2013 EMS STATE OF THE SCIENCE: Gathering of Eagles XVI

Nosocomial Injection:

Intranasal Midazolam for Pediatric Seizures

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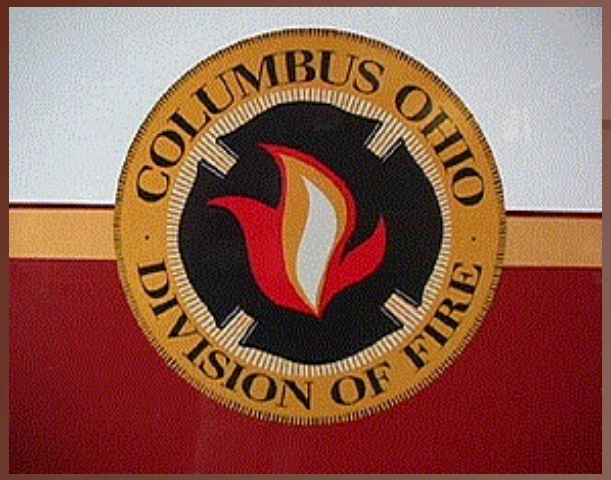
Medical Director Columbus Division of Fire

DISCLOSURE

- Dr. Keseg has no financial interest in any companies that are involved in the manufacture of products related to this presentation.

CFD EMS OVERVIEW



Geographical Information

Area	Size	Population
Metro Columbus	399.1 square miles	1,742,798
City of Columbus	239.9 square miles	791,868

CFD EMS OVERVIEW

First Line Apparatus Summary

Emergency Units in Service

34	Engines	7	EMS Supervisors
15	Ladders	1	Air Supply
5	Rescues	1	Bomb Squad
7	Battalion Chiefs	1	Safety Officer
32	Medics	11	Boats
1	HazMat		

CFD EMS OVERVIEW

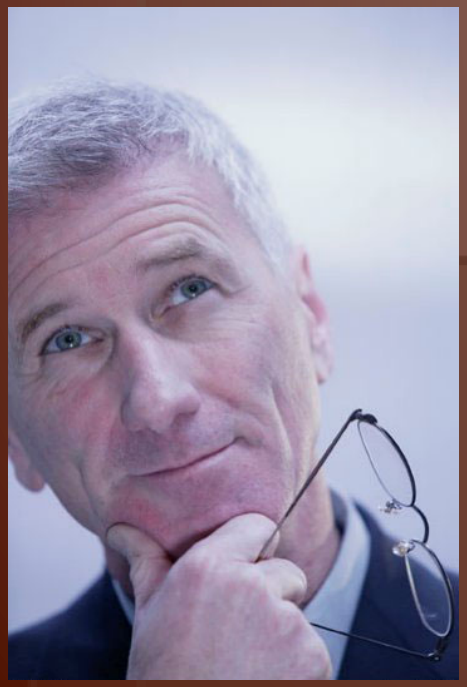
- All ALS Fire based EMS System
- Two EMT-Ps on each Medic Vehicle (32)
- At least one EMT-P on each engine (34)
- Engine/medic stations
- Seven EMS Officers

FOUR-YEAR COMPARISONS

	2008	2009	2010	2011
Total Incidents	146,144	142,981	148,918	161,693
Fire Incidents	24,868	21,470	21,861	23,715
EMS Incidents	110,739	110,398	115,311	137,442

Do you know Columbus???

- What was the name of the vehicle that the Columbus Fire Department deployed in 1969 to take care of cardiac patients?



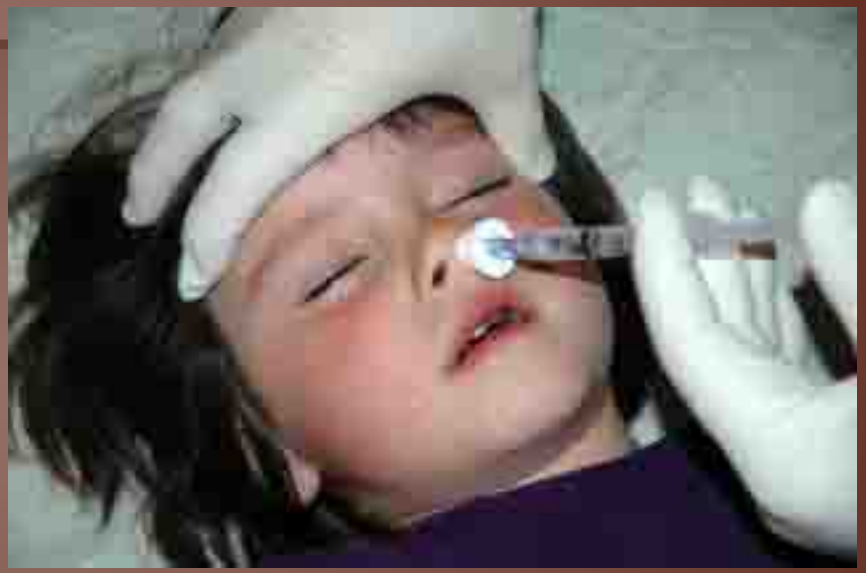
Do you know Columbus???

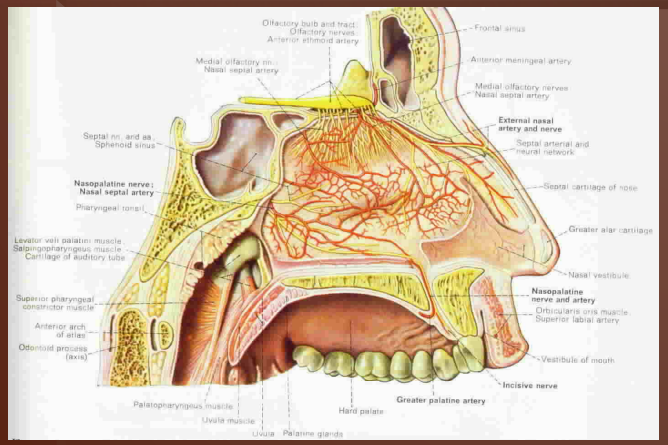
- THE HEARTMOBILE

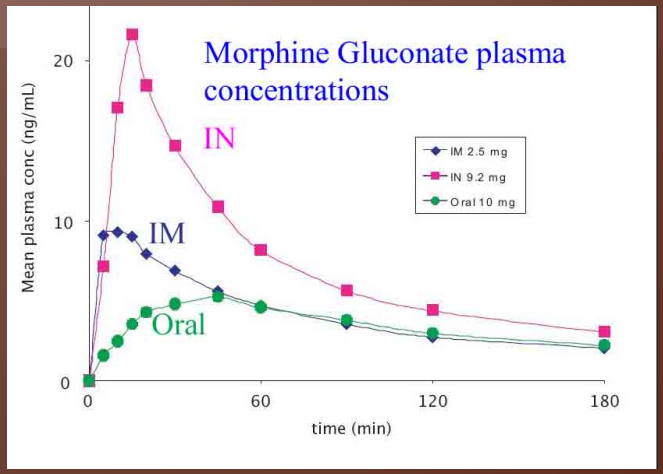
IN Midazolam for seizure control

- 150,000 cases of status epilepticus annually
- Morbidity and mortality are at least partially dependent on the duration of seizure activity
- **HYPOTHESIS**
  - ***Intranasal delivery of Midazolam provides a very effective, safe and inexpensive means to rapidly achieve seizure control.***

