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Response to: improvements to out-of-hospital cardiac arrest and opioid overdose treatment algorithms to enhance positive outcomes

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Dear Editor,

In a recent Perspective/Viewpoint, Davis et al.[1] outlined strategies aimed at better differentiating an out-of-hospital cardiac arrest (OHCA) from an opioid overdose or poisoning event to improve treatment algorithms and clinical outcomes. We commend the authors on this effort. However, as the opioid crisis continues to evolve, 2 of the proposed revisions to the treatment algorithm merit comment and reconsideration.

At face value, there is a compelling rationale to support the authors' recommendation of a pupillary exam to assess for miosis. Thus, miosis is a cardinal symptom of opioid overdose[2] and a better predictor of response to prehospital naloxone than restoration of respiratory rate.[3] However, within the past 5 years, the veterinary anesthetic xylazine and other alpha2-adrenergic agonists (e.g., dexmedetomidine, medetomidine) have been identified as adulterants in the illicit opioid supply ("tranq dope") with increasing frequency.[4] Alpha 2-adrenergic agonists not only exacerbate opioid toxicity by increasing respiratory depression, bradycardia, and ultimately brain hypoxia[5] but also produce miosis as part of their toxidrome[6] that is not reversed by opioid antagonists. While the presence of miosis remains useful in eliminating a diagnosis of OHCA, its value both as a definitive sign of an opioid overdose in an unresponsive, apneic patient and as a predictor of response to an opioid antagonist is diminished with changes in the illicit drug supply. Despite the presence of adulterants in the illicit opioid supply,[4,7] administration of an opioid antagonist remains a critical intervention to reverse the opioid-mediated component of the toxidrome.

In an era when synthetic opioids are linked to about 90% of opioid overdose deaths in the United States,[8] the authors' recommendation to carry 4 mg naloxone nasal spray puts patients at unnecessary risk when an overdose involves a potentially lethal dose of a synthetic opioid like fentanyl. As a competitive μ-opioid receptor antagonist, naloxone can reverse the pharmacological actions of any opioid, including synthetic opioids. However, converging lines of evidence indicate that higher naloxone doses are needed to reverse synthetic opioid overdoses compared to overdoses caused by opium-based alkaloids such as morphine.[9–11] Notably, data show that the 4-mg dose of intranasal (IN) naloxone, now generally viewed as the standard of care in a community setting, is neither fast enough nor strong enough to effectively reverse the majority of potentially lethal synthetic opioid overdoses.[9–11] The rapid onset of respiratory depression produced by synthetic opioids compared to opium-based alkaloids[12] reduces the window of opportunity to intervene and reverse an overdose. In the community setting, where ventilatory support, cardiopulmonary resuscitation, and intravenous (IV) access are generally unavailable, reversal agents are the first and often only means of restoring respiration. Within this setting, reversal strategies that rapidly deliver an opioid antagonist provide overdose victims the best chance of a successful outcome.

A validated translational model of synthetic opioid overdose was developed by the Food and Drug Administration (FDA) to provide an unbiased approach to compare the effectiveness of intramuscular (IM) and IN naloxone dosing strategies on respiratory depression and cardiac arrest following a synthetic opioid overdose.[10,13] Strauss et al.[10] reported that following an IV bolus dose of fentanyl (1.63 mg) resulting in cardiac arrest in 52% of simulated patients, a single dose of IN naloxone (4 mg) reduced the cardiac arrest rate to 21%, corresponding to a 40% mortality rate. Administering additional IN naloxone doses every 2.5 minutes (up to a total of 4 doses) did not result in a further reduction in the incidence of cardiac arrest, although the simultaneous administration of 2 doses (i.e., 8 mg) produced an additional decrement in the incidence of cardiac arrest. Qualitatively similar results were evident across overdose scenarios evaluating both a higher dose of fentanyl and a more potent synthetic opioid, carfentanil, albeit with a higher percentage of simulations resulting in cardiac arrest.[10] Based on the pharmacokinetic data obtained following simultaneous and sequential dosing of IN naloxone, the authors concluded that the absorption of naloxone following a 4 mg IN dose was too slow to effectively reverse a potentially lethal dose of fentanyl, with no benefit of additional doses administered based on the FDA's approved prescribing information (additional doses every 2–3 minutes).[10] Using this model, Laffont et al.[14] compared the effectiveness of IN naloxone (4 mg) to a single dose of IN nalmefene (2.7 mg) using the same overdose scenarios described by Strauss et al.[10] Following the 1.63 mg IV dose of fentanyl, rescue with 4 mg IN naloxone resulted in a cardiac arrest in 19.2% of simulations. Nalmefene, with a higher affinity for mu-opioid receptors[15] and an IN formulation that is more rapidly absorbed than IN naloxone,[16] reduced the incidence of cardiac arrest to 2.2%.[14] Across dosing scenarios, 4 doses of IN naloxone administered simultaneously (i.e., 16 mg) were needed to reduce the incidence of cardiac arrest to levels approaching those following 1 dose of IN nalmefene.[14] The risks associated with using a 4-mg dose of IN naloxone in a synthetic opioid overdose based on simulations

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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using the FDA's model[10,14] are consistent with a recent clinical study comparing the effectiveness of 4 mg IN naloxone to 5 mg IM naloxone in reversing fentanyl-induced apnea.[11] This study employed a crossover design in a cohort of healthy volunteers and a smaller sample of individuals who chronically used opioids. In the experimental design, apnea was produced by an IV fentanyl bolus, and naloxone was readministered every 2 minutes until adequate ventilation (defined as 80% of baseline minute ventilation) was restored. A Kaplan-Meier survival analysis in healthy volunteers demonstrated that IM naloxone restored ventilation more rapidly compared to IN administration: at 2 minutes post-administration, only one (1/16) of the subjects receiving IN naloxone had adequate ventilation restored compared to nearly half (7/16) of the subjects who received an IM injection. Complete reversal of fentanyl-induced respiratory depression was observed in all subjects by 9.2 minutes following IN administration compared to 3.9 minutes following IM administration (P = 0.0002, log-rank test). Furthermore, significantly more doses of IN naloxone (range, 2–4 doses; mode 2 for 56% of subjects) were required to fully restore respiration compared to IM administration (range, 1–2 doses; mode 1 for 50% of subjects; P = 0.0002). Qualitatively similar trends were seen in the smaller sample (n = 5) of chronic opioid users, and rescue with IV naloxone was needed in 2 subjects receiving IN naloxone. Pharmacokinetic analysis of these data demonstrated that the higher plasma naloxone concentrations produced by IM dosing in the critical early period following administration were responsible for this difference in effectiveness.[11]

Given the prevalence of synthetic opioids in the illicit drug supply,[7] these data indicate that the use of both higher strength formulations of naloxone[10,11] and a rapid acting, more potent opioid antagonist (nalmefene)[14,17] should now be reconsidered as the standard of care when an opioid overdose is suspected. Naloxone is on the WHO essential medicines list and widely available in both parenteral and IN formulations. Nalmefene (both IN and parenteral) is FDA-approved for the treatment of natural and synthetic opioid overdose.

Conflict of interest statement

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Author contributions

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