TRUE NASAL

Migraine and Nasal Drug Delivery

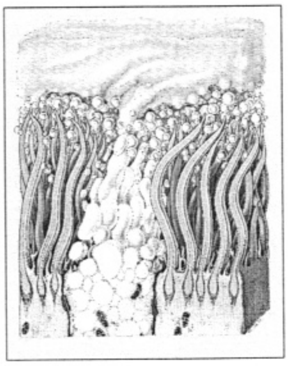
Frans W.H.M. Merkus, Ph. D.
Professor of Biopharmaceutics, Leiden University
Founder and Chairman of InnoScience Technology
Merkus.f@skynet.be

Advantages nasal delivery

- No first pass metabolism
- Pulsed absorption profile
- Easy administration
- Nasal absorption not disturbed by gastric stasis or vomiting
- Not expensive and not painful, compared to injection therapy

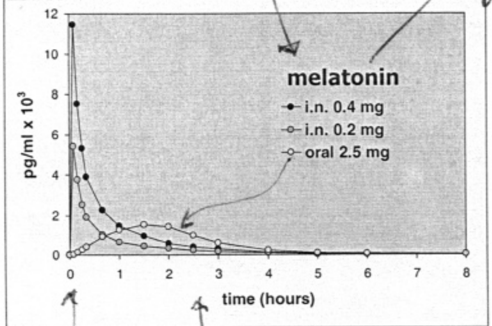
Disadvantages nasal delivery

- Only for drugs that are really absorbed nasally
- Only for drugs that are active in a low dose
- Drug substance should be water soluble or in solution
- Drug itself and excipients should be non-irritant
- Not suitable for drugs which need slow absorption profile and/or relatively constant blood level



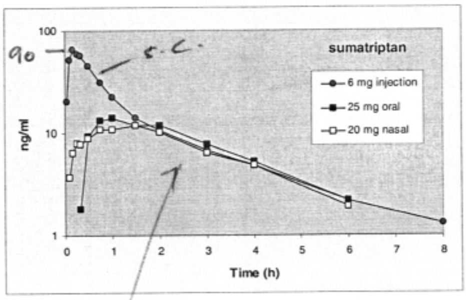
150 cm²

10-15 minutes transport



100% absorptie

nasaal



Duquesnoy et al., Europ. J. Pharm. Sci. 1998; 6: 101

Solution → stomach

because it is a liquid.

Intranasal Sumatriptan

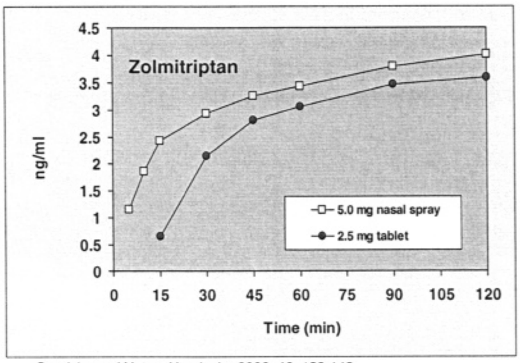
- Overall oral and intranasal administration have equal efficiency
- Intranasal usually faster onset of effect
- Higher recurrence rates (34-46%) than with DHE (8-14%)
- Most pronounced AE: taste disturbance

Sumatriptan Comparative Pharmacokinetics

	T_{max}	F (%)	$T_{½}$ (h)
Oral	0.7	14	2.0
Intranasal	0.7	16	2.0

20 mg.

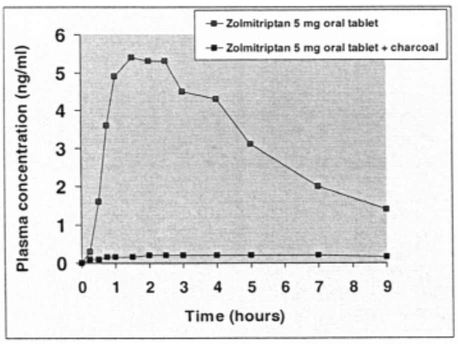
- Similar rate of absorption
- Multiple peaks after intranasal administration
- Intranasal / oral absorption



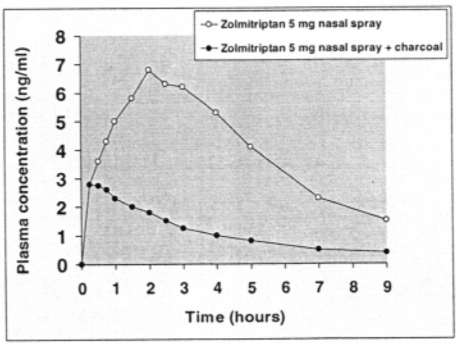
Goadsby and Yates, Headache 2006; 46: 138-149

