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Does Pancuronium Cause Prolonged Postoperative Intubation in Cardiac Patients?

To the Editor:—I read with interest the recent report of a study by Murphy *et al.*,[1] in which they compared the effects of two muscle relaxants, the intermediate-duration drug rocuronium and the longer-duration drug pancuronium. Even using a nerve stimulator to titrate dosing, their patients were not able to be extubated for several hours after cardiac surgery (350 min for rocuronium *vs.* 500 min for pancuronium). I am concerned that some readers may draw the inference from these results that pancuronium is not indicated in cardiac surgery, as it is responsible for protracted postoperative intubation.

One certainly cannot find fault with a major conclusion of the paper, namely the tautology that the duration of a shorter-acting drug is shorter than the duration of a longer-acting drug. However, this report raises an additional question. How much of the authors' results do they think are artifacts of experimental design? The patients in the study received muscle relaxants until approximately 30 min before the end of surgery. In their discussion, Murphy *et al.*[1] describe the known sensitivity of cardiac surgical patients to nondepolarizing neuromuscular blocking drugs, and it is the routine clinical practice of many cardiac anesthesiologists to administer neuromuscular blockers at induction and prior to initiation of cardiopulmonary bypass only for most patients. The continued administration of these drugs according to the study's protocol may have resulted in a protracted duration not seen in clinical practice.

If these drugs are, indeed, responsible for prolonged postoperative intubation of 6–8 h, how do the authors account for the practice in some adult cardiac centers of extubating cardiac surgical patients very early, or the fact that children and adolescents can have their tracheas routinely and safely extubated in the operating room with pancuronium as the sole muscle relaxant?[2]

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2. Kloth RL, Baum VC: Very early extubation in children after cardiac surgery. Crit Care Med 2002; 30:787–91

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In Reply:—We appreciate the interesting comments made by Dr. Baum. Dr. Baum suggests that the experimental design may have produced the delays in tracheal extubation that were observed in the pancuronium group. In particular, the study requirement to maintain a moderate level of neuromuscular blockade in the operating room (1 to 2 twitches to train-of-four stimulation) may have resulted in a relative overdosage of the neuromuscular blocking agent (NMBA). We utilized neuromuscular monitoring to determine when additional doses of NMBAs were to be administered. In the pancuronium group, all subjects required maintenance dosing during cardiopulmonary bypass. However, no patients required additional pancuronium in the postbypass period. Although the study design allowed for the administration of NMBAs until the last 30 min of the surgical procedure, no patient in the pancuronium group received maintenance dosing during the last 90 min in the operating room. In contrast, approximately 30% of the subjects in the rocuronium group received additional NMBAs following separation from cardiopulmonary bypass. We believe that most cardiac anesthesiologists administer NMBAs during cardiopulmonary bypass. This belief is supported by the results of a national postal survey of cardiac anesthesiologists that assessed practice patterns in the use of NMBAs.[1]

We agree with Dr. Baum's statement that many cardiac surgical patients who receive pancuronium intraoperatively are routinely extubated within a few hours of the end of the surgical procedure. It is possible that some of these patients are extubated before full recovery of neuromuscular function has occurred. Previous studies have demonstrated that significant residual neuromuscular blockade may persist for up to 8 h in the intensive care unit when pancuronium is used.[2,3] The high incidence of symptoms of moderate to severe muscle weakness following extubation in the pancuronium group in our study suggests that residual neuromuscular blockade may be present during the ventilatory weaning and extubation process. We believe that all cardiac surgical patients who receive a long-acting NMBA in the operating room should be carefully evaluated, using clinical criteria or neuromuscular monitoring, for residual neuromuscular blockade prior to extubation.

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Preemptive Analgesia: What Do We Do Now?

To the Editor:—The recent meta-analysis by Møiniche *et al.*[1] makes it clear that preemptive analgesia as currently envisioned by a large number of anesthesiologists is of limited clinical efficacy. In the accompanying editorial, Hogan[2] suggests reasons why this may be the case and proposes that current practice be modified accordingly. We are concerned that this may provide the impetus for less aggressive perioperative pain management, and that such a trend may have negative implications for perioperative pain relief, recovery of function, morbidity, and mortality.

As first conceived,[3] preemptive analgesia was based on the idea that systemic or regional analgesic regimens initiated before the onset of surgery could have effects that outlast the pharmacokinetic presence of the intervention. This view recognized that sensitization of the pain pathways was ongoing throughout the entire perioperative period. However, most trials of preemptive analgesia and all of those included in the meta-analysis involve interventions that differ only for the intraoperative portion of the perioperative period, generally permitting patients to enter the postoperative period with at least moderately effective analgesic interventions already active. Such studies parallel laboratory investigations of relatively discrete, low-intensity, noxious stimuli in which an animal receives the analgesic intervention either before or after the stimulus. As repeatedly emphasized by Kissin,[4,5] this approach to the clinical evaluation of preemptive analgesia is fraught with problems because of the limited ability of many analgesic interventions to prevent sensitization, the intensity and duration of the stimulus relative to the intervention, and the benefits of the analgesic regimen received by the control group.

