

Case Study II: Systemic Delivery of Small Molecules

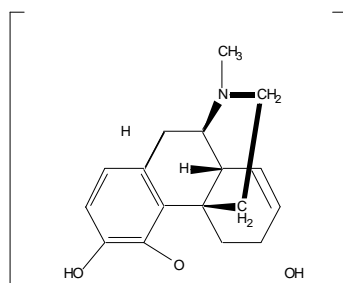
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Presentation Outline

- Introduction: Inhaled Morphine
 - Product concept
- Case Study of Development/Regulatory Issues
 - Regulatory Strategy
 - CMC
 - Preclinical
 - Clinical
- Conclusions

Small Molecule: Morphine



- Most widely used opioid
- Schedule II drugs (DEA controlled substance)
- Indicated for severe acute and chronic pain
- Hepatic metabolism; renal excretion;
- Pharmacologic effects include analgesia, euphoria, somnolence, respiratory depression, reduced gastric motility and physical dependence
- Inhalation route used for years

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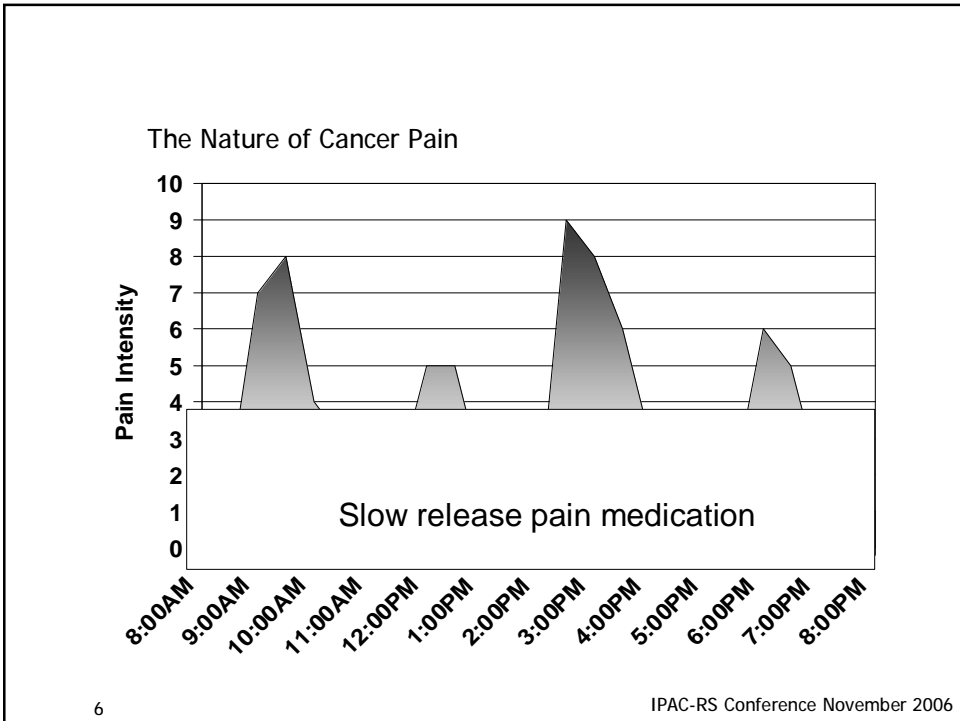
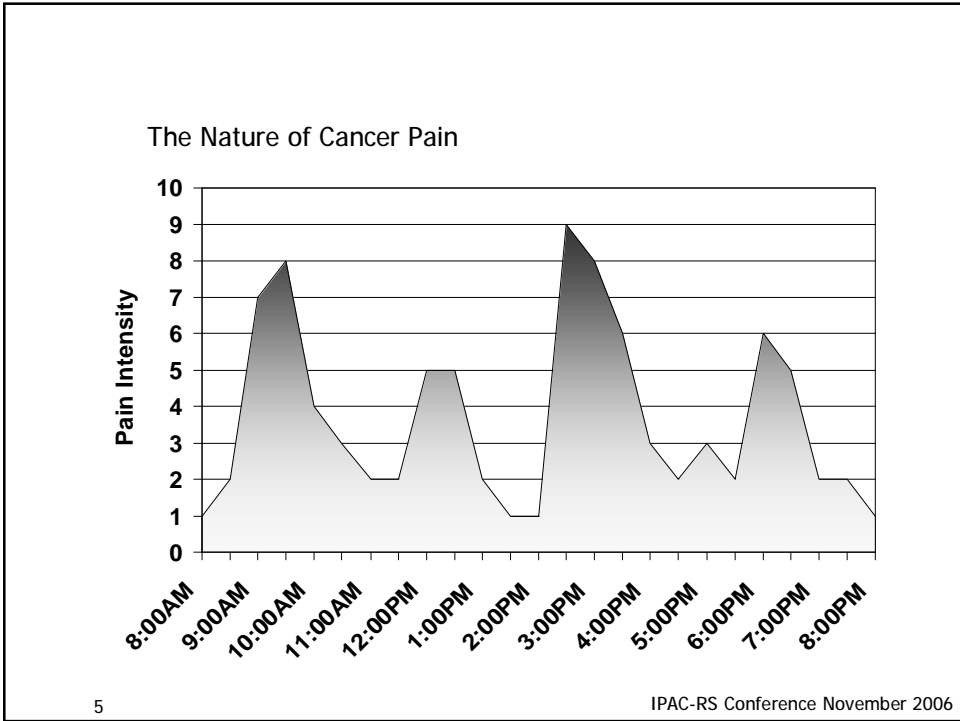
The AERx[®] Pain Management System