Intranasal Zolmitriptan

- More rapid absorption following intranasal administration
- Nasal-oral absorption profile ($T_{max} \approx 2h$)
- Absorption not impeded by xylometazoline
- Sustained efficacy demonstrated in long-term study
- Main AE: mild local nasal symptoms

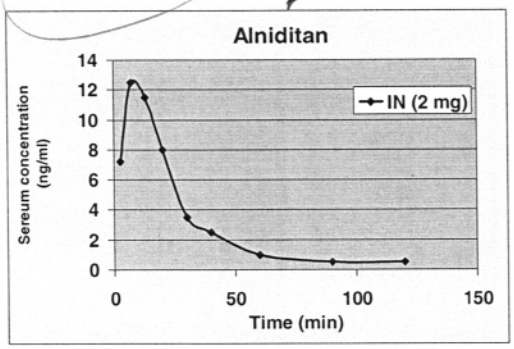


Goadsby and Yates, Headache 2006; 46: 142



Goadsby and Yates, Headache 2006; 46: 142

geen goed design
study: 3 groepen
1 NS + char
2 NS oraal + char
3



Roon et al. Br J Clin Pharmacol 1999; 47: 285-90

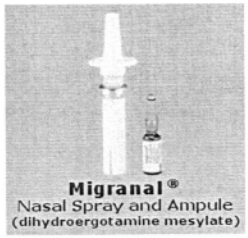
Butorphanol

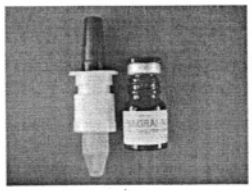
- Mixed opioid agonist-antagonist
- Oral bioavailability 5-17%
- Intranasal bioavailability 48-70%
- True intranasal absorption
- Effective and rapid pain relief
- AEs: dizziness, nausea/vomiting, drowsiness
- Addiction potential (multiple-dose sprayer!)
- Reserve for occasional rescue therapy

Dihydroergotamine

- Introduced for migraine therapy in 1945
- Binds to adrenergic, dopaminergic and serotonergic receptors
- Tight tissue binding explains long duration of effect
- Headache recurrence has low frequency
- Intranasal formulation: Migranal®, Diergo®
- Clumsy formulation(4 puffs needed)

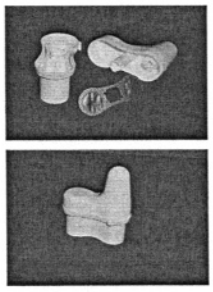
Migranal® Nasal Spray





Pfeiffer BiDose® Nasal Powder Device

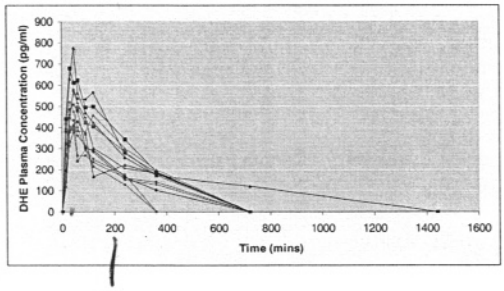
- Contains two doses per device
- Passive operation
- Visual confirmation of dose delivery
- Discreet
- Simple to use
- Disposable



DHE 1mg Nasal Powder Phase I Study

- Six healthy male volunteers
- Comparison with Diergo® Nasal Spray
- Single 1mg dose delivered to one nostril (powder) vs 2 x 0.5mg as one spray per nostril (spray)
- Pharmacokinetic samples collected over 24 hours

DHE 1mg Nasal Powder



PK Parameters

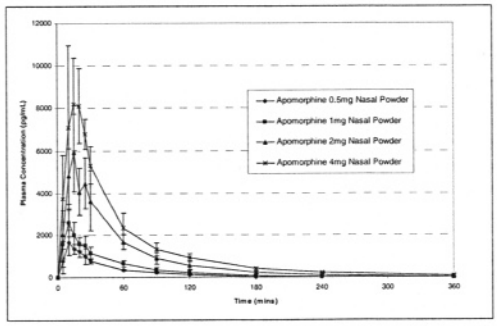
	C_{max} (pg/ml)	T_{max} (h)	AUC_{0-24} ([pg/ml/mg].h)
DHE 1mg Nasal Powder	503 (58.4)	0.82 (0.57)	1554 (404)
Diergo® Nasal Spray	669 (147.0)	0.71 (0.17)	2272 (670)

- All DHE Nasal Powder values normalised for delivered dose
- Standard deviation in parentheses

Apomorphine Nasal Powder Ascending Dose PK Study

- Six healthy male volunteers
- Open, ascending dose design
  - 0.5mg
  - 1mg (0.5mg/ nostril)
  - 2mg
  - 4mg (2mg/ nostril)
- Pfeiffer BiDose device

