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Shock Values

ACCORDING to anesthesia lore, we killed more sailors with thiopental than the Japanese did with bombs after the attack on Pearl Harbor.[1] The story is apocryphal,[2] but it makes a vivid teaching point that the potency of intravenous anesthetics is greatly increased during hemorrhagic shock, which is probably why we drill this story into our residents to this day.

Since that time we have learned to resuscitate trauma patients aggressively with fluid, usually crystalloid, before induction of anesthesia. In this issue of ANESTHESIOLOGY, Johnson *et al.* demonstrate that aggressive fluid resuscitation after massive hemorrhage in a pig model fails to completely reverse the profound increase in propofol potency induced by hemorrhage[3] even though hemodynamics were nearly restored to baseline levels. Figure 5 of this paper tells the entire story: a 4 mg/kg bolus of propofol drops the bispectral index of control animals to 50. However, the same dose drives the bispectral index to 0 (isoelectricity) in animals after severe hemorrhage, even though they have been aggressively fluid resuscitated.

This manuscript is the most recent installment in a series of papers from this laboratory, documenting the influence of shock on the clinical pharmacology of fentanyl,[4] remifentanil,[5] etomidate,[6] and propofol.[7] These articles tell a consistent story. Shock decreased the size of the central compartment and systemic clearance for fentanyl[4] and remifentanil,[5] resulting in increased concentrations. Shock decreased the central and peripheral volumes of etomidate, increasing the blood levels by about 20%.[6] In the case of propofol, shock decreased the intercompartmental clearance of propofol, significantly raising concentrations and resulting in increased propofol potency.[7]

Compartmental models of pharmacokinetics are an attempt to provide physiologic insight into the mathematical relationship between dose and concentration. With the probable exception of systemic clearance, there is little physiologic or anatomical "truth" to the volumes and clearances identified in pharmacokinetic models. In all likelihood, the reported changes in volumes and clearances for propofol, etomidate, fentanyl, and remifentanil tell the same story, regardless of the specific details: in shock the body becomes a blood-brain circuit, at the expense of circulation to the gut, liver, and muscles. This results in higher brain concentrations, more rapid onset, and more profound effect.

Propofol, however, has another dimension to the increased potency in shock. Hemorrhagic shock has little effect on intrinsic brain sensitivity to etomidate[6] or remifentanil.[5] Only for propofol does the brain become more sensitive in shock.[3,7,8] This may reflect the complex relationship propofol has with its lipid vehicle[9,10] and blood proteins.[11] However, propofol's combination of higher brain concentrations and increased brain sensitivity in hemorrhage is profound and dangerous.

In a series of simulations using the pharmacokinetics from these series of manuscripts, I calculated the reduction in dose to achieve the same effect with a bolus or a 10-min infusion. The results are shown in figure 1. With propofol, the dose should be reduced by 80 to 90% for a patient (or at least a pig) in hemorrhagic shock. The reduction is the same, whether anesthesia is induced by a bolus or a 10-min infusion. I will repeat this for emphasis: **a patient in hemorrhagic shock should receive only 10–20% of the propofol dose that a healthy patient would receive.** Even after vigorous fluid resuscitation, the propofol dose should be about half of what a healthy patient would receive.

The real surprise is etomidate. There is virtually no change in etomidate dose requirement with hemorrhage. Etomidate is often thought of as the drug of choice for hemodynamically compromised patients. However, I never expected its pharmacokinetic and pharmacodynamic profile to be so resistant to hemorrhage-induced alteration.

Figure 1 suggests that perhaps etomidate could be combined with 50% of the typical fentanyl dose. Although these articles indicate that no more than half of a typical fentanyl dose should be used in trauma, it might need to be reduced even further. To date Johnson *et al.* have not explored drug interactions in massive hemorrhage. The interaction between opioids and hypnotics may be more profound in hemorrhagic shock than in control patients. This would be a logical next study in this line of research. It would also be very interesting to know why etomidate does not show the pharmacokinetic changes expected from the physiologic alterations that accompany shock. Surely it does not undo the physiologic shunting of cardiac output to a blood-brain circuit: that would be catastrophic. Similarly, why does brain sensitivity increase to propofol, but not to etomidate, when both work at the $GABA_A$ receptor?

