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Articles You Might Have Missed

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Johnson FK, Ciric S, Boudriau S, et al., Effects of alcohol on the pharmacokinetics of morphine sulfate and naltrexone hydrochloride extended release capsules. J Clin Pharmacol 2012; 52:747–756.

Background: The coingestion of ethanol and opioids can lead to potentially life-threatening effects. Prior studies of hydromorphone extended release preparations showed that ethanol altered extended release characteristics, leading to product withdrawal.

Research Question: Does coadministration of ethanol affect the bioavailability or kinetics of morphine or naltrexone from a morphine sulfate/naltrexone (MS-sNT) extended release capsule?

Methods: An open-label, randomized, single-dose, four-way crossover, four sequence pharmacokinetic drug interaction study between MS-sNT (EMBEDA) 60 mg capsules and ethanol was conducted. MS-sNT 60 mg was given with 4, 20, and 40 % ethanol or water. Serial blood samples for ethanol, morphine, naltrexone, and 6-β-naltrexol concentration were obtained and used to determine standard kinetic descriptors.

Results: A total of 32 participants enrolled in the study and 31 completed all four study arms. Peak ethanol concentrations occurred within 1 h post-ingestion in all three ethanol treatment groups. MS-sNT administration with 4 and 20 % ethanol displayed profiles similar to MS-sNT with water, while MS-sNT administered with 40 % ethanol resulted in an increased rate of morphine absorption and a twofold increase in peak plasma morphine concentrations. Bioavailability of morphine across all three ethanol groups was similar to the reference arm. Naltrexone was largely undetectable in the majority of samples. Thus, kinetics were not determined.

Conclusion: Administration of MS-sNT with 4 or 20 % ethanol did not significantly alter the pharmacokinetics of the morphine dose. The administration of MS-sNT with 40 % ethanol (equivalent to more than five 1.5 oz shots of hard liquor) resulted in a modified extended release profile of morphine that was different from that of immediate-release morphine solution. Ethanol coingestion does not appear to alter naltrexone sequestration. Thus, the risk of opioid withdrawal following coingestion of ethanol and MS-sNT with alcohol may be low.

Critique: This generally well-conducted study specifically examined the single-dose kinetics of morphine and naltrexone when intact MS-sNT (EMBEDA) was coadministered with ethanol under fasting conditions. There are two methodological questions from the report. First, it is not clear how many data points were excluded in patients that experienced vomiting. Second, the subjects in this study did not receive regular release morphine, so comparing results from the current study to a prior study may not be valid. We agree with the authors that it is not feasible to extrapolate the study results to instances in which the MS-sNT is deliberately tampered with and coingested with ethanol. Unfortunately, in a majority of coingestions, it is exceedingly difficult to estimate the amount of ethanol consumed with any degree of accuracy. This makes predictive estimates as to the effects of ethanol on opioid concentrations unreliable.

Implication for Toxicologists: This study demonstrates that ethanol can disrupt the pharmacokinetics of opioid extended release preparations, leading to early release of morphine,

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and potentially posing a risk of excessive opioid effect. This phenomenon of "dose dumping," the increased peak plasma concentrations of hydromorphone, secondary to the coingestion of ethanol with other sustained release preparation like Palladone has been clearly defined.

Lofwall MR, Moody DE, Fang WB, et al. Pharmacokinetics of intranasal crushed Oxycontin™ and intravenous oxycodone in nondependent prescription opioid abusers. J Clin Pharmacol 2012; 52:600–606.

Background: The rate of misuse and unintentional overdose resulting in death from prescription opioids is increasing. Although immediate release oxycodone products are prescribed approximately five times more frequently than extended-release preparations, the nonmedical use of sustained release products is reported four times more frequently by emergency departments. A preferred method of administration among users of these sustained release products is intranasal (IN) insufflation, in the attempt to bypass the extended-release features. The pharmacokinetics of Oxycontin™, a commonly prescribed extended-release preparation, has never been studied via the IN route.

