To the Editor—We read with interest the article by Ramsay and Luterman and accompanying editorial discussing the use of high-dose dexmedetomidine as a single-agent intravenous anesthetic. We have several concerns, both with the technique described and the journal’s editorial position.

As to the case series itself, we wonder what was the basis for the clinical choice to use doses of dexmedetomidine at more than 7 to 50 times the recommended dose range of 0.2–0.7 μg·kg⁻¹·h⁻¹ as the sole anesthetic. Ebert et al.’s work with volunteers was extremely limited and in no way established dexmedetomidine as a safe single-agent anesthetic. Indeed, doses of dexmedetomidine lower than those in the case series have been recently reported as “accidental overdose” and are accompanied by guidelines for the management of same. Although Ramsay and Luterman’s cases imply that the doses were increased when the patients could not tolerate the procedures at lower dose levels, there is no mention of the initial anesthetic plan. Did the authors undertake the anesthetics with the expectation of using dexmedetomidine at massive, unstudied doses? Given the properties of dexmedetomidine at its usual clinical dose range, it is unlikely that patients would be able to tolerate the procedures described without either supplementation or rapid escalation to massive doses, as actually occurred. We find no convincing evidence in the literature to believe that their course of action could be chosen with confidence in its safety and efficacy. The intraoperative management of the cases is also unusual. We fail to understand their need to avoid the use of supplemental oxygen except when absolutely necessary. The argument regarding electrocautery is unconvincing. It is almost as if the decreased margin of safety is used as a demonstration of dexmedetomidine’s properties with respect to maintenance of ventilation. In the two cases that did not receive supplemental oxygen, were the patients subsequently placed on oxygen in the postanesthesia care unit? Finally, we question the assertion that recovery time in these patients was not significantly prolonged when compared with many conventional anesthetic techniques. A recovery time and postanesthesia care unit stay of 2 to 3 h is considered by many to be significantly prolonged and is not a desirable side effect.

We are therefore concerned that Anesthesiology tacitly endorses this anesthetic technique by calling it “another arrow for the clinician’s quiver” in the accompanying editorial. On the basis of Ebert et al.’s two volunteers and the three cases described by Ramsay and Luterman, are we to assume that this is now an acceptable practice? Certainly, we all daily administer many medications “off-label” in a safe and reasonable manner. There comes a point, however, when the off-label use of a drug crosses the line of “reasonable” and becomes a deviation from the standard of care. Until properly controlled, Institutional Review Board or hospital ethics committee was consulted regarding this “case series.” The practice of anesthesiology is neither a contest of skills nor a game of what one can get away with. The essence of the practice of anesthesiology is the planning and administration of the safest and most efficient anesthetic for a given individual patient using principles grounded in science and controlled clinical studies. An unusual technique that worked in three patients does not rise to this standard and sidesteps the checks and balances of ethical scientific investigation.

Finally, the lack of complete disclosure of conflicts of interest on Dr. Ebert’s part is disturbing. The attestation states, “Dr. Ebert is not supported by, nor maintains any financial interest in, any commercial activity that may be associated with the topic of this editorial.” This may be true only in the strictest and most limited interpretation of the statement, but ignores Dr. Ebert’s long and close association with Abbott Laboratories (Abbott Park, IL) and previous substantial financial support and honoraria. In fact, the study cited by Ebert in the editorial, examining high-dose dexmedetomidine in volunteers, was itself supported by a grant from Abbott Laboratories. At best, this is dishonourable. The casual reader of the journal should be fully aware that an unproven anesthetic technique, utilizing an expensive drug manufactured by Hospira, Inc. (Lake Forest, IL), a wholly-owned spin-off company of Abbott Laboratories, is advocated by an Abbott-funded investigator and is trumpeted by editorial writers with a long history of close association and support from Abbott Laboratories. It is difficult to understand how one can consider this an objective review of scientific data.

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CORRESPONDENCE

Anesthesiology 2005; 102:1067–8

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in the last sentence of the editorial did they offer the suggestion that dexmedetomidine may have a place in the management of the difficult airway. They recommended further comparative studies to establish the clinical role of dexmedetomidine in difficult airway algorithms. I certainly agree that three case reports are not even enough data to claim an ‘outcomes’ clinical trial; these reports were just observations. However, I am collecting more case reports to add to my initial database. I am also involved in a multicenter prospective clinical trial that is including the use of higher doses of dexmedetomidine than currently on the label and administering them for longer periods of time.

I wholeheartedly support the notion of evidence-based medicine following rigorous randomized controlled clinical trials, but the low incidence of the types of cases we reported will make this difficult to achieve in this patient population.

The “off-label” use of drugs is not unusual in the practice of anesthesiology, especially in some of our more sensitive patient groups such as the pediatric population. I agree with Mychaskiw and Badr that the use of “off-label” drugs needs to be done with extreme caution and is only justified when current therapies are less than optimal.