The "take home" message to the clinician is that

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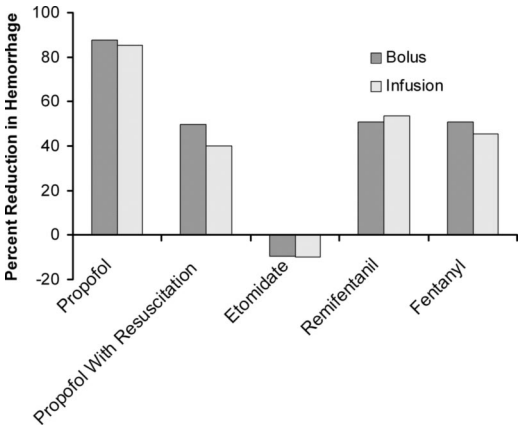

Fig. 1. The reduction in the dose to achieve a given drug effect in animals with hemorrhage, compared to control animals, based on simulations using the pharmacokinetic/pharmacodynamic models described in references 3–7.

propofol is a particularly poor choice for induction of anesthesia in patients with shock even after adequate fluid resuscitation. Even with adequate fluid resuscitation, propofol remains substantially more potent in patients with hemorrhage. In marked contrast, the potency of etomidate is nearly unchanged in shock. Thus, etomidate may be the drug of choice for anesthetic induction in patients with recent hemorrhage, even after adequate fluid resuscitation.

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Dexmedetomidine: Another Arrow for the Clinician's Quiver

ALPHA$_2$-adrenergic receptor agonists, as a class of compounds, have been widely used as adjuncts in the perioperative period to exploit their sedative/hypnotic, analgesic, anxiolytic, and sympatholytic properties for the benefit of surgical patients.[1–3] In this issue of ANESTHESIOLOGY, Ramsay and Luterman have provided three interesting case reports involving the use of high doses of the alpha$_2$-adrenoceptor agonist, dexmedetomidine, as a sole agent for anesthesia.[4] The rationale for this new, off-label use of dexmedetomidine is based on known properties of alpha$_2$-agonists to provide analgesia[5–7] while avoiding depression of respiratory function.[2,8–10] In all three cases, airway control or ventilatory dysfunction was an issue of concern. That dexmedetomidine could be used for general anesthesia had been alluded to by Ebert *et al.*,[2] who earlier demonstrated that two volunteers who received a targeted infusion to a concentration of 8 ng/ml could not be aroused. Although Ramsay and Luterman have reported successful results from the use of dexmedetomidine in high doses for surgical procedures, several caveats need to be highlighted if the application of this technique is to be more commonly applied to select patients. There are potential side effects of large concentrations of dexmedetomidine that could result in undesirable effects on the cardiovascular system. A brief review of the attributes of dexmedetomidine seems warranted.

The alpha$_2$-receptors are involved in regulating the autonomic and cardiovascular systems. Alpha$_2$-receptors are located on blood vessels, where they mediate vaso-

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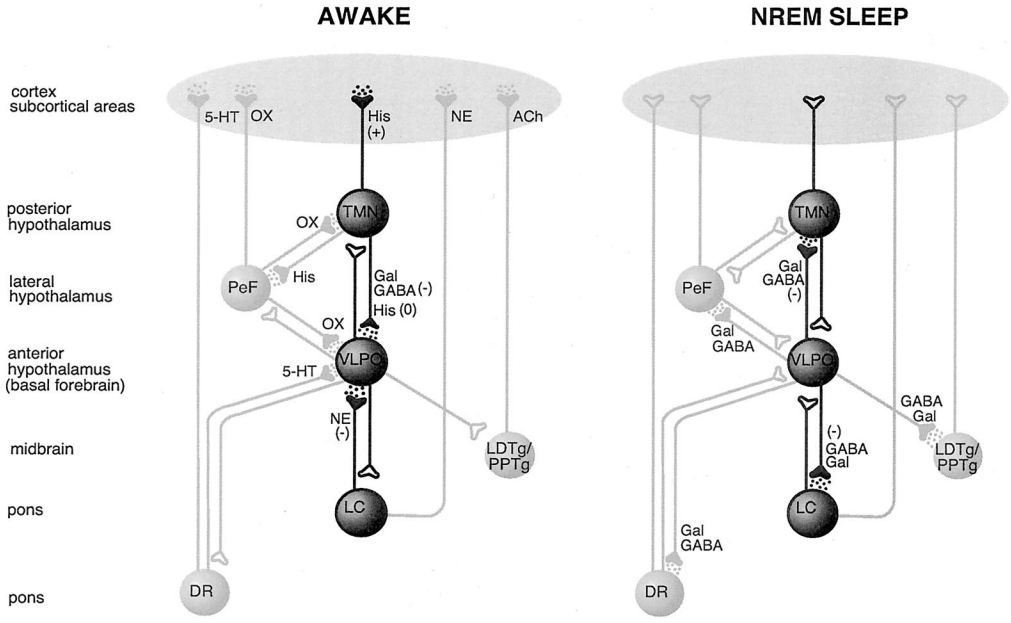

Fig. 1. Cartoon of a simple nonrapid eye movement sleep (*NREM*)-promoting pathway activated by the α_2-adrenergic agonist, dexmedetomidine.[15] The locus coeruleus (*LC*) is the site that initiates the hypnotic response to dexmedetomidine. Firing of noradrenergic neurons within the LC is inhibited thereby releasing tonic inhibition of the ventrolateral preoptic nucleus (*VLPO*). The activated VLPO is believed to release γ-aminobutyric acid (*GABA*) into the tuberomammillary nucleus (*TMN*), which inhibits its release of arousal-promoting histamine into the cortex and forebrain to induce loss of consciousness. Other aminergic pathways are thought to be similarly affected.