Research Question: How do the pharmacokinetics of intranasal oxycodone and its key metabolites compare to the pharmacokinetics of immediate release oxycodone solution given intravenously?

Methods: A double-blind design study was performed using eight healthy adult volunteers. The pharmacokinetics was evaluated from blood samples taken from a no-pain control condition and was compared to two IN drug conditions (crushed Oxycontin™ 15 and 30 mg/70 kg) and one IV condition (oxycodone 5 mg/70 kg). Plasma oxycodone, noroxycodone, and oxymorphone concentrations were measured using a liquid chromatography–electrospray ionization–tandem mass spectrometric method and used to determine kinetics.

Results: All drug doses were well-tolerated by participants. Oxycodone was first detected in the plasma at 5 min postdose for the IN groups and 2 min for the IV group. Time to maximum (T_{max}) parent drug concentration was 7±5, 65±73, and 51±32 min for the 5-mg/kg IV dose, 15 mg/kg IN dose, and 30 mg/kg IN doses of Oxycontin™. The mean T_{max} was significantly longer in the low-dose IN group compared to the IV dose. Noroxycodone was the major metabolite in all three conditions. The maximal plasma concentrations (C_{max}) for oxycodone, noroxycodone, and oxymorphone were significantly different among drug conditions (dose dependent). The $t_{1/2}$ of oxycodone was 3.3, 3.5, and 3.6 h in the IV, low-dose IN, and high-dose IN conditions, respectively, and was not significantly different. The $t_{1/2}$ of noroxycodone was significantly longer in the IV group as compared to the IN groups.

Conclusion: Crushed Oxycontin™ administered via intranasal route is rapidly absorbed. Intranasal Oxycontin™ was also found to have a high bioavailability. The $t_{1/2}$ of IN Oxycontin™ was not significantly different than IV oxycodone. By crushing and snorting Oxycontin™ tablets, one can effectively bypass the extended-release characteristics of this preparation.

Critique: Although the intranasal administration appeared to release drug faster than intended, the study did not contain an oral administration arm to allow a direct comparison. Head to head comparison would have been more appropriate. Another limitation is the small (N=8) sample size and the limited IN dose range of Oxycontin™. No mention was made of the formulation of Oxycontin™ used in this study. Newer formulations are intended to prevent tampering by crushing, chewing, or cutting the opioid medications in effort to release more medication. Lastly, the effects of excipients on bioavailability are unknown and future studies are needed to see if these might enhance IN Oxycontin™ delivery.

Implications for Toxicologists: By crushing and snorting extended-release opioid preparations, one might effectively bypass the extended-release properties of these products thereby increasing the risk of adverse events and mortality. Additional studies are needed to further our understanding of the pharmacokinetics of intranasally administered opioids.

Kelty E, Hulse G. Examination of mortality rates in a retrospective cohort of patients treated with oral or implant naltrexone for problematic use. Addiction. 2012 Apr 5. doi: 10.1111

Background: Since 1984, oral naltrexone has been used to treat opioid dependence. However, there have been several causes for concern on naltrexone therapy: observed increase in opioid overdose, potential for increase of non-opioid overdose, and increase in depression and suicide. Recently, surgically implanted naltrexone delivery devices have been introduced that provide stable blood levels for 145 days and have been shown to be superior to oral naltrexone in preventing opioid relapse.

Research Question: Is there a difference between mortality rates in opioid-dependent individuals prescribed with oral naltrexone versus those who had naltrexone surgically implanted?

Methods: This was a retrospective cohort study done in Western Australia from August 1997 to December 2009. Death statistics from the Australia Institute of Health and Welfare (AIHA) were compared from opioid-dependent individuals who received either oral naltrexone or implanted naltrexone. Differences among gender age, treatment period, and cause specific morality were also investigated.

