# Naloxone Intranasal Administration in the Pre-hospital Setting – Basic Life Support (BLS) Pilot Program


**A Joint Project of the Wisconsin EMS Advisory Board and the Wisconsin EMS Office**

# Naloxone Pilot Project

- Why is this project needed?
  - Increased number of narcotic overdoses.
  - Accessibility to Advanced Life Support (ALS) is not the same in all areas of Wisconsin.
  - Safety of EMS providers.

# Decrease in Needles = Decreases in Risk

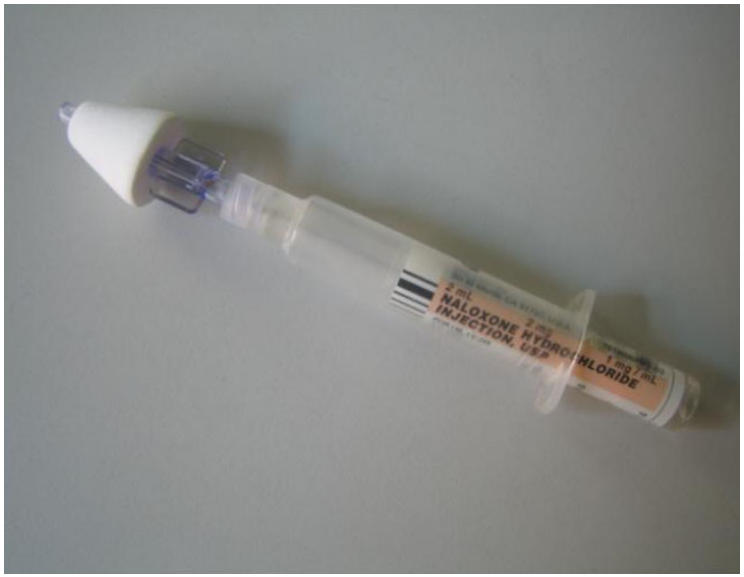
- The Centers for Disease Control and Prevention (CDC) estimates 600,000 percutaneous injuries occur each year involving contaminated sharps in the United States.
- Technological developments can increase protection.
- Education and training are the keys to a positive resolution.

# Communicable Disease Population

- Not all infected people know they are infected.
- EMS scenes can be high risk events due to patient and bystander behavior, as well as environmental aspects.

# Intranasal Medication Administration

- Intranasal medication administration offers a "Needleless" solution to drug delivery.



# Intranasal Administration: Basic Concepts

- The intranasal delivery route has several advantages:
  - It's easy and convenient.
  - The nose is a very easy access point for medication delivery (even easier than the arm, especially in winter).
  - No shots are needed.
  - It is painless.
  - It eliminates any risk of a needle stick *to you, the medical provider.*

# Naloxone (Narcan)

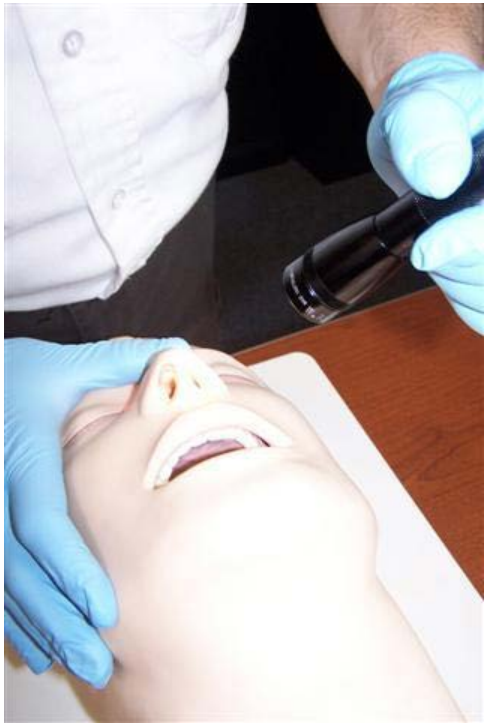
- Pure opiate antagonist –reverses respiratory & central nervous system (CNS) depression
- High lipid solubility so rapidly enters CNS
- Roughly $10-$30 per 2 mg
- Long shelf life: 18-24 months