In the editorial, Hogan[2] states that regardless of any intraoperative intervention, it should be possible to manage postoperative pain effectively. However, for reasons that are not always clear, and as illustrated by many of the trials included in the meta-analysis, this appears to be very difficult to do, even in the context of the increased sensitivity to the patient's analgesic needs that accompanies a clinical study of perioperative analgesia. Furthermore, even if sufficient analgesics can be administered in a highly structured environment to equalize pain between groups, very little is known about more typical clinical conditions, and even less is known about what happens once the patients leave this environment. For example, of the 80 studies included by the meta-analysis, only 9 report data for more than 72 h after surgery. However, long-term, painful sequelae following surgical procedures are more common than generally appreciated,[6–10] and even low-level pain can be associated with decreased function.[10,11] Thus, we still know little about limiting the very morbidity that we would most prefer perioperative analgesic regimens to prevent.

Unfortunately, pain scores alone might not be sufficient to evaluate the efficacy of perioperative analgesic regimens. As demonstrated in one longer-term positive evaluation of preemptive epidural analgesia that did not meet the inclusion criteria of the meta-analysis, even when pain scores are similar, functional differences may still be present.[12] Meaningful functional measures might be able to associate a benefit from the longer-term decreases in wound hyperalgesia seen after relatively simple interventions,[13,14] even when pain scores alone could not.

Given the lack of evidence of significant clinical efficacy of preemptive analgesia in the meta-analysis, the editorial advocated avoiding intraoperative opioid use and initiating epidural blockade only upon emergence "when analgesic needs can be directly assessed."[2] This may result in many more patients emerging with pain that must then be treated, and this pain may further sensitize the nociceptive pathways. The editorial also overlooks many of the other beneficial effects of intraoperative epidural blockade, which may include modulation of the stress response, decreased blood loss, ability to tolerate hemorrhagic shock, improved immune function, and decreased thromboembolic events.[15–18] Some of these effects may account for differences in morbidity and mortality when anesthetics involving regional anesthesia are compared with general anesthesia alone.[19–21]

In summary, the authors of the meta-analysis have made a valuable contribution by demonstrating that relatively modest interventions made for relatively brief periods of time are, at best, of limited efficacy. This should not obscure the fact that surgical procedures are frequently associated with residual long-term pain and other morbidities, which might benefit from aggressive analgesic interventions throughout the entire perioperative period. Rather than limiting preemptive analgesia, the results of the meta-analysis should focus clinicians and clinical investigators on the broader definition of preemptive analgesia and the longer-term impact of such interventions on pain, functionality, and morbidity.

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In Reply:—We thank Dr. Gottschalk and Dr. Ochroch for their interest in our work and their pertinent comments. We agree with the concerns they express. A major reason for the confusion and misunderstanding of the concept of preemptive analgesia is the variation in its definition. Original observations in experimental studies suggested that the timing of analgesic treatment was important to obtain efficient reduction of postinjury pain hypersensitivity phenomena. Accordingly, a tremendous number of studies have focused on the role of the timing of analgesia, *i.e.*, preoperative *versus* intraoperative or postoperative initiation of analgesia. The results of our overview of clinical studies showed that this one aspect of the discussion, namely the timing of analgesic administration, had no or only limited clinical impact on postoperative pain relief. Therefore, we believe that there is no need for further trials to investigate the role of timing of preemptive single-dose (and often short-lasting) analgesic treatment when postoperative pain is the end point. However, as emphasized also by Dr. Gottschalk and Dr. Ochroch, a number of reasons may explain the negative results from clinical trials compared with those from the experimental setting: intensity of the noxious stimuli, insufficient afferent blockade and insufficient analgesia, insufficient central inhibition, insufficient duration of the treatment, and so forth. Thus, although the overall results are negative when timing *per se* is the variable, this conclusion does not preclude a possible beneficial effect of aggressive, perioperative analgesic treatment of short- and long-term postsurgical pain. As indicated by Dr. Gottschalk and Dr. Ochroch, and already suggested in our overview, future studies should redirect their focus from the timing of perioperative analgesia to protective analgesia aimed at preventing pain hypersensitivity. The agenda would then be to investigate the effects of a prolonged, multimodal (protective) analgesic intervention *versus* less aggressive, conventional perioperative analgesia. Eventually, we agree that there may be other potentially beneficial effects of, for instance, intraoperative epidural blockade, such as modulation of the surgical stress response, reduced blood loss, stable intraoperative hemodynamics, and so forth.

