Value added medicines

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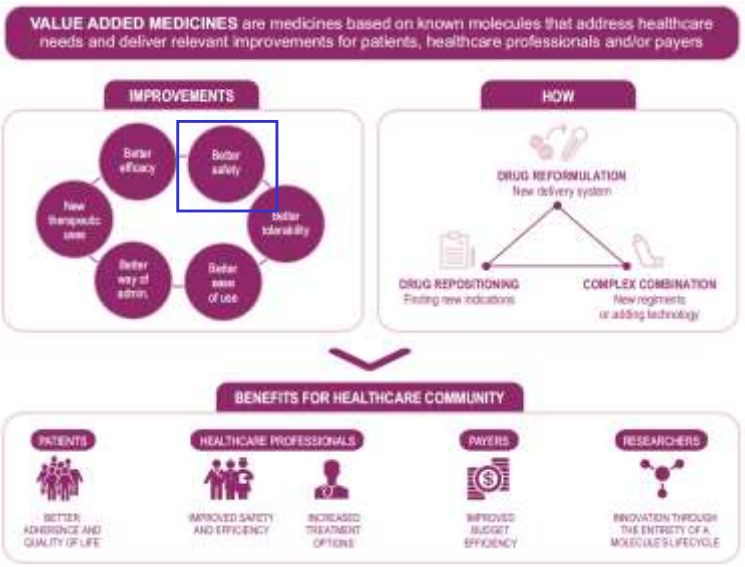

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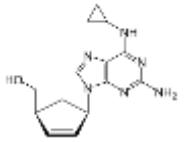
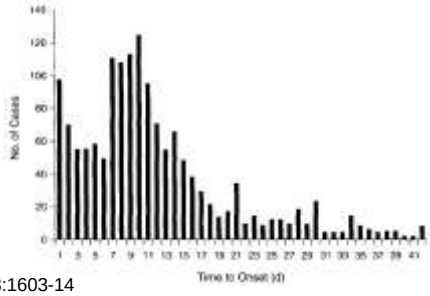
Abacavir (ABC) hypersensitivity - clinics



NRTI

- Occurs in approximately 4.5% of patients
- Multiorgan reaction: fever, rash, fatigue, nausea, liver and/or kidney injury
- Occurs mostly within the first 6 weeks after starting abacavir
- Rechallenge positive within hours

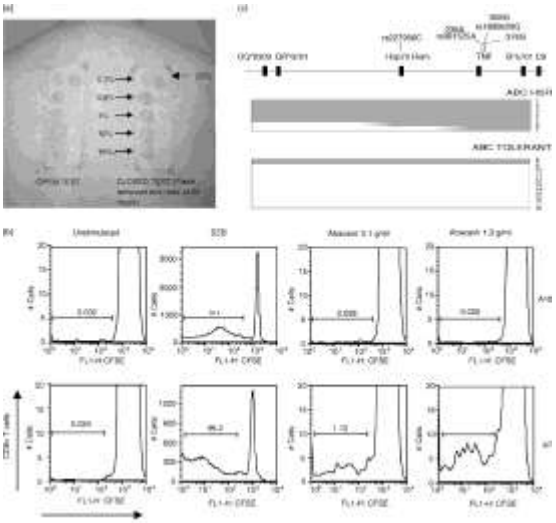
Symptom	Initial Presentation, No. (%)	Rechallenge Presentation, No. (%)
Fever	72 (56)	91 (71)
Rash	65 (51)	80 (63)
Gastrointestinal symptoms[†]	58 (45)	56 (44)
Constitutional symptoms[‡]	40 (31)	44 (34)
Respiratory symptoms[§]	19 (15)	27 (21)
Chills	16 (13)	26 (20)
Abnormal hepatic function	14 (11)	25 (20)
Headache	13 (10)	12 (9)
Pruritus	12 (9)	15 (12)
Abnormal blood count	11 (9)	17 (13)
Hypotension	7 (5)	32 (25)
Abnormal renal function	6 (5)	13 (10)
Edema	6 (5)	15 (12)
Tachycardia	1 (1)	14 (11)