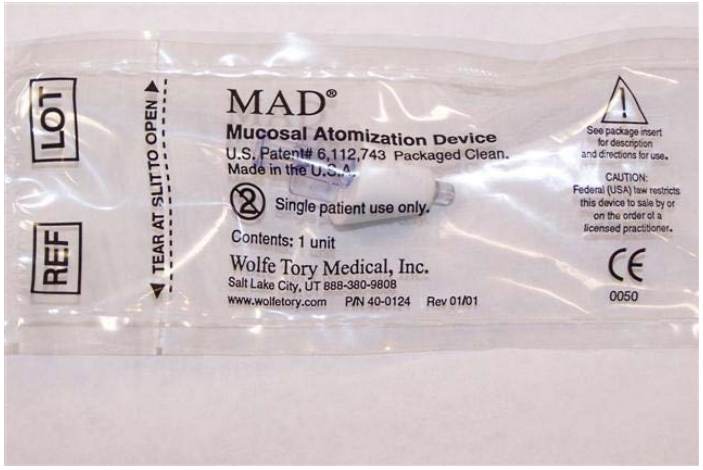
# Naloxone Complications

- Patient withdrawal:
  - Agitation
  - Vomiting
- Patient Combativeness
- Rare: Less than 1% of the time
  - Seizures
  - Pulmonary edema
    - <1 % complicated by non-cardiogenic pulmonary edema – 95 % of cases occur at onset of OD
  - Arrhythmias

