for their interest in our study on the influence of modalities of administration of sevoflurane on its cardioprotective properties in patients undergoing coronary surgery with cardiopulmonary bypass.[1] We regret that their review of the cardioprotective properties of volatile anesthetic agents was limited to the article of Conzen *et al.*[2] During the past years, there has been increasing evidence that these cardioprotective effects that had been demonstrated in experimental studies could also been observed in clinical practice.[2–6]

Demonstration of these cardioprotective effects was not solely based on analysis of troponin I concentrations but also on the evaluation of systemic hemodynamics parameters and variables of left ventricular function. When analyzing the literature, it was striking to observe that the clearcut clinical beneficial effects were only apparent in protocols where the volatile anesthetic was administered throughout the entire procedure and not in protocols where the volatile anesthetic was given solely before aortic cross clamping (preconditioning protocols) (references 12–16 from De Hert *et al.*[1]). This suggested that the beneficial effects on myocardial function of anesthetic preconditioning protocols observed in the experimental setting do not necessarily hold for the clinical setting. This was what our most recent study confirmed.[1] In this study, the cardioprotective effects of an anesthetic regimen were clinically most apparent when sevoflurane was administered throughout the surgical procedure. This was evident from a lower postoperative release of troponin I but also from better early postoperative hemodynamic and left ventricular function. When sevoflurane was administered only before aortic cross clamping or after completion of the coronary anastomoses, the postoperative troponin I release was not different from that observed with the total intravenous anesthetic regimen. However, postoperative recovery of stroke volume occurred earlier, suggesting that some cardioprotection may also be present with these pre- and post–cardiopulmonary bypass protocols.

The question on the effects of sevoflurane administered only during the period of cardiopulmonary bypass deserves some attention. During total cardiopulmonary bypass, the heart is "bypassed" from the circulation, and as such, virtually no sevoflurane could be administered to the myocardial tissue. The alternative approach to address this question is to add sevoflurane to the cardioplegic solution.

It should be noted that in our study, coronary anastomoses were performed using intermittent aortic cross clamping. This implies that during cardiopulmonary bypass, periods of ischemia are alternated with periods of reperfusion. As such, two protective mechanisms may be involved, which are ischemic and anesthetic preconditioning, and potential beneficial effects cannot unequivocally be attributed to sevoflurane. Therefore, this specific clinical situation does not allow one to address the question of whether sevoflurane administered only during cardiopulmonary bypass would be cardioprotective.

Substantial efforts were made by Drs. Djalali and Sadovnikoff to comment on the interpretation of troponin I as a marker of myocardial damage. Troponin is currently the routine marker used to determine extent of myocardial damage. As clearly stated in the methodology of the current study—as in the others— careful attention was paid to the random assignment of the patients to groups. There were no differences in patient characteristics or in perioperative variables such as number of grafts, duration of aortic cross clamping, and cardiopulmonary bypass time. Random assignment of the patients to the different groups was such that each individual surgeon operated a similar number of patients in each group in each study. The consequence is that the only variable between the groups in all our studies was the anesthetic protocol used, and any difference in any of the variables could therefore be essentially related to this difference in anesthetic protocol. It should again be emphasized that the conclusions on the cardioprotective properties of the volatile agent were not based solely on postoperative concentrations of troponin I but also on different variables of myocardial function.

Finally, isoflurane has indeed been shown in many experimental studies to exhibit cardioprotective properties. As such, it can be expected that these properties should also be apparent in the clinical setting. There are many reasons to choose one particular anesthetic agent, among which economical concerns certainly are to be considered. However, the real economical impact relies not on the individual cost of the specific agent but rather on the fact that cardioprotective properties of some anesthetic techniques may result in a reduction of intensive care unit and hospital durations of stay.[6]

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(Accepted for publication November 19, 2004.)

