

Take-Home Naloxone: the revolution, the convolutions and the necessary evolutions

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NALOXONE NASAL SPRAY

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DISCLAIMER

The following presentation describes the Naloxone Nasal Spray product approved by U.S. FDA and Health Canada but not licensed in other territories. Accordingly, at this time as it pertains to ex-US and Canada, all test data and product information are presented for informational purposes only, and must be considered experimental

AGENDA

- **Opioid Overdose Deaths**
- **Role of Naloxone**
- **Narcan Nasal Spray**
- **Pharmacokinetics and Dose**
- **Field Experience**

OPIOID OVERDOSE DEATHS

Opioid overdose deaths are growing worldwide

- Estimated at least 6,800 – 8,000 deaths EU in 2014¹
- England & Wales almost 2,000 deaths in 2015 up >50% since 2012²
- Ireland over 75% of the 219 drug related deaths in 2014; 71.1 deaths per million in 2013, three time the most recent European average³
- Over 33,000 deaths in US in 2015⁴
- Increase in use of potent and synthetic opioids¹

Many deaths may be preventable

- Most overdoses are witnessed

Naloxone routinely used for opioid overdose over 40 yrs¹

- Treats overdose symptoms if an adequate dose is administered in time

Clinical Use Dosing

- Initial dose in range of 0.4-2 mg injection with titration up to 10mg²

Community Setting Special Considerations

- Easy-to-use emergency naloxone treatment as bridge to medical care
- Lack of medical expertise and equipment means titration not practical

NALOXONE MoA

- Competitively binds to opioid receptors¹
- Literature suggests 50% opioid receptor occupancy is achieved with 1mg naloxone by injection but 2mg provides 80% occupancy^{1,2}
- Lower doses have been used successfully but success rate unknown

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

Warnings

- Duration of efficacy¹
- Limited efficacy in partial agonists; mixed agonist/antagonists¹
- Possible CV effects in those with pre-existing condition¹
- Neonates safety concern¹

Potential For Acute Withdrawal In Some Opioid Dependent Patients¹

- Incidence, severity vary by opioid dependent patient and opioid¹
- Unpleasant but generally transitory and non-life threatening²⁻⁵
- In non-opioid dependents high bolus doses of 90mg well tolerated²

NARCAN NASAL SPRAY

Collaborated with NIDA to Develop Naloxone Nasal Spray

Regulatory status 4mg and 2mg

- Approval by U.S. FDA and Health Canada in 2016
- Application under review in Europe

Commercialisation

- Launched 2/16 and Canada 7/16
- Rapidly adopted and now most prescribed naloxone in U.S.



NARCAN NASAL SPRAY

- 4mg naloxone in 0.1ml
- Single-use, needle-free, nasal delivery system
- Pre-filled, ready-to-use, no-assembly, priming, or training
- Non-titratable
- Supplied with back-up device

