Opioid overdose deaths can occur in patients with naltrexone implants

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From Australian coronial records, we identified five deaths involving implantable naltrexone between 2000 and 2004. One man died from acute narcotism with a naltrexone implant in place and a blood naltrexone level of 0.3 mg/L. A woman died of combined drug effect (including naltrexone) accompanied by severe pain from a naltrexone implant site. These cases indicate that patients can die from opioid overdose with a naltrexone implant and blood naltrexone levels higher than reported blockade levels. **(MJA 2007; 186: 152-153)**

Clinical records

Treatment with implanted naltrexone has been claimed to prevent relapse to opioid use[1-3] and therefore fatal opioid overdose.[4,5] We evaluated this claim by examining a series of deaths related to implanted naltrexone in the treatment of opioid dependence identified through Australia's National Coroners Information System (NCIS). This research was approved by the University of New South Wales Human Research Ethics Committee and the Monash University National Centre for Coronial Information.

The NCIS database provides access to all coronial cases in Australia, and is likely to capture most opioid-related deaths. Each database record is linked to available documents, including coronial finding, autopsy, toxicology and police reports. Naltrexone-related deaths were determined by searching for the keyword "naltrexone". All closed cases were searched in December 2005 for deaths occurring between 2000 and 2004 inclusive. Ninety-one records were identified containing the keyword, of which five involved an implantable form of naltrexone (Box).

The average age of the five people was 26 years (range, 22–32 years). Naltrexone was detected at autopsy in two and not tested for in the remaining three. All five deaths were related to the use of drugs. Two deaths occurred while undergoing naltrexone implant treatment, one shortly after naltrexone implant removal, and two about 6 months after insertion of an implant. In these last two cases, it is not known whether these people received an implant designed to last 6 months, or if shorter-acting implants were used. Both types are available in Australia.[5]

Blood concentrations of naltrexone were quantified in two cases. Male 1 died of acute narcotism with 0.3 mg/L total (0.2 mg/L free) naltrexone and 0.05 mg/L total (0.03 mg/L free) naltrexol detected. Heroin (as morphine and codeine) was the only other drug detected in toxic levels, and the autopsy report specifically highlights the danger of using excess heroin to overcome the blockade given by the active naltrexone implant.

The only woman among the five people died of a combined drug effect, including naltrexone. Soon after the insertion of a naltrexone implant and 2 days before her death, she began to experience strong pain from the implant site (abdomen). She used methamphetamine the day before her death and was discovered by her carer to be delirious, in severe pain and clutching her abdomen on the morning of her death. Her blood levels of free naltrexone and naltrexol were 0.004 mg/L and 0.035 mg/L respectively, close

Details of deaths in people with naltrexone implants listed in the National Coroners Information System, 2000–2004

Case	Cause of death*	Substances detected post mortem†	Comments
Male 1	Acute narcotism	Naltrexone 0.3 mg/L total (0.2 mg/L free), naltrexol 0.05 mg/L total (0.03 mg/L free), morphine 1.9 mg/L, codeine 0.2 mg/L, alprazolam < 0.1 mg/L, methamphetamine < 0.1 mg/L, benzoylecgonine 0.09 mg/L	Autopsy reports the danger of using excess heroin to overcome naltrexone blockade. Had a current naltrexone implant (small scar and 10 naltrexone tablets in left groin).
Female	Combined drug effect (amphetamine, naltrexone, propranolol, doxepin, diazepam, paracetamol)	Naltrexone 0.004 mg/L free, naltrexol 0.035 mg/L free, methamphetamine 1.2 mg/L, amphetamine 0.07 mg/L, propanolol 0.7 mg/L, doxepin 1.1 mg/L, desmethyldoxepin 0.7 mg/L	Worsening stomach pain near recent naltrexone implant site for 2 days before death. Also had depression and had been prescribed numerous medications.
Male 2	Multiple drug toxicity (heroin, diazepam)	Naltrexone not tested, morphine 1.9 mg/L, codeine 0.2 mg/L, diazepam 0.3 mg/L, nordiazepam 0.5 mg/L, amisulpride 0.5 mg/L	Naltrexone implant was removed 2 weeks before death for unknown reasons.
Male 3	Mixed drug toxicity (heroin, codeine, diazepam)	Naltrexone not tested, morphine > 15 mg/L (urine), codeine 11.2 mg/L (urine), diazepam trace, nordiazepam 0.1 mg/L	Naltrexone implant 6 months previously.‡
Male 4	Combined drug toxicity (heroin, alcohol and diazepam)	Naltrexone not tested, ethanol 0.04 g/100 mL, morphine 0.2 mg/L free, codeine 0.06 mg/L free, diazepam 0.4 mg/L, nordiazepam 0.5 mg/L	Naltrexone implant approximately 6 months earlier with scar.‡ Doctor who inserted implant noted that after implant his opioid tolerance would have been low and the risk of opioid overdose high.

