Management of Acute Pain in Emergency Medicine: Sufentanil Sublingual Tablet 30 mcg

EMS World Expo, Learning Center - ALS Tract
Thursday, Oct 6 2016 12:15PM - 12:45PM
Pamela P. Palmer, MD, PhD
Disclosures

- AcelRx employee
Course Outline

- Overview of acute pain in emergency medicine
- Review of advantages/limitations of current analgesic therapies
- Provide context for the science behind sublingual sufentanil
- Presentation of Sufentanil Sublingual Tablet 30 mcg clinical program
- Implications for nursing/paramedic practice
- Q&A
Acute Pain in Emergency Medicine
Acute Pain: Physiology

- The body's response to acute pain can cause adverse physiological effects.¹

- Untreated pain has the potential to:
  - impede the return of normal pulmonary function
  - modify certain aspects of the stress response to injury
  - alter hemodynamic values and cardiovascular function
  - produce immobility and contribute to thromboembolic complications¹.

- Clinical research has demonstrated that patients with poorly treated pain were more likely to end up with chronic pain conditions, post-traumatic stress, depression, and other physical and psychological problems.²

- Proper pain management can help with wound healing and get people home from the hospital sooner.²

2. J. Goodwin. How to Manage Pain. EMSWorld; September 2013
Acute Pain: Management

“Unrelieved pain is a major, yet avoidable, public health problem. Despite 20 years of work by educators, clinicians and professional organizations and the publication of clinical practice guidelines, there have been, at best, modest improvements in pain management practices”


Acute Pain: Emergency Medicine

- Pain is the primary reason people call 9-1-1 and the most common reason they present to the ED.¹,²

- As hospitals and healthcare systems put greater emphasis on pain management, pressure is also increased on paramedics and EMTs to better assess, treat and relieve pain—whether it’s through the use of opioids and other pain relievers, or other techniques to ease the anxiety and distress that can make pain seem even worse²

- Emergency Medicine guidelines support use of opioids for moderate-to-severe acute pain³,⁴

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² J. Goodwin. How to Manage Pain. EMSWorld; September 2013
Acute Pain: ACEP Policy Statement¹

- The American Society for Pain Management Nursing (ASPMN) and the Emergency Nurses Association (ENA) in collaboration with the American College of Emergency Physicians (ACEP) and the American Pain Society (APS) support efforts to improve pain management for patients in all healthcare settings.

- These organizations recognize the need for prompt, safe, and effective pain management.

- Analgesic management should begin as soon as possible when indicated and diagnosis of the pain etiology should not delay administration of analgesics.

- Development and adoption of analgesic protocols are encouraged and measurement of patient response to pain relief interventions from these protocols is required by accrediting agencies.

- Protocols should be physician/nurse developed and nurse initiated.

Introduction to Sublingual Sufentanil

Unmet Analgesic Needs in Battlefield & Emergency Medicine
Sufentanil Sublingual Tablet 30 mcg Development

- **U.S. Department of Defense** aware of small sublingual sufentanil tablet in development in post-operative pain
  - Requested durable, single-dose, easy to use applicator for field scenarios

- **Sublingual delivery of sufentanil considered optimal for field-based analgesia**
  - More rapid onset of analgesia than morphine\(^1\)
  - Sublingual tissue perfusion maintained during shock\(^2\)
  - Eliminate needle-stick injury and reduce risk of IV infection

- **Standard IM morphine is not readily bioavailable during hypovolemic shock (severe vasoconstriction to muscles limits uptake of drug)\(^2\)**
  - Soldiers can vasodilate following warm IV saline infusion
  - Repeated doses of morphine cross blood-brain barrier → overdose/death\(^3\)

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Current Concerns with Acute Pain Management in Emergency Medicine

- Clinical need remains for rapid-acting, potent analgesic that does not require an invasive route of delivery

**Emergency Medicine**

- **IV route**
  - IV lines can be challenging to start in the field or in ambulances
  - Difficult access: obese, elderly and vasoconstricted (e.g., dehydration or shock) patients
  - Patients presenting directly to ED can experience long delays in obtaining IV access and obtaining treatment

- **IM route**
  - Reduced bioavailability during shock
  - Painful to administer