- Electromechanical device
- Breath monitoring and feedback
- Compliance monitoring and download capability
- Single-use, 50 μ L dosage form: 50 mg/ml aqueous formulation (=2.5 mg morphine sulfate per strip)
- ED approx 65%, lung absorption approx. 100% (=1.6 mg/strip in the blood)

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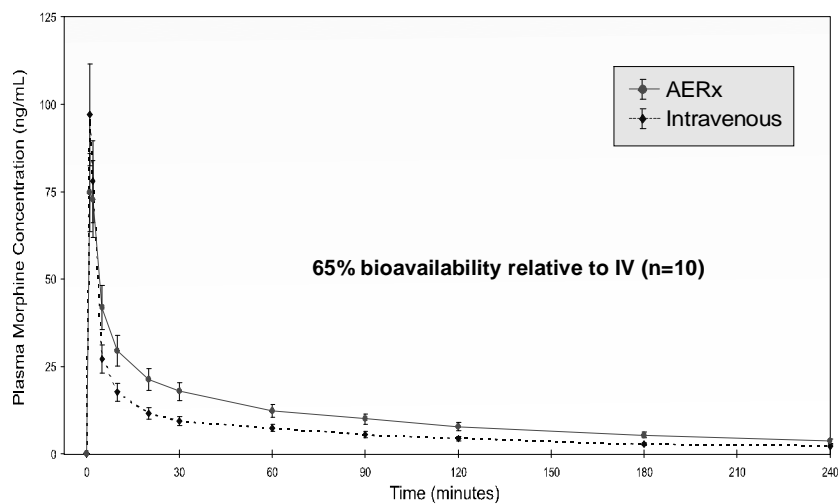
Possible Advantages of Inhaled Opioids

- Compared to intravenous:
 - greater convenience; lower risk of site infection or thrombosis.
 - may allow early hospital discharge
- Compared to oral or transmucosal:
 - superior time to analgesia; may translate into improved quality of life
 - may be able to decrease baseline analgesia; fewer side-effects
- Provides the most rapid-acting option for non-invasive treatment of breakthrough pain

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AERx Morphine: Phase 1 Pharmacokinetic Study



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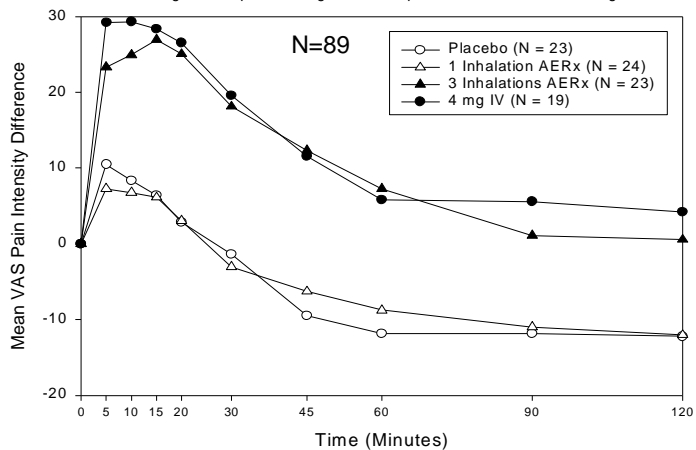
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AERx Morphine: Phase 2 Post-Op Pain Study

Mean VAS Pain Intensity Difference from Baseline by Study Group and Time

All available data before remedication/rescue

Missing data imputed using LOCF. All points have N's shown in legend.



