Rapid Development of Tolerance to Adverse Events After Oral Morphine Administration to Opiate Naïve Subjects

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Abstract

Background:
Tolerance to opiate adverse events (AEs) has been observed to occur with repeated dosing, but the time course of its development is not well understood. We sought to determine whether tolerance would develop to the initial, unpleasant effects of morphine after repeated exposure in opiate-naïve subjects.

Methodology:
Three common morphine-related AEs (nausea, sedation and headache) were assessed for 24 hrs post-dose during the course of in-clinic, single-dose, two-period crossover bioequivalence studies of brand morphine 120mg ER (Avinza ®) versus bioequivalent generic versions, administered orally. Healthy, opiate-naïve volunteers (n = 90, ages 18-55) completed both periods, which were separated by 7 days.

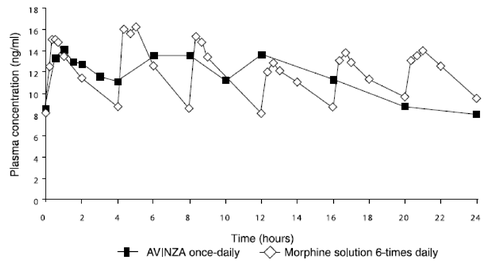
Results:
Out of all subjects, 20% (18/90) experienced one or more AE in the first period compared to 6.6% (6/90) in the second, which was a significant difference (χ^2=5.81, p= .016). The incidence of all individual AEs (nausea, sedation and headache) was lower in the second dosing period compared to the first. Nausea was the most common AE. In addition, females experienced significantly more AEs over both periods than males (32.4% vs. 13.2%; χ^2=3.75, p= .05). Most AEs (>70%) occurred within 4 hrs post dose.

Conclusion:
Overall, results demonstrate that tolerance to common initial AEs of opiates can develop even after a single exposure in opiate-naïve subjects. The potential influences of this finding, including the relationship between AE appearance and PK, subject expectations, and the therapeutic implications for initiating opiate therapy in naïve patients will be discussed.

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.
- While tolerance to repeated morphine dosing is a clinically well-recognized phenomenon, little data exists about the development of tolerance, including its time course and effect on common adverse events (AEs).

AVINZA® Extended Release (ER) versus Standard Morphine Plasma Concentrations[1]



Objective

The objective of this retrospective review was to use existing clinical trial data to examine the development of tolerance to morphine AEs in opiate naïve subjects.

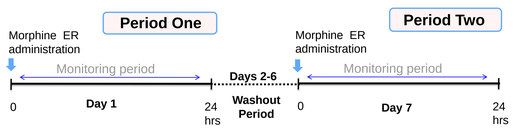
Methods

Study Design

Several morphine ER bioequivalence studies with similar methodologies were conducted at a large, phase I facility and provided comparative data.

- Avinza® 120mg or bioequivalent morphine ER 120mg was orally administered in separate in-clinic, single-dose, two-period crossover bioequivalence studies (A:B and B:A) under fasting conditions.
- A total of 90 healthy male and post-menopausal female subjects ages 18-55 participated in these studies and completed both periods.
- Naltrexone 50mg was given at 12 and 0.5 hours prior to each morphine dose to minimize potential for serious AEs (e.g. - respiratory depression).

Study Flow Sheet



Subjects

- Subjects in all studies were between 18 and 55 years of age, males or post-menopausal females, with BMI between 18 and 30.
- Subjects had no clinically significant abnormal finding 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 morphine ER.
- Subjects did not consume alcohol, caffeine/xanthine or poppy seed containing beverages and foods from 48 hours prior to the first dose of morphine ER until the study discharge.
- Subjects did not smoke or used tobacco products within 60 days prior to the first dose of morphine ER, 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).
- Subject did not take any OTC medication including cough and cold preparations, vitamins, and herbal supplements from 7 days prior to the first dose of morphine ER 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.

