Naloxone Meeting

Joint Meeting of the Anesthetic and Analgesic Drug Products Advisory Committee and the Drug Safety And Risk Management Advisory Committee

5 October 2016

Adapt Pharma
Radnor, PA
COMMUNITY USE NALOXONE DOSE

October 5 2016

SEAMUS MULLIGAN
CEO & Chairman
ADAPT PHARMA

Agenda

Introductions

1. Narcan Nasal Spray

2. Current Situation

3. Dosing Suggestions and Support
1. Narcan Nasal Spray: Summary

Developed With Input From NIDA

Approved by FDA Under Priority Review

Launched 7 Months Ago in Q1 2016

Rapidly Adopted

360,000 Doses Distributed

1. Narcan Nasal Spray: Profile

4mg naloxone in 0.1ml

Single-use, needle-free, nasal delivery

Pre-filled, ready-to-use

No-assembly, priming, or training

Non-titratable

Supplied with 2 devices per carton
1. Narcan Nasal Spray: Use

1. Narcan Nasal Spray: Affordable Access

**Public Interest Price**
- $37.50 per dose ($75/carton)

**Extensive Insurance Coverage\(^1\)**
- 46% co-pay $0
- 78% co-pay $10 or less

**CVS and Walgreen Partnerships**

---

\(^1\) IMS Health NPS Audit August 2016
1. Narcan Nasal Spray: Pharmacokinetics

**Naloxone Exposure**\(^1\)

- Each Narcan Nasal Spray approximates 5 times 0.4mg IM exposure
- Similar CV between Nasal and IM delivery

---

**FDA: Mean Plasma Naloxone Concentration Narcan Nasal 4mg v. 0.4mg IM 0-4Hrs (n=29)**\(^1\)

**Minutes post dose**

<table>
<thead>
<tr>
<th>Fold Higher Mean Naloxone Concentration (4mg Narcan Nasal Versus 0.4mg IM)(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
</tr>
<tr>
<td>5.0</td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>15</td>
</tr>
<tr>
<td>20</td>
</tr>
</tbody>
</table>

\(^1\) FDA: Fold Higher Naloxone Concentration (4mg Narcan Nasal Versus 0.4mg IM) 0 – 20 minutes. Healthy Subjects: N=29
2. Current Situation

Naloxone Approved Since 1971

Clinical Setting
- Initial dose in range of 0.4-2 mg injection with titration up to 10mg\(^1\)

Community Setting
- 76% of opioid overdose deaths happen in the community\(^2\)
- Emergency treatment as bridge to medical care
- Lack of medical expertise and equipment
- Clinical dosing titration approach not practical

\(^1\) Naloxone Hydrochloride Prescribing Information. \(^2\) CDC Wonder Database 2014 Data

2. Current Situation

Multiple Naloxone Products in Use
- Wide variety of possible pharmacokinetic profiles
- Confusion
- Potentially different reversal rates

Adequate Dose Depends on Multiple Factors
- Cannot predict appropriate initial naloxone dose needed

Minimize Risk of ‘Too Little Naloxone Too Late’
2. Dosing Suggestions

Delivery System: Safe and Easy Use and Allow Reliable, Rapid Administration

Plasma Exposure That Approximates the High End of Initial Dose Range
- Rapid Onset
- Back-up Device

3. Rationale For Dosing Suggestions

A. Exceptionally Favourable Risk/Benefit Profile

B. Dramatic Rise in Overdose Deaths from High Potency Opioids
3. Rationale: A. Risk/Benefit Profile Efficacy

Naloxone FDA Approved for 45 Years

- Effective if an adequate dose is administered in time
- Competitively binds to opioid receptors
- Literature suggests 50% opioid receptor occupancy is achieved with 1mg naloxone by injection but 2mg provides 80% occupancy
- American Academy Paediatrics recommended minimum 2mg at 20kg/5Yrs
- Lower doses have been used successfully but success rate unknown


3. Rationale: A. Risk/Benefit Profile PET Data

Narcan Nasal Spray $^{[11]}C$ Carfentanil

- PET study (8 healthy volunteers crossover placebo controlled design) using $^{[11]}C$ carfentanil and comparing the impact of Narcan Nasal Spray 4mg and naloxone nasal spray 2mg

- Naloxone competitively antagonizes carfentanil
- Narcan Nasal Spray 4mg displaced 88% $^{[11]}C$ carfentanil
- Faster and more extensive displacement – v – 2mg
3. Rationale: A. Risk/Benefit Profile Safety

Warnings

- Duration of efficacy\(^1\)
- Limited efficacy in partial agonists; mixed agonist/antagonists\(^1\)
- Possible CV effects in those with pre-existing condition\(^1\)
- Neonates safety concern\(^1\)

**Acute Withdrawal Potential In Some Opioid Patients\(^1\)**

- Incidence, severity vary by opioid dependent patient and opioid\(^1\)
- Unpleasant but generally transitory and non-life threatening\(^2-5\)
- In non-opioid dependents high bolus doses of 90mg well tolerated\(^2\)

---

3. Rationale: A. Narcan Field Experience

**Independent Field Survey of Narcan Nasal Experiences**

- 15 entities estimated they achieved over 1,400 reversals
- 8 entities with known outcomes data on 245 reversals: **99%** reversal rate

**Review of Case Reports in 196 Reversals**

- No adverse events in 62% of reports
- Most commonly reported events were withdrawal, nausea, irritability
- No new safety concerns identified
3. Rationale: B. High Potency Opioids

Dramatic Rise in Overdoses from High Potency Opioids

2. Rationale: B. High Potency Opioids

+80% in Deaths Related to Synthetic Opioid in 2014

Recent State Data Shows Alarming Trend has Continued

- Massachusetts 1H16 fentanyl and analogues implicated in 2 of every 3 opioid OD death

- New Hampshire fentanyl and analogues involved in 49% of 2014 deaths; Ohio fentanyl involved in 24% of 2014 deaths

Multiple Direct Warnings from CDC and DEA

3. Rationale: B. High Potency Opioids

**Potent Synthetic Opioids: Rapid and Increased Naloxone**

- Multiple times more potent than morphine
- Highly lipophilic: peak respiratory depression in 5-15 minutes
- Illicitly manufactured and covertly substituted into heroin, pills

**Increase in Multiple Uses of Lower Strength Naloxone**

- Media Reports, CDC, DEAWarnings
- EMS state level data: Massachusetts up 40% (2015-v-2013)

---

**Conclusion**

**Clinical Dosing Approach (Titration) Not Viable**

- Multiple unknowns, lack of medical expertise or equipment
- Fixed initial dose is required as a bridge to medical care

**Exposure at High End of Initial Range (2mg injection)**

- Exceptionally Favourable Risk/Benefit Profile
- Dramatic Rise in Overdoses from High Potency Opioids

**Delivery System: Safe and Easy Use**

- Allow Reliable, Rapid Administration