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

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We read with interest Connors et al.’s recent article, “The Evolution of Recommended Naloxone Dosing for Opioid Overdose by Medical Specialty” [1]. While the authors brought up interesting points suggesting that an initial low dose of naloxone may be sufficient and safer than the standard dose of 0.4 mg intravenously (IV) or intramuscularly (IM), the evidence supporting this hypothesis is debatable.

Naloxone is a very effective opioid antagonist successfully used for decades to rapidly reverse opioid-induced central nervous system (CNS)-depressant effects [2].

The authors discuss the fear of acute withdrawal symptoms provoked by naloxone with the release of circulating catecholamines. However, it is important to remember that these symptoms are rarely life threatening [3, 4].

This is a different risk than that of the Ultrarapid Opioid Detoxification (UROD) protocol, a controversial procedure consisting of withdrawal induction while under general anesthesia or heavy sedation, in which case patients can have symptoms for weeks or months after the procedure [5].

The authors cite a case report of pulmonary edema following the administration of naloxone post-operatively [1]. However, the causal relationship between naloxone, and this adverse event is not clear as many published case reports illustrate the potential risk of pulmonary edema with opioid toxicity [6]. Naloxone might solely unmask the opioid-induced pulmonary edema undiagnosed due to respiratory depression [3]. Dysrhythmias and seizures have also been reported; however, the distinction between the opioid-induced hypoxia, the patient’s underlying disease, and the effects of naloxone is difficult. Opioid-induced cardiotoxicity has been reported, therefore, the role of naloxone in dysrhythmias can be questioned [7]. To the best of our knowledge, if fatal events occurred due to naloxone administration, they are seldom reported [8].

On the other hand, 28,000 deaths, in 2014 alone, were attributed to opioid toxicity [9]. As the effectiveness of naloxone is time and dose dependent starting at very low doses could inappropriately delay the effective reversal of CNS depression [2, 10].

The evidence supporting low dose naloxone is largely based on unvalidated expert opinion. The single study cited by the authors to illustrate the efficacy of low dose naloxone suffered from several methodological shortcomings [11]. The retrospective design of the study as well the selection bias that was introduced with the patient inclusion requiring consultation of the medical toxicology consultation service limits the quality of the information extracted.

The evidence supporting the standard dose of 0.4 mg IV/IM is more robust. The American Heart Association recommends in the 2015 Advanced Cardiovascular Life Support (ACLS) guidelines 0.4 mg IM or 2 mg intranasally (IN) for a life-threatening opioid overdose, after the initiation of cardiopulmonary resuscitation (CPR) [12]. Several clinical trials and observational studies illustrated that doses ≥ 0.4 mg IV/IM

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are effective in improving the level of consciousness and spontaneous breathing and are associated with low rates of complications [4].

While it would be interesting to study lower doses of naloxone in order to limit withdrawal symptoms, the evidence supporting its efficacy at the moment is insufficient for wide acceptance. It is especially important for clinicians (and now, opioid users' family members with the take-home naloxone autoinjector) not to fear treating a patient with respiratory depression with the doses recommended by the 2015 ACLS guidelines, as the consequence of prolonging opioid respiratory depression with subtherapeutic doses of naloxone greatly outweigh the potential risks of withdrawal symptoms seldom reported with naloxone used at higher doses [12].

Compliance with Ethical Standards

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