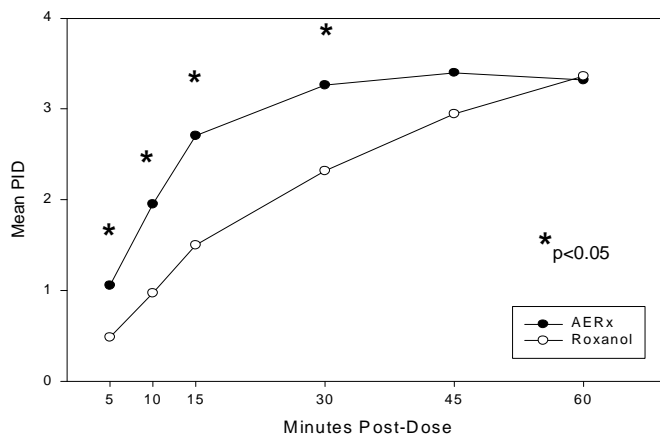
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AERx Morphine: Phase 2 Cancer Pain Study

Mean Pain Intensity Difference Scores Over Time by Treatment

(Based on 16 patients)



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Case Study: Product Development Issues

- Overall Regulatory Strategy:
 - 505(b)2
- CMC
 - Aerosol performance requirements: systemic vs topical
 - Drug-device combination issues
- Preclinical
 - Carcinogenicity
- Clinical development
 - Selection of Indication To Study
 - Safety, Abuse & Diversion

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- Regulatory Issues

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Regulatory Issues (1)

- Regulatory path: 505(b)2 :
 - application is one in which the studies on the drug itself “were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or whom the investigations were conducted”
 - applications regardless of the similarity or dissimilarity of the drug product to an already approved drug product... Such applications may be for variations of approved drug products,
 - applications for a change in an already approved drug supported by a combination of literature or new clinical investigations and the agency's finding that a previously approved drug is safe and effective

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Regulatory Issues (2)

- IND filed with the Anesthesiology Division
 - Consultative reviews with Pulmonary Division
 - CDRH involvement (no separate device application)
- Need for a Risk-Management plan
- Multiple interactions with the FDA

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- CMC

CMC Issues

- Solubility of morphine and dose-target
- Applicability of MDI/DPI *in vitro* aerosol specs:
 - Topical vs systemic drug
- Drug-device
 - Separate release of drug and device vs system release
- Testing of device:
 - Engineering tests (shock, vibration, drop tests, temp/humidity)
 - Device stability testing
 - Biocompatibility testing

- Preclinical

Preclinical

- Need for long-term toxicology data
 - Extensive human data on inhaled morphine
 - Testing of degradants in formulation
- Need for 2-year carcinogenicity testing
 - Extensive data on human use
 - Multiple formulations approved and widely used
 - Available data from NTP on codeine

- Clinical Development

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Clinical Development Issues (1)

- Selection of Indication(s)
 - Acute pain e.g. post-surgical pain
 - Breakthrough pain e.g. cancer pain
 - Chronic pain e.g. O-A, back pain
 - Precedents & off-label use issues
- Requirement of placebo-testing
- Satisfying the Pediatric Rule
- Size of exposure data required for filing

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Clinical Development Issues (2) – Abuse & Diversion control

- 1000-event memory offers automatic controlled substance record keeping
- Electronic ID port provides security via uniquely serialized ID keys
- Device “keyed” to a specific patient
- Healthcare professionals have a key to set/change dosing parameters:
 - Enable/disable patient key
 - Select drug type (confirm packet recognition)
 - Maximum dose
 - Lockout period to prevent overdosing



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Conclusions: Lessons learned so far...

- Applying new technology to generic drugs may still raise significant development issues
- A very good understanding of all aspects of the product development is critical for success
- Close interaction with regulatory authorities is essential
- Challenging the FDA is not necessarily a bad thing
 - Especially if your position is ultimately accepted!

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