# Patient Does Not Need to be Breathing for IN Administration

# IN Administration




LOT
REF
TEAR AT SLIT TO OPEN
MAD®
Mucosal Atomization Device
U.S. Patent# 6,112,743 Packaged Clean.
Made in the U.S.A.
Single patient use only.
Contents: 1 unit
Wolfe Tory Medical, Inc.
Salt Lake City, UT 888-380-9808
www.wolfetory.com P/N 40-0124 Rev 01/01
See package insert for description and directions for use.
CAUTION: Federal (USA) law restricts this device to sale by or on the order of a licensed practitioner.
CE
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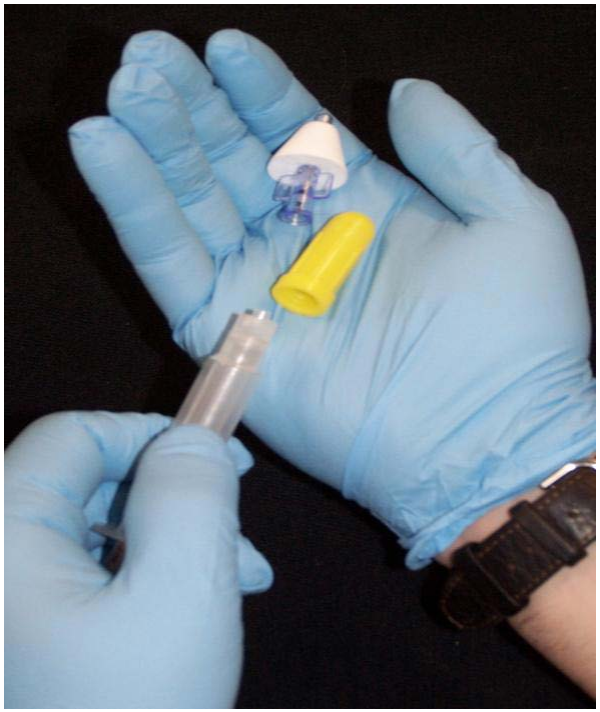
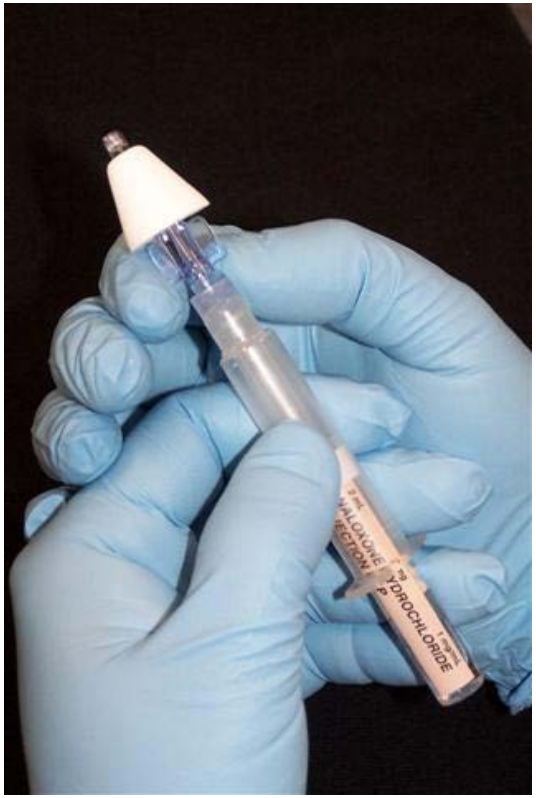
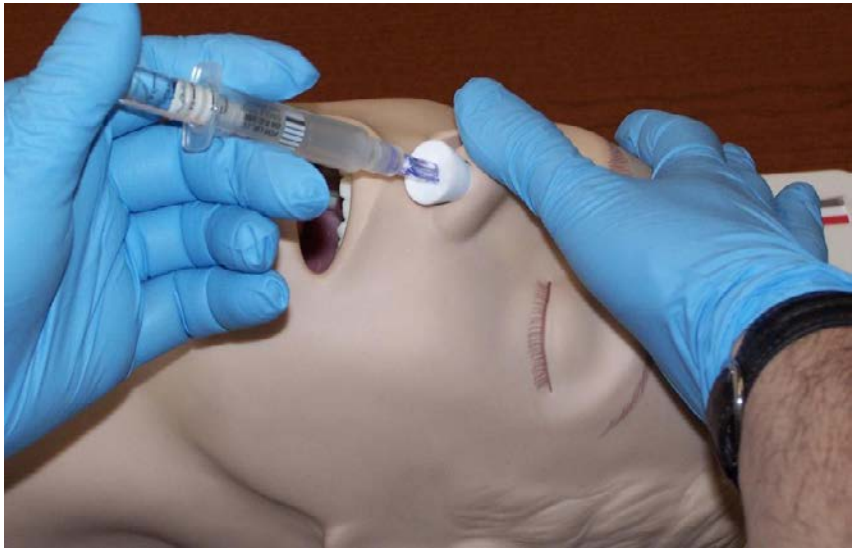
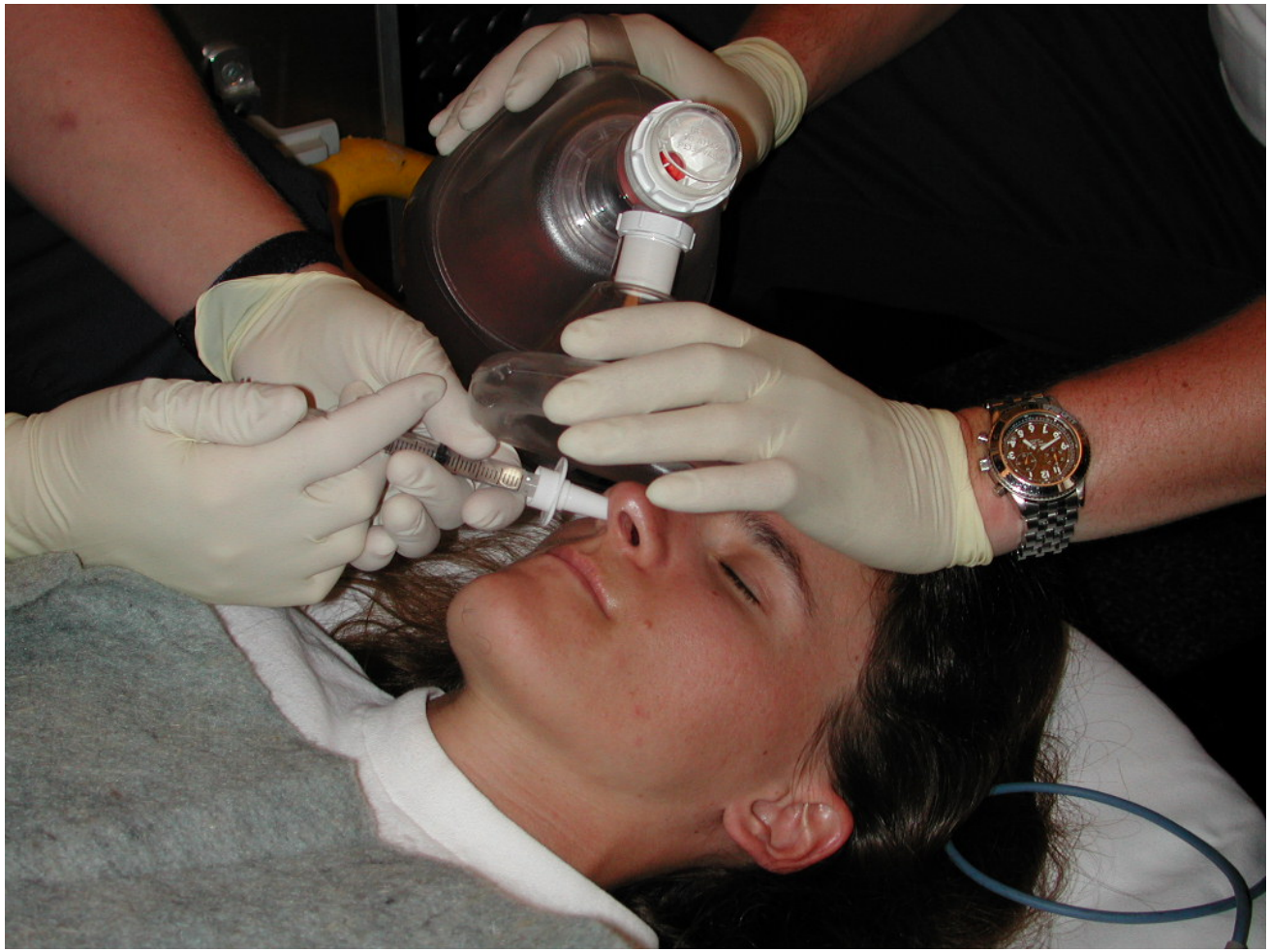