Assessment Procedures

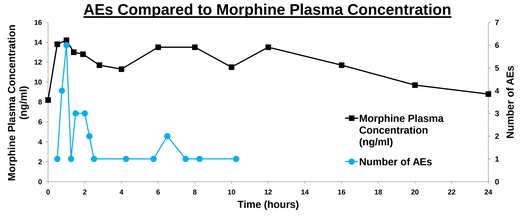
- Subjects were queried frequently with open-ended questions for each 24 hour period post-dosing (except when sleeping during designated bedtime).
- Investigator reviewed each AE and assessed its relationship to the study drug.
- Each AE was graded for severity, and the date and time of onset was recorded.
- AE times were rounded to the nearest ¼ hour.
- Only morphine ER related AEs with 10% or greater incidence as reported by the Physician's Desk Reference (2008) were included in the results.

Results

AEs Reported by Time (Hrs)

Subject	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Male/Female	M	F	M	F	F	F	F	F	M	F	F	F	F	F	M	M	M	M	F
Nausea *P1*		0.75	1.00		1.25			2.00	0.75		9.00	10.25	2.50			2.25	4.25	6.50	
Nausea *P2*	0.75							2.00										7.50	
Sedation *P1*	5.75					1.50	2.00			1.00		1.00	0.75						
Sedation *P2*	1.5									2.25				1.00					
Headache *P1*		1.00		1.50											8.25				0.50
Headache *P2*															1.00			6.50	

AEs Compared to Morphine Plasma Concentration



AEs Reported by Subject

Total Number of Subjects Experiencing AEs in Period 1= **18/90** (20%)

(χ^2=5.81, p=0.02)

Total Number of Subjects Experiencing AEs in Period 2 = **6/90** (6.6%)

AEs Reported by Gender

Men Experiencing at Least One AE in Study= **7/53** (13.2%)

(χ^2= 3.75, p=0.05)

Women Experiencing at Least One AE in Study = **12/37** (32.4%)

AEs Reported by Type[A]

AE Type	Nausea		Sedation		Headache	
Period	1	2	1	2	1	2
Number of AEs (mean onset + SD)	11 (3.7 ± 3.4 hours)	3 (3.4 ± 3.6 hours)	6 (2.0 ± 1.9 hours)	3 (1.6 ± 0.6 hours)	4 (2.8 ± 3.6 hours)	2 (3.8 ± 3.9 hours)
χ^2	3.795 (p=0.05)		0.468 (p= 0.49)		0.172 (p=0.68)	

[A] All AEs rated as mild.

Discussion

- There were significantly fewer subjects experiencing AEs in the second period (6) compared to the first period (18).
- The incidence of each AE by type was also reduced in the second period compared to the first period. This difference was significant for nausea. Sedation and headache were also reduced in the second period but the numbers were too small for statistical significance.
- All AE's occurred within the first 11 hours after treatment with morphine; most occurred within the first 4 hours (70%). There was no obvious relationship between AE appearance and plasma concentration.
- Most subjects who experienced AEs in the second period also did so in the first period.
- The 7 day washout period was sufficient to negate any pharmacokinetic (PK) carryover effect between treatments (i.e., morphine plasma concentration was zero prior to second dose). However, demonstration of tolerance to AEs suggests persistence of pharmacodynamic effects at the receptor level. Whether this tolerance develops more quickly than 7 days post-dose remains to be determined.
- An additional ten subjects experienced vomiting during the first period but were discontinued from further participation because the PK data in these bioequivalence studies would have been compromised.
- The ER formulation, with its relative persistence of morphine plasma concentrations over a 24 hour period, may also contribute to the rapid development of tolerance to AEs.
- Pre-treatment with naltrexone (identical dosing in both periods) may have minimized the AE profile, but did not eliminate any of the most common, expected AEs of morphine.
- Healthy subjects may be more sensitive to morphine related side-effects than patient populations presenting with severe pain.

Conclusion

These findings demonstrate that tolerance to common initial AEs of opiates can develop even after a single exposure in opiate-naïve subjects.

1. Reprinted from the U.S. National Library of Medicine (NLM) drug information website: http://dailymed.nlm.nih.gov/