Apomorphine Nasal Powder Ascending Dose PK Study



Pharmacokinetic Parameters

Dose (mg)	AUC_{0-6} ([pg/ml/mg].h)	C_{max} (pg/ml)	T_{max} (h)
0.5	1031 (± 148)	1710 (± 524)	0.21 (± 0.07)
1.0	1760 (± 281)	2658 (± 541)	0.23 (± 0.10)
2.0	4816 (± 1188)	6262 (± 1496)	0.25 (± 0.05)
4.0	7558 (± 1029)	9583 (± 1934)	0.27 (± 0.10)

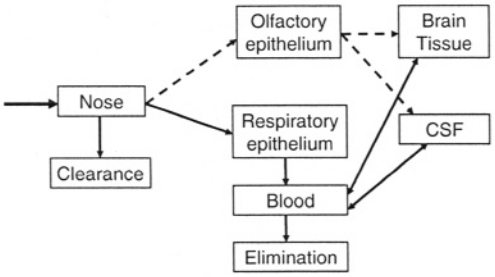
Intranasal Hydroxocobalamin

- Vitamin B_{12} analogue
- NO- scavenger
- NO involved in migraine attacks?
- Negligible oral absorption
- 5% intranasal bioavailability
- Promising effects as intranasal prophylactic in open-label study (n=19)
- 1 mg hydroxocobalamine daily

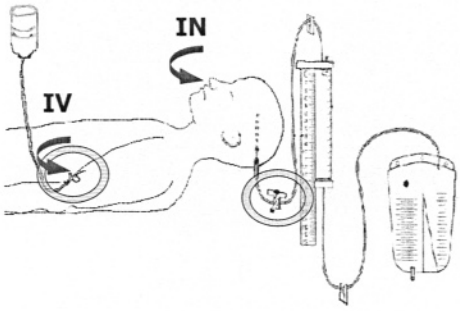
V B2 400µg

V B12

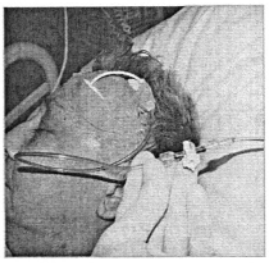
Theory: Nasal transport routes



Methods



Human study: taking CSF samples



A neurosurgery patient with a CSF drain, which allows the collection of serial CSF samples.

Human study

P. Merkus *et al.* (2003) Neurology **60** 1669-1671

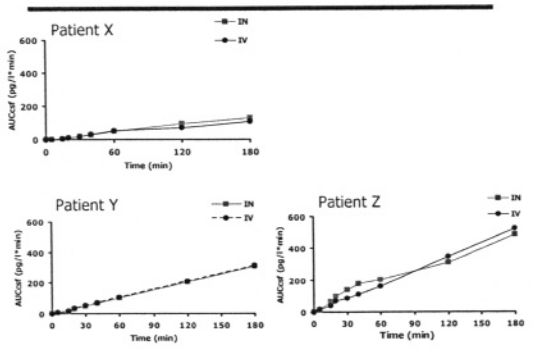
- Investigating the nose-to-CSF transport of melatonin and hydroxocobalamin after nasal and intravenous delivery in patients

Human study: melatonin

Melatonin

- 3 patients with a CSF drain
- IN: 0.4 mg (0.2/100 µl/nostril)
- Concentrations in plasma and CSF following IN and IV delivery

Melatonin: human AUC_{CSF} data

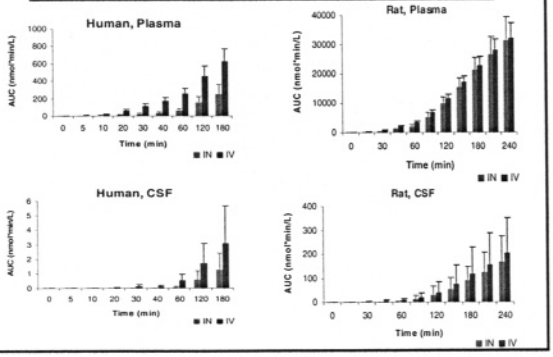


Human study: hydroxocobalamin

Hydroxocobalamin

- 5 patients with a CSF drain
- IN: 1.5 mg (0.75 mg / 70 μl / nostril)
- Concentrations in plasma and CSF following IN and IV infusion over 15 min

Hydroxocobalamin



conclusions

- Intranasal formulations increasingly popular
- Several formulations show nasal/oral absorption (sumatriptan, zolmitriptan)
- Development of true intranasal formulations would enhance advantages of intranasal administration