New Opioid Formulations: Hope on the Horizon

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Outpatient: Critical Issues

- Utilize Optimal Opioids
- Optimize Route of Delivery
- Abuse-Resistant Formulations
- Safe Dosing/Prescribing
- Opioid Tolerance/Dose Escalation

Utilizing Optimal Opioids

- Avoid opioids with active metabolites
- Avoid untoward effects (e.g., histamine release)
- Match opioid half-life to indication to avoid lack of titration for acute pain and extended-release formulations for chronic pain
- Decreased respiratory depression
- Decreased physical dependence
- Decreased opioid tolerance

Optimize Route of Delivery

- Choose route that avoids poor bioavailability, thereby avoiding excess opioid loading
- Choose route that matches the opioid's intrinsic characteristics
- Pick route of delivery to match indication (acute vs. chronic pain)

Need to Improve Bioavailability

Oral Route Bioavailability:

- Oral morphine (MSContin, Avinza) – 30%
- Oral oxymorphone (Opana IR, ER) – 10%
- Oral hydromorphone (Dilaudid) – 30-35%
- Oral oxycodone (OxyIR, OxyContin) – 60-80%

Other Routes:

- Fentanyl patch (IonSys, Duragesic) – 30-70%
- Fentanyl TM (Actiq, Fentora) – 50-65%

Double Trouble:
Extended-Release Low Bioavailable Drug Formulations

IV dose: 0.2mg

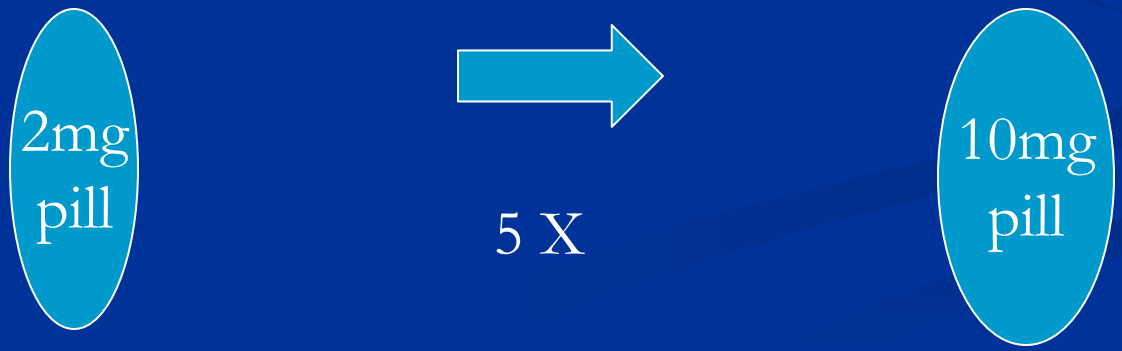
50 X

Crushed IV dose: 10mg

10 X

Oral BA = 10%

Extended-Release



Optimal Scenario:
Methadone Resists Abuse

IV dose: 5mg

1 X

Oral BA = 90%

5mg pill

1 X

Crushed IV dose: 5mg

Extended-Release not necessary

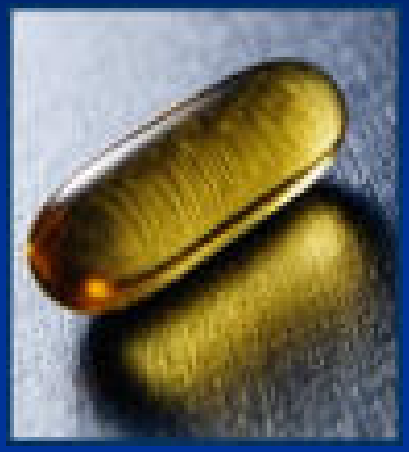
5mg pill

Abuse-Resistant Formulations

- Need to avoid the ability to crush or rapidly extract drug with ethanol (OxyContin, Palladone)
- Remoxy – SABER technology (Durect/Pain Therapeutics/King Pharmaceuticals)
- Naloxone/Naltrexone additive
  - Suboxone (buprenorphine/naloxone)
  - Oxytrex (oxycodone/naltrexone)