Tolerance to Miotic Effects of Opioids

To the Editor:—Embedded in an excellent review of acute pain management for the opioid tolerant patient[1] is an error that has been faithfully transmitted in the medical literature for the past 50 yr by diverse authors. The 1956 edition of Goodman and Gilman's pharmacology textbook contains the following unreferenced statement: ". . . tolerance does not develop to the excitatory responses elicited by the opium alkaloids. Also the actions on the bowel and the pupil persist, and the morphine addict thus manifests constipation and miosis."[2] The only studies that have professed to support this statement came from the Addiction Research Center in Lexington, Kentucky, where unconsenting federal prisoners were given addictive doses of methadone[3] or morphine[4] and then withdrawn from the drugs to study the physiologic responses to long-term opioid therapy. These studies did not find any differences during long-term opioid treatment in the tolerance to decreased respiratory rate and miosis. Nevertheless, this statement has been regularly transmitted, in one form or another, through all of the subsequent editions of Goodman and Gilman's pharmacology textbooks, even in chapters written by other authors. The unreferenced statement also appears in several other pharmacology textbooks, as well as in the other reference given to Stoelting and Dierdorf.[5]

Meanwhile, several excellent human studies[6–9] have shown that tolerance does indeed develop to the miotic effects of μ-opioid agonists. It is not our intent to review these studies because it can be readily observed that patients taking large doses of opioids over a long term do not have miotic pupils, unless they are measured in bright light or have other conditions that produce miosis. Certainly, however, as the opioid dose is escalated above the usual dose, the pupil constricts, just as these patients can also experience oversedation and respiratory depression.

Why measure dark pupil size? It makes no sense to measure the pupil diameter in ambient light because opioids do not interfere with the light reflex. Therefore, a patient looking directly at the room light might have a pupil size of 3 mm. This patient might not even be taking opioids, but the pupil would be termed *miotic*. The effect of lighting intensity on the miotic effect of opioids has been studied and revealed

that dark pupil size should be used to assess the effect of opioids on the pupil.[10] If a subject is given a standard dose of morphine in bright daylight, the pupil changes from 2.5 mm to 2.2 mm, and the change would not be noticeable, but the same pupil would constrict from 6 mm to 3 mm if the measurements were taken in the dark.

With this information in mind, proper dark pupil measurement can be of value in opioid-tolerant patients. Other classes of drugs, such as benzodiazepines or anticonvulsants, can produce sedation, and with patients using these agents, the constricting pupil is a useful confirmatory sign of opioid toxicity. Furthermore, as the authors[1] suggest, a dilated pupil at the end of a case can mean inadequate opioid has been given to provide a pain-free emergence. However, with the idea that the pupil does not become tolerant to the miotic effects of opioids, the observation of pupil size in tolerant patients at that time would have no value at all.

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David C. Warltier, M.D., Ph.D., acted as Handling Editor for this Correspondence.

This Letter was sent to the authors of the referenced report. The authors did not feel that a response was required.—David C. Warltier, M.D., Ph.D.

(Accepted for publication November 16, 2004.)

Epidural Hematoma after Epidural Steroid Injection in a Patient Withholding Enoxaparin per Guidelines

To the Editor:—We present a case of a patient with renal insufficiency in whom an epidural hematoma developed after an epidural steroid injection while enoxaparin was withheld per guidelines.

An 85-yr-old woman referred to the Anesthesia Pain Clinic for epidural steroid injection (ESI). She reported worsening left-sided lumbar radicular pain with left foot numbness for approximately 1 yr. Conservative therapy had provided minimal relief.

Neurologic examination results were normal, except for a positive straight leg raise test result on the left. No magnetic resonance imaging study of the lumbar spine was available. However, two-view radiogra-

phy demonstrated a wedge compression deformity of the L1 vertebra, mild to moderate degenerative joint disease, and mild scoliosis.

The patient was taking warfarin for chronic atrial fibrillation and a St. Jude aortic valve. Warfarin was withheld 6 days before the ESI, and the patient received 1 mg/kg subcutaneous enoxaparin every 12 h for 4 days before her appointment. On the day before her appointment, she received only her morning dose. Therefore, at the time of injection, it was more than 24 h since her last dose. Her international normalized ratio on the day of injection was 1.2.

