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How to Use Non-Clinical Models in Intranasal Drug Development

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NASAL INNOVATION FORUM

Disclosures

Philip Kuehl is an employee of Lovelace Biomedical. Some of this work was contract to Lovelace by external sources and some funded by internal research and development funds.

No other disclosures.

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Presentation Outline

- Cover quickly
  - In vitro methods
  - Small animal vs. large animal models
  - Small animal vs. large animals deliver tools
- Spend more time on
  - Anatomical differences
  - Case studies
  - Scientific team thought process on study design development and how to use this in your programs.

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Intranasal Drug Delivery – What tools exist?

- Nasal Casts
  - Human casts available and routinely used
  - Animal cast models are limited and not well standardized
- Non-clinical nose to brain models are limited
  - Nasal Cast
  - Animal model(s)
- Rodent Models
  - Rats, mice, ferrets, etc
- Large animal
  - NHP or canine

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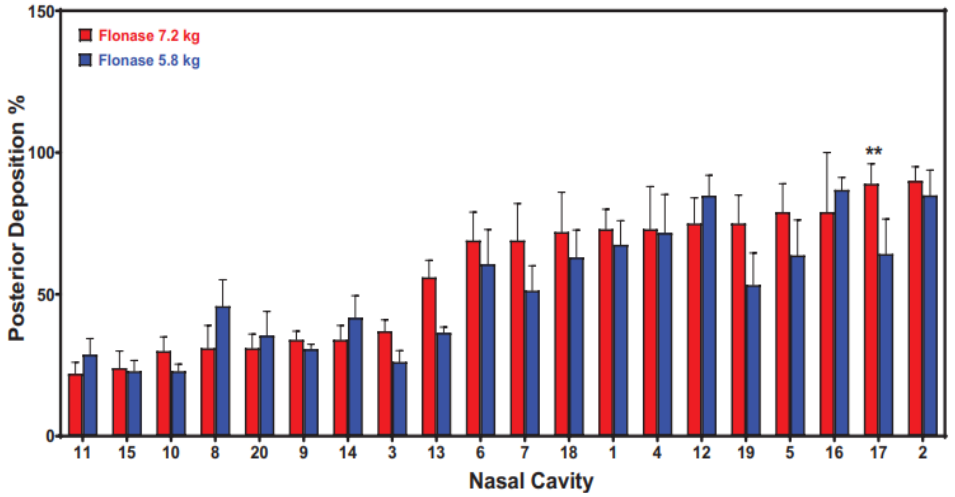
Intranasal Drug Delivery – In vitro Models

- In vitro models – Nasal Casts
  - Clinical and non-clinical casts exist
  - Over 20 existing nasal casts
  - Vary in complexity and source data
- How does the user select which one best suits their problem statement?

Williams and Suman Pharmaceutics 2022; 14, pp. 1353



Golshahi, L., etc. In Vitro Bioequivalence Testing of Nasal Sprays Using Multiple Anatomically-Correct Nasal Airway Models. In Respiratory Drug Delivery 2020; River Grove, IL, USA, 2020; Volume 1, pp: 155–164

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Intranasal Drug Delivery – In vitro Models

- There are publications that discuss differences in anatomy between NHP's and humans but there are no available NHP nasal casts
- Similar results with other non-clinical species.

ELSEVIER

Computers in Biology and Medicine

Volume 141, February 2022, 105150

Detailed comparison of anatomy and airflow dynamics in human and cynomolgus monkey nasal cavity

Lin Tian, Jingliang Dong, Yidan Shang, Jiyuan Tu

Comparative Study > J Aerosol Med. 1997 Winter;10(4):319-29. doi: 10.1089/jam.1997.10.319.