Clin Ther 2001;23:1603-14

Abacavir hypersensitivity - mechanism

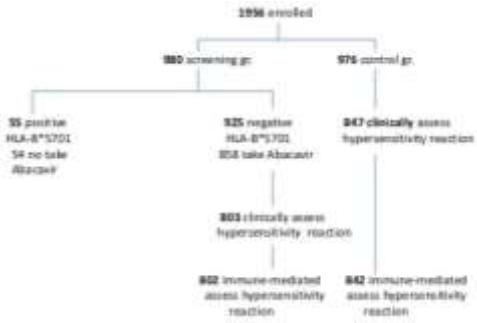
- Immunological studies in a patient 41 months after an ABC-associated hyper-sensitivity reaction (HSR)
- **(a)**: positive patch test
- **(b)**: positive CD8 proliferation (A10: control, A7: patient; SEB: staphylococcal enterotoxin)
- **(c)**: Increased frequency of MHC alleles of the 57.1 ancestral phenotype in patients with ABC HSR



AIDS 2005;19:979-987

HLA-B *5701 screening for ABC HSR

- Prospective, randomized, double-blind multicenter study
- 1956 patients with HIV type 1 infection not having been treated with ABC
- Prospective screening group (980 patients): HLA-B *5701 positives → no ABC. Remaining patients ABC
- Control group (976 patients): no screening, all ABC
- Endpoints: incidence of clinical HSR and positive patch testing



N Engl J Med 2008;358:568-79

HLA-B *5701 screening for ABC HSR

Hypersensitivity Reaction	Prospective Screening	Control	Odds Ratio (95% CI)*	P Value
	no. of patients/total no. (%)			
Clinically diagnosed				
Total population that could be evaluated	27/803 (3.4)	66/847 (7.8)	0.40 (0.25–0.62)	P<0.001
White subgroup	24/679 (3.5)	61/718 (8.5)	0.38 (0.23–0.62)	P<0.001
Immunologically confirmed				
Total population that could be evaluated	0/802	23/842 (2.7)	0.03 (0.00–0.18)	P<0.001
White subgroup	0/679	22/713 (3.1)	0.03 (0.00–0.19)	P<0.001

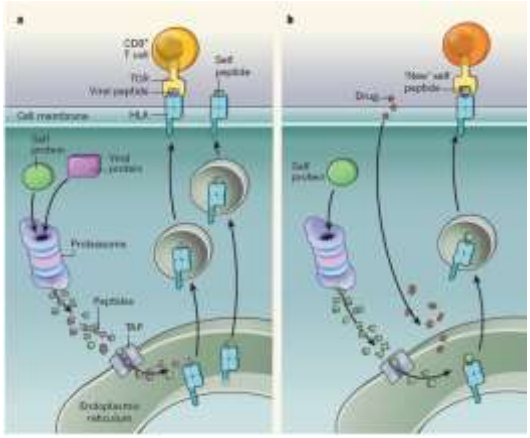
- HLA-B *5701 genotyping reduces clinically diagnosed hypersensitivity reactions
- HLA-B *5701 genotyping eliminates immunologically confirmed (patch clamping) hypersensitivity reactions (NPV 100)

N Engl J Med 2008;358:568-79

Abacavir hypersensitivity - molecular mechanism

a: normal recognition of antigens on cell surfaces: viral proteins are recognized as «foreign», «self-proteins» not

b: Abacavir binds in the ER to HLA-molecules and changes binding sites of the HLA. «Self protein»-fragments, which normally don't bind, can now bind and are recognized as foreign



Nature 2012;28;486:554-8

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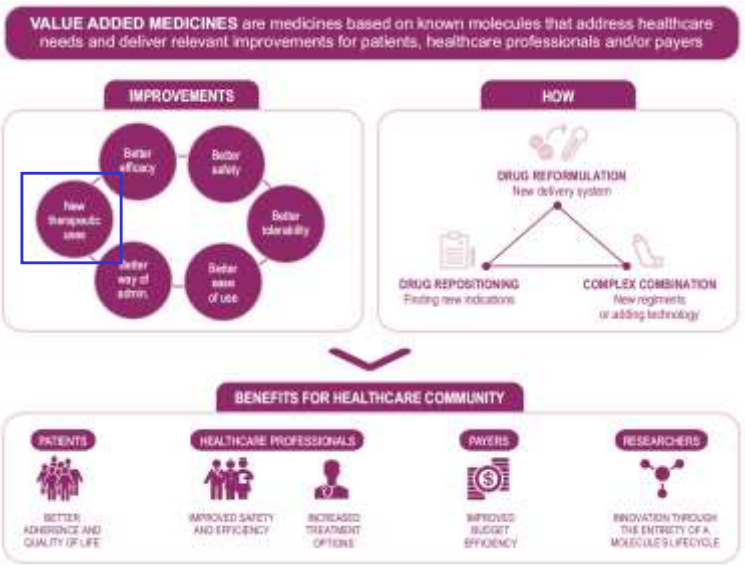