Epidural steroid injection was performed atraumatically with use of an 18-gauge Tuohy needle and the loss-of-resistance technique into the L4–L5 interspace. The vertebral level of the injection was not confirmed radiologically. It is possible that the injection was performed at

Fig. 1. Magnetic resonance imaging views, with *arrows* indicating margins of epidural hematoma on the day of admission to the hospital (*left*) and after expansion of hematoma (*right*).

the L3–L4 interspace. No paresthesias or blood were encounter during needle placement. Methylprednisolone, 80 mg, was injected into the epidural space. The patient experienced no exacerbations of her sciatica and was discharged from the clinic with no acute distress.

She received strict written instructions to resume her warfarin treatment on the evening of the injection and to return to the anticoagulation clinic the next day for measurement of her prothrombin time. At that time, she was instructed to continue to take 1 mg/kg subcutaneous enoxaparin every 12 h and 2.5 mg oral warfarin once daily.

Again, the enoxaparin regimen was reinstituted 24 h after the procedure. The patient had received a total of three doses when, 48 h after the procedure, she reported "100-times-worse" back pain in the same location as before ESI. History and physical examination revealed no other neurologic findings and no other signs or symptoms of infection. Her blood pressure in the emergency department was 145/43 mmHg. The patient had a history of well-controlled hypertension, but no blood pressure readings were available from the day of her ESI. Straight leg raise test results were positive at 30° on the left and negative on the right, with no change from previous to ESI. An initial magnetic resonance imaging study (fig. 1) showed severe central spinal canal stenosis centered at L3–L4 from a posterior epidural hematoma. The craniocaudal extent of the hematoma was from L2–L3 through mid L4. There was mild to moderate central canal narrowing from the hematoma above L3–L4. The patient was admitted to the hospital, and neurosurgery was consulted. Her anticoagulation regimen was discontinued. Intravenous opioids, steroids, and baclofen were instituted, and serial neurologic examinations were ordered to monitor for development of neurologic signs or symptoms.

On the second day of hospitalization, the patient experienced increasing numbness and weakness in the lower extremities and urinary retention. Subsequent magnetic resonance imaging (fig. 1) revealed increasing size of the epidural hematoma, extending from the inferior L1 level to L4–L5. Decompression laminectomies were performed at L2–L4, and dexamethasone was continued for 3 days. On postoperative day 1, the patient's urinary retention resolved, and her pain improved dramatically. After 1 week of physical rehabilitation, she was ambulating well without assistance and reporting only mild intermittent low back pain and numbness in her toes on the left.

This patient developed an epidural hematoma after ESI, despite strict

adherence to current American Society of Regional Anesthesia guidelines for neuraxial anesthesia and anticoagulation regarding administration of low-molecular-weight heparin (LMWH). These guidelines state that patients should discontinue warfarin for 4–5 days before neuraxial procedures and check prothrombin time and international normalized ratio before the procedure. These guidelines also recommend delay of the procedure until 24 h after the last dose of LMWH. If needle placement is traumatic or if blood is encountered during needle placement, a 24-h delay is recommended before restarting LMWH.[1]

It is well recognized that when neuraxial anesthesia (epidural/spinal anesthesia) is used, patients receiving LMWH are at risk of development of an epidural hematoma. The risk of this event is increased by the use of indwelling epidural catheters or by concomitant use of other drugs affecting homeostasis, such as nonsteroidal antiinflammatory drugs, platelet inhibitors, or other anticoagulants. The risk also seems to be increased by traumatic or repeated epidural or spinal puncture.[2]

In our case, the needle placement was atraumatic, and no catheter was placed. Although the patient's warfarin had been withheld for 6 days previously, on the day of the ESI, her international normalized ratio was still mildly increased at 1.2. Warfarin treatment was resumed that evening, and the patient's international normalized ratio was 1.2 the next day in the anticoagulation clinic. Of course, the administration of warfarin, even in subtherapeutic concentrations, in combination with LMWH may have contributed to the development of the epidural hematoma.

No imaging studies were available to confirm that a hematoma was not present before the ESI. It is possible that a preexisting hematoma expanded after the ESI.