NARCAN NASAL SPRAY

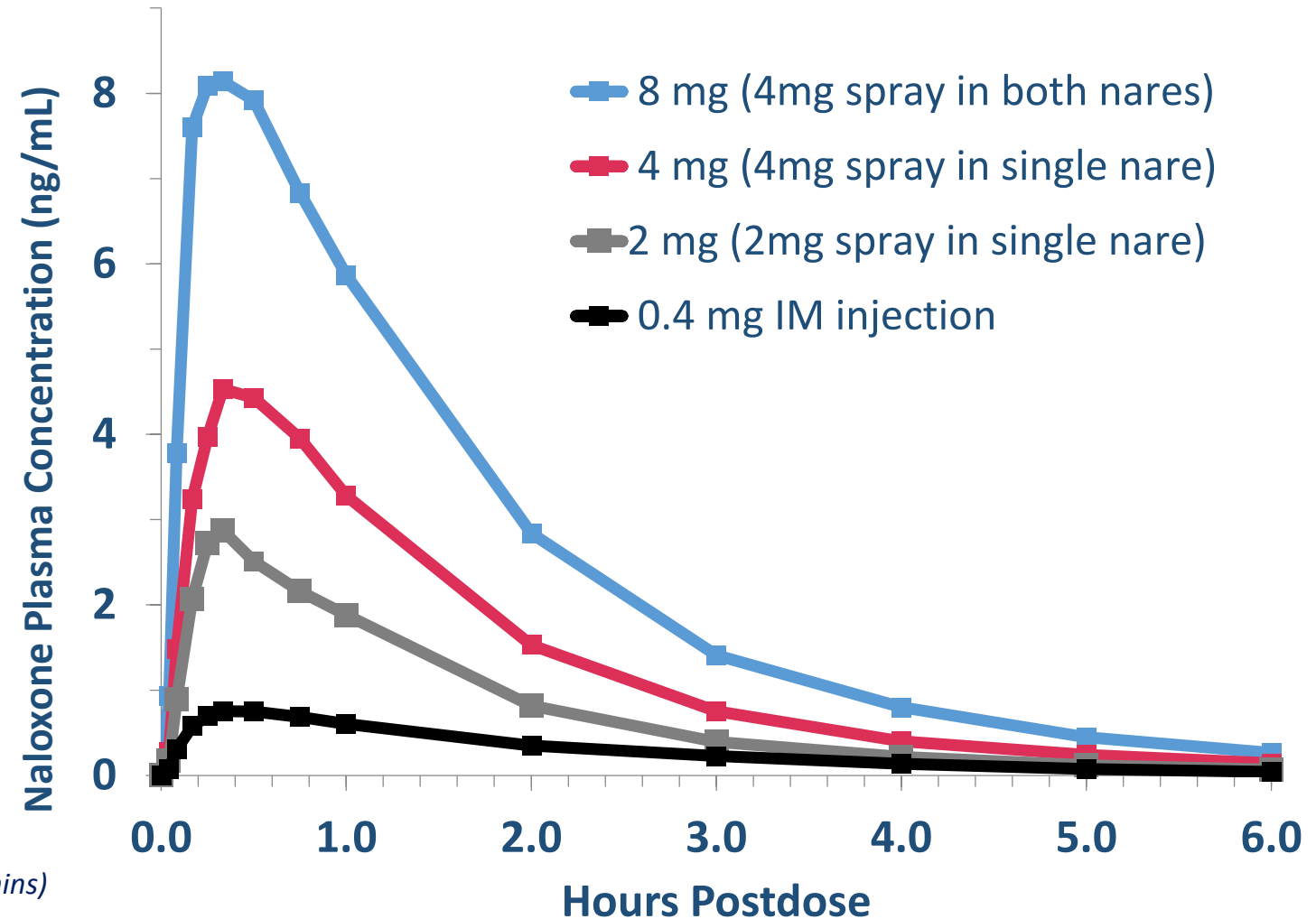


Naloxone Exposure¹

- Narcan Nasal Spray
4mg blood levels = 5X
0.4mg IM exposure,
- Approx. 50% relative
bioavailability to IM.
- Similar RSD%
between IM and
Nasal delivery

[1] FDA: Mean plasma concentration time profiles of naloxone (0 to 60 mins)
Narcan Nasal 4mg, 2mg 2X 4mg v 0.4mg IM healthy subjects (N = 29)

FDA: Mean Plasma Naloxone Concentration Narcan Nasal 8mg, 4mg, 2mg v 0.4mg IM 0-6 Hrs (n=29)¹

