In Reply: “The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty”

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Received: 5 October 2016 / Accepted: 6 October 2016 / Published online: 24 October 2016
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Keywords Naloxone · Opioid overdose · Opioid withdrawal

In reply:

We appreciate the interest of Lombardi et al. in our work and agree that naloxone is a very effective antidote for opioid toxicity. Though acute iatrogenic opioid withdrawal in the ED is not typically life-threatening, measures to control an agitated patient, such as chemical or physical restraint or paralysis and intubation, carry significant negative consequences and may utilize valuable resources and risk complications. These further measures may be avoided if a balance can be struck between the reversal of consequential opioid toxicity and the precipitation of opioid withdrawal. To achieve this, we believe the lowest naloxone dose that reverses respiratory depression should be utilized. The optimal dose cannot be predicted because it is impossible to know the exact opioid, the dose used, the timing, or the concomitant exposures for each patient.

Behavioral disturbances after iatrogenic acute withdrawal in opioid-dependent patients place both patients and staff at risk. Additionally, there is strong evidence documenting elevated circulating epinephrine and norepinephrine concentrations after naloxone administration, even in anesthetized

subjects [1]. This is most pronounced, in animal models, in the setting of opioid-induced hypercapnea [2]. In the opioid toxic ED patient not under general anesthesia, catecholamine release following naloxone may even be more pronounced. The elevated concentrations of catecholamines may worsen pulmonary capillary permeability and have other adverse cardiovascular consequences.

The American Heart Association (AHA) recommendation, like many others in our analysis, does not cite data for their recommendation and is likely expert opinion. Further, the recommendation for 0.4 mg IV or 2 mg IN naloxone after initiation of chest compressions is in the setting of cardiac arrest, a much more severe clinical presentation than bradypnea, hypopnea, and respiratory acidosis commonly seen in the ED. Acute withdrawal is an acceptable risk compared to the potential benefit in the former setting. However, the ability to provide oxygenation and ventilation in the ED reduces the need for rapid and complete opioid reversal in patients with the latter set of circumstances.

We agree that evidence regarding an initial naloxone dose of 0.04 mg IV is limited. Given the difficulty in prospectively studying this dosing regimen, the extensive use by a substantial number of authors who recommend this approach provides added support for its value. The risk-benefit profile of naloxone today, once under medical care that can provide respiratory support, falls towards a deliberate and cautious approach. There should not be a significant time delay to adequate dosing by starting with a low dose as naloxone can be rapidly titrated with escalating doses.

There are over 28,000 opioid deaths annually in the USA, and the number of nonfatal overdoses is obviously much higher. Naloxone will continue to be a widely used tool to reverse opioid toxicity and potentially save lives, and the more we can refine our knowledge on the dosing

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and regimen of naloxone, the better we will be able to effectively reverse opioid toxicity while avoiding precipitated opioid withdrawal.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Sources of Funding There are no sources of funding.

References

1. Kienbaum P, Thurauf N, Michel MC, Scherbaum N, Gastpar M, Peters J. Profound increase in epinephrine concentration in plasma and cardiovascular stimulation after mu-opioid receptor blockade in opioid-addicted patients during barbiturate-induced anesthesia for acute detoxification. *Anesthesiology*. 1998;88(5):1154–61.
2. Mills CA, Flacke JW, Miller JD, Davis LJ, Bloor BC, Flacke WE. Cardiovascular effects of fentanyl reversal by naloxone at varying arterial carbon dioxide tensions in dogs. *Anesth Analg*. 1988;67(8):730–6.