A comparative analysis of primate nasal airways using magnetic resonance imaging and nasal casts

H C Yeh [1], R M Brinker, J R Harkema, B A Muggenburg

Affiliations + expand

PMID: 10175962 DOI: 10.1089/jam.1997.10.319

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Intranasal Drug Delivery – In vivo Models

- Non-clinical models should be based on what the problem statement is, what the current program data exists and what the overall program goals are
- All animal models can be considered – rodents to non-rodents
- Keep in mind that ‘all models are wrong, some models are useful’

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Intranasal Drug Delivery – In vivo Models

- Team review of the Problem Statement:
  - What is the compound class
  - What/Where is the biological target
  - What is the formulation (aqueous, dry powder, etc.)
  - What data exist?
  - What methods exist?
- Considerations for delivery location:
  - Volume
  - Anesthesia depth and type

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Intranasal Anatomy

- The nasal anatomy is widely different from non-clinical species to humans and within non-clinical species
- This specifically means no animal model is perfect for all intranasal studies

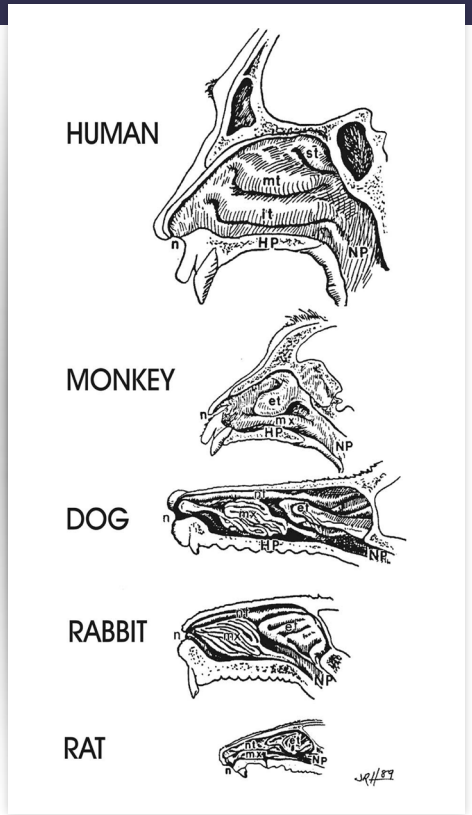

Figure from: Harkema, Jack R., Stephan A. Carey, and James G. Wagner. "The Nose Revisited: A Brief Review of the Comparative Structure, Function, and Toxicologic Pathology of the Nasal Epithelium." *Toxicologic Pathology* 34, no. 3 (April 1, 2006): 252–69. https://doi.org/10.1080/01926230600713475.T

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Intranasal Anatomy

- Compare and contrast the differences in each of the species volume and surface area
- As animal models evolve it is clear that some species are not included in the current literature

Species	Volume (mL)	Total Surface Area (cm^2)	Turbinate Complexity
Human	19	181	Simple scroll
Dog	20	220.7	Very complex, membranous scroll
Monkey	8	61.6	Simple scroll
Rat	0.4	20	Complex scroll
Mouse	0.03	2.8	Complex scroll

Table from: Emami, et. al. Int. J. Toxicol 2018, 37(1)

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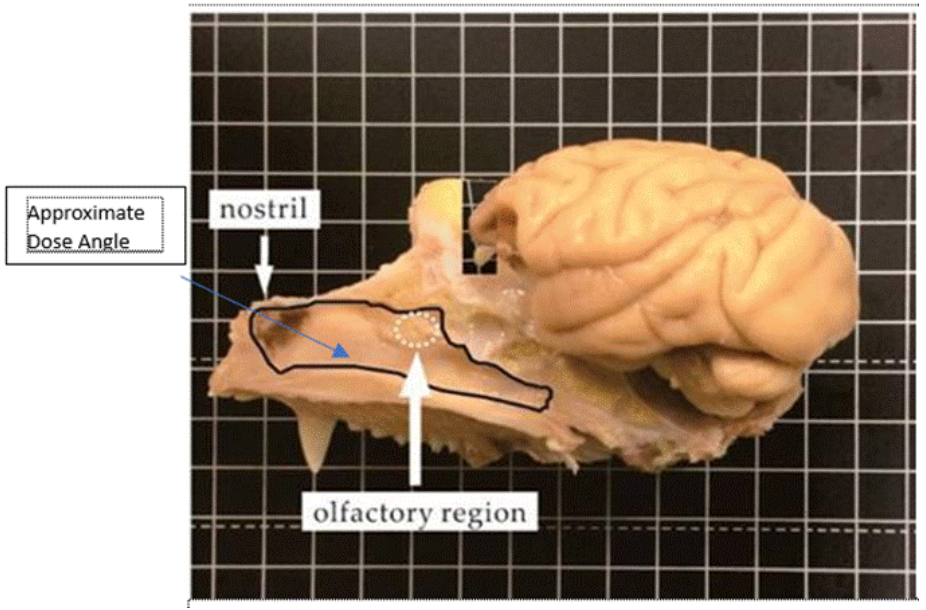
Intranasal Anatomy