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Myocardial Ischemic Preconditioning Decreases Postischemic Oxygen Free Radical Production

To the Editor:—We read with great interest the article by Müllenheim *et al.*[1] published in the April 2002 issue of ANESTHESIOLOGY. They report that the release of free radicals is an important feature of isoflurane-induced myocardial preconditioning. According to recent reports, ischemic preconditioning induces a cascade with the opening of mitochondrial K_{ATP} channels, followed by the generation of free radicals to trigger the preconditioning state.[2] The preconditioning cascade continues with the activation of kinases, if the heart again becomes ischemic. Kersten *et al.*[3] have shown that isoflurane mimics ischemic preconditioning by the activation of K_{ATP} channels. We have shown that hydroxyl free radicals are released during events of ischemia and reperfusion.[4] These free radicals are known for their harmful effect on the myocardium, both directly, by damaging membranes and enzymes, and indirectly, by initiating the inflammatory process. The release of these hydroxyl radicals could be blocked effectively by halothane, ischemic preconditioning, and by the chelating compound desferral–zinc.[4,5] Isoflurane was found to have only a small, insignificant effect on free radical production. In their study, Müllenheim *et al.*[1] demonstrated that the use of antioxidants blocked the preconditioning cascade, which might have already been initiated with the opening of K_{ATP} channels by isoflurane. Their *in vivo* rabbit model indirectly evaluated postischemic oxygen free radical production, as they measured the preconditioning effect in the presence of scavengers. In our model, however, the release of hydroxyl radicals is identified by 2,3-dihydroxybenzoic acid and 2,5-dihydroxybenzoic acid measurement, the direct product of the interaction between hydroxyl radicals and salicylate given intravenously.[4] This method monitors free radical–related events *in vivo* as they are formed in the tissues. Salicylate is a highly effective hydroxyl radical trap, which, upon scavenging the hydroxyl radical, forms the stable adducts 2,3-dihydroxybenzoic acid and 2,5-dihydroxybenzoic acid by hydroxylation reaction.

Thus, during reperfusion and during preconditioning, there are free radical–related events that act in a contradictory manner. This warrants further investigation of free radical–related damage to intracellular organelles and, conversely, of free radical signaling for preconditioning.

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In Reply:—We thank Dr. Gozal for his comments. He stresses an important point: the dual role that the release of free radicals has been shown to play in myocardial preconditioning and in reperfusion injury.

The relationship between free radicals and ischemic preconditioning was shown by Tanaka *et al.*,[1] who tested the ability of various oxygen radical scavengers to prevent the development of preconditioning. They reported that the administration of the radical scavenger mercaptopropionyl glycine, or superoxide dismutase, was able to blunt the protective effect of ischemic preconditioning on infarct size in rabbits.[1] Thus, the generation of a low amount of free radicals during a short ischemic episode is not sufficient to cause cell necrosis but enough to modify cellular activity and induce preconditioning effects. This result has been confirmed in numerous studies, not only in animals but also in humans. By measuring the free radical content in coronary sinus blood during coronary artery bypass surgery, Wu *et al.*[2] demonstrated that ischemic preconditioning generates a small amount of free radicals after ischemic preconditioning compared with the larger amount seen after declamping. It has been shown in several subsequent studies that the opening of mitochondrial K_{ATP} channels is a key step in triggering the signal transduction cascade of both ischemic and pharmacologic preconditioning (*e.g.*, by opioids or volatile anesthetics).[3,4] The opening of these channels causes the release of free radicals (superoxide and hydroxyl radicals, hydrogen peroxide[3]), which, in turn, activate different kinases (*e.g.*, protein kinase C).[5]

In contrast to their beneficial effect in triggering preconditioning, a very large number of studies indicate that free radicals play a detrimental and major role in the pathogenesis of reperfusion injury. Gozal *et al.*[6] have shown that halothane prevents the postischemic production of hydroxyl radicals. A very recent study by Kevin *et al.*[7] demonstrated that not only ischemic preconditioning but also pharmacologic preconditioning by sevoflurane reduces free radical formation during ischemia and reperfusion. The extent of this decrease correlates with functional and structural protection. Thus, the reduction of postischemic free radical release by volatile anesthetics may contribute to their well known protective effects against reperfusion injury.[8] We have shown in a previous study that, in contrast to desflurane and sevoflurane, isoflurane did not reduce myocardial reperfusion injury.[8] Therefore, volatile anesthetics might differ in their effect on free radical release during reperfusion. This suggestion is supported by a recent study by Gozal *et al.*,[9] who reported that isoflurane was not effective in reducing hydroxyl radical production during myocardial reperfusion.