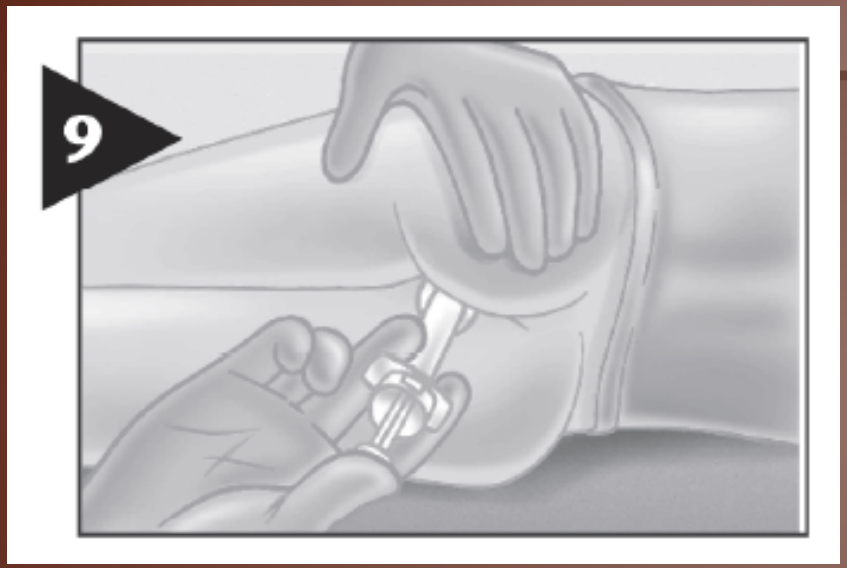
Why Intranasal?

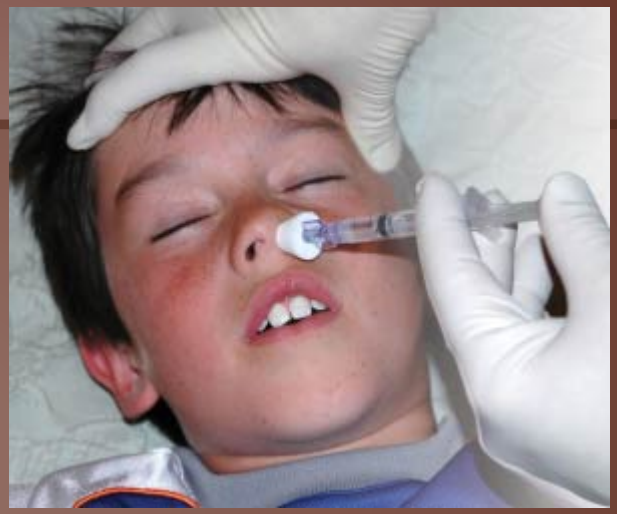


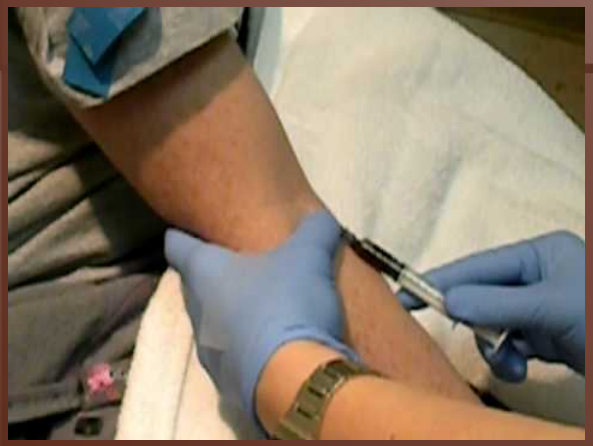


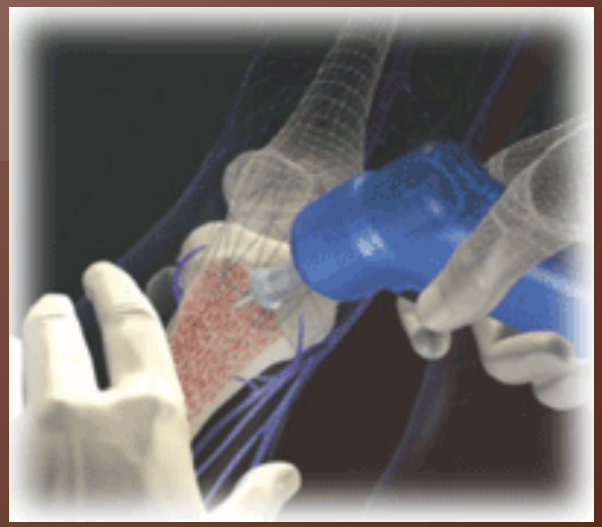


Which would YOU prefer?



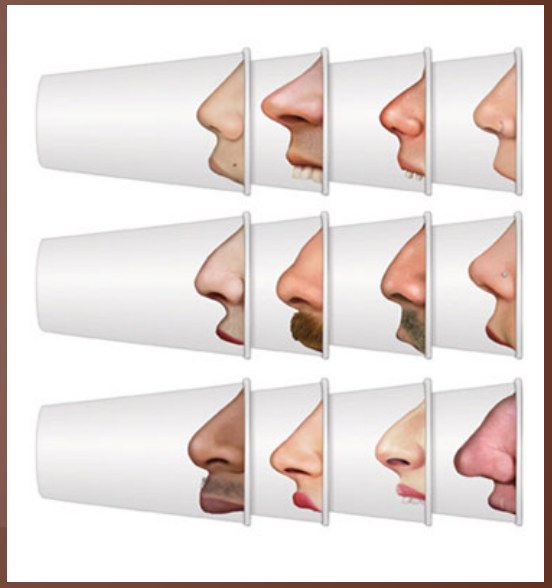






Why Intranasal?

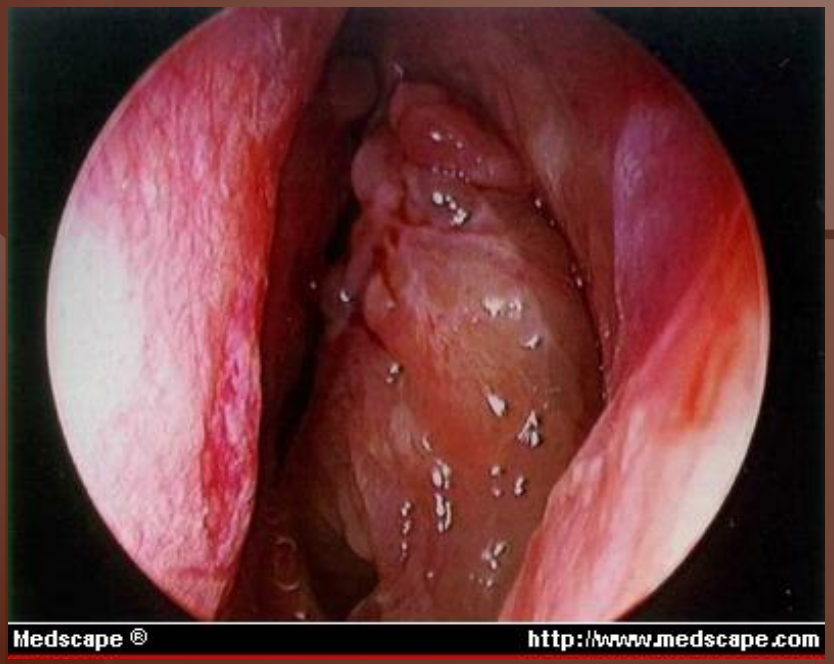
The nose is a preferred access point for medication administration because:

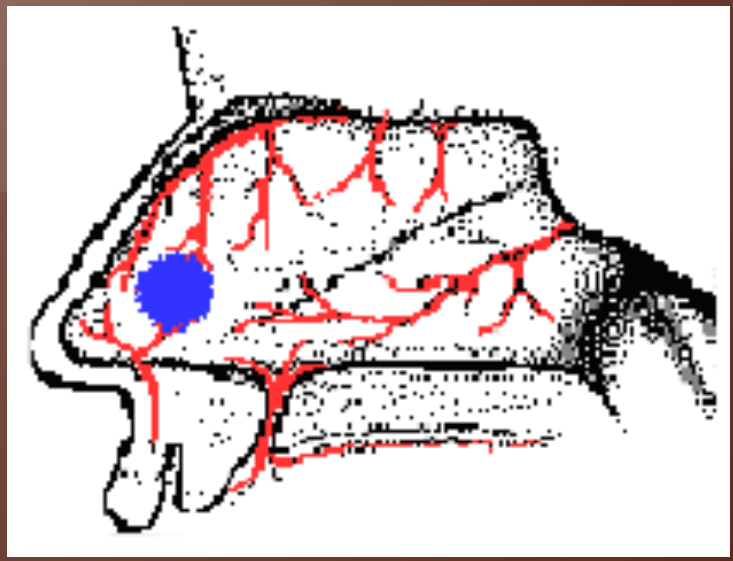


- ***Training is minimal***
- ***No shots are needed***
- ***It is virtually painless***
- ***It eliminates any risk of a needle stick***

Nasal Mucosa

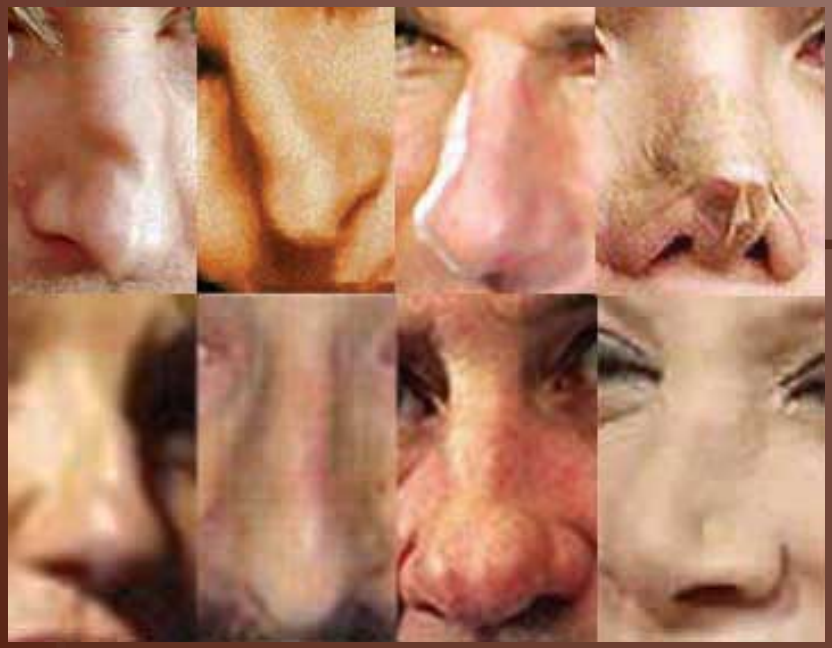
- *The rich vascular plexus of the nasal cavity provides a direct route into the blood stream for medications that easily cross mucous membranes.*