- Think about and evaluate angle for delivery



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Rodent Models

Advantages

- Small weights – less API needs
- Simple delivery systems (pipette)
- Serial sacrifice for tissue collections
- Wide range of laboratories that can work with rodents

Disadvantages

- Significant differences in anatomy (nasal breathers)
- Can't utilize clinical devices
- Limited number of devices available for novel formulations
  - Liquid vs. dry powder

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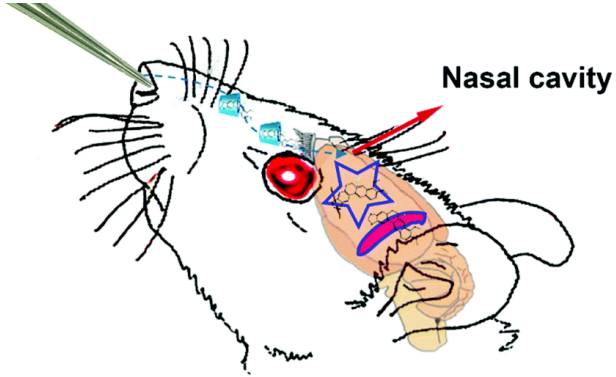
Rodent Delivery - Liquid

- Liquid formulations – pipette into the nose
  - Volumes can be varied to support dose based on formulation concentration typically ~ 10 µL / nostril in a rat
  - Pipette / novel devices for liquid aerosols



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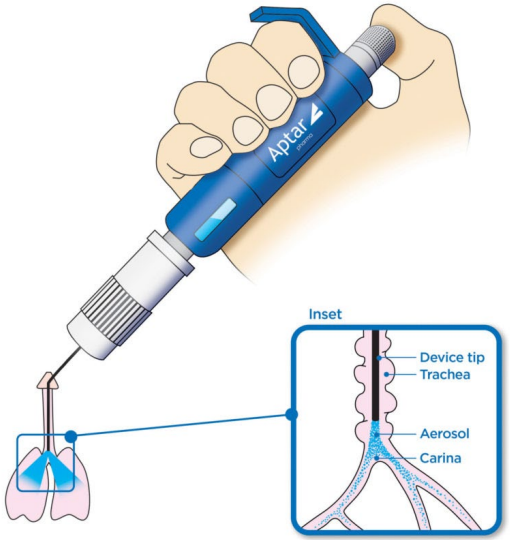
Rodent Delivery – Dry Powder

- Dry powder formulations: there really aren't any purpose built systems but some dry powder devices may be 'enabled' to work
- Also consider nose only inhalation delivery and assess localization of delivery based on particle size



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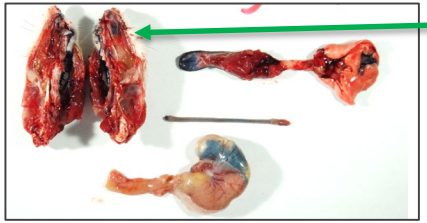
Rodent Models – Positioning Matters