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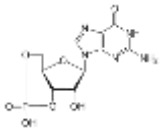
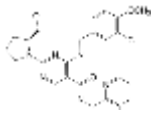
PDE5 inhibitors on the market

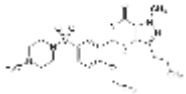
Drug	Dose (mg)	Ingestion before sex (h)	Metabolism (CYP)	Half-life (h)	Duration of effect (h)
Avanafil (Spedra®)	50-200	0.5	3A4, 2C9	6-17	ca. 6
Sildenafil (Viagra®)	25-100	ca. 1	3A4	4	4-6
Tadalafil (Cialis®)	10-20	1-36	3A4	17	24-36
Vardenafil (Levitra®)	5-20	ca. 1	3A4, 2C9	5	4-6



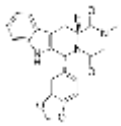
cGMP



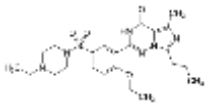
Avanafil



Sildenafil



Tadalafil



Vardenafil

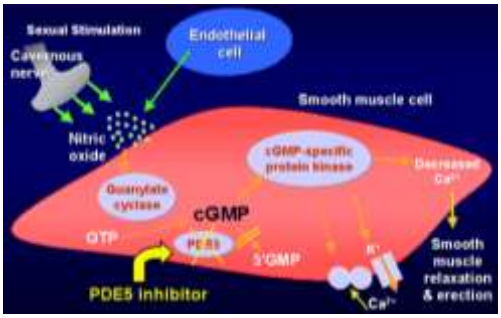
Mode of action of PDE5 inhibitors

Inhibition of PDE5

- Degradation of cGMP ↓
- cGMP dilates smooth muscles and stimulates blood flow into corpus cavernosum

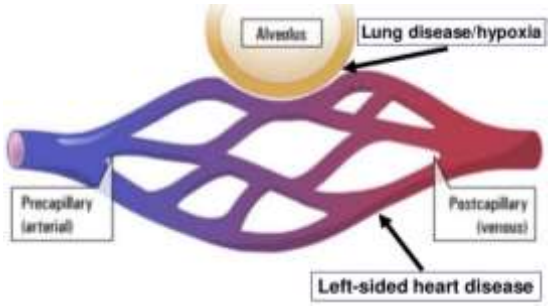
No "chemical" erection

- Sexual stimulation is necessary for NO synthesis → stimulation of cGMP-synthesis
- Neurovascular function must be intact

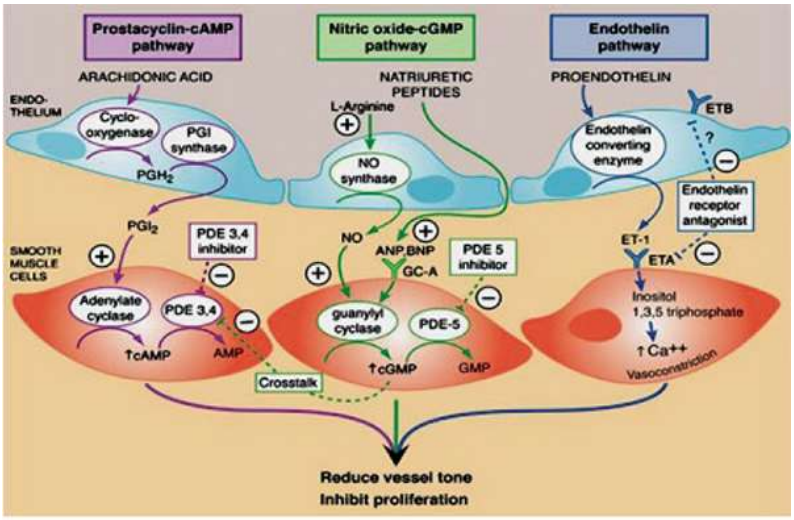


Pulmonary arterial hypertension - pathogenesis

Resting pulmonary arterial pressure >25 mmHg



Pharmacological modulation of pulmonary arteries

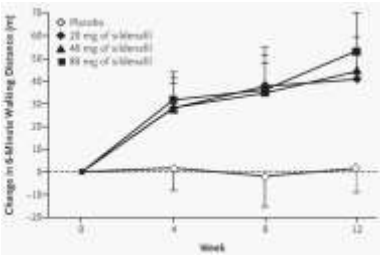


Source: Agarwal et al: Am Heart J 2011;162:201-13

Sildenafil in pulmonary arterial hypertension

- Double-blind placebo-controlled study in patients with PAH (idiopathic, lung fibrosis, left-right shunts)
- Placebo or sildenafil (20, 40 or 80 mg q8h) for 12 weeks
- End points: 6-minute walking distance, pulmonary arterial pressure, safety

