The Name of the Game: No Anesthesia by Cookbook

How does one optimally match anesthetic and neuromuscular blocking drugs with patient disease and concurrent drug therapy to result in the most advantageous cardiovascular response? That’s really “the name of the game” in anesthesia, especially when managing patients with severe cardiovascular disease, whether for cardiac or noncardiac surgery.

Current practice in such patients often appears relatively uniform; that is, many anesthesiologists routinely administer a synthetic narcotic-based anesthetic consisting of fentanyl (50–100 μg/kg)\(^1\) (or less commonly sufentanil\(^2\) or morphine\(^3\)) accompanied by pancuronium. The rationale behind this regimen is that the vagolytic\(^4\) and indirect sympathomimetic\(^5-8\) effects of the pancuronium will counter any untoward circulatory effects of the narcotic. Thus, it is hoped, the bradycardia that is a pharmacologic effect of the narcotic will not become manifest.

In this issue of ANESTHESIOLOGY, Thomson et al.\(^9\) challenge the wisdom of this practice. They report standard hemodynamic variables and the ECG observed in patients with severe coronary artery disease about to undergo coronary artery bypass grafting. Anesthesia was induced with fentanyl (100 μg/kg at a rate of 5 μg · kg\(^{-1}\) · min\(^{-1}\)).

Concomitantly with the narcotic, the patients received either pancuronium, metocurine, or the pancuronium–metocurine combination\(^10\) to prevent muscular rigidity and provide relaxation. The relaxant was selected and administered in a randomized, double-blind fashion, and dosage was precisely equipotent. Endotracheal intubation was accomplished after 50 μg/kg fentanyl. The experimental conditions were carefully controlled.

The rather disturbing outcome of the study, which will surprise many, is that 25% (three of 12) of the patients in the pancuronium group showed ECG evidence of myocardial ischemia, whereas no patient in the metocurine or pancuronium/metocurine group developed similar ECG changes. Ischemia occurred during heart rate increases of 28–57% above control. That such heart rate increases may occur even when fentanyl is administered rapidly is attested to by figure 1, in which a bolus of 50 μg/kg fentanyl was delivered followed by increments totaling 5 mg pancuronium. Importantly, in the Thomson et al. study, major heart rate increases were observed only in the pancuronium group.

The article by Thomson et al. again emphasizes the role of heart rate control in the prevention of myocardial ischemic episodes during anesthesia in patients with coronary artery disease. Since the recent demonstration that ischemic episodes are associated with an increased incidence of postoperative myocardial infarction,\(^11\) we can state with confidence that the increased heart rate associated with this anesthetic regimen is undesirable in patients at risk.

The vagolytic effect of pancuronium\(^4\) is well known to anesthesiologists, but the specifics of pancuronium’s various effects on the sympathetic nervous system are probably less well appreciated\(^5,8\) (fig. 2). Pancuronium can block muscarinic receptors on sympathetic postganglionic nerve terminals.\(^9\) These receptors are part of a negative-feedback mechanism whereby excessive catecholamine release is modulated or prevented. Their blockade by pancuronium removes this modifier.\(^2\) Pancuronium can block the so-called M\(_1\) muscarinic receptors located on the cell bodies of interneurons in sympathetic
Fig. 1. Hemodynamic variables in a patient with aortic stenosis and coronary artery disease undergoing anesthetic induction with a bolus of fentanyl (50 μg/kg) administered at point "F." One milligram of pancuronium was administered 2 min prior to "F," and an additional 4 mg administered in the next 4 min. There was no evidence of airway obstruction or chest wall rigidity, and ventilation was easily controlled without an oral airway. Note the precipitous increase in heart rate from 60 to 90 beats/min. SAP = systemic arterial pressure; HR = heart rate.