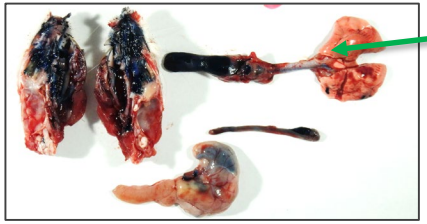
- Ventral Recumbency

50 µL



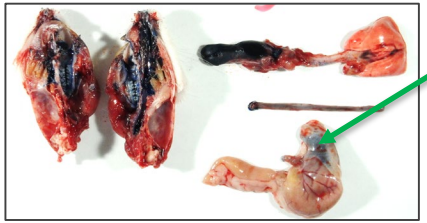
Nasal Cavity

100 µL



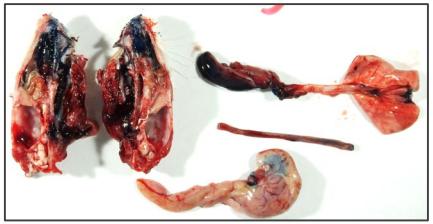
Trachea and lungs

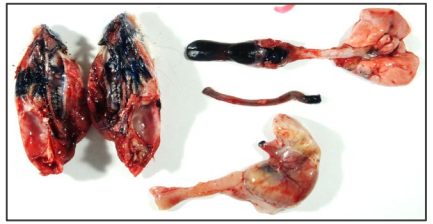
150 µL

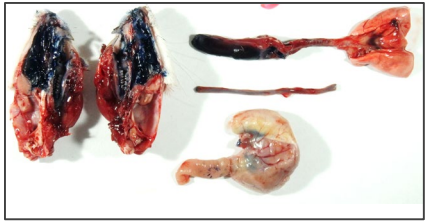


Stomach and esophagus

- Dorsal Recumbency







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Canine Models

Advantages

- Clinical devices can be used
  - Liquid and dry powder
- Large blood volumes for serial sampling
- Well established model often with other published data or methods in place

Disadvantages

- Significant differences in anatomy (sense of smell)
- Limited ability to collect tissue samples

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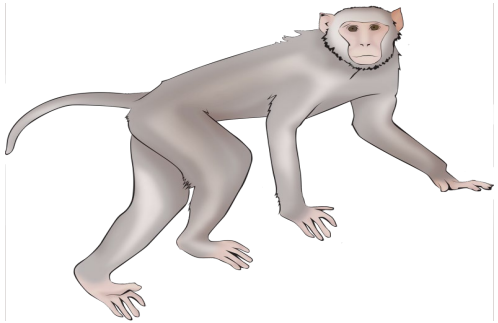
NHP Models

Advantages

- Clinical devices can be used
  - Liquid and dry powder
- Large blood volumes for serial sampling
- Well established model often with other published data or methods in place
- Anatomy similar to humans

Disadvantages

- Limited ability to collect tissue samples
- Higher ordered species (limited locations that can work with NHP's)



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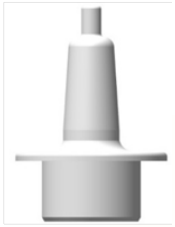
Large Animal Delivery - Liquid

- Liquid formulations
  - Clinical devices can be used without modifications
  - Adapters are available to support unique dosing requirements (if needed)
  - Additional off the shelf devices that directly fit to syringes are also feasible
- Enable the teams to lavage CMC section for dose, dose uniformity, analytical methods, and remove device questions



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Large Animal Delivery – Dry Powder

- Dry Powder formulations
  - Must be active devices as the animals can't be trained to inhale
  - Adapters are available to support unique dosing requirements (if needed)
  - Additional off the shelf devices that directly fit to syringes are also feasible

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Case Studies Based on Problem Statements

- All models are wrong, some models are useful
- Each problem statement should be evaluated and considered by the team to determine what is the best system to ask/answer the question based on the data at hand
- The answer today might be different than the answer after you generate more data
- Don't let the pursuit of perfection stop progress

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Can a Non-Clinical Model be Used to Quantify Nose to Brain Delivery