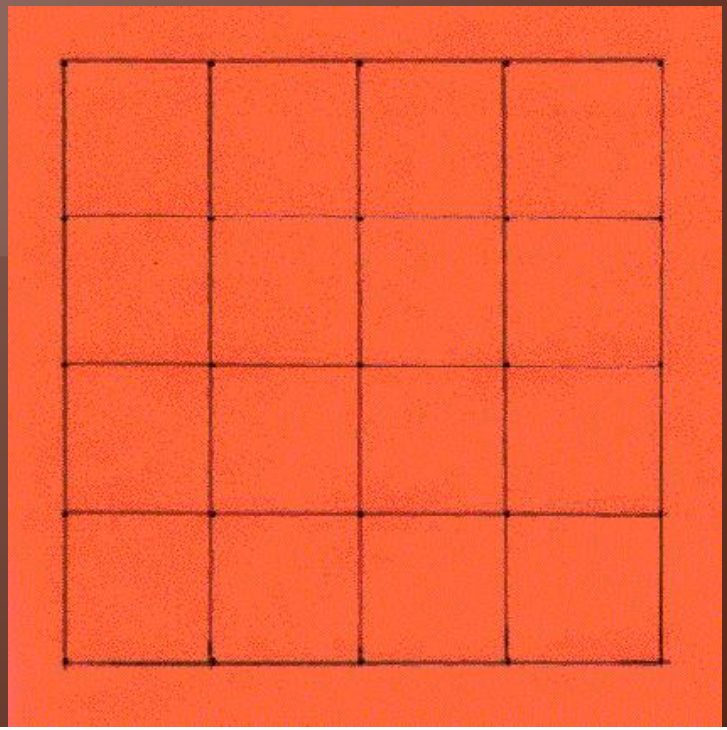




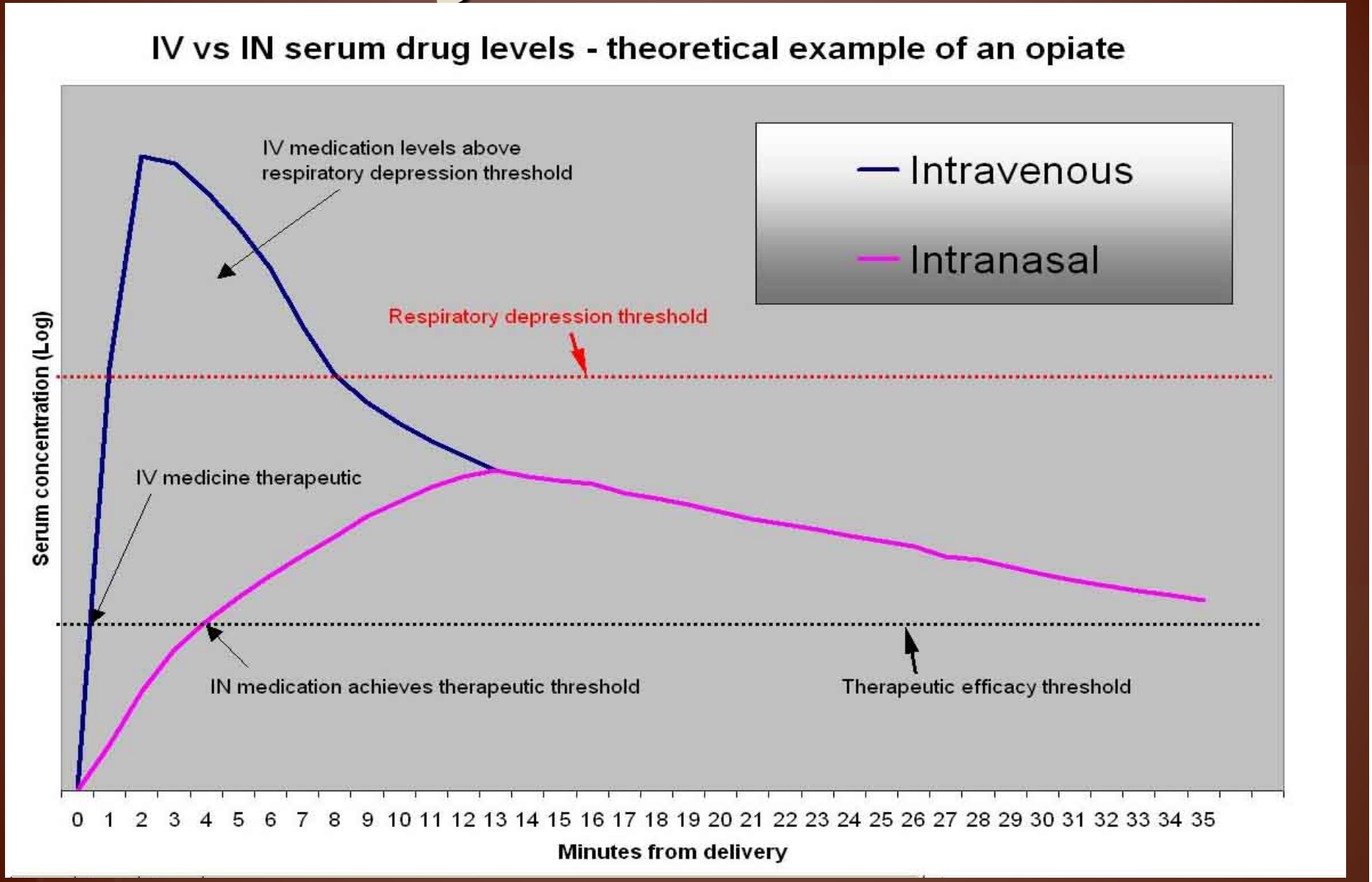
Nasal Mucosa

- *The total surface area available in the nasal mucosa is estimated to be about 28 square inches*



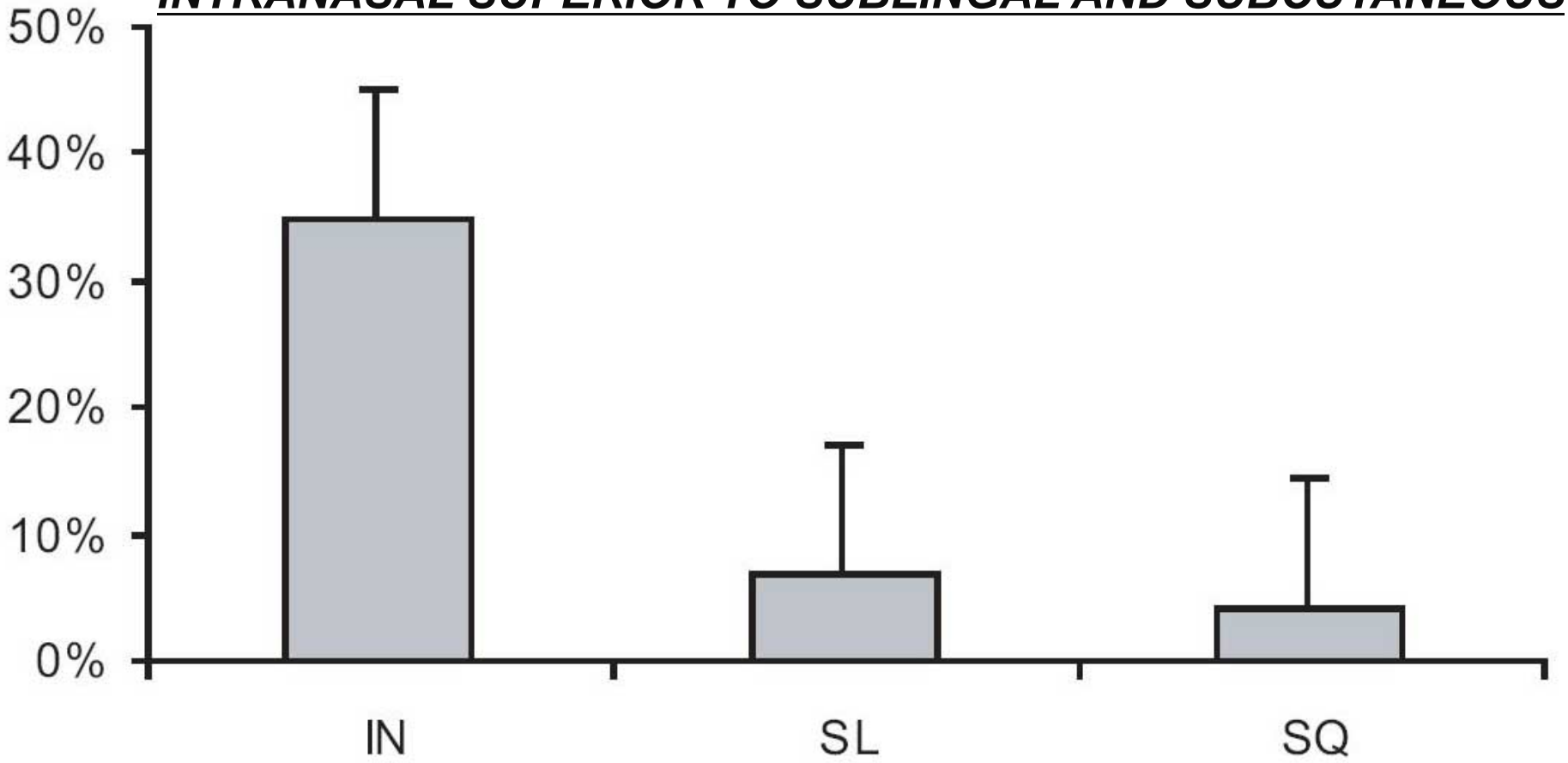


Why Intranasal?



Comparison of CSF/plasma ratios for IN, SL and SC apomorphine

INTRANASAL SUPERIOR TO SUBLINGAL AND SUBCUTANEOUS



Key Features:	Nasal	Oral	I.V.
High Serum Drug Levels	✔	NO	✔
Rapid Onset	✔	NO	✔
Titratable	✔	NO	✔
Painless	✔	✔	NO
Easy to Use	✔	✔	NO
Low Resource Utilization	✔	✔	NO

How to give drugs intranasally

- Fragment the medication into fine particles so:
  - ***maximal*** *nasal mucosal surface is covered and*
  - ***minimal*** *volume runs out the nose or into the throat*

Mucosal Atomization Device MAD device

- Device designed to allow emergency personnel to delivery nasal medications as an atomized spray.
- Broad 30-micron spray ensure excellent mucosal coverage.
- Cost: **$3.32 apiece**
  - Translation: CHEAP!!!!