ganglia. These receptors control part of an inhibitory preganglionic pathway, which may act as a "braking" mechanism during heightened sympathetic activity. If these receptors are rendered less effective by pancuronium, there is less modulation of sympathetic traffic. Pancuronium may actually stimulate catecholamine release from adrenergic nerve terminals. This response undergoes tachyphylaxis (a tyramine-like effect). Lastly, pancuronium also inhibits catecholamine re-uptake by sympathetic postganglionic nerve endings, which can lead to indirect augmentation of sympathetic responses. These mechanisms, together with possible release of catecholamines by fentanyl or anesthetic or surgical stimulation despite the presence of fentanyl, may be critical factors underlying the development of ischemia in susceptible individuals. Whether this latter release is tantamount to a light level of anesthesia is a matter of conjecture. The fact is that the study of Thomson et al. documents that the phenomenon occurs more commonly when pancuronium is the primary muscle relaxant regardless of the specific mechanism responsible.

The study's emphasis upon the importance of heart rate control suggests that perhaps, at least under a "pure" narcotic technique, nonvagolytic neuromuscular blocking drugs without stimulatory effects on the sympathetic nervous system may be preferable to pancuronium. If another neuromuscular blocker is substituted, we can expect to observe other disadvantages. Thomson et al., for example, noted that while no ischemia developed in the mivacurium-treated group, one patient did become sufficiently hypotensive to require treatment with a vasoconstrictor. Mivacurium is a relatively weak histamine releaser that is nonvagolytic and does not block sympathetic ganglia. Its hypotensive effect in humans is related to this histamine-releasing property. Perhaps more importantly, it has no stimulatory effect on the sympathetic nervous system. According to Thomson et al., these properties of mivacurium may be more desirable when fentanyl is employed than the autonomic effects of pancuronium. However, several new relaxants may offer better alternatives than mivacurium alone, in terms of prevention of heart-rate increases with minimal vasodilation and blood pressure decline. Thus, atracurium, vecuronium, pipercuronium, and BWA-9381 are all nonvagolytic and should not be expected to augment sympathetic responses. In addition, the well-established, pancuronium/mivacurium combination produces little or no cardiovascular effect, ostensibly because the two drugs markedly potentiate each other's


Fig. 2. Effects of pancuronium on the sympathetic nervous system. Besides stimulating catecholamine release from adrenergic nerve terminals, pancuronium may stimulate sympathetic nervous system function indirectly in the three ways shown in the diagram. See text for explanation. Reprinted with permission from Lebowitz and Savarese, ASA Refresher Courses in Anesthesiology, vol 8, 1980, pp 103-115.
neuromuscular blocking actions, thereby facilitating paralysis with small doses that do not ordinarily appear to reach the threshold for heart rate or blood pressure changes in humans.18

On the other hand, precipitous bradycardia may be a hazard when no vagolytic drug is employed with a potent narcotic. This most frequently occurs at the commencement of administration, or during such vagotonic maneuvers as laryngoscopy, endotracheal intubation, chest incision, or sternal splitting. Whether this hazard is accentuated by such commonly prescribed medications as beta-adrenergic blockers or calcium channel blockers is not entirely clear. (In this respect, it is noteworthy that only 1 of 33 patients in the Thomson et al. study was receiving at least one of these medications, but that this did not provide protection against heart rate acceleration.) When bradycardia does occur to the extent that hypotension ensues, we prefer to treat this with either electrical pacing or a small dose (10–20 mg) of gallamine, which appears to provide a relatively predictable increment in heart rate, restoration of blood pressure, and protection from further episodes of bradycardia. We have been less impressed with the efficacy and predictability of either atropine or pancuronium for this purpose.

The article by Thomson et al. thus calls into question the common wisdom. Can even a well-designed and well-executed study in such a small number of patients really effectively cause a decline in the use of so popular an anesthetic–neuromuscular blocking drug combination? Only time will answer this question. However, the study has certainly brought to light a difference that has not been widely appreciated, which appears important to outcome, and that may add impetus to the increased use of neuromuscular blockers other than pancuronium in patients at risk for myocardial ischemia. Thus, at the least, it represents a call for greater diversity in the anesthetic management of patients with heart disease: less rote and more art; less "reflex" response and more thought; less fast-food and more cuisine. After all, isn't that really the name of the game?

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