- Problem Statement:
  - Is there a non-clinical model that enables evaluation of nose to brain delivery?
- NHP
  - Similar anatomy
  - Clinical devices
  - Serial blood collections
  - Serial CSF collections
  - Tissue collection was not needed

Kuehl, et. al: Proceedings of Respiratory Drug Delivery, 2020, Vol 1, pp. 165-174

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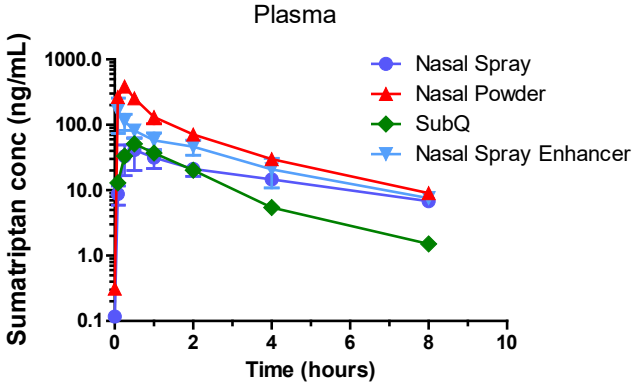
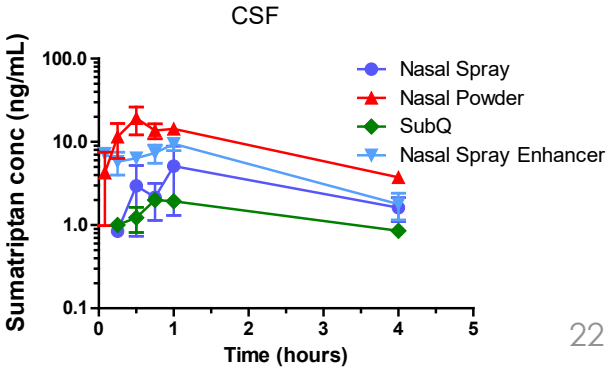
Can a Non-Clinical Model be Used to Quantify Nose to Brain Delivery

- Plasma
  - Significant exposure from all routes of delivery
- CSF
  - Significant exposure and potentially increased in nasal delivery
  - NCA to quantify





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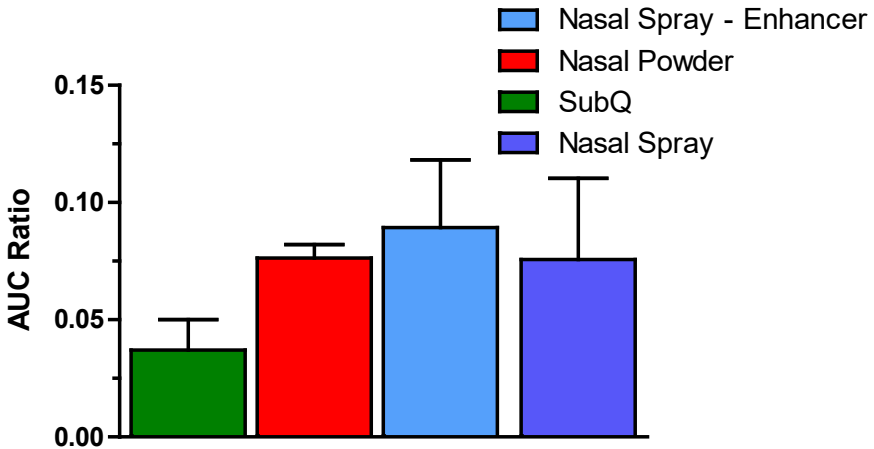
Kuehl, et. al: Proceedings of Respiratory Drug Delivery, 2020, Vol 1, pp. 165-174

Can a Non-Clinical Model be Used to Quantify Nose to Brain Delivery

- Ratio of CSF AUC/Plasma AUC enables comparison between routes of delivery
- NHP model allows the quantification of nose to brain delivery in a non-terminal model
- Limitation – does CSF reflect the target tissue in the CNS system?



