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Commentary

Time to Hit Opioids Early and Hard

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A turning point in the HIV epidemic was the introduction of protease inhibitors. It was clear to some that treatment of HIV infected individuals with these potent antiviral agents was needed as early as possible, and with this paradigm shift, HIV became a livable chronic disease (1). There are some lessons learned from the HIV epidemic relevant to the current synthetic opioid epidemic. In the current opioid epidemic, the largest increases in deaths due to opioids appears to be driven by rises in illicitly manufactured synthetic opioid use, such as fentanyl (2). In order to differentiate this rise in deaths from previous increases, many have characterized the current epidemic as the synthetic opioid era. Naloxone is a critical weapon against acute opioid overdoses. Naloxone is an opioid antagonist capable of displacing opioids at the mu receptor in the central nervous system.

Recent studies have documented the benefit in decreasing overdose deaths with take-home naloxone kits (3). In this study it was estimated that a take-home naloxone kit in British Columbia averted 33% of the deaths within a 9-month period (226 deaths). Adequate funding for better naloxone access is also critical and can become an additional challenge to countering the current opioid epidemic (4).

We and others have proposed that higher doses of naloxone than are currently available (4 mg intranasal or 2 mg intramuscular) are needed to outcompete the mu receptors that are rapidly occupied by the more potent synthetic opioids (5). The potency of fentanyl has been estimated to be 100 times more potent than morphine. In addition, fentanyl has a fast onset of action, and a high therapeutic index (6). Much of fentanyl's potency is related to its lipophilicity. For example, fentanyl and morphine have similar affinities for the mμ receptor (1.346uM and 1.168uM, respectively) (7). Morphine has a longer duration and onset of action compared to fentanyl. This is thought to be due to the more rapid influx and efflux of fentanyl in and out of the CNS compared to morphine. Extremely high levels of fentanyl have been found in the blood of overdose patients and one study suggested a mean fentanyl blood level of 52.9 ng/ml (8,9, 10). Thus, high levels of fentanyl bind a large number of mu receptors in the brain. Naloxone receptor occupancy increases as naloxone dose increases (11). Thus, high levels of naloxone must be available to compete out the large number of mu receptors bound by fentanyl.

Of public health concern are the recent reports noting that multiple sequential doses of naloxone are needed for clinical reversal in response to overdoses involving the synthetic opioids. Sommerville, et al., reported (12) a study where 83% of patients required greater than 2 naloxone doses prior to a clinical response. Of particular concern is that 36% had a fatal death within seconds to minutes after drug use. Upon Emergency Medical Service (EMS) arrival, 90% were pulseless. This rapid reversal of opioid toxicity is needed to treat overdoses involving the more potent opioids. Higher doses of naloxone should bind more mu receptors displacing the large number of receptors rapidly. This report and others support the notion that higher doses of naloxone are needed for adequate synthetic opiate reversal. Higher doses and the ability to rapidly compete out the synthetic opioids at the mu receptor may mean the difference between life and death.

The lesson learned from the HIV epidemic is applicable to the current synthetic opioid epidemic. Hitting early and hard with higher doses of naloxone may be an important countermeasure to the current synthetic opioid epidemic. As the exposure level of fentanyl cannot be determined in most overdoses, giving a higher dose of naloxone than currently being used should translate into improved mortality. The risk of underdosing naloxone far exceeds the risk of over antagonizing the effects of the potent synthetic opioids observed in the current opioid epidemic (13).

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