- **Intra-nasal**
  - Route off-label for most analgesics; unpredictable absorption
  - Immediate access to an atomizer required
  - Burning sensation of nasal mucosa not uncommon

Pharmacokinetic Limitations of Current IV Opioid Therapy

**IV morphine**
- Delayed CNS penetration resulting in poor analgesic onset and slow offset which can delay discharge
- Active metabolite morphine-6-glucuronide can cause delayed side effects\(^1\)

**IV hydromorphone**
- Slightly more rapid onset than morphine but known for delayed and prolonged side effects (e.g., sedation, respiratory depression)\(^1\)

**IV fentanyl**
- Known brain penetration results in rapid onset of analgesia but alpha distribution of this lipophilic drug (1.7 minutes) results in quick offset and requires frequent re-dosing to maintain analgesia\(^2,3\)

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Sufentanil Sublingual Tablet 30 mcg Single-Dose Applicator

- Designed in collaboration with DoD (light-weight, extreme-environment tested, easily handled with gloves)¹

1. AcelRx data on file (2015-2016)
Sublingual Sufentanil
The Science
Why Sublingual Sufentanil?

Sufentanil first synthesized by Janssen in 1974¹

First approved in US for IV delivery in 1984¹

- Approved for induction of anesthesia
- Later approved for epidural delivery as an analgesic in combination with bupivacaine¹

Molecular Properties

- Lipophilic: 1500 times more fat-soluble than morphine
- 20% non-ionized at physiological pH (fentanyl only 8%)
- Fat-soluble, non-ionized molecules = more rapid brain penetration than lipid-insoluble, charged molecules²

Sufentanil Penetrates CNS Due to Lipophilicity ($t_{1/2}k_e$)

Commonly used IV opioids have a delayed equilibration time between plasma and CNS

- Morphine $t_{1/2}k_e = 2.8$ hours\(^1\)
- Hydromorphone $t_{1/2}k_e = 46$ min\(^2\)

Sufentanil rapidly penetrates the CNS due to its very lipophilic nature

- Sufentanil $t_{1/2}k_e = 6$ min\(^3\)

1. Lotsch et al., *Anesthesiol* 95:1329-38, 2001
Plasma Versus Brain Morphine Concentrations

- Delayed brain uptake leads to disconnect between IV dosing and effect\(^1\)

Plasma concentrations with IV morphine dosing

\[\text{Morphine} + \text{M6G}\]

\[\text{Cp}/\text{Ce (ng/mL)}\]

\[\begin{align*}
0 & \quad 20 & \quad 40 & \quad 60 & \quad 80 & \quad 100 \\
0 & \quad 2 & \quad 4 & \quad 6 & \quad 8 & \quad 10 & \quad 12
\end{align*}\]

\[\text{Time (hours)}\]

\[\text{Morphine/M6G in brain}\]

\[\text{Plasma}\]

\[\text{Effect Site}\]

\(^*\text{Assumes equipotency of morphine and M6G; other potency ratios achieved similar results}\]

1. IV PCA dosing frequency based on IAP309 Phase 3 study; plasma and brain concentrations modelled from published plasma and CNS equilibration values by D. Fisher – consultant to AcelRx
Sufentanil has Rapid Plasma/CNS Equilibration ($t_{1/2}k_{e0}$)

- Uptake of sublingual sufentanil leads to potential for real-time tracking between dosing and effect\(^1\)

1. Sublingual sufentanil dosing frequency based on IAP309 Phase 3 study; plasma and brain concentrations modelled from published plasma and CNS equilibration values by D. Fisher – consultant to AcelRx
# Sufentanil: High Therapeutic Index and No Active Metabolites

<table>
<thead>
<tr>
<th>Opioid</th>
<th>Therapeutic index</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>[lethal dose (\text{LD}<em>{50})/effective dose (\text{ED}</em>{50}) in animal studies]</td>
</tr>
<tr>
<td>Meperidine</td>
<td>5¹</td>
</tr>
<tr>
<td>Morphine</td>
<td>71¹</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>232²</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>277¹</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>26,716¹</td>
</tr>
</tbody>
</table>

2. Kumar, Eur J Pharmacol 2008; 597:39 (ED50) and Purdue Pharma MSDS, 2009 (LD50)

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**Other Opioid Active Metabolites³⁻⁷**