Pediatric Nasal Device

How To Use the Nasal Device

Remove and discard the green vial adapter cap.

Pierce the medication vial with the syringe vial adapter.

Aspirate the proper volume of medication required to treat the patient (an extra 0.1ml of medication should be drawn up to account for the dead space in the device).

Remove (twist off) the syringe from the vial adapter.

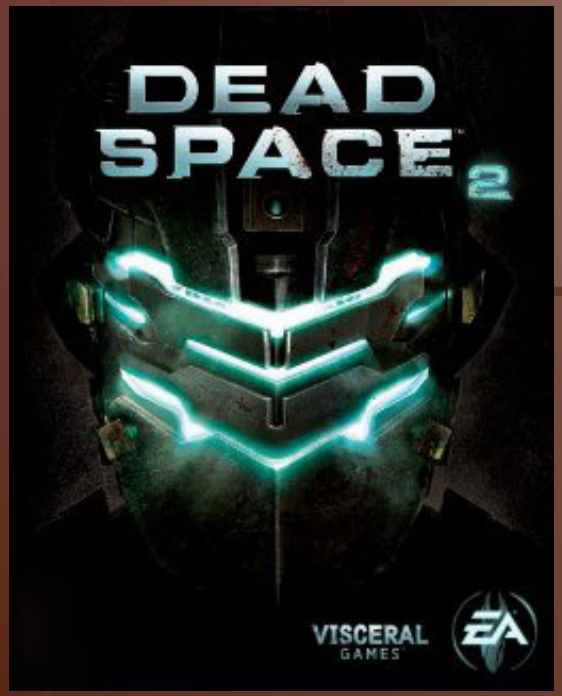
BOTTOM LINE: IT'S EASY!!!!!

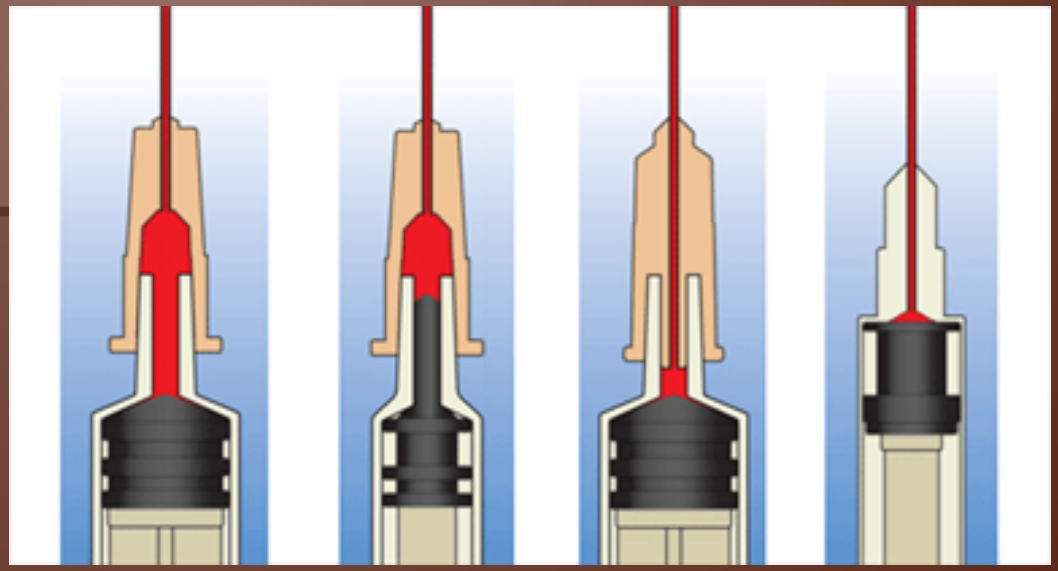
Tips on IN Administration

- Utilize both nostrils

Tips on IN Administration

- Be knowledgeable of the “dead space” within the MAD





Tips on IN Administration

Minimize volume,

- ***1/3 mL per nostril is ideal, 1 mL is maximum***

Maximize concentration

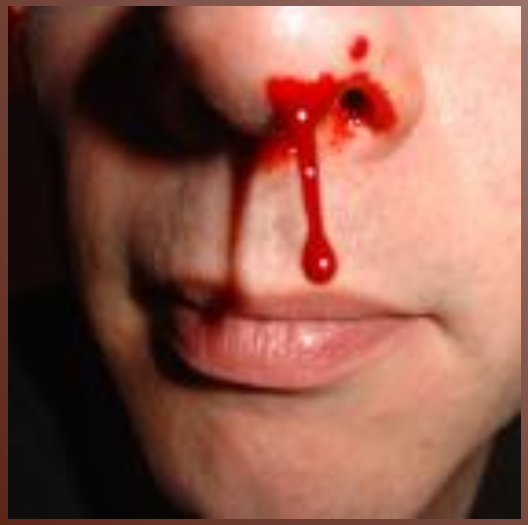
- ***Use the appropriately concentrated drug***

Tips on IN Administration

Beware of abnormal mucosal characteristics

- ***Mucous, blood and vasoconstrictors reduce absorption***

- ***Suction nostrils or consider alternate drug delivery method in these situations***



Nasal Drug Delivery in EMS: What Medications?

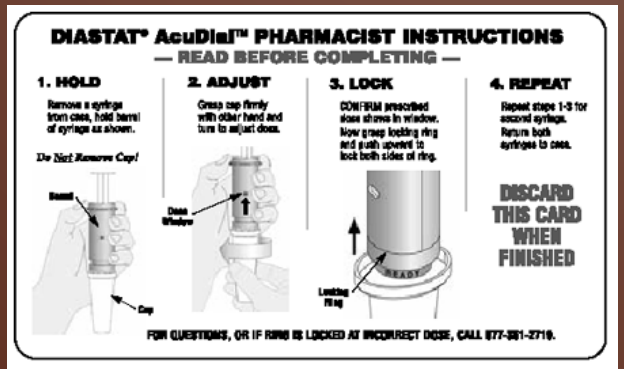
- Drugs of interest to EMS systems:
  - Intranasal naloxone (Naloxone)
  - Intranasal midazolam (Midazolam)
  - Intranasal Fentanyl
  - Intranasal Glucagon
  - Intranasal Ketamine
  - Intranasal Epinephrine
  - Others

EAGLES Experience

- 30 responses
  - 25 using IN
    - 3 soon
  - 24 using Naloxone
  - 18 using midazolam
  - 11 using fentanyl
  - 3 using glucagon
  - 1 dilaudid
  - 1 influenza vaccine

SUMMARY
Intranasal Midazolam: advantages in EMS seizure treatment

- *No needles*
- *Rapid delivery*
- *Training is easy*
- *Socially acceptable*



But does intranasal Midazolam work in Pediatric seizures?