Although the patient was receiving the twice-daily treatment dose (1 mg/kg) of LMWH, the ESI was approximately 28 h after her last dose in accordance with current American Society of Regional Anesthesia consensus statement recommendations. The postprocedural dose of LMWH was administered 24 h afterward, again in compliance with current recommendations.[1]

The therapeutic anticoagulant effect of enoxaparin, which correlates with plasma antifactor Xa activity, peaks within 3–5 h, is 50% at 12 h, and is 0% at 24 h. The patient had taken her third post-ESI enoxaparin dose before admission. Her plasma anti-Xa concentration was increased at 0.6 U/ml, which is still within therapeutic range, 12 h after her last dose.[3] The potential risk factors that may prolong the half-life of LMWH and predispose to bleeding complications are renal insufficiency and advanced age.[4] Initially, the studies done on the effects of renal insufficiency on the half-life of LMWH were contradictory.[5,6] However, it has been shown recently that renal insufficiency delays the elimination of enoxaparin, and patients with renal dysfunction are at increased risk for major bleeding complications.[7–11]

There is currently no clear consensus to which degree of renal insufficiency requires dose adjustment.[7,8,10,12] In 2002, Becker *et al.*[7] determined that patients with marked renal impairment (creatinine clearance < 40 ml/min) had higher trough and peak anti-Xa activity compared with those with normal renal function and were more likely to have major hemorrhagic events. A study conducted by the manufacturer concluded that the elimination half-life increased with a degree of renal impairment, and this relation was more evident after repeated dosing.[8] One manufacturer of enoxaparin recommends dosage adjustment in severe renal impairment (creatinine clearance ≤ 30 ml/min). Although dosage adjustment is not recommended in patients with moderate (creatinine clearance = 30–50 ml) and mild (50–80 ml/min) renal impairment, they caution that such patients should be observed carefully for signs and symptoms of bleeding.[3] Using the Cockcroft-Gault equation, our patient's creatinine clearance at the time of instituting her regimen and at the time of admission to the hospital were 41 and 38 ml/min, respectively. We recognize that this equation allows only for an estimation of creatine clearance from the plasma creatinine in patients with stable plasma creatine and is not a direct measure of renal function. The American Society for Regional Anesthesia's Consensus Statement on Neuraxial Anesthesia and Anti-

Coagulation recognizes concern where sustained therapeutic levels of anticoagulation are present but does not recommend monitoring of the anti-Xa concentration or increasing the time from last dose of enoxaparin when performing neuraxial procedures in these patients.[1] In 2002, Bastani and Gonzales[11] presented a patient who had moderate degree of renal insufficiency with a very prolonged duration of anticoagulation after treatment with subcutaneous enoxaparin. This case emphasizes that even a low dose of enoxaparin administered over the course of days could produce a very prolonged anticoagulation effect such that even 36 h after its discontinuation, the patient may remain anticoagulated. In fact, the authors suggest that it is prudent that physicians caring for patients with a higher risk of the delayed elimination of LMWH (*i.e.*, patients with renal insufficiency and the elderly) monitor antifactor Xa concentration on a regular basis, particularly before any invasive procedures. In conclusion, current American Society for Regional Anesthesia recommendations for treatment of patients receiving LMWH may not apply to patients with renal insufficiency. To reduce the risk of bleeding complications, one should check for sustained therapeutic concentrations of enoxaparin by measuring factor Xa concentrations in the elderly and in patients with renal insufficiency.

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Potentially Dangerous Fracture of the Needleless Interlink Vial Access Cannula

To the Editor:—The "needle-less" Interlink Vial Access Cannula manufactured by Becton Dickinson and Co. (Franklin Lanes, New Jersey; part No. 303405) is being commonly used at a large number of institutions in the United States. It minimizes the use of needles and thereby limits the risks of needle-stick injuries. To our knowledge, there are no risks to the patient that have as yet been reported from the use of this needleless system.

The Interlink Vial Access Cannula consists of a syringe, a cannula, and a blue plastic dart within the cannula. The dart pierces the vial, allowing the cannula to enter the vial for aspiration of drugs. After the drug is aspirated, the blue dart is retained within the vial, and the cannula along with the syringe is withdrawn (fig. 1).

