δ Opioid Receptor Antagonists

Do They Buy Time for Traumatic Hemorrhagic Shock Patients?

IN this issue of ANESTHESIOLOGY, Liu *et al.*[1] reported that the selective δ opioid receptor antagonist (ICI 174,864) may be beneficial for the early management of traumatic hemorrhagic shock in rats. With or without a small volume of fluid infusion, this δ opioid receptor antagonist increased 24-h survival rate in a model of traumatic hemorrhagic shock. Furthermore, treated animals showed improvements in mean arterial pressure (MAP), cardiac function, and increased blood flow in the liver and kidney. More interestingly, these effects were seen irrespective of whether bleeding was stopped 1, 2, or 3 h after treatment initiated.

Hemorrhage remains the major cause of preventable death after trauma.[2] The primary focus of strategies aiming to decrease mortality after trauma has been to reduce the delay between the initial trauma and hemorrhage control. However, in rural areas or in situations where prolonged prehospital transport time is expected (war trauma or mass casualty incident), there is an important need for a therapy which can prevent the hemodynamic deterioration in patients before damage control. Consequently, the concept of "buying time" until hemorrhagic control can be obtained has emerged as a research focus.

The novelty of the study by Liu *et al.* is that δ opioid receptor antagonist (ICI 174,864) provides an alternative approach to "buying time" in hemorrhagic shock. This beneficial effect on outcome was superior to a hypotensive resuscitation strategy which is considered to be the ideal strategy in hemorrhagic shock until bleeding is under control. The δ-receptor antagonist ICI 174,864 was found to reduce by half bleeding volume and to markedly reduce the amount of fluids given for resuscitation.

"The novelty of the study by Liu* et al. *is that δ opioid receptor antagonist ... provides an alternative approach to 'buying time' in hemorrhagic shock."

The study by Liu *et al.* revives the debate on the role of opioid receptor in the hemorrhagic shock. As early as 1979, it was speculated that endogenous opioids were involved in the pathophysiology of uncompensated hemorrhagic shock.[3] Several experimental studies have reported that naloxone, an opioid antagonist (highest affinity for the μ-opioid receptor and less for the κ- and δ-subtype), prolongs survival and improves hemodynamic stability in animals during hemorrhagic shock.[4–7] In humans, the clinical studies on the efficacy of naloxone in shock states have produce conflicting results. Lightfoot *et al.*[8] found in healthy volunteers that naloxone reduced the tolerance to hypovolemia induced by lower body negative pressure by 17% and was not capable to delay the onset of the uncompensated hypovolemia in humans. A meta-analysis evaluated the effectiveness of naloxone in human shock.[9] Six prospective, randomized, double-blind clinical trials were included (126 patients with septic, cardiogenic, hemorrhagic, or spinal shock). No serious adverse events or complications were reported in these six clinical trials. The MAP was significantly higher in the naloxone groups than in the placebo groups (weighted mean difference + 9.3 mmHg; 95% CI, 7.1–11.6). The conclusion of the meta-analysis was that the clinical usefulness of naloxone to treat shock remains to be determined. Clearly, there is a need for randomized controlled trials in traumatic hemorrhagic shock to assess the usefulness of δ opioid receptor antagonists.

The mechanisms involved in the hemodynamic effects of δ opioid receptor antagonists have not completely been elucidated, but it has been shown that endogenous opioids contribute to the pathophysiology of hypovolemic shock through central and peripheral sympathetic inhibition and contributes to hypotension during severe hemorrhage.[10]

Photo: J. P. Rathmell.

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◆ This Editorial View accompanies the following article: Liu L, Tian K, Zhu Y, Ding X, Li T: δ opioid receptor antagonist, ICI 174,864, is suitable for the early treatment of uncontrolled hemorrhagic shock in rats. ANESTHESIOLOGY 2013; 119:379–88.