Impact of a protocol using intranasal midazolam for managing seizures

Margaret Kyrkou[1], Michael Harbord[2], Nicole Kyrkou[3], Debra Kay[4], Kingsley Coulthard[1] & Kylie Bailey[2]

[1]Children, Youth and Women's Health Service, [2]Flinders Medical Centre, [3]Flinders University, [4]Department of Education and Children's Services, South Australia

Dr Margaret Kyrkou

Midazolam was first used in 1982 (O'Regan, Brown & Clarke, 1996). Unlike rectal diazepam (RD), which has a number of disadvantages including the need for privacy, intranasal midazolam (INM) can be easily administered in the community. Scheepers, Scheepers & Clough (1998) also claimed that fear of RD administration has been cited as a reason for truancy among older children with epilepsy. Additionally, they pointed out that the long half life of 20-40 hours may result in drowsiness which in itself may paradoxically lower the seizure threshold, leaving the patient more susceptible to further seizures.

Nasal administration of midazolam results in rapid absorption from an area rich in blood supply, cerebrospinal fluid concentrations peaking 5-12 minutes after administration. INM does not have the disadvantage of being processed through the liver, unlike buccal administration, and has a mean elimination half life of two hours in healthy subjects.

Statistics of status epilepticus (SE)

Aicardi (1994) demonstrated that the outcome of SE was worse in children (especially those less than 3 years of age), with neurologic sequelae in 20%, and death in 3-7%, a claim supported by Wilson, McLeod & O'Regan (2004). Soon after an episode of SE, magnetic resonance imaging studies demonstrated regions of focal cerebal oedema which resolved, but later changes of cerebral atrophy appeared in those regions (Meierkord, Wieshmann, Niehaus, & Lehman, 1997). Young (1996) noted seizure duration to be the single major predictor of mortality, with a 10% mortality rate if SE was controlled within 10 hours, but rising to 85% mortality rate if SE persisted for more than 20 hours.

Timing of administration of emergency anticonvulsants

Although it is now generally accepted that prolonged seizures can cause neuronal injury, there is considerable uncertainty regarding the duration and intensity of seizures required before injury occurs (Alldridge & Lowenstein, 1999), largely due to an extremely limited ability to validate in humans the findings of experimental models. Lowenstein & Alldredge (1993, 1998) showed that treatment of SE within 30 minutes of onset was associated with an 80% response rate to first line anti-epileptic drugs (AEDs), but only 40% if the seizure had persisted for longer than 2 hours. Walker (2003); Gilbert, Gartside & Glauser (1999); Hirsch & Claassen (2002); and Livingston (2004) all claimed treatment in the premonitory stages of a seizure is more likely to be successful than treatment in the later stages, with Hirsch & Claassen (2002), and Livingston (2004) advocating treatment by caregivers at home to allow extremely fast treatment, prevent SE, and reduce the need for emergency room visits. Hirsch & Claassen (2002) were of the opinion that failure to treat aggressively in the early stages increased the likelihood of refractory SE (RSE), which Gilbert, Gartside, & Glauser (1999) demonstrated in a meta-analysis to have a mortality rate of 16%. This is an important recommendation, considering approximately 5 % of adults and 10-25% of children with epilepsy will have at least one episode of SE (Shorvon, 2001), and 13% of all patients with SE will have a further episode of SE (Fountain, 2000).

Studies involving pre-hospital treatment of SE

Alldredge, Wall & Ferriero (1995) in a prospective study reported that pre-hospital treatment of SE not only reduced the seizure duration, but also reduced the incidence of respiratory complications. Holsti, Sill, & Firth et al, (2004) compared 25 paediatric patients administered either INM or RD by emergency services before being transported to a paediatric emergency service in Salt Lake County. The first 17 children were administered RD, with a subsequent 8 administered INM. Children given INM had less need for bag-valve-mask ventilation (0% versus 31%), or endotracheal intubation (0% versus 33%), were less likely to have further seizures prehospital (0% versus 22%), or in the emergency department (60% versus 78%), and less likely to require hospitalisation (40% versus 88.8%). A study by ambulance paramedics in New South Wales (Rainbow, Browne, & Lam, 2002)

Intranasal Midazolam Research Studies

- **Seizures.**
  - Lahat et al, *BMJ*, 2000.
    - Prospective study: ***IN midazolam*** versus ***IV diazepam*** for prolonged seizures (>10 minutes) in children.
    - ***Similar efficacy*** in stopping seizures (app. 90%).
    - ***Time to seizure cessation***:
      - ***IV Diazepam: 8.0 minutes.***
      - ***IN Midazolam: 6.1 minutes.***

Pediatric Neurology

Volume 34, Issue 5 , Pages 355-359, May 2006

Intranasal Midazolam vs Rectal Diazepam in Acute Childhood Seizures

Madhumita Bhattacharyya, MD

Veena Kalra, MD,

Sheffali Gulati, MD

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Received 21 June 2004; accepted 14 September 2005.

One hundred eighty-eight seizure episodes in 46 children were randomly assigned to receive treatment with rectal diazepam and intranasal midazolam with doses of 0.3 mg/kg body weight and 0.2 mg/kg body weight, respectively. Efficacy of the drugs was assessed by drug administration time and seizure cessation time. Heart rate, blood pressure, respiratory rate, and oxygen saturation were measured before and after 5, 10, and 30 minutes following administration of the drugs in both groups. Mean time from arrival of doctor to drug administration was 68.3 ± 55.12 seconds in the diazepam group and 50.6 ± 14.1 seconds in the midazolam group ($P = 0.002$). Mean time from drug administration to cessation of seizure was significantly less in the midazolam group than the diazepam group ($P = 0.005$). Mean heart rate and blood pressure did not vary significantly between the two drug groups. However, mean respiratory rate and oxygen saturation differed significantly between the two drug groups at 5, 10, and 30 minutes after drug administration. Intranasal midazolam is preferable to rectal diazepam in the treatment of acute seizures in children. Its administration is easy, it has rapid onset of action, has no significant effect on respiration and oxygen saturation, and is socially acceptable.

IN Midazolam is preferable to rectal diazepam in the treatment of seizures in children. It's administration is easy, it has a rapid onset of action, has no significant effect on respiration and oxygen saturation and is socially acceptable.

Epilepsy Behav. 2004 Apr;5(2):253-5.

Comparison of intranasal midazolam with intravenous diazepam for treating acute seizures in children.

Mahmoudian T, Zadeh MM.

Source

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Abstract

Midazolam, a water-soluble benzodiazepine, is usually given intravenously in status epilepticus. The aim of this study was to determine whether **intranasal midazolam** is as safe and effective as intravenous diazepam in the treatment of acute childhood **seizures**. Seventy children aged 2 months to 15 years with acute **seizures** (febrile or afebrile) admitted to the **pediatric** emergency department of a general hospital during a 14-month period were eligible for inclusion. **Intranasal midazolam** 0.2 mg/kg and intravenous diazepam 0.2 mg/kg were administered after intravenous lines were established. **Intranasal midazolam** and intravenous diazepam were equally effective. The mean time to control of **seizures** was 3.58 (SD 1.68) minutes in the **midazolam** group and 2.94 (SD 2.62) in the diazepam group, ***not counting the time required to insert the intravenous line.*** No significant side effects were observed in either group. Although **intranasal midazolam** was as safe and effective as diazepam, **seizures** were controlled more quickly with intravenous diazepam than with **intranasal midazolam**. **Intranasal midazolam** can possibly be used not only in medical centers, but also in general practice and at home after appropriate instructions are given to families of children with recurrent **seizures**.