N Engl J Med 2005;353:2148-57



Event	Placebo (N=70)	Sildenafil		
		20 mg (N=69)	40 mg (N=67)	80 mg (N=71)
	number (percent)			
Headache	27 (39)	32 (46)	28 (42)	35 (49)
Flushing	3 (4)	7 (10)	6 (9)	11 (15)
Dyspepsia	5 (7)	9 (13)	6 (9)	9 (13)
Cough	4 (6)	5 (7)	3 (4)	6 (8)
Epistaxis	1 (1)	6 (9)	5 (7)	3 (4)
Pyrexia	2 (3)	4 (6)	2 (3)	7 (10)
Insomnia	1 (1)	5 (7)	4 (6)	3 (4)
Influenza	2 (3)	4 (6)	4 (6)	3 (4)
Visual disturbance	0	0	3 (4)	5 (7)
Gastritis	0	2 (3)	2 (3)	3 (4)

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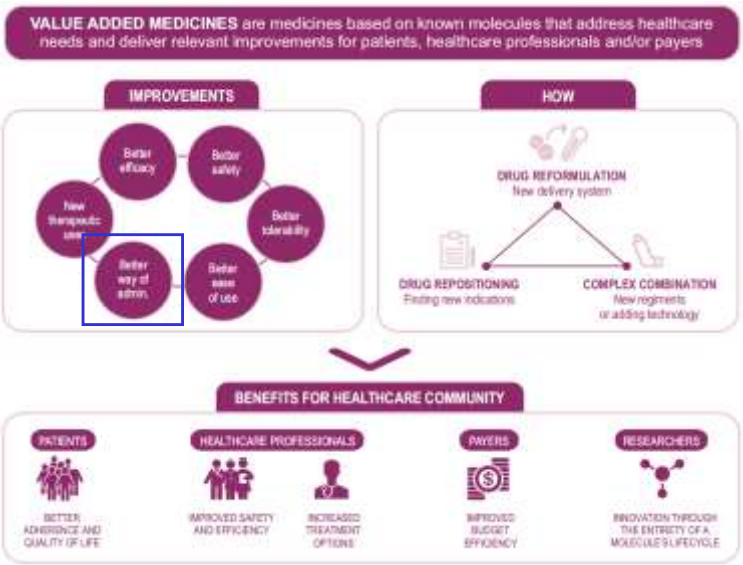

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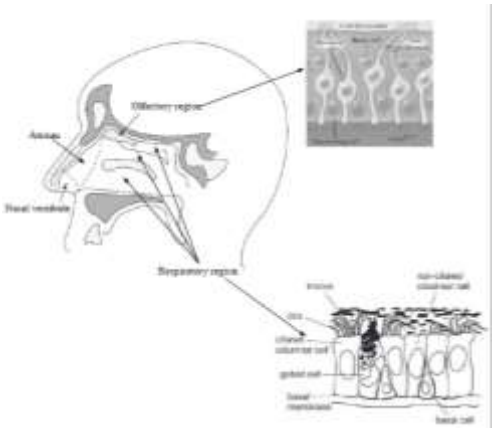
Nasal application of drugs - anatomy

Respiratory region

- 130 cm2
- Columnar cells, goblet cells (mucus), basal cells (progenitors)
- Very high vascularization, good permeability

Olfactory region

- 15 cm2
- Receptor cells, supporting cells and basal cells
- High vascularization, direct access to CNS



J Pharm Pharmaceut Sci 2009;12:288-311

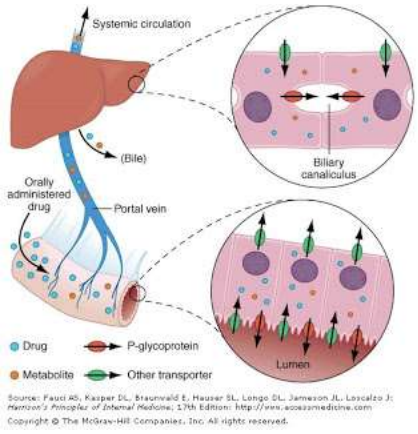
Nasal application of drugs – pharmacy & pharmacology

