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

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Abstract

A retrospective review of common adverse events (AEs) associated with morphine (headache, nausea, vomiting and sedation) was conducted across a series of inpatient bioequivalence (BE) studies that compared generic versions of morphine extended release with brand morphine extended release (Avinza®).

A review of three identical studies of Avinza® 60mg, with the exception of naltrexone pretreatment (non-naltrexone n=18; naltrexone n = 32), suggested the incidence of morphine-related AEs in the 24hr post-dose period was lower when naltrexone was employed (15.6%) than not (27.8%), including reduction in the incidence of vomiting from 11% to 0%.

A further evaluation of 324 subjects across 12 BE studies differing in dose of naltrexone (100mg dose n = 132; 50mg dose n = 192) 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; $\chi 2$ =0.20, p>.05) or specific AEs related to Headache ($\chi 2$ = 1.5); Nausea ($\chi 2$ = .91); Vomiting ($\chi 2$ = 1.6); or Sedation ($\chi 2$ = 0.05).

Food/fasting 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) studies all using 50mg naltrexone, no significant differences were seen in combined (22% AEs fasting vs. 18% AEs fed; $\chi 2$ = 0.39) or specific AEs related to Avinza® 120mg treatment (Headache $\chi 2$ = 0.60; Nausea $\chi 2$ = 0.39; Vomiting $\chi 2$ = 0.0; Sedation $\chi 2$ = 0.60).

Importantly, more AEs leading to discontinuation before dosing with Avinza® 120mg were associated with 100mg naltrexone pretreatment (n = 13) than 50mg pretreatment (n = 3) ($\chi 2$ = 8.76, p < .0003). The comparable effectiveness of blocking common unwanted opioid side effects while having a somewhat better tolerability profile supports the relative merits of using 50mg over 100mg naltrexone dose for pretreatment.

Introduction

- Morphine sulfate is a potent opiate analgesic 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 oral formulations of morphine such as Avinza® offer the advantage of a longer interval (24 hrs) between dosing and a more continual pain relief profile, but do not allow for dose modulation to control drug induced side-effects.
- Common side effects of extended-release morphine (incidence 10% or greater, 2008 PDR) include nausea, vomiting, sedation, headaches, and constipation.
- Naltrexone is an μ-opioid antagonist used in the treatment of narcotic and alcohol addiction that is believed to compete for the same receptor sites as morphine and can reverse opioid toxicity.
- Little data exists showing whether naltrexone can prevent the initial common side-effects seen with morphine administration.
- Little data exists comparing the effectiveness of different doses of naltrexone and of food/fasting on blocking common unwanted opioid side effects.

Objective

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

Methods

Subjects

- All subjects across all studies were between 18 and 55 years of age, body mass index (BMI) between 18 and 30 kg/m^2, males or non-pregnant, non-breast-feeding females.
- Subjects had no clinically significant abnormal findings on a physical exam, medical history, ECG or clinical laboratory results at screening.
- Subjects did not use any prescription medication or consume grapefruit within 14 days prior to the first dose of study.
- Subjects did not consume alcohol, caffeine/xanthine or poppy seed containing beverages and foods from 48 hours prior to the first dose of study medication until the study discharge. Subject did not engage in strenuous exercise from 48 hours prior to the first dose of study medication until study discharge.
- Subjects did not smoke or use tobacco products within 60 days prior to the first dose of study medication, had no history of treatment for substance abuse (including alcohol) in the past 5 years and had a negative urine screen for drugs of abuse (amphetamines, barbiturates, benzodiazepines, cocaine, cannabinoids, opiates).
- Subjects did not take any OTC medication including cough and cold preparations, vitamins, and herbal supplements from 7 days prior to the first dose of study medication until study discharge without evaluation and approval by the Investigator.
- All protocols were approved by a Human Subject Review Board and all subjects signed informed consent.
- All subjects remained in the CEDRA Clinical Research study unit for the entire duration of each confinement period.

AE Assessment Procedures

- Subjects were queried frequently with open-ended questions.
- Investigator reviewed each adverse event (AE) and assessed its relationship to the study drug.
- Each AE was graded for severity, and the date and time of onset was recorded.
- Only AEs judged "related to study medication" between 5 minutes to 24 hours after first morphine administration were included in results.
- Very early AEs (<5 minutes) were not included in results due to extensive start-up procedures.
- All AE results used in analysis were taken from period using Avinza® brand morphine for consistency.
- Only AEs with 10% or greater incidence as reported by the Physician's Desk Reference (2008) were included in the results.
- Constipation was not included in the results due to its occurrence typically outside of the 24 hour observation period.

I. First set of comparative studies – *blocking effects*

Three sets of morphine bioequivalence studies with similar methodologies.

Morphine Alone

- 18 healthy male or female subjects.
- Compared Avinza® 60mg extended release morphine capsule to investigative formulation with same bioequivalence.
- Three periods with at least seven day washout period in-between (Avinza® fasting, test capsule fed, test capsule fasting).
- Subjects both fasted and fed.
- No naltrexone administered.

Morphine + Naltrexone

- 32 healthy male or female subjects.
- Compared Avinza® 60mg extended release morphine capsule to investigative formulation with same bioequivalence.
- Two periods for fasting subjects and fed subjects with at least seven day washout period in-between (Avinza® and test capsule).
- Subjects either fasted or fed.
- 100mg naltrexone administered 24 hours prior, 0 hours, and 24 hours after morphine dose.