Thus, the release of free radicals has been shown to play a dual role in myocardial preconditioning and reperfusion injury. Volatile anesthetics might differ in their effects on free radical signaling for preconditioning and reperfusion injury.

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Bispectral Index and Mitochondrial Myopathies

To the Editor:—I am troubled that Morgan *et al.*[1] used the Bispectral Index (BIS) to measure anesthetic sensitivity in 16 patients with mitochondrial myopathy. There is no evidence (Medline search, June 5, 2002) that supports the use of the BIS as a valid measure in the abnormal brain. Patients with mitochondrial myopathy who have central nervous system dysfunction have abnormal electroencephalographic activity.[2–4] How can the BIS algorithm, based on the effects of hypnotic agents in presumably normal brains,[5] be considered valid in patients who suffer from seizures, encephalopathy, and stroke-like episodes?

Equally troubling is that the study was performed without informed parental consent. The authors state that this was not a study, and patients received "normal care," but this is incorrect. The 16 affected patients and 25 healthy "noncontrol" subjects were given (1) no premedication that might affect BIS results, and (2) a slow, nonstandard sevoflurane induction. This is hardly "normal care." This was a research protocol, and informed consent should have been obtained. That the authors' institutional review board did not require it is very disquieting.

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In Reply:—We appreciate the letter from Dr. Allen and share his concerns for the care of children. It is important to remember that most of these patients were only suspected to have mitochondrial disease and were presenting for diagnostic studies. One of us (P. G. M.) had noticed that some of the children seemed abnormally sensitive to anesthetics and, thus, had started using slow inductions and Bispectral Index® monitoring (BIS®; Aspect Medical Systems, Inc., Newton, MA) as prudent clinical care. Only in retrospect, after diagnostic muscle biopsies were performed, did we note that the apparent increased sensitivity was found in some patients with abnormal mitochondrial function.

Dr. Allen raises two separate points that we will address. The first point questions the validity of the BIS measurement as an end point for central nervous system function in the abnormal brain. The problem is, of course, that any anesthetic end point is questionable when central nervous system function is abnormal. The use of minimum alveolar concentration (MAC), or any of the derivatives of MAC, such as MAC_{awake}, is also likely to be a debatable measure of anesthetic concentration. Our point was not that BIS® definitely indicated anesthetic concentration; rather, we noted only that there were differences among patients in responses to sevoflurane when using this monitor. We did not suggest that this measurement necessarily correlated with the MAC in these patients. This is especially true since we did not attempt to reach a true steady state anesthetic concentration.

Having said this, one is left with the desire not to be entirely nihilistic. Clinically, we feel that patients with mitochondrial myopathies are at increased risk from anesthetic exposure. What, then, is a useful end point to guide our care for these patients? In each of our patients, we measured the BIS value with the patient awake and obtained a value of 96–100. Thus, none of the patients started with an extremely low value. In addition, none of these patients clinically appeared somnolent preoperatively. In the absence of a gold standard to guide our anesthetic delivery, it seems prudent to use all of the information we can gather. With our patients, we used all of the usual data (heart rate, blood pressure, arousal, breathing patterns) and added the BIS to help us determine the anesthetic concentration. In each of the patients who exhibited abnormal decreases in BIS at low concentrations of anesthetic, we also noted that the other parameters indicated that they were "asleep." Since the BIS® readings are objective, we reported the differences between patients with this parameter. We stand by our report that such differences do exist; the interpretation of their implications awaits prospective studies.

This brings us to the second point that Dr. Allen raises. He states that our approach does not reflect "normal care" and represents a research protocol. Most anesthesiologists have cared for unstable or elderly patients in whom a heightened sensitivity to induction agents was suspected. It is common to "go slowly" with the induction agent in such patients in order to gauge their response. Does this represent a departure from "normal care?" In the case of these patients, we merely went slowly so that we could gauge their response. Our department normally uses preoperative sedation in less than half of our pediatric patients, so this omission does not represent a deviation from normal care and was part of our attempt to induce anesthesia slowly, with minimum drug exposure. P. G. M. began noting the relation of the BIS and sevoflurane induction after observing unusual responses in a subset of these patients. We should point out that during this time, some children with mitochondrial myopathies were agitated preoperatively, required sedation, or did not seem appropriate for such a slow induction. They were not considered in this report since the BIS measurements were not obtained under similar conditions. In each case, however, we carefully told the parents what our anesthetic approach would be and described the reasons behind it. Thus, informed parental consent was obtained regarding the administration of the anesthetic technique, as it is in all pediatric cases handled at our institution. However, we did not intend this to be a study, and we did not set it up as one. The data were gathered through a chart review. Institutional Review Board approval was obtained for the chart review, as noted in the report.

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