APS Intranasal workshop 2022

Intranasal nonclinical models

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Overview

- Preclinical drug development for intranasal administration
  - Species similarities and differences
  - How
    - Nonclinical delivery techniques
  - Limitations: bad news
    - Alternative administration
  - Regulations: good news
- Moving forward
  - Improvements for better in vivo modelling

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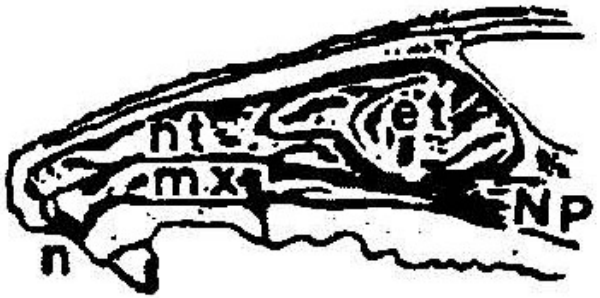
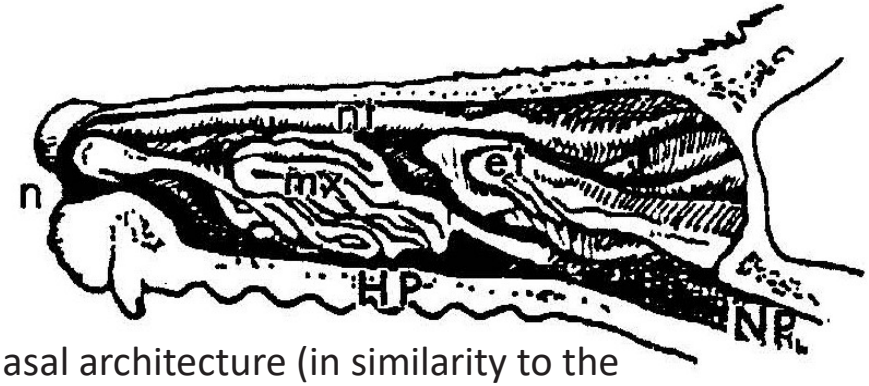
Nasal architecture

RAT



The rat shows a low volume high complexity nasal architecture.

DOG



The dog retains the relative complexity of the nasal architecture (in similarity to the rat) at an overall increase in volume.

Harkema et al, Toxicologic Pathology, 34; 252-269, 2006

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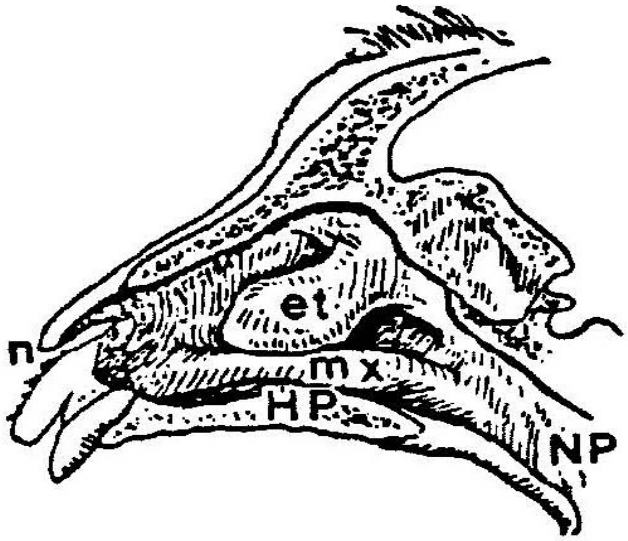
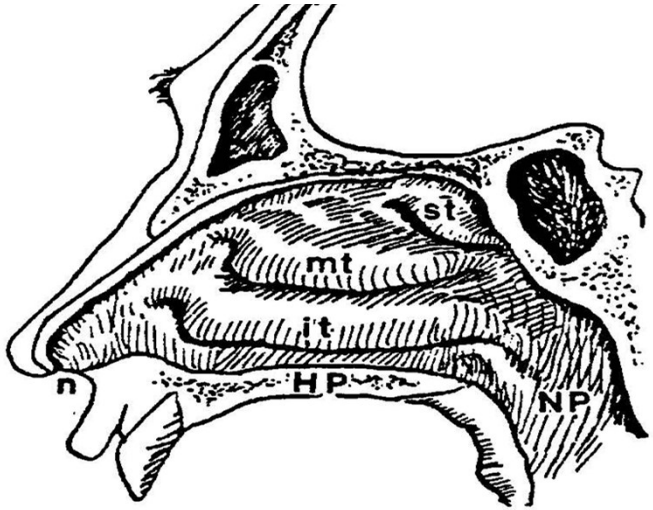
Nasal architecture

MONKEY



Note the less complex nasal architecture of the monkey in relation to the rat and the dog.