We thank Drs. Mychaskiw and Badr for raising a cautionary note about the use of these high doses of dexmedetomidine and we certainly emphasize that this should only be done by those practitioners with extensive experience with this drug in well-controlled circumstances and where current technologies are less than ideal. However, as our experience with dexmedetomidine increases, its role in the management of the difficult airway may well become “Another Arrow in the Clinician’s Quiver”!

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Depth of Anesthesia Monitors and Shock

To the Editor.—In the article by Johnson et al.1 and in the follow-up editorial by Shafer2, the sensitivity of pigs to propofol after severe hemorrhage is described. In the editorial, the “take-home message” is that propofol is a poor choice for induction. My supplementary “take-home” message is that a monitor of anesthetic depth, such as the Bispectral Index, should be used for all critically ill patients. If a dose of propofol drives the Bispectral Index to 0 (isoelectricity), the patient is probably too deeply anesthetized. Certainly, it is possible that the Bispectral Index is not accurate during shock, i.e., a decrease in Bispectral Index score might not necessarily represent a change in depth of anesthesia. In a case report of a patient who underwent elective abdominal aortic aneurysm repair with total intravenous anesthesia, the Bispectral Index score decreased shortly after the aortic clamp was released; 10 min later other monitored variables suggested clinical deterioration.3 Although no study has formally analyzed the relationship of Bispectral Index to shock, there are electroencephalographic changes during shock. In awake animal studies of controlled hemorrhagic shock, electroencephalography frequency slows and amplitude increases; the electroencephalograph is flat when blood pressure is inadequate to support respiration.4–6 It is not always clear how much anesthesia critically ill patients need. In such situations, I use a depth of anesthesia monitor, use much less anesthesia than I would otherwise have planned to use, and I believe that I also have an easier job of managing blood pressure.

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References

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Pharmacodynamics of Propofol during Hemorrhagic Shock

To the Editor.—It has been reported that hemorrhagic shock altered pharmacodynamics of propofol: the potency of propofol increased during hemorrhagic shock.1–3 A proposed explanation for this increase of propofol potency is that hemorrhagic shock leads to an increase in circulating beta endorphins.4 Recent work by Depaepe et al., however, has revealed that endorphin antagonism with naloxone does not influence end-organ sensitivity during hemorrhagic shock in the rat.5 Other potential sources of increased end-organ sensitivity to propofol is the increase of unbound propofol; this can be achieved through competitive displacement interactions with other drugs or endogenous substances or decreases in the level of proteins.

It is now widely accepted that the pharmacological effects of a drug are elicited by the unbound fraction in the blood. Only those drug molecules that are not bound to plasma protein are able to pass through blood vessels and reach their target sites within the tissue. Therefore, changes in the protein-binding characteristics of a drug may alter its pharmacological potency and pharmacokinetics.

For drugs that are restrictively cleared, regardless of route of admin-
istration, an increase in the unbound fraction leads to accelerated total body clearance, thereby reducing the total concentration of drug. The unbound concentration at steady state is unchanged because an increase in the unbound concentration gradually returns to the control value after redistribution. Thus the ultimate effect of changes in protein binding is only transient.

In contrast, for drugs that are nonrestrictively cleared and administered intravenously, an increase in the unbound fraction could not affect total body clearance because such drugs are extracted by the eliminating organ so efficiently that protein binding dose not limit their removal. The total concentration of drug would initially fall because an increase in the unbound fraction leads to an increase in the volume of distribution. However, after redistribution the concentration returns to the control value. Thus, the total concentration at steady state is unchanged and an increase in the unbound fraction leads to an immediate and sustained increase in the unbound concentration. This is of clinical significance for highly protein-bound drugs with narrow therapeutic indices such as propofol.

Recently, we reported that a significant (twofold) increase in the concentration of unbound propofol occurred without alteration in the total propofol concentration in blood during cardiopulmonary bypass. This increase in the unbound fraction was caused mainly by a lower total propofol concentration in blood during cardiopulmonary bypass. Therefore, the total concentration at steady state is unchanged and an increase in the unbound fraction leads to an immediate and sustained increase in the unbound concentration. This is of clinical significance for highly protein-bound drugs with narrow therapeutic indices such as propofol.

We thank Drs. Lichtor and Takizawa et al. for their interest in our study and thought-provoking observations. Dr. Lichtor points out that in settings of hypotensive extremes from blood loss i) perfusion to the brain can be compromised to the point of significantly altering electrical activity in the brain and ii) delivering an anesthetic that results in brain isoelectricity is clearly excessive. It is interesting to note that in our experimental protocol, we performed a series of pilot studies directed at characterizing the impact of our hemorrhage and resuscitation protocol on a processed measure of brain electrical activity, the Bispectral Index score, in the presence of isoflurane. Although hemorrhage was severe (+2 ml/kg) and resuscitation restored hemodynamic parameters to near-baseline levels, we observed no significant change in the Bispectral Index (i.e., no Bispectral Index decrease beyond that initially produced by isoflurane). We point out, however, that in our protocol, the mean arterial blood pressure never dropped below 40 mmHg and resuscitation was initiated just at the onset of cardiovascular decompensation. The clinical correlates here are twofold: 1) although hypotensive, compensatory mechanisms most likely maintained adequate cerebral perfusion to accompany hemorrhage—especially followed by crystalloid resuscitation.

