#59

Pharmacokinetic Characteristics of Oral and Intranasal Administration of Morphine ARER (MorphaBond™ ER), a Novel Abuse-Deterrent Formulation of Morphine

Lynn Webster, MD[1]; Carmela Pantaleon[2]; Matthew Iverson, MPH[2]; Michael D Smith, PharmD[1]; Eric R Kinzler, PhD[2]; Stefan Aigner, MD[2]

[1]PRA Health Sciences, Salt Lake City, Utah; [2]Inspirion Delivery Sciences, LLC, Morristown, New Jersey

BACKGROUND

- Extended-release (ER) opioid formulations are often targeted for misuse and abuse because they contain high amounts of opioid[1]
- Drug abusers frequently use physical manipulation to increase the bioavailability of the opioid for intravenous, intranasal, and oral abuse[2]
- Abuse-deterrent opioid formulations provide pain relief while deterring common methods of manipulation and extraction to reduce the potential for abuse and misuse
- An oral abuse-deterrent formulation of ER morphine sulfate tablets (morphine ARER [abuse-resistant extended-release], MorphaBond™ ER, Daiichi Sankyo, Inc., Basking Ridge, NJ) resists physical manipulation and chemical extraction, forms a nonsyringeable material in liquid environments, and retains its ER characteristics despite manipulation[3-5]
  - Morphine ARER is formulated with multiple overlapping physiochemical barriers instead of antagonists or aversive agents to deter misuse and abuse
- We previously demonstrated that when crushed and taken intranasally, morphine ARER has a 40% lower mean maximum drug-liking score than crushed intranasal morphine ER (MS Contin®, Purdue Pharma L.P., Stamford, CT)[6]
  - There was no significant difference in drug liking between crushed intranasal morphine ARER and intact oral morphine ARER
  - These data suggest that intranasal administration of morphine ARER has a lower abuse potential when compared with intranasal administration of ER morphine

OBJECTIVE

- To assess the pharmacokinetics (PK) of morphine ARER when administered intranasally after physical manipulation, and explore the correlation between morphine PK and the pharmacodynamic (PD) parameter of drug liking

METHODS

Study Design and Treatments

- Randomized, double-blind, double-dummy, placebo-controlled, single-dose, 4-way crossover, single-center study
  - Qualification period: 3-night in-clinic double-blind naloxone challenge (1 day) and drug discrimination test (2 days)
  - Treatment period: double-blind; 4 treatment sequences with a 2-night stay for each; each treatment appropriately blinded to route of administration, and separated by a 7-day washout period
    - Crushed intranasal morphine ARER 60 mg
    - Intact oral morphine ARER 60 mg
    - Crushed intranasal morphine ER 60 mg
    - Placebo

Subjects

- Key inclusion criteria:
  - Healthy male and female subjects 18 to 55 years of age
  - Nondependent, recreational opioid users (nonmedical use of opioids on at least 10 occasions in the past year and at least once in the preceding 12 weeks)
  - Subjects must have insufflated drugs at least 3 times in the past year
- Key exclusion criteria:
  - Current treatment for a substance abuse disorder
  - History of drug or alcohol dependence
  - Positive urine drug screen

Pharmacokinetic Assessments

- Blood samples were obtained predose and at prespecified timepoints postdose (at 0.25, 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hours)
- Plasma morphine levels were assessed using a validated liquid chromatography, tandem mass spectrometry method (calibration range, 0.725 to 145 ng/mL); values below the lower limit of detection were reported as 0 ng/mL
- PK parameters were calculated using a noncompartmental model (Phoenix WinNonlin 6.3; Certara®, Princeton, NJ)
  - Maximum observed plasma concentration (C_{max})
  - Time associated with C_{max} (T_{max})
- Abuse quotient (AQ; C_{max}/T_{max}), a surrogate measure associated with drug liking and abuse potential, was also calculated[7]

Pharmacodynamic Assessment

- As previously reported,[6] drug liking was assessed at various times postdose (at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, and 24 hr) using a bipolar visual analog scale (0 = strong disliking, 50 = neither like nor dislike, 100 = strong liking)
  - Subjects recorded their response to the question "Do you like the drug effect you are feeling now?"
- The maximum drug liking score (E_{max}) was used in the PK/PD correlation analyses

Safety Assessments

- Adverse events (AEs) were recorded using the *Medical Dictionary for Regulatory Activities* (MedDRA version 7.1)