- Normeperidine
- M6G
- M3G
- H6G
- H3G
Sufentanil: Pharmacokinetics

- Sublingual delivery of sufentanil blunts $C_{\text{max}}$ and extends plasma half-time compared to IV administration\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>ARX-04 30 mcg</th>
<th>IV</th>
<th>Sublingual</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioavailability, %, mean</td>
<td>100</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{max}}$, pg/mL, mean</td>
<td>1074</td>
<td>63</td>
<td></td>
</tr>
<tr>
<td>CST(\frac{1}{2}), h, median</td>
<td>0.1</td>
<td>2.3</td>
<td></td>
</tr>
</tbody>
</table>

\(\text{CST}\frac{1}{2} = \text{context-sensitive half-time (time from } C_{\text{max}} \text{ to 50\% of } C_{\text{max}})\)

1. SAP101, data on file, AcelRx
Sublingual Sufentanil 30 mcg Tablet

Clinical Program Update
ARX-04: Clinical Studies

<table>
<thead>
<tr>
<th>Study number</th>
<th>Phase #</th>
<th>Clintrials.gov NCT #</th>
<th>Patient population</th>
<th>Current status of study</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP202</td>
<td>Phase 2</td>
<td>NCT01710345</td>
<td>Postoperative bunionectomy</td>
<td>Published 2014&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Dose-finding</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pivotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP301</td>
<td>Phase 3</td>
<td>NCT02356588</td>
<td>Ambulatory surgery - Postoperative abdominal</td>
<td>Completed 2015; Manuscript Accepted&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Pivotal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAP302</td>
<td>Phase 3</td>
<td>NCT02447848</td>
<td>Trauma/injury in the ED</td>
<td>Enrollment complete; manuscript in process</td>
</tr>
<tr>
<td>SAP303</td>
<td>Phase 3</td>
<td>NCT02662556</td>
<td>Postoperative; elderly and organ impaired</td>
<td>Enrollment complete; manuscript in process</td>
</tr>
</tbody>
</table>


<sup>2</sup> Manuscript formally accepted by Pain Practice Journal September 2016
SAP301
Outpatient Abdominal Surgery
SAP301: Study Design

Postoperative ambulatory surgery patients following abdominal surgery

- Open hernia repair
- Abdominoplasty
- Any laparoscopic abdominal surgery

Randomized 2:1, active:placebo

- Total of 163 randomized and 161 dosed (ITT population)

Pain score had to be ≥ 4 prior to administration of first dose

Minimum time between doses: 60 minutes

Study completed at 24 hours after first dose

- Dosing could extend out to 48 hours if needed
SAP301: Key Endpoints

Primary efficacy variable: Time-weighted SPID-12

- Essentially an area under the curve measurement of the drop in pain intensity from baseline over the first 12 hours of the study
- Pain intensity (PI) measured on a 0–10 NRS
  (0 = no pain, 10 = worst pain imaginable)

Safety:

- Adverse events
- Vital signs and oxygen saturation
- Concomitant medications
## SAP301: Demographics

<table>
<thead>
<tr>
<th>Category</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, female, %</td>
<td>Surgery, %</td>
</tr>
<tr>
<td>68</td>
<td></td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>Abdominoplasty</td>
</tr>
<tr>
<td>41</td>
<td>50</td>
</tr>
<tr>
<td>Race/ethnicity, %</td>
<td>Laparoscopic</td>
</tr>
<tr>
<td>Caucasian</td>
<td>30</td>
</tr>
<tr>
<td>40</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>Open hernia</td>
</tr>
<tr>
<td>38</td>
<td>20</td>
</tr>
<tr>
<td>African American</td>
<td>ASA status, %</td>
</tr>
<tr>
<td>19</td>
<td>64</td>
</tr>
<tr>
<td>Asian</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>32</td>
</tr>
<tr>
<td>BMI &lt;30, %</td>
<td></td>
</tr>
<tr>
<td>70</td>
<td>4</td>
</tr>
</tbody>
</table>

**ASA status:**
- African American: 1
- Asian: 2
- Caucasian: 1
- Hispanic: 3
- Open hernia: 2
- Pneumonia: 3
- Respiratory failure: 4
- Surgery, %: 30
- Abdominoplasty: 50
- Laparoscopic: 30
- Open hernia: 20
- BMI <30, %: 70
SAP301: Primary Endpoint: SPID-12