constriction, and on sympathetic terminals, where they inhibit norepinephrine release.[11,12] Alpha$_2$-receptors also are located within the central nervous system,[13] and their activation leads to sedation, a 60–80% reduction of tonic levels of sympathetic outflow and catecholamines,[2,10–14] and an augmentation of cardiac-vagal activity.[15] In addition, alpha$_2$-receptors within the spinal cord modulate pain pathways, thereby providing some degree of analgesia.[5–7]

Alpha$_2$-induced sedation qualitatively resembles normal sleep;[10] specifically, the endogenous, nonrapid eye movement, sleep-promoting pathways may mediate alpha$_2$-mediated sedation. Nelson *et al.* used a combination of immunohistochemistry (to monitor activity in brain nuclei), discrete application of ibotenic acid (to lesion specific nuclei), and pharmacologic antagonists as well as genetically-altered mice (to probe the participation of specific receptors) to show that endogenous sleep pathways are causally involved in dexmedetomidine-induced sedation (fig. 1).[16] Thus, the participation of nonrapid eye movement sleep pathways seems to explain why patients who appear to be "deeply asleep" from dexmedetomidine are relatively easily aroused in much the same way as occurs with natural sleep.

However, the mechanisms that have been elucidated in rodents do not completely explain why arousal was not possible in both Ebert *et al.*'s two volunteers and now in Ramsay and Luterman's three patients. Possibly, at very high levels of dexmedetomidine, nociceptive transmission is sufficiently blocked to prevent the arousing signal from disrupting the patient's hypnotic state. Dexmedetomidine and other alpha$_2$-agonists are known to interrupt nociceptive processing in the periphery, in the spinal cord, and in supraspinal sites.[3]

The respiratory sparing effects of alpha$_2$-agonists have been closely examined.[2,8–10,17–21] They are associated with minimal respiratory depression and a preservation of the ventilatory and occlusion pressure response to CO_2. In healthy volunteers, plasma levels of dexmedetomidine eightfold to 10-fold higher than the clinical range resulted in unarousable volunteers who did not respond to a painful stimulus but maintained their respiratory drive.[2] The $Paco_2$ increased from a baseline of 43 mm Hg to only 47 mm Hg. However, several reports indicate that obstructive apnea can occur with either a bolus administration or high doses of dexmedetomidine.[2,9] This first caveat suggests that patients with a history of obstructive sleep apnea might also obstruct during high concentrations of dexmedetomidine.

The second concern with the use of high concentrations of dexmedetomidine is the potential for both systemic and pulmonary hypertension and direct or reflex bradycardia. In the previously mentioned volunteer study, central pressures responded to increasing concentrations of dexmedetomidine in a biphasic manner. In the lower, clinical range, infusions decreased pressure, presumably as a result of a central sympatholytic effect. At higher plasma levels, peripheral alpha$_2$-receptor mediated vasoconstriction overrode the sympatholytic effects, resulting in increased pulmonary artery and sys-

temic blood pressures. In healthy patients with intact baroreflexes, this can lead to bradycardia. Reflex bradycardia in conjunction with the vagal mimetic property of alpha$_2$-agonists could lead to severe bradycardia or asystole. In the three case reports from Ramsay and Luterman describing the use of high doses of dexmedetomidine in surgical patients, decreases, rather than increases, in blood pressure were noted. Perhaps in an older population, the alpha$_2$-receptor vascular effects of dexmedetomidine are diminished. Nonetheless, a second caveat with administering high doses of dexmedetomidine is to be wary of increases in blood pressure and excessive slowing of heart rate.

Although both Ebert *et al.*[2] and now Ramsay and Luterman[4] have described the possible monotherapeutic application of alpha$_2$-agonists to provide an anesthetic state suitable for general anesthesia, it is much more likely that this class of compound will be used in combination with other anesthetic adjuvants in the perioperative period. Clinical studies in humans have validated the long-practiced veterinary anesthetic technique of combining alpha$_2$-agonists with ketamine to obviate both the cardiostimulatory and psychomimetic effects of the latter drug.[22] Furthermore, combining alpha$_2$-agonists with opiate narcotics or nonsteroidal antiinflammatory drugs can enhance the analgesic efficacy without increasing the respiratory depressant effect of the latter. Past studies have revealed that the dose of many induction and maintenance agents for anesthesia can be significantly reduced when combined with alpha$_2$-agonists without adverse effects.[23]

Ramsay and Luterman's interesting series of cases provides another arrow in the quiver of clinicians for the management of surgical patients with compromised airways. We anticipate further comparative studies to establish the clinical role of dexmedetomidine in difficult airway algorithms.

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