* Causes of death were recorded directly from findings or autopsy documents. † Substances were detected in blood unless otherwise specified. ‡ Some naltrexone implants available in Australia are claimed to provide "effective" blood naltrexone levels up to 6 months after implanting.[4] Without reported blood naltrexone levels we cannot be certain of the duration of action of these implants, as shorter-acting implants may have been used. ◆

to reported "therapeutic" levels.[6] Naltrexone was viewed by the coroner as playing a causal role in the death.

Discussion

Naltrexone is an opioid antagonist that acts to inhibit the effects of opioids,[7] and is used for treating opioid dependence. Non-compliance with naltrexone is common, and is usually followed by relapse to heroin use,[8] with a substantially increased risk of fatal overdose.[9] Implanted forms of naltrexone have been advocated to reduce non-compliance.[1,10] These devices are not currently registered in Australia, but can be accessed through the Therapeutic Goods Administration Special Access Scheme.[2,4]

In this series of deaths in people treated with naltrexone implants, we have identified a case of fatal opioid overdose with detectable post-mortem levels of naltrexone. The blood level of naltrexone (0.3 mg/L = 300 ng/mL) was several orders of magnitude higher than the 2.8 ng/mL previously reported to block 500 mg doses of pure diamorphine[11] or the 2.4 ng/mL reported to completely antagonise 25 mg of heroin.[12] Blood naltrexone levels of 1–2 ng/mL are commonly quoted as being sufficient to offer protection from fatal opioid overdose.[6,13]

The case of Male 2 highlights the risks of opioid overdose after chronic naltrexone treatment. The deaths of Males 3 and 4 by multiple drug toxicity 6 months after insertion of their naltrexone implants cannot be definitively linked to the naltrexone implant treatment, as it is not known if they were using long-acting (6-month) implants. In Male 4, the possible relationship between the naltrexone implant and the subject's higher risk of opioid overdose death was noted by his doctor in the coronial finding.

The likely under-detection of oral naltrexone-related death through the NCIS database has been previously reported,[14] and naltrexone implant-related deaths might be even more under-reported. Naltrexone implants are highly likely to be overlooked at autopsy, unless the pathologist had prior knowledge of their presence (Associate Professor J Duflou, Chief Forensic Pathologist, New South Wales Department of Forensic Medicine, Sydney, personal communication). For this reason, this case study should not be used to estimate the naltrexone implant-related death rate in Australia.

The clinical implications are clear: patients can die from an opioid overdose while undergoing naltrexone implant treatment with blood naltrexone levels higher than reported "blockade" levels. Although the risk of fatal overdose is probably reduced in naltrexone implant treatment, a risk still exists. Medical professionals have a duty to consider the risks of naltrexone implant treatment and to warn patients of the possibility of opioid overdose death during compliant naltrexone implant treatment as well as after treatment cessation.

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Competing interests

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