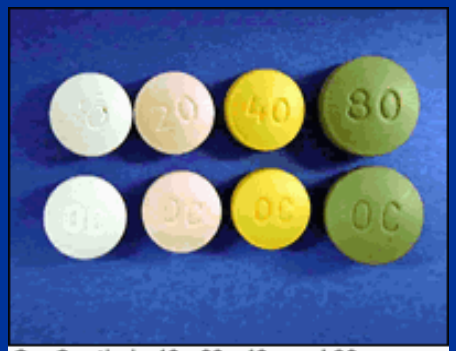
Abuse-Resistance In Practice

Remoxy Intact



Crushed

Oxycontin® Intact



OxyContin in 10-, 20-, 40-, and 80-mg forms seized by the DEA Washington, DC, Field Division

Crushed

No Rapid Release of Oxycodone = No Euphoria

Transdermal Opioids

- Due to delay in onset of plasma levels, this route appears best for chronic pain conditions
- Opioids delivered transdermally:

  Fentanyl (Duragesic, IonSys)

  Sufentanil (Endo, in development)

  Buprenorphine (Europe, Australia)

  Hydromorphone (Altea, in development)

Outpatient Cancer Breakthrough Pain

- Actiq, Fentora (buccal TM delivery of fentanyl)
- Rapinyl (sublingual fentanyl tablet)
- Many other fentanyl formulations in pipeline
- Saliva response results in at least half of the drug being swallowed, lowering bioavailability
- AcelRx sublingual sufentanil NanoTab™ formulation – above 90% bioavailability

Safer Dosing/Prescribing

- Scheduled drugs less trackable than UPS
- Patient reported usage, pill counting and urine testing only methods to determine opioid usage
- Need better tracking around opioid dosing history
- RFID chip on OxyContin bottles only helps track from manufacturer to pharmacy
- AcelRx electronic NanoTab™ dispensers will allow download of dosing history

Opioid Tolerance

- Opioid dose escalation at all time high
- Pain now the "5th Vital Sign", fears slightly abating around high-dose prescribing
- Dose escalation driven by tolerance and disease progression
- Research into novel mechanisms to treat or avoid opioid tolerance are vital
- Until then, opioid rotation is only option

Opioid Tolerance

- Complex clinical phenomenon, not easy to study
- Studies not run long enough, nor detailed enough
- Recent studies suggest age plays important role
- Targets: NMDA antagonists, mu-receptor antagonists, bivalent mu/delta ligands, RGS protein modulators

Inpatient: Critical Issues

- #1 hospital medication error: Analgesics
- Most common mistake: Wrong Dose
- Patient-Controlled Analgesia (PCA)

  IV PCA – misprogramming, basal rates, etc

  IonSys – trandermal fentanyl on-demand

  AcelRx – sublingual sufentanil NanoTabs™ with hand-held PCA dispenser

Is Morphine the Gold Standard?