We report two incidences in the ambulatory surgery center of the same institution where the blue dart of the Interlink Vial Access

Cannula was fractured during the process of aspiration of drugs. This resulted in breakage of a small segment of the distal-most part of the dart. The broken end of the blue dart was retained in the syringe (fig. 2). This is seen floating in the syringe in figure 2. These incidents occurred using the 10-ml syringes on two separate occasions in a period of 3 weeks with two different anesthesiologists.

Although the blue color of the dart helps to identify the broken piece, it is possible that such incidents may occur and go unrecognized. Accidental injection of broken plastic pieces may occur through peripheral or central veins and result in injury to the patient. We have removed this product from our clinical practice until modifications in the manufacturing of needleless systems are made.

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Fig. 1. Normal appearance of needleless Interlink Vial Access Cannula and the blue dart before and after aspiration of drug from the vial.

Fig. 2. Retained piece of the broken distal end of the blue dart in the syringe, with the other end in the vial.

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In Reply:—The Interlink Vial Access Cannula consists of a blunt plastic cannula with a removable spike inserted into the lumen of the cannula. The blue plastic spike allows for needleless access of a single-dose vial. When the cannula is removed from the vial, the spike remains embedded in the stopper, and the blunt plastic cannula can then be used to access InterLink injection sites.

Becton Dickinson initially became aware of instances of fracturing of the end of the blue spike of the Interlink Vial Access Cannula in August 2003, in which small solitary fragments of the spike were found in syringe barrels. Our investigation revealed the root cause of the fracturing was related to the product assembly process. To reduce the potential for broken spikes, immediate action was taken to correct the manufacturing process. Modification of the process was completed in August 2003, and since the change was made, 413,188 samples have been inspected during manufacturing, and no broken spikes have been detected. In addition, a sampling and simulated-use evaluation of 5,000 units (1,000 units from each of five lots) of current inventory was undertaken in November 2004 to further confirm the effectiveness of the corrective action. No fractures or fragments were observed during this testing, in which the product is used to penetrate and draw fluid from medication vials in a laboratory setting.

When the issue was first reported in 2003, to assess the potential risk of product manufactured before correction of the problem, Becton Dickinson evaluated more than 14,000 units through simulated use testing. Only one broken spike was found, and the single resulting fragment was drawn into the syringe barrel during the simulation, in much the same way that the fragment reported by Drs. Kohli and Florence was drawn into the syringe. However, the piece was elon-

gated and could not be readily flushed through the lumen of the Interlink Vial Access Cannula, which has a diameter equivalent to that of a 15-gauge intravenous catheter (0.054 inches or 1.37 mm in diameter). (In order for an irregularly shaped fragment that exceeds the diameter of the cannula in any dimension to be flushed through the cannula, it would need to be oriented as it enters the cannula so as to allow its narrower profile to clear the walls of the cannula lumen.)

Intravenous catheters normally have a lumen gauge that is higher than 15 and is therefore smaller than that of the cannula. In the event that a small piece was flushed through the Interlink plastic cannula, it would most likely be prevented from entering the circulation by the yet narrower catheter lumen. In the unlikely situation that a fragment detaches that is small enough to be flushed through both the cannula and catheter (the ID of a 20-gauge peripheral intravenous catheter is 0.030 inches, whereas the ID of a 24-gauge peripheral intravenous catheter is 0.019 inches), given the inert nature of the polycarbonate spike material and the small size of the particle released, there is minimal risk of such an embolized particle causing harm to a patient. Consistent with this assessment is the lack of patient injury reports received by Becton Dickinson during the 24 months preceding the August 2003 reports.

Becton Dickinson believes we have addressed the problem reported here by Drs. Kohli and Florence but is continuing to monitor the product to ensure that the problem does not reoccur. Becton Dickinson appreciates the information provided to us by clinicians regarding the performance of our devices. We take very seriously any complaints or issues related to our products, and we are committed to resolving such issues as rapidly as possible.

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