Pain intensity (PI) measured on a scale of 0–10

<table>
<thead>
<tr>
<th>Assessment</th>
<th>ARX-04</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline PI</td>
<td>5.6</td>
<td>5.5</td>
<td>NS</td>
</tr>
<tr>
<td>SPID-12</td>
<td>25.8</td>
<td>13.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NS, not significant

(p<0.001)
SAP301: 
PID Over First Hour by Surgery Type

- Abdominoplasty
- Hernia repair
- Laparoscopic Abd
- Placebo (All)

* p<0.01
** p<0.001
SAP301: Drug Utilization & Rescue

Number of 30mcg tablets dosed

<table>
<thead>
<tr>
<th>Time period</th>
<th>Number of tablets, median (range)</th>
<th>Inter-dosing interval, mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 Hours</td>
<td>4 (1–9)</td>
<td>185 minutes</td>
</tr>
<tr>
<td>0–24 Hours</td>
<td>7 (1–15)</td>
<td>221 minutes</td>
</tr>
</tbody>
</table>

Rescue Medication - 1mg IV Morphine

<table>
<thead>
<tr>
<th></th>
<th>ARX-04</th>
<th>Placebo</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients using rescue, %</td>
<td>27.1</td>
<td>64.8</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>
SAP301: Adverse Events (>3% in Either Group)

No statistical difference between cohorts

<table>
<thead>
<tr>
<th>Adverse Event, %</th>
<th>Sufentanil Sublingual Tablet 30 mcg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Adverse Event</td>
<td>42.1</td>
<td>37.0</td>
</tr>
<tr>
<td>Nausea</td>
<td>32.7</td>
<td>29.6</td>
</tr>
<tr>
<td>Headache</td>
<td>19.6</td>
<td>18.5</td>
</tr>
<tr>
<td>Vomiting</td>
<td>7.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5.6</td>
<td>3.7</td>
</tr>
<tr>
<td>Hypotension</td>
<td>4.7</td>
<td>3.7</td>
</tr>
<tr>
<td>Flatulence</td>
<td>3.7</td>
<td>7.4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2.8</td>
<td>3.7</td>
</tr>
<tr>
<td>Procedural nausea</td>
<td>2.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Pruritus</td>
<td>1.9</td>
<td>3.7</td>
</tr>
</tbody>
</table>
SAP302
Emergency Department
## SAP302: Study Design

### Study Details

**Multicenter, Single-Arm, Open-Label Study**

**Two Cohorts:**
- Single-dose (after 1 hour, other opioids administered if needed)
- Multiple-dose up to 5 hours (rescue opioids allowed if study drug not effective)

### Inclusion/Exclusion

**Inclusion:**
- 18 years and older
- moderate-to-severe acute pain due to trauma or injury

**Exclusion:**
- Opioid-tolerant (>15mg oral MSO₄ equivalent daily)
- Dependent on supplemental oxygen
- Pregnant
SAP302: Outcome Measures

Study sites
Hennepin County Medical Center, Minneapolis, MN (James Miner, MD)
Memorial Hermann-Memorial City Medical Center, Houston, TX (Harold Minkowitz, MD)
Baylor College of Medicine, Ben Taub General Hospital, Houston, TX (Zubaid Rafique, MD)

Primary Endpoint
- Sum of the pain intensity difference to baseline over the first hour of treatment (SPID1)

Key Secondary Efficacy Endpoints
- PID assessments
- Patient and Healthcare Global Assessment
- Use of rescue medication
- Drop-outs due to inadequate analgesia

Safety Endpoints
- Adverse Events
- Vital Signs
- Six-item Cognitive Screener
- Concomitant Medications
### SAP302: Demographics (n=76)

<table>
<thead>
<tr>
<th>Category</th>
<th>Category</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, %</td>
<td>61</td>
</tr>
<tr>
<td>BMI, %</td>
<td>61</td>
</tr>
<tr>
<td>Age, years, mean</td>
<td>42</td>
</tr>
<tr>
<td>&lt; 30kg/m²</td>
<td>61</td>
</tr>
<tr>
<td>&gt; 30kg/m²</td>
<td>39</td>
</tr>
<tr>
<td>Race, %</td>
<td>45</td>
</tr>
<tr>
<td>Caucasian</td>
<td>45</td>
</tr>
<tr>
<td>African American</td>
<td>34</td>
</tr>
<tr>
<td>Native American</td>
<td>7</td>
</tr>
<tr>
<td>Ethnicity, %</td>
<td>3</td>
</tr>
<tr>
<td>Hispanic/Latino</td>
<td>16</td>
</tr>
<tr>
<td><strong>Baseline Pain</strong></td>
<td><strong>8.1/10</strong></td>
</tr>
</tbody>
</table>
## SAP302: Demographics (n=76)