# IN Administration



# IN Administration



# The Pilot IN Protocol

## Suspected Opioid Overdose Protocol for BLS Providers

- Inclusion Criteria:
  - Suspected narcotic or opiate overdose, with at least one of the following:
    - History of overdose provided by bystanders
    - Paraphernalia consistent with opiate/narcotic use
    - Medical history consistent with opiate/narcotic use
    - Respiratory depression with pinpoint pupils
  - Blood glucose level >60 mg/dl. If blood glucose < 60 mg/dl, treat low glucose first.
  - Patients age >8
  - Alteration of consciousness (defined as P or U on the AVPU scale)
  - Respiratory rate <8

# The Pilot IN Protocol

## Suspected Opioid Overdose Protocol for BLS Providers

- Exclusion Criteria:
  - Documented allergy to naloxone
  - Alteration of consciousness or respiratory depression of presumed traumatic etiology
  - Epistaxis, nasal trauma or nasal mucosal abnormality for IN administration. Deviate to IM administration.

# The Pilot IN Protocol

## Suspected Opioid Overdose Protocol for BLS Providers

- Procedure (based upon local packaging)
  - Ensure all BLS assessments and procedures are being adequately delivered.
  - Check blood glucose to assure a reading of greater than 60mg/dl.
  - Verify that inclusion and exclusion criteria support administration.

# The Pilot IN Protocol

## Suspected Opioid Overdose Protocol for BLS Providers


- Procedure (cont.)
  - Pre-filled syringe
    - Un-package and remove prefilled syringe
    - Remove the pop-off caps and screw together
    - Withdraw 0.4 mg - 0.5 mg of the naloxone using the 1 cc luer lock syringe and needle
    - Remove needle from 1 cc luer lock syringe
  - Vial
    - Confirm the medication
    - Remove top from the naloxone and clean the rubber top with an alcohol pad
    - Draw equal amount of air into syringe as you want to administer
    - Inject air into vial and withdraw medication to appropriate amount
    - Remove needle from 1 cc syringe

# The Pilot IN Protocol

## Suspected Opioid Overdose Protocol for BLS Providers

- Procedure (cont.)
  - Once medication is drawn into 1 cc syringe:
    - Attach mucosal atomizer device to the 1 cc luer lock syringe
    - Insert atomizer until flush with external nare
    - Depress plunger rapidly to ensure delivery of 0.4 mg - 0.5 mg of syringe contents
    - Remove syringe and atomizer from the patient's nare
    - Dispose of syringe and atomizer in approved receptacle
    - Monitor patient respirations and mental status for signs of improvement and/or deterioration
    - If no improvement after five minutes and/or deterioration in the patient's respiratory status is noted, repeat procedure using the other nare. This procedure can be continued until a max dose of 2 mg has been administered.