Advantages

- Non-invasive, easy drug application
- Circumvents intestinal and hepatic presystemic metabolism
- Rapid effect for a non-invasive application
- Preparation has not to be sterile

Disadvantages

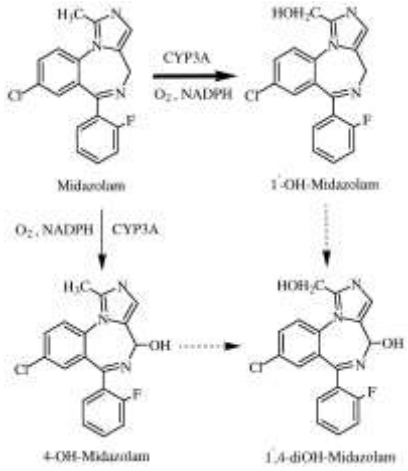
- Low volume (100-150 µL)
- Nasal irritation and/or systemic toxicity if adjuvants are used
- Absorption may be altered in patients with nasal diseases



J Pharm Pharmaceut Sci 2009;12:288-311

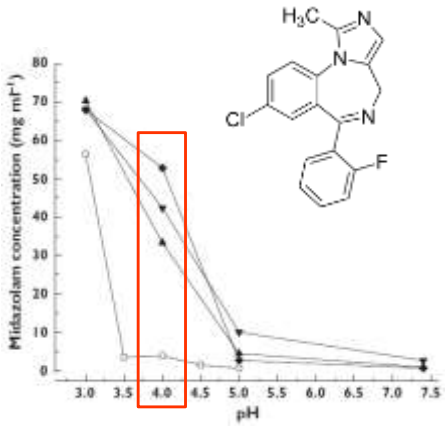
Midazolam - pharmacokinetics

- Rapid absorption
- Bioavailability ≈30% (intestinal and hepatic presystemic metabolism)
- Protein binding 98%, V_{ss} ≈1 L/kg
- Almost complete metabolism by CYP3A4/A5 to 1'-OH-midazolam and 4-OH-midazolam
- Half-life midazolam 1.5 – 2.5 h (1'-OHMDZ ≈1 h)
- Lipophilic, limited water solubility
- Nasal application might be preferable for patients with seizures



Midazolam – pH-dependent solubility

- Saturation concentrations of MDZ at different pH
- Britton-Robinson (BR) buffer alone (○)
- BR buffer with 10% solubilizer hydroxypropyl-β-cyclodextrin (HPβCD) (▼)
- Randomly methylated β-cyclodextrin (RMβCD) (▲)
- Hydroxypropyl-γ-cyclodextrin (HPγCD) (♦)



Br J Clin Pharmacol 2010;69:607–616

Midazolam – nasal preparations assessed

	Applied MDZ dose	MDZ concentration (base)	Delivered volume	RMβCD (w : v)	Chitosan HCl (w : v)	NaCl (w : v)
Formulation 1 MDZ	1 mg	5 mg ml^{-1}	2 × 0.1 ml	–	–	0.9%
Formulation 2 MDZ + RMβCD	1 mg	5 mg ml^{-1}	2 × 0.1 ml	2%	–	0.8%
Formulation 3 MDZ + RMβCD	1 mg	10 mg ml^{-1}	0.1 ml	4%	–	0.8%
Formulation 4 MDZ + RMβCD	3 mg	30 mg ml^{-1}	0.1 ml	12%	–	0.2%
Formulation 5 MDZ + RMβCD + Chitosan	3 mg	30 mg ml^{-1}	0.1 ml	12%	0.5%	0.1%

Composition of aqueous midazolam solution for intranasal application. MDZ, midazolam; RMβCD, randomly methylated-β-cyclodextrin. Concentration of RMβCD is equimolar to MDZ. Osmolality adjusted to 300 mosmol kg^{-1} with NaCl. Formulations 1 and 2 were applied bilaterally to deliver total dose of 1 mg.