II. Second set of comparative studies – *dose effects*

Twelve sets of BE studies with similar methods with the exception of dosing.

Naltrexone 100mg

- 5 studies using 100mg naltrexone.
- 132 healthy male or female subjects.
- Compared Avinza® 120mg extended release morphine capsule to investigative formulation with generic bioequivalence.
- 2 and 3 periods with at least 7 day washout period in-between.
- Collapsed across 2 studies fed, 2 studies fasted, 1 sprinkle.

Naltrexone 50mg

- 7 studies using 50mg naltrexone.
- 192 healthy male or female subjects.
- Compared Avinza® 120mg extended release morphine capsule to investigative formulation with generic bioequivalence.
- 2 and 3 periods with at least 7 day washout period in-between.
- Collapsed across 3 fed, 3 fasted and 1 sprinkle.

III. Third set of comparative studies – *food/fast effects*

Six sets of BE studies with similar methods with the exception of feeding.

Fed Condition

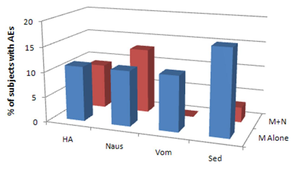
- 3 studies fed.
- 72 healthy male or female subjects.
- Naltrexone dosed at 50mg.
- Compared Avinza® 120mg extended release morphine capsule to investigative formulation with same bioequivalence.
- 2 periods with at least 7 day washout period in-between.

Fasted Condition

- 3 studies fasted.
- 72 healthy male or female subjects.
- Naltrexone dosed at 50mg.
- Compared Avinza® 120mg extended release morphine capsule to investigative formulation with same bioequivalence.
- 2 periods with at least 7 day washout period in-between.

Results

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

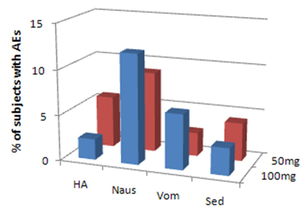


Naltrexone +/-	Number of Subjects	Headache	Nausea	Vomiting	Sedation
Morphine Alone	18	2	2	2	3
Percent of total subjects		11.1%	11.1%	11.1%	16.7%

Naltrexone +/-	Number of Subjects	Headache	Nausea	Vomiting	Sedation
Morphine + Naltrexone	32	3	4	0	1
Percent of total subjects		9.4%	12.5%	0.0%	3.1%

Results (cont)

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



Dose of Naltrexone at 100mg	Number of Subjects	Headache	Nausea	Vomiting	Sedation
	36	1	5	4	0
	36	0	4	3	2
	36	1	4	1	0
	12	1	1	0	1
	12	0	2	0	1
Totals	132	3	16	8	4
Percent of total subjects		2.3%	12.1%	6.1%	3.0%

Dose of Naltrexone at 50mg	Number of Subjects	Headache	Nausea	Vomiting	Sedation
	48	4	3	2	2
	48	2	6	1	4
	48	4	6	1	1
	12	0	1	1	0
	12	0	0	0	0
	12	0	0	0	1
	12	1	1	0	0
Total	192	11	17	5	8
Percent of total subjects		5.7%	8.9%	2.6%	4.2%

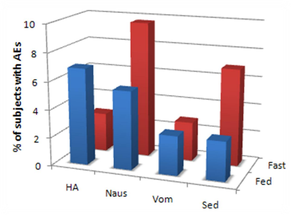
Chi-squared values	$\chi 2$=1.5 (p=0.22)	$\chi 2$=0.91 (p=0.34)	$\chi 2$=1.6 (p=0.20)	$\chi 2$=0.05 (p=0.82)

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

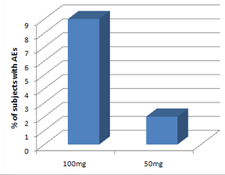
Fed state	Number of Subjects	Headache	Nausea	Vomiting	Sedation
	48	4	3	2	1
	12	0	0	0	1
	12	1	1	0	0
Totals	72	5	4	2	2
Percent of total subjects		6.9%	5.6%	2.8%	2.8%

Fast state	Number of Subjects	Headache	Nausea	Vomiting	Sedation
	48	2	6	1	4
	12	0	1	1	0
	12	0	0	0	1
Totals	72	2	7	2	5
Percent of total subjects		2.8%	9.7%	2.8%	6.9%

Chi-squared values	$\chi 2$=0.60 (p=0.44)	$\chi 2$= 0.39 (p=0.53)	$\chi 2$=0.0 (p=1.00)	$\chi 2$=0.60 (p=0.44)



Discontinuation due to Naltrexone AEs



Importantly, more AEs leading to discontinuation before dosing with Avinza® 120mg were associated with 100mg naltrexone pretreatment **(n = 13, or 9%)** than 50mg pretreatment **(n = 3, or 2%) ($\chi 2$ = 8.76, p < .0003).**

Conclusions

- The incidence of morphine-related AEs was lower in the 24 hour post-dose period when naltrexone was administered.
- Severity of AEs was also reduced in the naltrexone administered population.
- There were no dose dependent differences in naltrexone's ability to block unwanted common opioid side effects.
- There did not appear to be any differences between fed and fasted conditions in blocking opioid side effects.
- The pretreatment naltrexone 50mg dose was just as effective as the 100mg dose at blocking common unwanted opioid side effects, and also had a better tolerability profile, supporting its future use in the treatment of opioid toxicity.
- This effect will need to be verified in patients since they may have a different tolerability profile to morphine, and a different response to naltrexone, than healthy subjects.