# Understanding IN delivery: Definitions

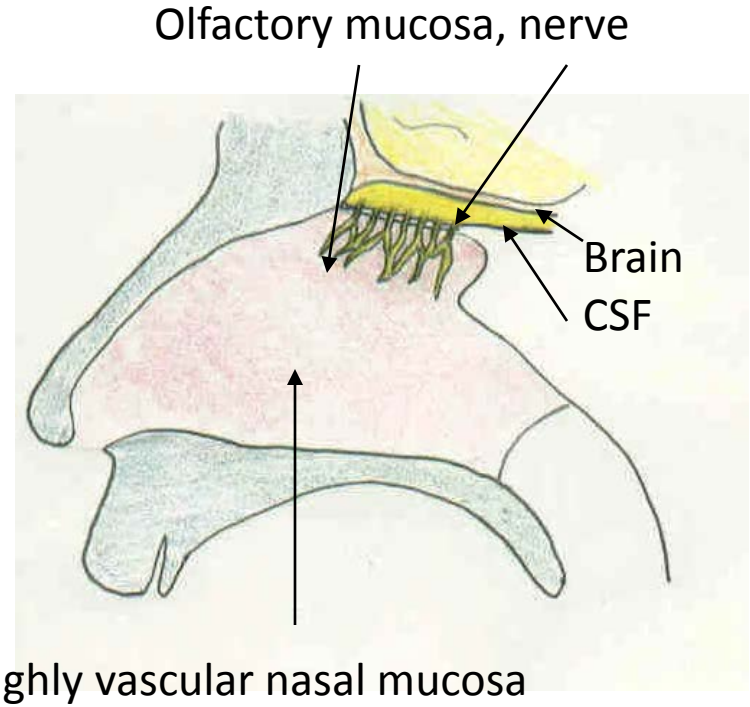
- First pass metabolism
- Nose brain pathway
- Lipophilicity
- Bioavailability

# First pass metabolism

- Molecules absorbed through the stomach, including all oral medications, enter the "portal circulation" and are transported to the liver.
- Liver enzymes then break down most of these drug molecules and only a small fraction enter the body's circulation as active drug.
- This process is called "First Pass Metabolism."
- Nasally delivered medications avoid the digestive system so do not suffer first pass metabolism.