Intranasal Midazolam can possibly be used not only in medical centers but also in general practice and

AT HOME

after appropriate instructions are given to families of children with recurrent seizures.

JOURNAL CLUB Arch Pediatr Adolesc Med. 2010;164(8):747-753

Intranasal Midazolam vs Rectal Diazepam for the Home Treatment of Acute Seizures in Pediatric Patients With Epilepsy

Maija Holsti, MD, MPH; Nanette Dudley, MD; Jeff Schunk, MD; Kathleen Adelgais, MD, MPH; Richard Greenberg, MD; Cody Olsen, MS; Aaron Healy, BS; Sean Firth, PhD, MPH; Francis Filloux, MD

We found no detectable difference in efficacy between IN-MMAD and RD as a rescue medication. However, our data suggest that there may be a trend toward faster seizure control in the IN-MMAD group. The published literature in the ED setting also suggests that IN midazolam may stop seizures more quickly than RD. Adverse effects appear to be minimal. Given the ease of administration/overall satisfaction, IN-MMAD may be considered an alternative to rectal diazepam as a rescue medication for the in-home treatment of prolonged seizures in children.

Intranasal Midazolam
MORE Research Studies

- *Rectal diazepam fails to abort about 40 percent of seizures in randomized controlled trials.* ♪
  - (*Lancet* 1999;353:623; *J Pediatr* 1999;135:398; *J Child Neurol* 2002;17:123.) ♪

♪

- *Several randomized trials now demonstrate that transmucosal intranasal midazolam is as effective as intravenous diazepam and more effective than rectal diazepam in aborting prolonged seizures.* ♪
  - (*J Child Neurol* 2002;17:123; *Brit Med J* 2000;321:83; *Epilepsy Behav* 2004;5:253.) ♪

♪

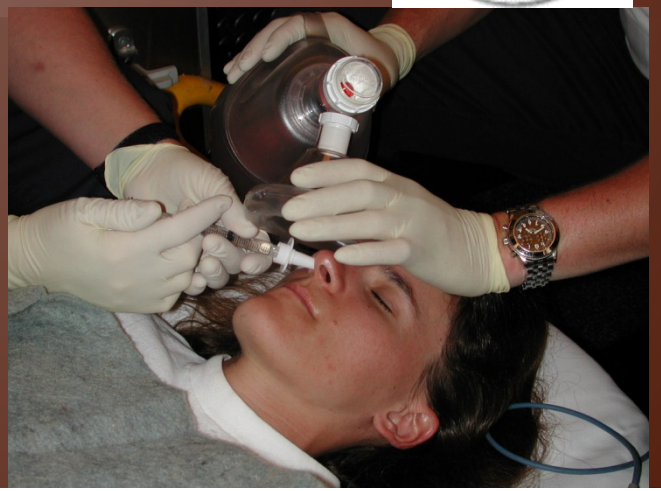
- *In addition, its preference over rectal diazepam by caregivers and its safety as home therapy have been established in multiple small studies.* ♪
  - (*Arch Dis Child* 2004;89:50; *J Paediatr Child Health* 2004;40:556; *Eur J*

BOTTOM LINE:

IN Midazolam as good and probably better than PR Diazepam in pediatric seizures

CFD Implementation of IN Midazolam

- Analysis of product: Jan-May 2003
- Recommendations Nasal Device: June 2003
- Nasal Device arrives: September 2003
- Training/Protocol development: Oct 2003
- Training completed: December 2003
- Devices deployed: Feb 2004



CFD Protocol for IN Midazolam

- For treatment of persistent seizure activity
- Procedure:
  - Assess ABC's – Airway, Breathing, Circulation
  - For pulseless patients, proceed to ACLS guidelines
  - Apply 100% oxygen NRB mask to seizing patient
  - Use age based table to determine proper volume of Midazolam for atomization:

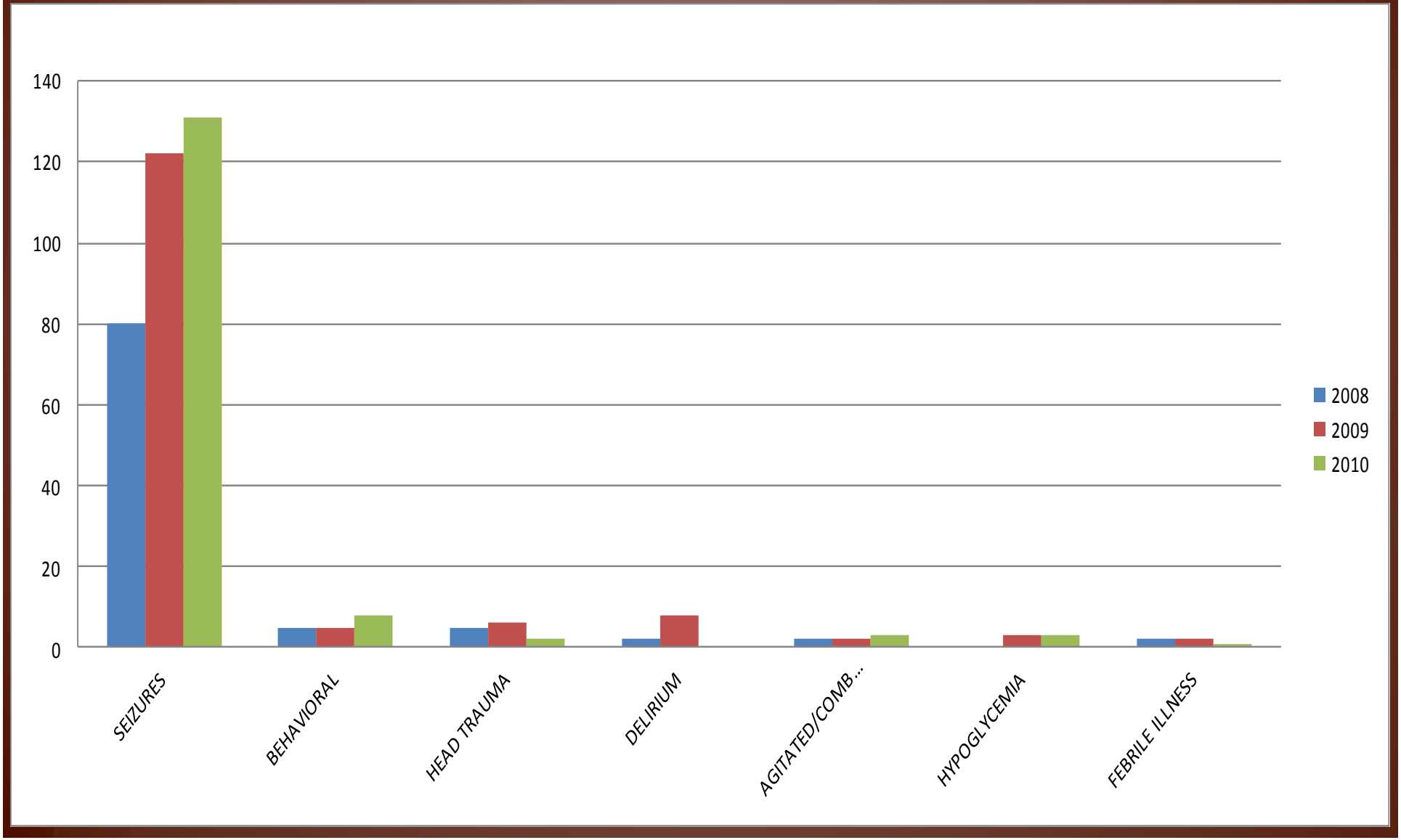
IN Midazolam Dosing Table

Patient age (years)	Weight (kg)	IN Versed volume in ml* 5mg/ml concentration	
		IN volume (ml) 5 mg / ml	Dose (mg)
Neonate	3 kg	0.3 ml	0.6 mg
<1 yr	6 kg	0.4 ml	1.2 mg
1 yr	10 kg	0.5ml	2.0 mg
2 yr	14 kg	0.7 ml	2.8 mg
3 yr	16 kg	0.8 ml	3.2 mg
4 yr	18 kg	0.9 ml	3.6 mg
5 yr	20 kg	1.0 ml	4.0 mg
6 yr	22 kg	1.0 ml	4.4 mg
7 yr	24 kg	1.1 ml	4.8 mg
8 yr	26 kg	1.2 ml	5.2 mg
9 yr	28 kg	1.3 ml	5.6 mg
10 yr	30 kg	1.4 ml	6.0 mg
11 yr	32 kg	1.4 ml	6.4 mg
12 yr	34 kg	1.5 ml	6.8 mg
Small teenager	40 kg	1.8 ml	8.0 mg
Adult or full-grown teenager	≤ 50 kg	2.0 ml	10.0 mg

Survey on IN Midazolam use

- Distributed to all EMS personnel on medics:
  - *IN Midazolam used most often for seizures (81%)*
  - *IN Midazolam used 0 - 5 times per month (97%)*
  - *96% felt comfortable administrating IN Midazolam*
  - *93% felt it somewhat or somewhat or greatly enhanced their practice*

IN Midazolam Indications



Pediatric seizure patients given Intranasal Midazolam

Year	Number treated
2008	**10**
2009	**21**
2010	**21**
2011	**25**
2012	**14** (as of 8/2012)

Conversion Rate of pediatric seizure patients given Intranasal Midazolam

Year	Conversion Rate
2008	**50%**
2009	**80%**
2010	**64%**
2011	**75%**
2012	**72%**(as of 8/2012)

The NEW ENGLAND JOURNAL of MEDICINE

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Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

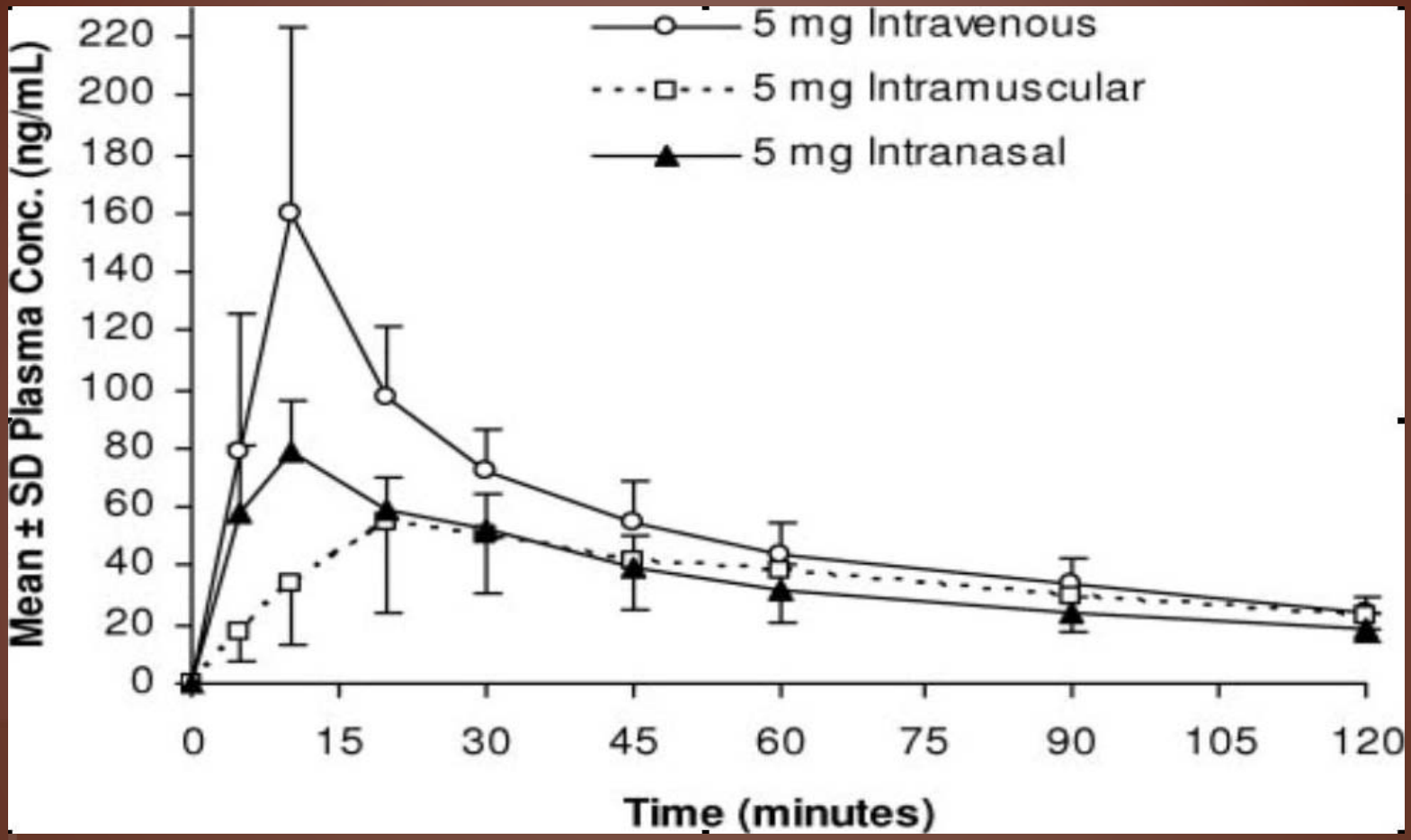
Robert Silbergleit, M.D., Valerie Durkalski, Ph.D., Daniel Lowenstein, M.D., Robin Conwit, M.D., Arthur Pancioli, M.D., Yuko Palesch, Ph.D., and William Barsan, M.D., for the NETT Investigators*

CONCLUSIONS

For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

NO HEAD TO HEAD COMPARISON WITH INTRANASAL MIDAZOLAM

IN Midazolam for seizure control



IN MIDAZOLAM MUCH MORE RAPID ONSET THAN IM

Take away lessons for nasal midazolam:

- Dose and volume:
  - Higher concentration: 5mg/ml IV solution.
- Dosing calculations can be difficult:
  - Use a predefined weight based table
- Deliver immediately on decision to treat:
  - Atomize into nose with MAD, then begin standard care.
- Efficacy:
  - Not quite 100% effective so failures with nasal may need follow-up with IV therapy.

NASAL MIDAZOLAM IS AN EFFECTIVE EMS TREATMENT FOR PEDIATRIC SEIZURES

- Questions???????????