Kuehl, et. al: Proceedings of Respiratory Drug Delivery, 2020, Vol 1, pp. 165-174

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Non-Clinical Model to Quantify Systemic Epinephrine following Intranasal Delivery?

- Problem Statement:
  - What non-clinical model would enable the comparison of IM vs. IN delivery of epinephrine for systemic exposure?
- Canine
  - Clinical devices
  - Serial blood collections
  - Published LCMS method

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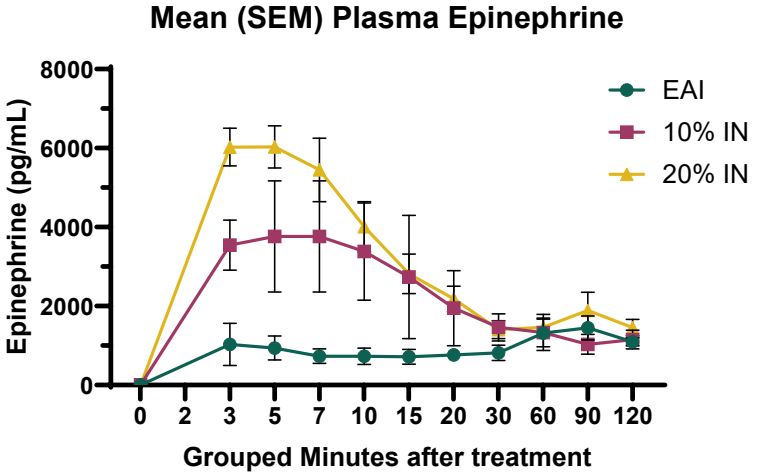
Kuehl, Wargin, Lyman and Taubenheim: Proceedings of Respiratory Drug Delivery, 2024, Vol 1, pp. 201-204

Non-Clinical Model to Quantify Systemic Epinephrine following Intranasal Delivery?

- Canine
  - Partial AUCs between 2x and 4x increase for IN
  - IN exposures much more rapid (C_{max} and T_{max})
  - IN appears to follow dose dependency



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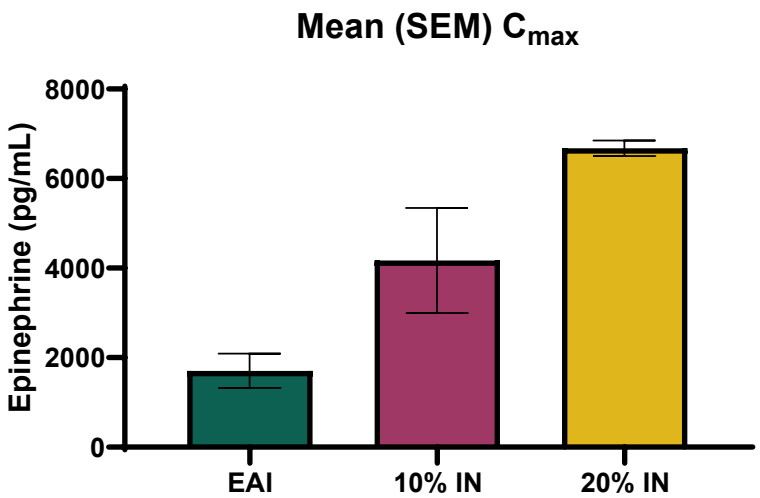
Kuehl, Wargin, Lyman and Taubenheim: Proceedings of Respiratory Drug Delivery, 2024, Vol 1, pp. 201-204

Non-Clinical Model to Quantify Systemic Epinephrine following Intranasal Delivery?

- Canine model allows the assessment of C_{max} and Tmax of different formulations and delivery routes
- Limitation – did the increased surface area in the canine impact the PK?



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Kuehl, Wargin, Lyman and Taubenheim: Proceedings of Respiratory Drug Delivery, 2024, Vol 1, pp. 201-204

Can a Dry Powder be Delivered Intranasally to a Rodent?