# Nose brain pathway

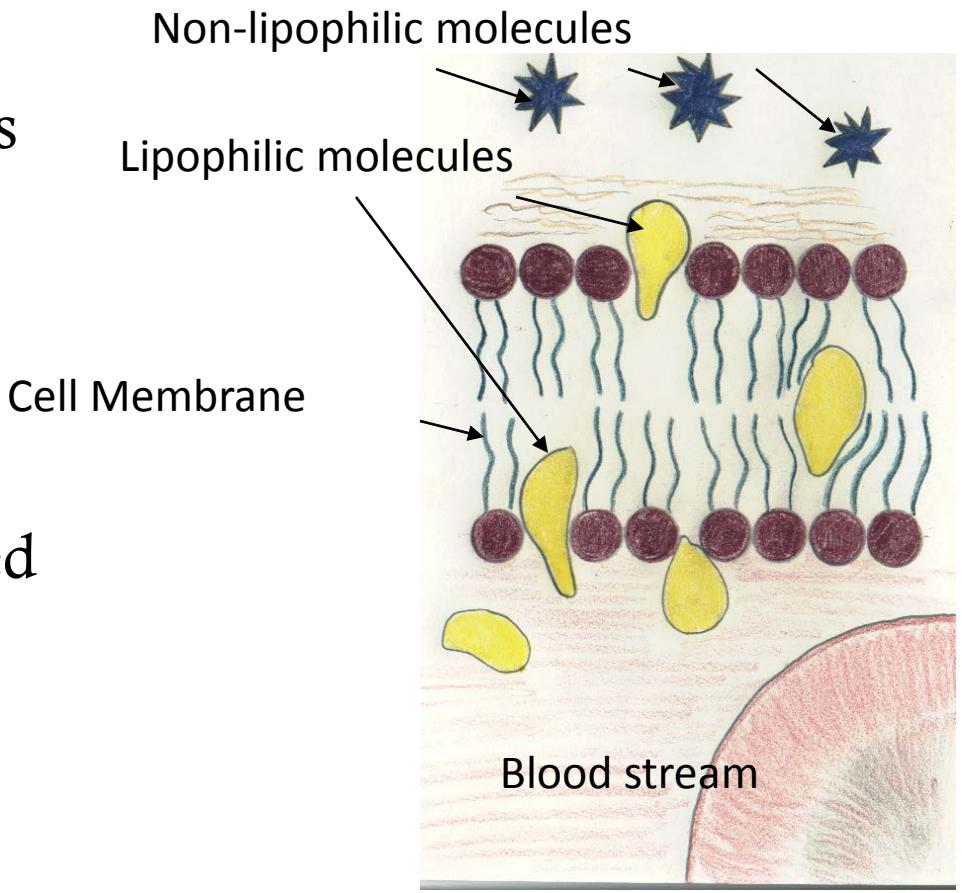
- The olfactory mucosa (smelling area in nose) is in direct contact with the brain and cerebrospinal fluid (CSF).
- Medications absorbed across the olfactory mucosa directly enter the CSF.
- This area is termed the nose brain pathway and offers a rapid, direct route for drug delivery to the brain.



# Lipophilicity

"Lipid Loving"

- Cellular membranes are composed of layers of lipid material.
- Drugs that are lipophilic are easily and rapidly absorbed across the mucous membranes.

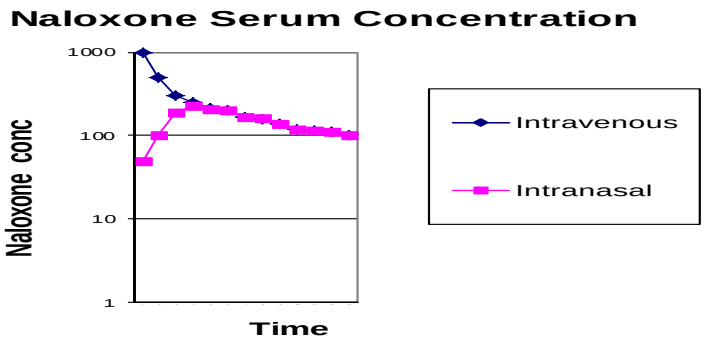


# Bioavailability

- How much of the administered medication actually ends up in the blood stream?
  - IV medications are 100% bioavailable.
  - Most oral medications are about 5 to 10 percent bioavailable due to destruction in the GI tract and liver.
  - Nasal medications vary, but nasal Naloxone approaches 100 percent, the same as when given intravenously.

# Bioavailability

- Table demonstrating naloxone serum concentrations when given via IV and IN routes.
- Note that IV and IN serum levels are identical after about two to three minutes.



# Intranasal Medication
## Administration: Bioavailability

- Not all drugs can be delivered via the nasal mucosa.
- Factors affecting bioavailability:
  - Medication characteristics
  - Medication volume and concentration
  - Nasal mucosal characteristics
  - Delivery system characteristics
    - Mucosal surface area coverage
    - Medication particle size

# Intranasal Medication Administration: Factors Affecting Bioavailability

- Medication Characteristics:
  - Drug characteristics that affect bioavailability via the nasal mucosa include
    - Molecular size
    - Lipophilicity
    - pH
    - Drug concentration
    - Properties of the solution the drug is solubilized within

# Intranasal Medication Administration: Factors Affecting Bioavailability

- Volume and concentration
  - Too large a volume or too weak a concentration may lead to failure because the drug cannot be absorbed in high enough quantity to be effective.
  - Volumes over 1 ml per nostril are too large and may result in runoff out of the nostril.
    - 1/3 to 1/2 ml per nare is *ideal* in an adult.