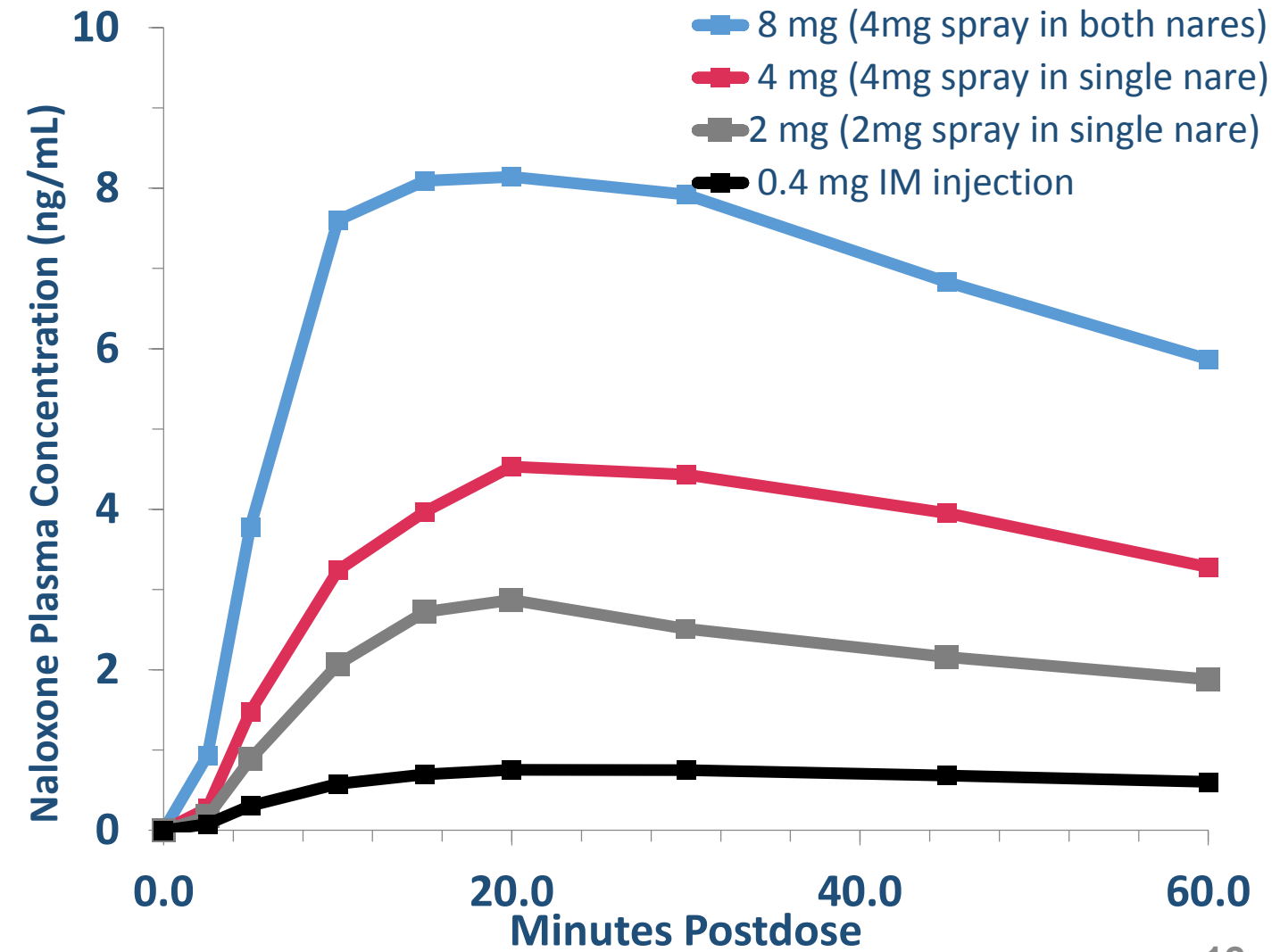


PHARMACOKINETICS

Mins post dose **Fold Higher Naloxone Concentration**
(4mg Narcan Nasal V 0.4mg IM)² **(2mg Narcan Nasal V 0.4mg IM)**

Mins post dose	Fold Higher Naloxone Concentration (4mg Narcan Nasal V 0.4mg IM) ²	Fold Higher Naloxone Concentration (2mg Narcan Nasal V 0.4mg IM)
2.5	3.5	2.2
5.0	4.8	2.9
10	5.6	3.6
15	5.7	3.9
20	6.0	3.8

FDA: Mean Plasma Naloxone Concentration Narcan Nasal 8mg, 4mg, 2mg v 0.4mg IM 0-60 Mins (n=29)¹



[1] FDA: Mean plasma concentration time profiles of naloxone (0 to 60 mins) Narcan Nasal 4mg, 2mg 2X 4mg v 0.4mg IM healthy subjects (N = 29)

[2] FDA: Fold Higher Naloxone Concentration (4mg and 2mg Narcan Nasal Versus 0.4mg IM) 0 – 20 minutes Health Subjects: N=29

Delivery System

- Safe and Easy Use and Allow Reliable, Rapid Administration
- Back-up Device

Target Plasma Exposure

- Approximate the High End of Initial Clinical Dose Range as Multiple Unknown Factors and Absence of Clinical Expertise and Assets to Titrate
- Ensure Rapid Onset in Initial Few Minutes Post Dosing
- Avoid Delivering 'Too Little Naloxone Too Late'

Independent Field Survey of Narcan Nasal Spray 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

Offers Potential New Option

Delivery System: Safe and Easy Use

- Allow Reliable, Rapid Administration

Naloxone exposure at High End of Initial Range

- Favourable Risk/Benefit Profile
- Appropriate for community use setting