Statistics

- Relative bioavailability was calculated for C_{max} using the ratio (and 90% confidence intervals) of geometric means for morphine
  - Analysis of variance models were used to test the differences in PK parameters between crushed intranasal morphine ARER and crushed intranasal morphine ER. The SAS (SAS Institute Inc., Cary, NC) mixed-effect linear model procedure (PROC MIXED) with the PK parameter as the dependent variable, treatment, sequence, and period as fixed effects, and subject nested within sequence as a random effect was used. PK parameters were $\log_e$-transformed with the exception of T_{max}
  - Confidence intervals were based on the least square (LS) means estimation using the mean square error from analysis of variance models
- Logarithmic regressions were fitted to PK/PD dose-response plots to assess correlation between mean PK parameters and mean drug liking; coefficient of determination (R^2) was calculated

RESULTS

- 48 subjects entered the study and passed the naloxone challenge; of these, 27 passed the drug discrimination test and 25 completed the treatment phase
  - Most were white males with a history of alcohol and tobacco use and an average age of 25 years **(Table 1)**
  - All subjects had used opioids recreationally in the past 12 weeks, with a mean of 12.1 times for men and 9.0 times for women
  - All intranasal doses were completely (100%) insufflated as confirmed by intranasal check

Table 1. Baseline Demographics

Characteristic	Subjects (n = 27)
Age, years	
Mean (SD)	25.4 (6.57)
Median (range)	23.0 (19.0–53.0)
Sex, n (%)	
Male	23 (85.2)
Female	4 (14.8)
Body mass index, kg/m^2	
Mean (SD)	24.9 (3.89)
Median (range)	24.3 (19.1–32.9)
Alcohol use, n (%)	24 (88.9)
Tobacco use, n (%)	20 (74.1)

Pharmacokinetics

- Mean maximum plasma morphine concentration was lower for crushed intranasal morphine ARER (26.2 ng/mL) compared with crushed intranasal morphine ER (49.5 ng/mL) **(Figure 1 and Table 2)**
  - The morphine C_{max} was 47% lower for crushed intranasal morphine ARER than for crushed intranasal morphine ER
- The median T_{max} for morphine was 46% longer for crushed intranasal morphine ARER than for crushed intranasal morphine ER
- The PK profile of crushed intranasal morphine ARER was similar to that of intact oral morphine ARER, albeit the overall exposure to morphine was lower for crushed intranasal morphine ARER than for intact oral morphine ARER (data not shown)

Figure 1. Mean Plasma Concentration-Time Profile of Morphine by Treatment

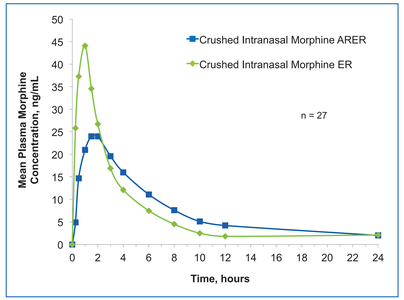


Table 2. Pharmacokinetic Parameters of Morphine

Parameter	LS Mean*			Ratio %† (95% CI) of Crushed Intranasal Morphine ARIR vs	
	Intact Oral Morphine ARIR	Crushed Intranasal Morphine ARIR	Crushed ER Morphine	Intact Oral Morphine ARIR	Crushed ER Morphine
C_{max}, ng/mL	17.72	24.03	46.85	135.6 (118.4–155.3)	51.3 (44.8–58.7)
T_{max}, hr	1.83	1.74	0.98	-0.09 (-0.374–0.192)	0.76 (0.483–1.042)
AQ, ng/mL/hr	12.1 (7.2)	16.7 (8.5)	74 (67.4)	N/A	N/A

AQ = abuse quotient; CI = confidence interval; C_{max} = maximum observed plasma concentration; N/A = not available; T_{max} = time associated with C_{max}.

*Least squares (LS) means are backtransformed from Ln-transformed least squares mean calculations, except for T_{max}, which was based on nontransformed least squares mean calculations. AQ values are untransformed means (standard deviation).

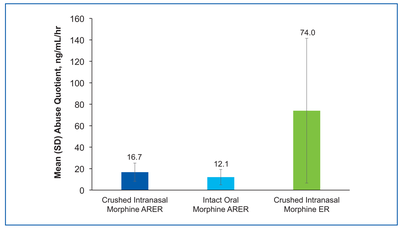
†Values are the ratio of the LS mean values, except for T_{max}, which is the difference between the test and reference products.

n = 27 for crushed intranasal morphine ER and n = 26 for both morphine ARIR treatments.

