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

ADAPT PHARMA

COMMUNITY USE NALOXONE DOSE

October 5 2016

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Agenda

Introductions

1. Narcan Nasal Spray
2. Current Situation
3. Dosing Suggestions and Support

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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

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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

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1. Narcan Nasal Spray: Use

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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

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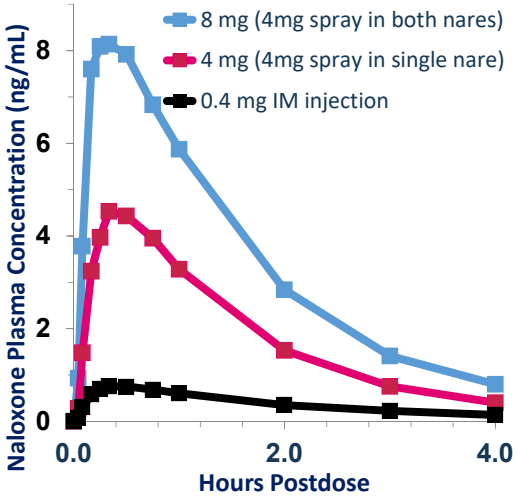
1. Narcan Nasal Spray: Pharmacokinetics

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]



[1] FDA: Mean plasma concentration time profiles of naloxone (0 to 4 hours) Narcan Nasal 4mg v 0.4mg IM healthy subjects (N = 29)

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1. Narcan Nasal Spray: Pharmacokinetics

Minutes post dose	Fold Higher Mean Naloxone Concentration (4mg Narcan Nasal Versus 0.4mg IM)[1]
2.5	**3.5**
5.0	4.8
10	5.6
15	5.7
20	**6.0**

[1] FDA: Fold Higher Naloxone Concentration (4mg Narcan Nasal Versus 0.4mg IM) 0 – 20 minutes Health Subjects: N=29

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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

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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'

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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

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3. Rationale For Dosing Suggestions

A. Exceptionally Favourable Risk/Benefit Profile

B. Dramatic Rise in Overdose Deaths from High Potency Opioids

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3. Rationale: A. Risk/Benefit Profile Efficacy

Naloxone FDA Approved for 45 Years[1]

- Effective if an adequate dose is administered in time
- Competitively binds to opioid receptors[1]
- Literature suggests 50% opioid receptor occupancy is achieved with 1mg naloxone by injection but 2mg provides 80% occupancy[2,3]
- American Academy Paediatrics recommended minimum 2mg at 20kg/5Yrs
- Lower doses have been used successfully but success rate unknown

[1] Naloxone Hydrochloride Prescribing Information [2] Melichar et al 2003 EurJPharmacol. 459:217-219; [3] Kim S et al. J Nucl Med. 1997;38:1726-1731

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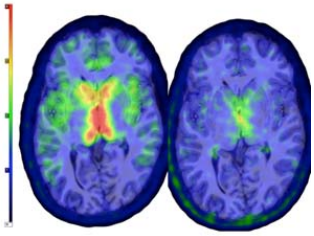
3. Rationale: A. Risk/Benefit Profile PET Data

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

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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]

[1] Naloxone Hydrochloride Prescribing Information [2] Clarke et al. Emergency medicine journal : EMJ. Sep 2005;22(9):612-616. [3] Wermeling DP. Therapeutic Advances in Drug Safety. 2015;6(1):20-31 [4] Buajordet I et al. Euro J Emerg Med. 2004; 11(1):19-23 [5] Boyer EW. N. Engl. J. Med. Jul 12 2012;367(2):146-155.

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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

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3. Rationale: B. High Potency Opioids

Dramatic Rise in Overdoses from High Potency Opioids

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2. Rationale: B. High Potency Opioids

+80% in Deaths Related to Synthetic Opioid in 2014[1]

Recent State Data Shows Alarming Trend has Continued

- Massachusetts 1H16 fentanyl and analogues implicated in 2 of every 3 opioid OD death[2]
- New Hampshire fentanyl and analogues involved in 49% of 2014 deaths; Ohio fentanyl involved in 24% of 2014 deaths[3,4]

Multiple Direct Warnings from CDC and DEA[5]

[1] CDC Wonder Database; [2] opioid related overdose deaths among ma residents august 2016;[3] New Hampshire Office of the Chief Medical Examiner [4] CDC Health Advisory Note October 2016; [5] CDC, DEA

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3. Rationale: B. High Potency Opioids

Potent Synthetic Opioids: Rapid and Increased Naloxone[1,2]

- Multiple times more potent than morphine
- Highly lipophilic: peak respiratory depression in 5-15 minutes[3,4,5]
- Illicitly manufactured and covertly substituted into heroin, pills

Increase in Multiple Uses of Lower Strength Naloxone

- Media Reports, CDC, DEA Warnings[5]
- EMS state level data: Massachusetts up 40% (2015-v-2013)[6]

[1] Melichar et al 2003 EurJPharmacol. 459:217-219; [2] Kim HK, Nelson LS. *Exp Opin Drug Saf*. 2015;14(7):1137-1146; [3] Fentanyl Citrate Prescribing Information; [4] Volpe DA, McMahon Tobin GA, Mellon RD, et al. *Regul. Toxicol. Pharmacol.* Apr 2011;59(3):385-390. [5] CDC HAN 00384 October 2015; [6]. Opioid-related EMS Transports Massachusetts Residents: 2013-2015;

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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

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