Human studies have demonstrated that naloxone can augment sympathetic nervous activity.[11] This effect has been attributed to the presence of presynaptic μ, κ, and δ opioid receptors with receptor-specific inhibitory effects on neurotransmitter release. The effect observed in the study by Liu *et al.*[1] could be due to an increase in catecholamine release and/or effectiveness of their pressor effects.[12,13] As opiates favor a parasympathetic over sympathetic tone dominance, an additional mechanism through which opioid receptor antagonists can improve cardiovascular function is a prevention of vagal activation during hemorrhagic shock, improving myocardial function, and compensation from the hypotensive insult.[10] Other potential mechanisms could contribute to the beneficial effects of opioid receptor antagonists as modulation of inflammation or modulation of the immune system, something that is not addressed by Liu *et al.*[1]

In the study by Liu *et al.*,[1] the observed increase in MAP was not associated with an increased blood loss and was lost when subjects received concomitant fluid loading. As ICI 174,864 decreases the bleeding independently of the level of MAP (≥60 mmHg in part I and approximately 55 mmHg in part II), these results lend credence to the notion that the true enemy during the initial management of hemorrhagic shock in trauma patients is more the high-fluid resuscitation than the level of MAP *per se*. This notion is supported by the study by Poloujadoff *et al.*[14] in an animal model during uncontrolled hemorrhage. Infusion of norepinephrine was found to reduce the amount of fluid required to achieve an arterial pressure target with lower blood loss and significant improvement of survival. This effect was observed when MAP was not only allowed to fall below 40 mmHg, but also when MAP was not allowed to fall below 80 mmHg. Therefore, may be it is not the level of MAP which is deleterious during hemorrhagic shock but the way you reach it. Trying to get a high level of MAP by only using fluid resuscitation could increase the bleeding and death and justify hypotensive resuscitation with low-volume resuscitation. Trying to reach the same level of MAP by addition of a vasopressor to fluid resuscitation appears to decrease the amount of fluid, the induced bleeding and death. However, we have to be cautious about overinterpreting the results of the Liu's study.[1] And, we have to keep in mind that the optimal level of blood pressure during the resuscitation in hemorrhagic shock patient is still in debate.

Liu *et al.*[1] provide very interesting findings regarding the use of δ opioid receptor antagonists in hemorrhagic shock, and its effect on MAP suggests that it may help to reduce the deleterious effect of excessive fluid loading. However, questions and concerns remain about the clinical usefulness of δ opioid receptor antagonists to treat hemorrhagic shock in trauma patients. First, we regret that the authors did not include a study group using naloxone. It may be a less selective opioid receptor antagonist, but naloxone is already available and its efficacy/safety ratio in human has been better described.[9] Second, a randomized controlled trial in traumatic hemorrhagic shock with positive results is needed before one can recommend δ opioid receptor antagonists as a standard treatment of hemorrhagic shock. However, despite the magnitude of the heath policy concern, large randomized control trials remain uncommon in trauma, largely as a result of the many methodological[15] and logistic limitations of working in this population. However, studies such as the Clinicial Randomization of an Antifibrinolytic in Significant Haemorrhage-2[16] demonstrate that it is possible to effectively evaluate trauma management strategies by using randomized control trials. The impact of trauma on society (young patients, high mortality rate) warrants the massive amount of work needed to be able to provide robust evaluations of new strategies to reduce mortality in trauma.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Hypnos, God of Sleep

Sculpted by an unknown artist, this bust of Hypnos (*above*) was curatorially acquired from The Netherlands. Known as Somnus by Imperial Romans, Hypnos was the God of Sleep to ancient Greeks and would eventually be regarded as the God of Anesthesia. According to the poet Ovid, Hypnos' dark palace was a massive cave around whose mouth flourished opium poppies and other hypnotic herbs. The cave's silence was unbroken, save for the River Lethe's rushing over loose pebbles. That river's gentle babbling induced drowsiness and forgetfulness. The palace of the God of Sleep had no doors or gates and thus no hinges to disrupt his quiet with creaking noise. At the center of the palace, the slumbering Hypnos lay sprawled out upon gray sheets on an ebony bed, surrounded by countless dreams…. From Hypnos we derive the word "hypnotic," and from the River Lethe ether pioneer William Morton coined "Letheon," the name he used for disguising his anesthetic's identity from curious onlookers. (Copyright © the American Society of Anesthesiologists, Inc.)

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