Abuse Quotient

- AQ for crushed and intact morphine ARER was 77% and 84% lower than that for crushed intranasal morphine ER, respectively **(Table 2, Figure 2)**
  - There was a large variability in the T_{max} for morphine ER, resulting in a wide range for AQ (15.9 to 298.7 ng/mL/hr)

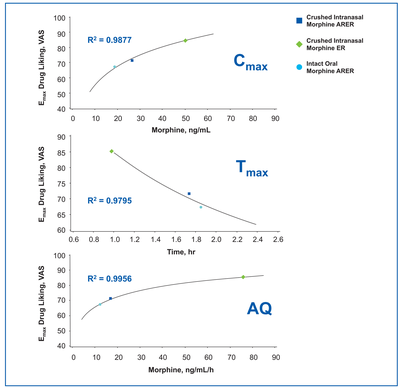
Figure 2. Abuse Quotient



Pharmacokinetic/Pharmacodynamic Correlation

- Logarithmic regressions were used to fit a curve based on the PK and PD data for all 3 active treatments; a strong association across all active treatments was observed between mean morphine PK parameters and drug liking **(Figure 3)**
  - There was excellent correlation between E_{max} of drug liking and C_{max}, T_{max}, and AQ with an $R^2 \geq 0.9795$ for all comparisons

Figure 3. Average Dose-Response Plots of Drug Liking E_{max} vs PK Parameters



Safety

- A full report on the safety data from this study was previously published[6]
  - All AEs were mild in intensity
  - The most frequently occurring AEs included nasal congestion, rhinorrhea, and epistaxis, all of which are associated with intranasal administration
  - Common opioid-related AEs including nausea, vomiting, and generalized pruritus were the only other AEs that occurred in more than 10% of subjects

CONCLUSIONS

- When morphine ARER was crushed and administered intranasally, the peak plasma morphine concentration was significantly lower compared with intranasal administration of crushed morphine ER
- The T_{max} of morphine ARER was similar between intranasal and oral administration and the C_{max} was slightly higher for intranasal administration, which support the retention of ER properties of morphine ARER when manipulated
  - These data are consistent with the similar maximum drug liking scores observed with intranasal and oral morphine ARER[6]
- The AQ of intranasal morphine ARER was approximately 3 to 4 times lower than that of intranasal morphine ER
- Mean morphine C_{max}, T_{max}, and AQ strongly correlated with drug liking, suggesting that the PK profile of morphine ARER was predictive of a lower abuse potential
  - However, given the inherent inter- and intraindividual variability associated with opioid absorption, additional research is needed to better evaluate the predictive value of PK parameters for PD response and abuse potential
- Data from this clinical abuse potential study suggest that morphine ARER has a lower abuse potential via the intranasal route of administration when compared with ER morphine

REFERENCES

1. Katz N, et al. *Am J Drug Alcohol Abuse*. 2011;37:205–17.
2. Moorman-Li R, et al. *P & T*. 2012;37:412–21.
3. Bianchi RP, et al. Extraction testing of a novel extended-release, abuse-deterrent formulation of morphine, Morphine ARER, in common solvents. Poster presented at the 33rd Annual Scientific Meeting of the American Pain Society; Tampa, FL; May 1–2, 2014.
4. DiFalco R, et al. Abuse-resistant, extended-release morphine is resistant to physical manipulation techniques commonly used by opioid abusers. Poster presented at PAINWeek; Las Vegas, NV; September 4, 2014.
5. Kinzler ER, et al. In vitro evaluation of morphine ARER potential for abuse via injection. Poster presented at PAINWeek; Las Vegas, NV; September 4, 2014.
6. Webster LR, et al. *Pain Med*. 2017;18:1303–13.
7. Webster LR, et al. The effect of different C_{max}/T_{max} ratios on euphoria and liking following oral oxycodone dosing in opioid-experienced, nondependent, recreational drug users. Poster presented at the American Academy of Pain Medicine 25th Annual Meeting; Honolulu, HI; January 28–31, 2009.

DISCLOSURES

LW is an employee of PRA Health Sciences, and has received honorarium for consulting or advisory boards from Alcobra, Daiichi Sankyo, Egalet, Elysium, Inspirion, Insys, Kempharm, Pain Therapeutics, Pfizer, Shionogi, and Teva. **MDS** was an employee of PRA Health Sciences at the time of the study; he is currently an employee of KalVista Pharmaceuticals Inc. **CP, MI, ERK, and SA** are full-time employees or consultants for Inspirion Delivery Sciences, LLC. The authors acknowledge Manish Shah and Ray DiFalco of Cerovene for their role in the study. This study was funded by Inspirion Delivery Sciences, LLC. Writing and editorial assistance was provided by Kelly Cameron, PhD, of JB Ashtin, and funded by Daiichi Sankyo, Inc.