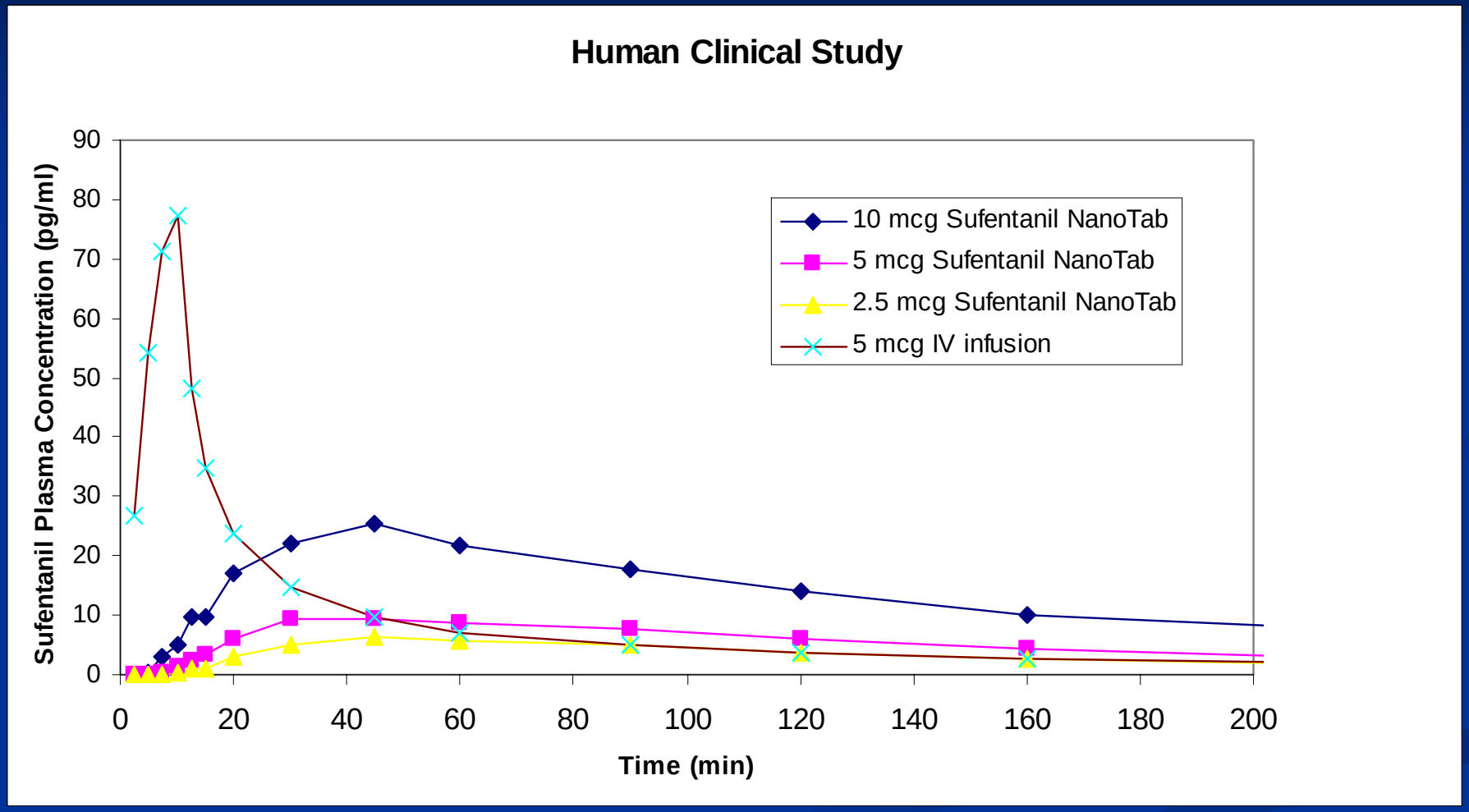
- Morphine suffers from a number of pitfalls
- Relatively high-level of side-effects compared to other opioids
- Active metabolites, M3G and M6G, that build up particularly rapidly in the elderly
- M3G produces dysphoria, anxiety, anti-analgesia
- Often leads to overdosing and death due to perceived patient discomfort by nurse/MD

Post-Operative Pain

Is IV Route the Gold Standard?

- For acute pain, IV route of administration often held up as the gold standard
- However, IV opioids often achieve rapid, high plasma drug levels that can lead to respiratory depression
- Sublingual sufentanil NanoTabs™ offer rapid onset with safer drug plasma profile

Phase I Data in 12 Subjects



Summary

- Need to pursue optimal opioids with optimal routes of delivery based on patient needs
- More aggressive tracking of patient dosing history in outpatient setting
- Pursue novel therapies to avoid or treat opioid tolerance to minimize dose escalation in chronic pain conditions
- Simplified patient-controlled opioid dosing
- Never avoid pursuing optimal pain therapies out of fear of abuse/diversion