### Trauma classifications

<table>
<thead>
<tr>
<th>Injury Type</th>
<th>Number</th>
<th>Percent Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fractures</td>
<td>25</td>
<td>32.9%</td>
</tr>
<tr>
<td>Sprains/strains</td>
<td>23</td>
<td>30.3%</td>
</tr>
<tr>
<td>Contusion/hematoma (soft tissue)</td>
<td>13</td>
<td>17.1%</td>
</tr>
<tr>
<td>Laceration</td>
<td>8</td>
<td>10.5%</td>
</tr>
<tr>
<td>Joint dislocation</td>
<td>4</td>
<td>5.3%</td>
</tr>
<tr>
<td>Burns</td>
<td>2</td>
<td>2.6%</td>
</tr>
<tr>
<td>Infections</td>
<td>1</td>
<td>1.3%</td>
</tr>
</tbody>
</table>
SAP302: Combined Cohorts Efficacy (n=76)

- Over 35% drop in pain intensity by 60 minutes
- A clinically significant drop in pain intensity when administering 0-10 point numerical rating scale (NRS) to measure pain is 1.3

SAP302: Multiple-Dose Cohort Efficacy (n=36)

- Redosing allowed hourly if needed
- 75% of patients did not require redosing
SAP302: Use of Rescue Analgesia

- **Low rate of rescue opioid usage**

<table>
<thead>
<tr>
<th>Study Period</th>
<th>Patients Requiring Use of Rescue Opioid</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Single-Dose Cohort (n = 40)</td>
</tr>
<tr>
<td>Use in First Hour</td>
<td>7.5%</td>
</tr>
<tr>
<td>Use after First Hour</td>
<td>NA</td>
</tr>
</tbody>
</table>
### SAP302: Adverse Events (> 2% of patients)

- **Majority of patients experienced no side effects**

<table>
<thead>
<tr>
<th>Adverse Event, n (%)</th>
<th>ARX-04 (30 mcg) n=76</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Adverse Event</td>
<td>79%</td>
</tr>
<tr>
<td>Nausea</td>
<td>9%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5%(^1)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4%</td>
</tr>
<tr>
<td>Oxygen Desaturation</td>
<td>3%(^2)</td>
</tr>
</tbody>
</table>

1. All 4 patients with somnolence were rated as mild
2. Two patients experienced transient room air oxygen desaturations below 95% (88% and 94% which immediately improved with nasal cannula oxygen)
SAP302: Six-Item Screener (SIS) Cognitive Test

Sublingual sufentanil not associated with cognitive impairment

- DoD requested cognitive test before and 1 hour after dosing of sublingual sufentanil 30 mcg
- Impaired cognitive skills a concern with other field-based analgesics used in the military (e.g., ketamine)
- 73 patients either had the same score or increased their score while only 2 patients had a decrease of 1 point compared to baseline.
Study Conclusions

- Single dose of sufentanil sublingual 30 mcg tablet results in approximately a 3-point drop in pain intensity within 60 minutes, with clinically meaningful analgesia in < 20 minutes
- Sublingual sufentanil was well-tolerated with most commonly reported AEs of nausea and somnolence
- Clinical studies showed no cognitive impairment
- Additional research is indicated to assess safety and efficacy in actual field-based environments
Questions?
Discussion: Emergency Medicine Pain Management

- What percentage of patients present with moderate-to-severe acute pain?
- How long does it take a typical patient to receive their first dose of analgesia for moderate-to-severe pain?
- Are there nurse-initiated protocols in place for nurses to place IV lines, assess and treat pain prior to physician assessment?
- What percentage of patients present with difficult venous access?
- What may be some benefits/limitations of using a sublingual therapy for patients in the EMS/emergency medicine setting?
Thank you