- Typically IN delivery to a rodent is done with a liquid formulation pipetted into the nare(s)
- Different delivery technique (anaesthesia/volume/etc.) can change the location of delivery
- Study has a need for serial collection of CNS tissue

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Can a Dry Powder be Delivered Intranasally to a Rodent?

- Aptar PADA Device
  - Designed for intratracheal delivery of dry powders in rodents

– Modify to enable insertion directly into naris

– Evaluate a dibenzoazepine while collecting blood and tissue

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Can a Dry Powder be Delivered Intranasally to a Rodent?

- Dose ~ 15 animals
  - ~ 10 animals the quantitative analysis of the PADA device (weight before and after delivery) showed good delivery
  - ~ 5 'failures'
- All animals with good delivery showed clear clinical signs of delivery
- Lessons learned and improvements:
  - Failed devices likely plugged with nasal mucus
  - How do engineers and veterinary technicians prevent the opening from plugging with mucus?

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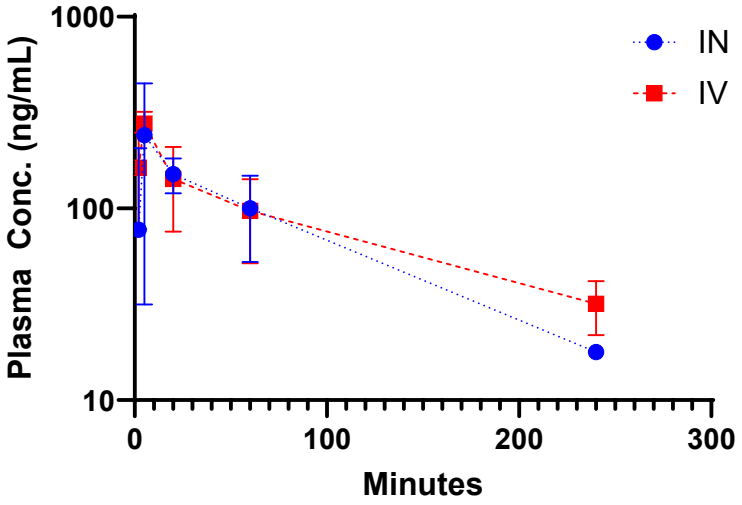
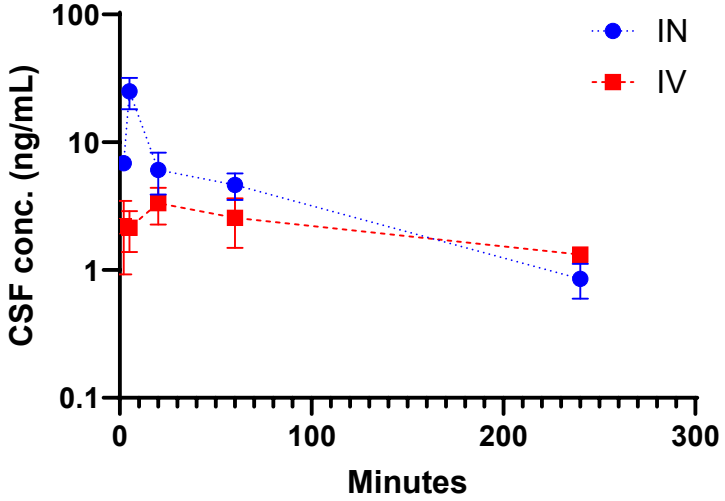
Can a Dry Powder be Delivered Intranasally to a Rodent?