References


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To the Editor—We report the case of a 68-yr-old obese male patient that was admitted in our university hospital for scheduled elective left carotid endarterectomy under regional anesthesia. Past medical history was significant, with controlled ischemic (four coronary artery bypass grafts at the age of 56 yr) and hypertensive cardiopathy and sleep apnea syndrome balanced with nocturnal ventilation support. Preoperative physical examination detected no abnormality. The patient received a deep cervical plexus block using a single-injection (15 ml 0.5% bupivacaine and 15 ml 2% lidocaine) nerve stimulator-assisted technique. The patient developed respiratory distress associated with bilateral diaphragm paralysis symptoms 15 min after the block was placed. Facemask noninvasive titrated inspiratory pressure-support ventilation resulted in normal breathing pattern and oxygen parameters. After an uneventful surgical procedure the patient was transferred to the ward 2 h after postanesthesia care unit admission. Postoperative ambulatory arterial blood gas analysis and pulmonary functional tests were considered normal but phrenic conduction measurements confirmed severe right phrenic nerve conduction alteration.

In this report the patient experienced acute ventilatory failure probably attributable to bilateral diaphragm weakness. Epidural or subarachnoid injection might have promoted similar clinical features. However, the deep cervical plexus block we performed remained strictly ipsilateral to the puncture side. The block concerned left C2-C4 sensory dermatomes but preserved distal motor function of the arm. Then, we believe that the spread of deep cervical plexus block promoted a left phrenic block, resulting in ventilatory failure because of preexisting contralateral phrenic damage. Usually, extension of the block to the phrenic nerve is common during cervical blocks but without significant clinical problems, even in patients with preexisting lung disease. In the present case, unrecognized coronary artery bypass graft-induced right phrenic nerve damage was revealed by the extension of left deep cervical plexus block.

Because up to 10% of cardiac surgery patients may suffer from postoperative electrophysiological abnormal phrenic nerve conduction, we recommend anesthesiologists performing cervical blocks in postcardiac surgery patients remain vigilant attending the patient, with the capacity to supply ventilatory failure.

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Is Recall during Sedation Being Confused with Recall during General Anesthesia?

To the Editor—Recall during general anesthesia has been reported to occur in approximately 1 to 2 per 1000 anesthetic procedures. Most providers are familiar with press reports and litigations by patients to recover damages as a result of recall and suffering while under general anesthesia. I would like to report a phenomenon which I have observed to be occurring more frequently in my practice.

During my preoperative visit, I commonly ask the patient about previous anesthetic exposures. Lately, several patients have stated that they remember most if not all of their last anesthetic. When asked what type of procedure they had that they recall so well, they have invariably replied, colonoscopy, cataract, cardiac catheterization, or similar procedures. When I question this recall event further, it is clear that the procedure they recall was done under sedation and not general anesthesia. Indeed, all of the patients I have interviewed so far who have had other procedures that required general anesthesia, e.g., cholecystectomy, were able to discern the difference in the depth of anesthesia and had no recall of the procedure they had that they recall so well, they have invariably replied, remember most if not all of their last anesthetic. When asked what type of procedure they had that they recall so well, they have invariably replied, conscious sedation or even moderate sedation are being told they will not experience the more invasive procedure. A brief explanation that sedation for endoscopy and similar procedures does not reliably ablate recall has been accepted by all patients and to date has eased apprehension that if the current procedure requires a general anesthetic, they will most likely not have any recall or intraoperative awareness.

I get the impression that many patients undergoing endoscopy, catheterization, cataract extraction, and many other procedures that utilize conscious sedation or even moderate sedation are being told they will not remember the procedure. I think it will serve us well to remind our colleagues in the endoscopy suites and the catheterization labs that such is not the case. In addition, we practitioners of anesthesia should not tell patients undergoing spinal, epidural, regional, or monitored anesthetic care that the sedation we may provide will ablate all intraoperative awareness and recall.

The general public has difficulty distinguishing between different levels of sedation and general anesthesia; in fact, this concept is not clearly defined within our own specialty. Caution needs to be exercised when discussing matters of recall and awareness with patients.

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First, find out if they truly had a general anesthetic. Second, do not make assurances of memory ablation if you do not plan a general anesthetic and even then be careful what you promise. Third, talk with your colleagues in the endoscopy and catheterization laboratories. I think they are making well-intentioned assurances of memory ablation and are unaware of how often they fail to provide the amnesia they wish to give.

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