- Comparison of the pharmacokinetics after nasal and iv application

Br J Clin Pharmacol 2010;69:607–616

Midazolam – pharmacokinetics of nasal preparations

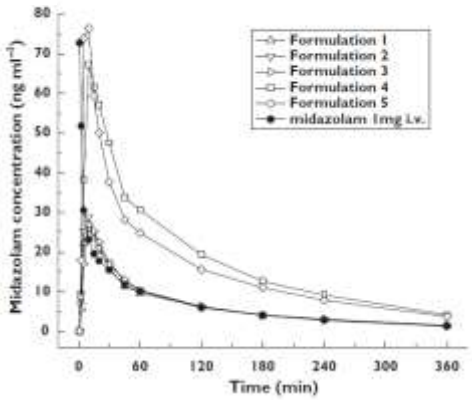
1: buffer (1 mg)

2: RMβCD 2% (1 mg)

3: RMβCD 4% (1 mg)

4: RMβCD 12% (3 mg)

5: RMβCD 12% + chitosan 0.5% (3 mg)



Br J Clin Pharmacol 2010;69:607–616

Midazolam – pharmacokinetics of nasal preparations

Formulation	t_{max} (min)	C_{max} (ng ml^{-1})	$AUC(0,\infty)$ (ng ml^{-1} min)	AUC(0,120 min) (ng ml^{-1} min)	$t_{1/2}$ (min)	F
Midazolam 1 mg, i.v.	2.1 ± 0.8	87.6 ± 58.7	2799 ± 589	1796 ± 418	113.5 ± 25.9	N.A.
Formulation 1 0.5 mg i.n. both sides	10.6 ± 5.0	28.1 ± 9.1	2461 ± 628	1424 ± 399	114.2 ± 23.0	88 ± 17%
Formulation 2 0.5 mg i.n. both sides	9.4 ± 3.2	30.1 ± 6.6	2596 ± 680	1535 ± 370	113.0 ± 22.8	92 ± 15%
Formulation 3 1 mg i.n. one side	11.3 ± 4.4	28.9 ± 5.4	2511 ± 541	1496 ± 269	105.4 ± 17.7	90 ± 16%
Formulation 4 3 mg i.n. one side	13.0 ± 4.3	68.9 ± 19.8	7143 ± 1568	4117 ± 798	117.5 ± 32.0	85 ± 8%
Formulation 5 3 mg i.n. one side	7.2 ± 0.7**	80.6 ± 15.2**	6320 ± 1458**	3741 ± 717*	111.4 ± 20.6	76 ± 12%*

Values are mean ± SD. i.n., intranasal application. C_{max}, maximum serum concentration; t_{max}, time to maximum serum concentration; $AUC(0,\infty)$, area under concentration–time curve extrapolated to infinity; $t_{1/2}$, elimination half-life; F, bioavailability. *Significantly different ($P < 0.05$) from formulation 4. **Significantly different ($P < 0.005$) from formulation 4.

1: buffer 2: RMβCD 2% 3: RMβCD 4% 4: RMβCD 12% 5: RMβCD 12% + chitosan 0.5%

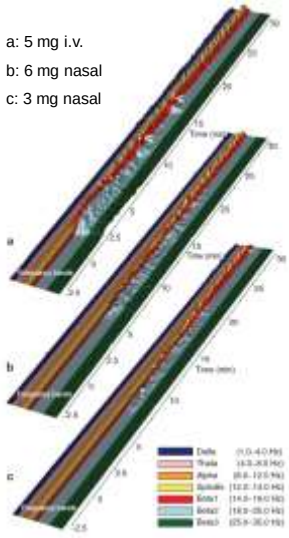
Br J Clin Pharmacol 2010;69:607–616

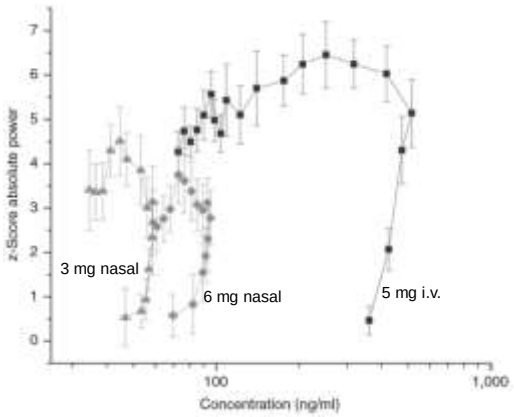
Midazolam – pharmacodynamics of nasal preparations

a: 5 mg i.v.

b: 6 mg nasal

c: 3 mg nasal





Clin Pharmacol Ther 2012;91:856-862

Conclusions

- Drugs that are on the market can be further developed in different ways
- Investigation for new indications is common – in particular for anti-cancer drugs
- New galenical formulations are particularly common in pediatrics (off-label or off-license formulations due to lacking studies)
- Pharmacists can initiate new developments and can help particularly well in designing new preparations