HUMAN



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Factors affecting successful nasal absorption of drugs in experimental animals

Anatomical factors	Physiological conditions of the nose	Dosage form factors	Techniques and devices of administration
Nasal volume and length	Speed of mucus flow	Concentration of the drug	Volume
Nasal epithelial surface area	Presence of infection	Viscosity/density properties of the dosage form	Droplet size or size of solid particles
The bend from the nostrils into the cavity	Mucosal enzymes and components	pH-tonicity of the dosage form	Site of deposition
Structure of the conchae	Atmospheric conditions	Surface tension of the drug and the dosage form	Spray characteristics
Presence of “septal window”		Excipient	Loss anteriorly from the nose
Cellular structure		Physicochemical properties of the drug	Loss into the esophagus

Interspecies Comparison of Nasal Cavity Characteristics

	Sprague-Dawley Rat	Guinea Pig	Beagle Dog	Rhesus Monkey	Man
Body weight	250 g	600 g	10 kg	7 kg	~70 kg
Naris cross-section	0.7 mm^2	2.5 mm^2	16.7 mm^2	22.9 mm^2	140 mm^2
Bend in naris	40º	40º	30º	30º	
Length	2.3 cm	3.4 cm	10 cm	5.3 cm	7–8 cm
Greatest vertical diameter	9.6 mm	12.8 mm	23 mm	27 mm	40–45 mm
Surface area (both sides of nasal cavity)	10.4 cm^2	27.4 cm^2	220.7 cm^2	61.6 cm^2	181 cm^2
Volume (both sides)	0.4 cm^3	0.9 cm^3	20 cm^3	8 cm^3	16–19 cm^3 (does not include sinuses)
Bend in nasopharynx	15º	30º	30º	80º	~90º
Turbinate complexity	Complex scroll	Complex scroll	Very complex membranous	Simple scroll	Simple scroll

Schreider, J.P., in Nasal Tumors in Animals and Man, vol. III, Experimental Nasal Carcinogenesis, CRC Press, Boca Raton, FL, 1983

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Non-clinical delivery devices

	Physical state	Devices
Small animal	Liquid	Micropipette, curved dose needle, syringe + foot pump, Vary volume with adaptors or syringe sizes (spacers)
	Powder	Debatable
Large animal	Liquid	LMA MADomizer, Kurve's ViaNase, PennCentury micro-sprayer, Optinose, Aptar BDS (2 x 100 mcL) Most clinical devices are suitable
	Powder	PennCentury DP4

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Available commercial devices: taken from Aptar website

Global overview of APTAR Pharma preclinical solutions

39

Device Available	Population	Molecule format	Administration route	Availability
PADA	Mice*	Powder	Pulmonary	Commercially available
LADA	Mice	Liquid	Pulmonary	Not available / under development
PADA LADA	Rats	Powder Liquid	Pulmonary	Not available / under development
UDS Powder standard actuator	Primates (with human like nostrils)	Powder	Nasal	Commercially available
UDS Powder + Animal tip	Medium animals (rabbits, mini pigs, cats and dogs) - Pediatric	Powder	Nasal	UDS Powder/ Commercial Animal Tip / Prototype samples available
UDS Liquid with pediatric tip	Medium animals (rabbits, mini pigs, cats and dogs) - Pediatric	Liquid	Nasal	Prototypes samples available
CPS (preservative free) multidose pump + soft snap actuator	Medium animals (rabbits, mini pigs, cats and dogs) - Pediatric	Liquid	Nasal	CPS (50 to 140 µL) / Commercial Soft snap actuator / Commercial
VP7 multidose pump + 232 NE actuator	Medium animals (rabbits, mini pigs, cats and dogs) - Pediatric	Liquid	Nasal	VP7-25 µL / Commercially available VP7-50 µL / Commercially available 232 NE actuator / prototype samples available

Taken from Aptar literature.
Other manufacturers of intranasal devices are available

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Limitations

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Nasal diameter and flexibility determines administration method

Instillation – essentially liquid only
"To put/place"

Insufflation – both liquid and powder
"To blow/aerosolize"

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Alternative strategy: Intratrachael vs Intranasal vs Inhalation

	Intratracheal	Intranasal	Inhaled delivery
Benefits	Good for very early screening studies	Good for upper airway or nasal disease targets	Clinical route of administration
Compound requirements 1 mg/kg n=8 rats	<6 mg	<6 mg	~400 -900 mg dependent on dead space
Deposition	• Localized upper airway • Variable respiratory tissue distribution • Limited distribution to periphery	• Localized upper airway • Variable respiratory tissue distribution Limited distribution to periphery	Diffuse throughout lung airways and parenchyma
Efficiency of delivery to lungs	100%	~40-60% (remaining swallowed) depending on volume	~10-20% of total animal dose deposits in lung tissue (dependent on particle size)
Formulation	Solution/fine suspension (and powder)	Solution/fine suspension (and powder)	Any including dry powder. Blend required for very low doses (<1 mg/kg)
Pre-dosing aerosol characterisation requirement	None relative to any other dose route	None relative to any other dose route	• Generation device • Chamber selection Aerosol concentration • Particle size

The Good News: regulatory expectation

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Improvements?

- Better intranasal dosing of rodents. We'll just have a cunning device please!
  - Not as simple as it sounds!
- Better understanding of distribution
  - No-one can guarantee brain exposure non-clinically

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In summary: Intranasal nonclinical models

- Intranasal nonclinical drug development
  - Assessment of localized pathology
  - Assessment of systemic toxicity and exposure
  - Species specific (size and anatomy) challenges
- The way forward
  - Better nonclinical delivery devices for smaller species
  - Better understanding of administered dose and brain distribution
    - More realistic expectations?

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Thank you
Any Questions?