# Intranasal Medication Administration: Factors Affecting Bioavailability

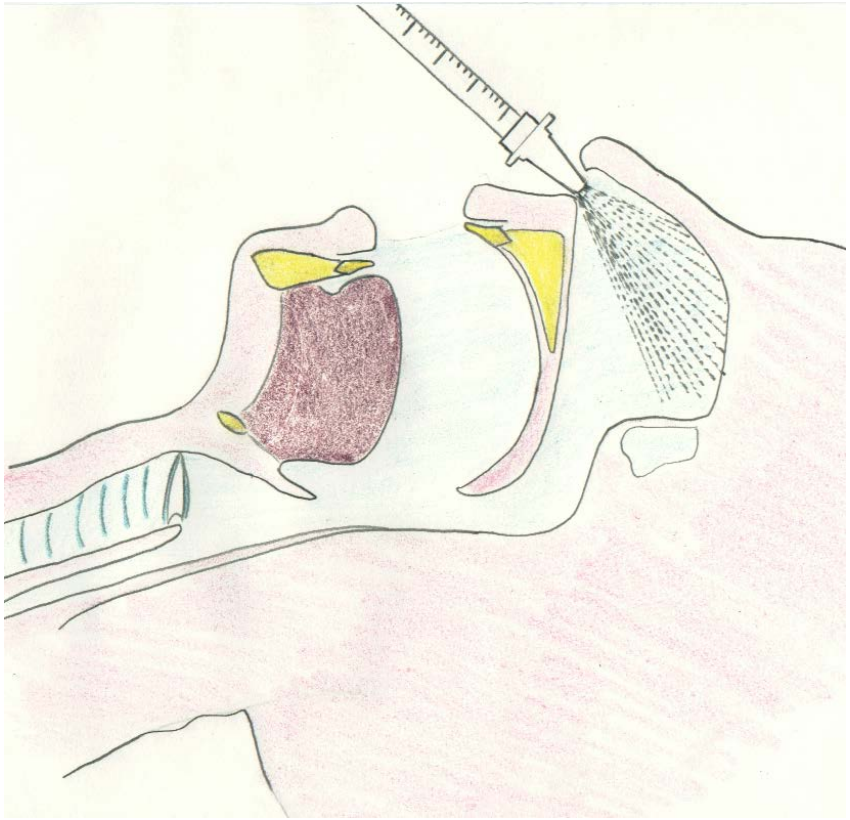
- Nasal mucosal characteristics
  - If there is something wrong with the nasal mucosa, it may not absorb medications effectively.
  - Examples:
    - Vasoconstrictors, such as cocaine, prevent absorption.
    - Bloody nose, nasal congestion, mucous discharge all prevent mucosal contact of drug.
    - Destruction of nasal mucosa from surgery or past cocaine abuse – no mucosa to absorb the drug.

# Intranasal Medication Administration: Factors Affecting Bioavailability

- Delivery system characteristics:
  - Nasal mucosal surface area coverage:
    - Larger surface area delivery = higher bioavailability.
  - Particle size:
    - Particle size 10-50 microns adheres best to the nasal mucosa.
    - Smaller particles (nebulized) pass on to the lungs.
    - Larger particles form droplets and run-out of the nose.

# Bioavailability and Particle size

- Compared to drops, atomized medication results in:
  - Larger surface area of coverage.
  - Smaller liquid particle size, allowing thin layer to cover mucosa.
  - Less run-off out the nasal cavity.



# Intranasal Medication Administration: Factors Affecting Bioavailability

- Nasal drug delivery is convenient and easy, but it may not always be effective.
- Nasal drug delivery cannot completely replace the need for injections.
- Being aware of the limitations and using the correct equipment and drug concentrations will assist you in predicting times when nasal drug delivery may not be effective.