Results: The study included 1,467 patients treated with oral naltrexone, 1,701 treated with naltrexone implant, and 688 with both. Subjects were predominantly male and ages ranged from 25 to 35 years. Of the 3,856 total patients, there were 228 fatalities; 77 deaths in the implant group and 151 deaths in the oral group ($P<0.0339$). The difference in mortality was especially evident in the first 4 months after therapy: the crude mortality rate was 26 vs 7 per 1,000 patient-years in the oral vs implant groups, respectively. The difference in overdose mortality was significant up to 12 months.
Conclusion: Both crude morality and opioid-specific overdose mortality were decreased in the implant group. The authors conclude that implanted delivery of naltrexone has a significant promise as a safer alternative to oral naltrexone.
Critique: Accuracy of the mortality rates reported is limited due to the potential for alternate names and the overall quality of the data submitted to AIHA. Cause of death was discerned from the ICD10 code and levels of naltrexone in the blood stream were not checked. Furthermore, conclusions made about the implanted naltrexone may not be applicable to other sustained-release naltrexone devices.
Implications for the Toxicologist: Patients taking naltrexone for opioid dependence remain at significant risk for continued opioid and non-opioid exposure with resultant toxicity. A surgically implanted naltrexone device may mitigate but not eliminate these risks.

Solhi H, Mostafazadeh B, Vishteh HRK, et al. Benefit effect of naloxone in benzodiazepines intoxication: findings of a preliminary study. Human Exp Toxicol 2011; 30:535–540

Background: Benzodiazepines have significant potential toxicity including lethargy and CNS depression. As an antidote, flumazenil is a specific benzodiazepine antagonist, but is expensive and has side effects such seizures. For this reason, centers with limited resources are in search of a cheaper and safer alternative treatment. Previous work indicates that naloxone may antagonize the GABA receptor.
Research Question: Does naloxone improve symptoms of benzodiazepine overdose?
Methods: This was a blinded random allocation study encompassing 116 patients with history and signs of benzodiazepine intoxication. Drugs included were diazepam, clonazepam, alprazolam, and lorazepam. Coingestion of opioids, tricyclics, or ethanol was an exclusion. Subjects in the treatment arms were given two doses of 0.4 mg of naloxone and then evaluated by a blinded observer 30 min later.
Results: There were no significant difference among the treatment arms when adjusting for gender, age, ingestion to treatment time, and symptoms. After treatment, the naloxone arm had significantly less patients who met the clinical judgment of lethargy ($P<0.001$), weakness ($P<0.001$), ataxic ($P>0.001$), hyporeflexic ($P<0.001$), or dysarthric ($P<0.008$). There were no statistical differences in nystagmus or hospital stay between the study arms.
Conclusion: The authors argue that this study supports naloxone as a viable reversal agent for the respiratory and CNS depression associated with benzodiazepine overdose, especially in healthcare systems with limited financial resources. They further advocate that additional studies are needed with a larger sample size.
Critique: This study had a number of design limitations that prevent accepting the results and conclusion. Regarding inclusion and exclusion, there is the inability of a sedated patient to give an accurate history, the possible secondary gains of denying other substances, and the poorly defined "screening tests" used to exclude substances such as opioids. It would be critical to definitively exclude coingested opioids in a trial to test the ability of naloxone to reverse CNS depression due to non-opioid toxicity. This is especially true in a country where tramadol abuse is common. Although the authors state that the different groups were similar prior to treatment, the control patients may have been sicker. Notation for Table 1 indicates that all bradypneic patients were in control groups. Except for GCS, all study criteria were subjective, so more than one blinded observer would have been appropriate. The paper does not state why the study included only a single observation time point of 30 min after naloxone treatment. The reported positive treatment benefits did not appear to change treatment or significantly decrease length of stay. Lastly, the study did not include potential adverse effects of naloxone treatment.
Implications for the Toxicologist: This study leaves more questions than it answers and will not impact clinical toxicology practice.