Plasma



CSF



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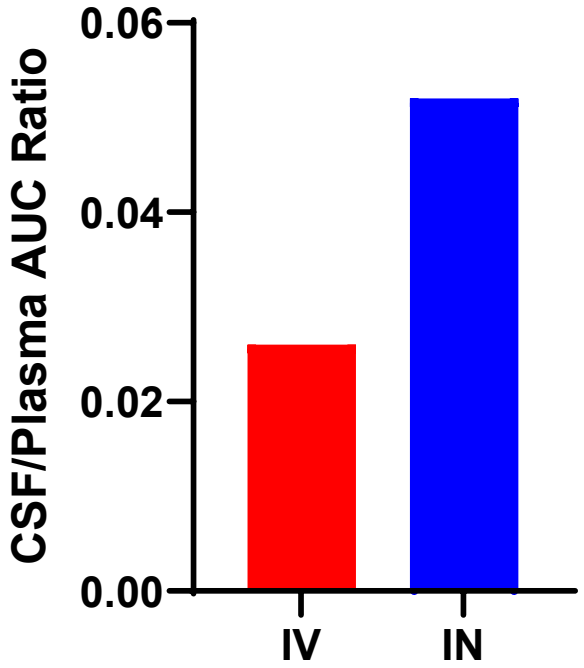
Can a Dry Powder be Delivered Intranasally to a Rodent?

- Working within the limits of our data: Did API go nose to brain with a dry powder in rats?
- Evaluate ratios of CSF/Plasma AUC
- IV represents blood to brain as a baseline
- Increase in ratio from IN represents nose to brain



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Can a Non-Clinical Model be Used to Evaluate Changes in Formulation

- NHP model enables the non-terminal evaluation of different formulations to compare PK parameters
- Non-terminal nature allows iterative study conduct
- Inform formulation development for each specific API

To be submitted Sept/Oct2025 JAMPDD

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Can a Non-Clinical Model be Used to Evaluate Changes in Formulation

- Problem Statement:
  - For a specific small molecule API what formulation technologies will provide greatest absorption (AUC) and highest C_{max}?
- Formulation:
  - Excipient composition for enhanced absorption, improved dissolution, permeation enhancer
- NHP
  - Similar anatomy
  - Clinical devices
  - Serial blood collections
  - Tissue collection was not needed

To be submitted Sept/Oct2025 JAMPDD

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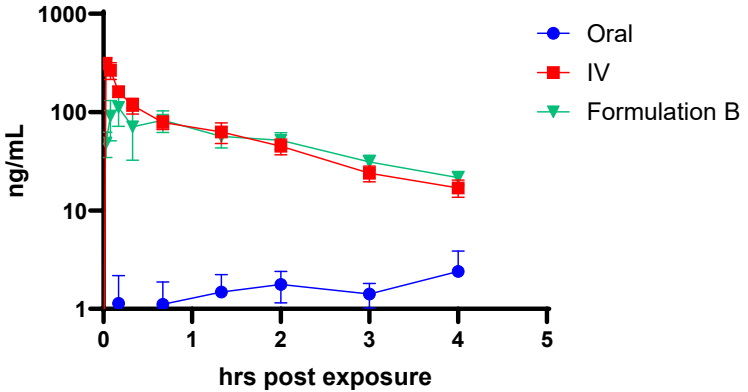
Can a Non-Clinical Model be Used to Evaluate Changes in Formulation

- Formulation:
  - API/HPMC/Mannitol (30/30/40)
- Aptar Unit Dose Powder Device
- 7 formulations evaluated (see manuscript for full details!)
- Plasma
  - Oral, IV and lead formulation shown
  - IN delivery provides similar profile as IV



To be submitted Sept/Oct2025 JAMPDD

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What Gaps Remain

- Rodents
  - Dry powder delivery needs additional refinement
  - Nasal casts
    - Should we develop them?
  - Translatability of IN / nose to brain in rodents to other species/humans
  - Formulation advances and feasibility of testing in rodents

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What Gaps Remain

- Large Animals
  - What animals are important?
    - NHP's, canines, swine
  - Nasal casts
    - Should we develop them?
  - Translatability of IN / nose to brain in rodents to other species/humans
  - Formulation advances and feasibility of testing in large animals

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Acknowledgments

- Conor Ruzycki, Jane Lindborg, Ted Barrett, Hammad Irshad
- Countless others from Lovelace and the groups below

Aptar pharma

Belhaven BIOPHARMA

MOD3 Pharma
YOUR CATALYST TO CLINIC

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Questions

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