Use of Naltrexone to Block Opioid Side Effects in Healthy Volunteers: Effects of Dose and Food

Neal R. Cutler, M.D.¹,2, Barbara Newberry², John Sramek, Pharm. D.¹,2, Sherilyn Adcock, Ph.D. R.Ph. ², Henry Riordian, Ph.D.²
¹Worldwide Clinical Trials, Inc., Beverly Hills, CA; ²CEDRA Corporation, Austin, TX

Abstract
A retrospective review of common adverse events (AEs) associated with morphine (headache, nausea, vomiting and sedation) was conducted. Two sets of BE studies with similar methods with the exception of dosing. Collapsed across 2 studies fed, 2 Studies had no clinically significant abnormal findings on a physical exam, 0 All protocols were approved by a Human Subject Review Board and all subjects =0.20, p>.05) or specific AEs related to Headache (χ²=0.60, p=0.43). The comparable effectiveness of blocking common unwanted opioid side effects while having a somewhat better tolerability profile shows the relative merits of using 50mg over 100mg naltrexone dose for pretreatment.

Introduction
Morphine is a potent opioid agonist used in the treatment of severe acute and chronic pain. Morphine achieves its effects primarily through interactions with the μ-opioid receptor in the brain and central nervous system. Extended-release and formulations of morphine such as Avinza® offer the advantage of a longer interval (24 hrs) between dosing and a more controlled opioid release profile, but do not allow for dose modulation to control individual pain needs. Common side effects of extended-release morphine include incidence greater than 10%, or greater incidence as reported by the Physician’s Desk Reference (2008) were included in results. The washout period in both investigative and control formulations was just as effective as the 100mg dose at washout period in between.

Objective
The objective of this retrospective review was to use existing clinical trial data from our Phase I to determine whether naltrexone could block typical opioid side effects, and to determine whether the ability was dose dependent and affected by food feeding conditions in order to guide future BE studies involving opioids in normal healthy volunteers.

Methods
Subjects
All subjects across six were between 18 and 55 years of age, body mass index (BMI) between 18 and 30 kg/m², male or non-pregnant, non-breastfeeding females.

AE Assessment Procedures
Subjects were queried frequently with open-ended questions. 12 BE studies differing in dose of naltrexone (100mg dose = 132; 50mg dose = 72) suggested that naltrexone dose did not significantly impact self-reported, common AEs following Avinza® 120mg when examining combined AEs (23%; for 100mg vs. 21% for 50mg, p=0.20; p=0.05) or specific AEs related to Headache (p = 1.5; Naltr zona = 3.0; Sedation = 0.05). Foodfasting did not appear to impact naltrexone’s ability to decrease common unwanted side-effects to opioids. When examining 3 fasted (n = 72) and 3 fed (n = 72) all studies using 50mg naltrexone, no significant differences were seen in combined (23% AE’s fasting vs. 18% fed; p = 0.39) or specific AEs related to Avinza® 120mg treatment (Headache p = 0.05; Naltr zona = 3.0; Vomiting p = 0.01; Sedation = 0.05). Importantly, more AEs leading to discontinuation before going with Avinza® 120mg were associated with 100naltrexone pretreatment (n = 19; 10 mg pretreatment (n = 3), or 2%.) The comparable effectiveness of blocking common unwanted opioid side effects while having a somewhat better tolerability profile shows the relative merits of using 50mg over 100mg naltrexone dose for pretreatment.

Results (cont)
Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with 50 vs 100mg of Naltrexone

Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with Naltrexone (100mg) under Fed and Fasting Conditions

Importantly, more AEs leading to discontinuation before going with Avinza® 120mg were associated with 100mg naltrexone pretreatment (n = 13, or 2%.) than 50mg pretreatment (n = 3, or 2%.) p = 0.05.

Conclusions
The incidence of morphine-related AEs was lower in the 24 hour post-dose period when naltrexone was administered.

Conclusion
• The incidence of morphine-related AEs was lower in the 24 hour post-dose period when naltrexone was administered.

Comparison of Adverse Events between Morphine Bioequivalence Studies with and without Naltrexone (100mg) Pretreatment

Discontinuation due to Naltrexone AEs

Results
Comparison of Adverse Events between Morphine Bioequivalence Studies with and without Naltrexone (100mg) Pretreatment

Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with 50 vs 100mg of Naltrexone

Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with Naltrexone (100mg) under Fed and Fasting Conditions

Importantly, more AEs leading to discontinuation before going with Avinza® 120mg were associated with 100mg naltrexone pretreatment (n = 13, or 2%.) than 50mg pretreatment (n = 3, or 2%.) p = 0.05.

Conclusions
The incidence of morphine-related AEs was lower in the 24 hour post-dose period when naltrexone was administered.

Conclusion
• The incidence of morphine-related AEs was lower in the 24 hour post-dose period when naltrexone was administered.

Comparison of Adverse Events between Morphine Bioequivalence Studies with and without Naltrexone (100mg) Pretreatment

Discontinuation due to Naltrexone AEs

Results
Comparison of Adverse Events between Morphine Bioequivalence Studies with and without Naltrexone (100mg) Pretreatment

Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with 50 vs 100mg of Naltrexone

Comparison of Adverse Events between Morphine Bioequivalence Studies Pretreating with Naltrexone (100mg) under Fed and Fasting Conditions

Importantly, more AEs leading to discontinuation before going with Avinza® 120mg were associated with 100mg naltrexone pretreatment (n = 13, or 2%.) than 50mg pretreatment (n = 3, or 2%.) p = 0.05.