# Intranasal (IN) Naloxone

- Background
  - Absorption of IN naloxone is almost as fast as IV in both animal and human models:
    - Hussain, A.A., *Mechanism of nasal absorption of drugs.* Prog Clin Biol Res, 1989. **292**: p. 261-272.
    - Loimer N., Hofmann P., Chaudhry H.R. (1994). *Nasal administration of naloxone is as effective as the intravenous route in opiate addicts. The International Journal of the Addictions; 29:6.*

# Intranasal (IN) Naloxone

- Atomized spray of medications show much better absorption via the IN route:
  - Bryant, M.L., et al., *Comparison of the clearance of radiolabelled nose drops and nasal spray as mucosally delivered vaccine.* Nucl Med Commun, 1999. **20**(2): p. 171-4.
  - Daley-Yates, P.T. and R.C. Baker, *Systemic bioavailability of fluticasone propionate administered as nasal drops and aqueous nasal spray formulations.* Br J Clin Pharmacol, 2001. **51**(1): p. 103-5

# "Intranasal Administration of Naloxone by Paramedics"

- Prospective clinical trial
- Preliminary study February, 2001
  - Barton et al, *Prehosp Emer Care* 2002
  - http://www.ihra.net/files/2010/08/23/Barton_-_Intranasal_Administration_of_Naloxone.pdf
- Final study completed
  - Barton et al, J Emerg Med 2005
  - Kelly et al, Med J Aust 2005 (a study in Australia)
  - https://www.mja.com.au/journal/2005/182/1/randomised-trial-intranasal-versus-intramuscular-naloxone-prehospital-treatment
- Study design:
  - Required all patients to get an IV and IV naloxone (standard care) – however nasal naloxone was administered first and if the patient awoke prior to IV therapy they could stop.

# Pre-hospital IN Naloxone

## Results

- 43/52 (83%) = Responded to IN Naloxone
  - Median time to awaken from drug delivery = **3 min**
  - Median time from first contact = **8 min**
- 9/52 (17%) = Did not respond to IN Naloxone
  - Fourpatients noted to have “epistaxis,” “trauma,” or “septal abnormality”
  - Note: no one waited for them to respond. Once an IV was started they got IV naloxone, so some cases were given IV naloxone before the nasal drug could absorb.

# Pre-hospital IN Naloxone

- Conclusions
  - IN naloxone is effective:
    - 83 % response in the field
    - Potentially higher if one waits a few minutes for its effect prior to giving IV naloxone
  - Inexpensive device
    - Syringe driven atomizer
  - May decrease pre-hospital blood exposures
    - 29 % of patients did not need an IV in the field (woke up before one could be started)

# Pre-hospital IN Naloxone

- Take away lessons for nasal naloxone:
  - Dose and volume – higher concentration preferred so use 1 mg/ml IV solution.
  - Delivery – immediately on decision to treat, inject naloxone into nose with atomizer. Then begin standard care.
  - Successful awakening eliminates the need for any IV or further ALS care.
  - Awakening is gradual-patient doesn't jump off the bed, but adequate respiratory efforts occur as fast or faster than IV naloxone due to no delays with IV start.
  - Not 100 percent effective- failures with IN naloxone need to be followed with IM naloxone.

# What if initial intranasal Naloxone does not work?

1) Continue ABCs to support breathing and circulation.
2) Administer additional Naloxone per protocol.
3) Consider other causes for respiratory depression/coma AEIOU-TIPS.

| | AEIOU |
|---|---|
| A | Alcohol |
| E | Epilepsy |
| I | Infection |
| O | Overdose |
| U | Uremia |

| | TIPS |
|---|---|
| T | Trauma |
| I | Insulin |
| P | Poisoning |
| S | Stroke |

# Give the Initial IN Dose Time to Work

- 0.5 mg can usually correct respiratory concerns in a large person.
- Give the drug three to five minutes to work before additional doses are given.

# Use of IM Administration

**Use only when IN route is contraindicated.**

# Conclusions

- Drugs can be given IN:
  - Rapid
  - Safe to patient and provider
  - Immediate access
  - Can be given to almost anyone
    - Exception = Nasal mucosal abnormalities

# Conclusions

The purpose of this medication is **NOT** to wake someone up. The purpose of this medication is to increase their spontaneous respiratory effort.

- Intranasal drug delivery is a "needleless" system.
- Reduce bloodborne exposure risks:
    - HIV
    - Hepatitis B, C

# Questions?

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# Resources and References


- www.intranasal.net
- http://www.ihra.net/files/2010/08/23/Barton-Intranasal_Administration_of_Naloxone.pdf
- https://www.mja.com.au/journal/2005/182/1/randomised-trial-intranasal-versus-intramuscular-naloxone-prehospital-treatment
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