MEDICAL PROPHYLAXIS TO MITIGATE CHEMICAL THREATS

Assessment Of Naltrexone And Nalmefene As Prophylactic Treatment Against Carfentanil Exposure In A Non-human Primate Model

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Exposure to highly potent opioids such as fentanyl and carfentanil can rapidly cause a loss of consciousness and a potentially fatal respiratory depression at micrograms doses. Consequently, they pose both a threat to the Warfighter and are a public health hazard.

Naltrexone and nalmefene are both competitive antagonists at opioid receptors. Oral naltrexone is licensed in the US, UK and elsewhere in the world for the treatment of opioid and alcohol dependence and oral nalmefene is licensed in the UK and elsewhere in the world for the treatment of alcohol dependence. The drugs' competitive antagonism at opioid receptors means that they effectively prevent opioids from binding to and activating the receptors, thus mitigating the effects of the opioids. This action makes them suitable to protect against the effects of poisoning by opioids in a military scenario. The two drugs have very similar chemical structures, similar mechanisms of action and very similar side-effect profiles.

The aim of this study was to determine whether prophylactically administered naltrexone and nalmefene, at clinically achievable plasma concentrations could protect against lethal intravenous doses of carfentanil.

The study was carried out in the marmoset (a small non-human primate) with naltrexone and nalmefene delivered by surgically implanted osmotic pumps. The plasma concentrations were targeted to match those seen clinically following oral dosing of the licensed doses of naltrexone hydrochloride (50 mg) and nalmefene hydrochloride (20 mg) at both Tmax (approx. 1 hour) and a trough value that was still detectable (approx. 12 hours for naltrexone and 24 hours for nalmefene).

Carfentanil was administered as intravenous bolus doses at 5 minute intervals with all animals receiving 5 to 6 doses. Initially, the first pair received 1 LD50 of carfentanil at each administration. For subsequent animals, the dose was doubled at each administration following an initial 1 LD50 dose. The maximum individual dose of carfentanil administered was 16 LD50s and the maximum cumulative dose (i.e. total of 6 administrations) was 47 LD50s.

Both naltrexone and nalmefene provided protection against multiple lethal doses of intravenous carfentanil challenge. This protection was measured in terms of improved survival, through prevention of profound respiratory depression, and through reduction of both depth and duration of observed incapacitation. This effect was dependent on the dose (plasma concentration) of naltrexone or nalmefene with the higher dose providing more protection. There was little difference between the protective effects provided by naltrexone or nalmefene in these pilot studies.

Ongoing studies are assessing the ability of prophylactic naltrexone and nalmefene to prevent the effects of exposure to lethal doses of inhaled carfentanil. In this scenario, an effective prophylactic will protect respiratory drive, which will then lead to an increased inhaled dose of carfentanil, therefore it is important to understand the impact of this.

The use of prophylactic naltrexone or nalmefene would preclude the use of opioids for battlefield analgesia and anaesthesia so alternative medications would be required for these purposes.