

NEW SEDATIVE HYPNOTICS

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Disclosures

- None


Definition

- [Soft drugs are] “novel active compounds [that] are specifically designed to be vulnerable to rapid biotransformation to inactive metabolites”

* Egan T Anesthesiology 2009; 111(2):229-30

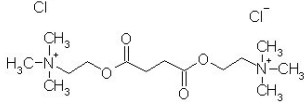
The Problems

- Patients are older
- Patients are sicker
 - Liver - Metabolism
 - Kidney - Excretion



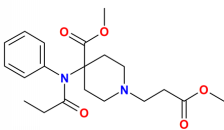
Succinylcholine- A Classic (1951)

- Acts by opening ACh channels
- Onset 45 seconds
- Duration 3-5 minutes
- Relatively resistant to AChE
- Metabolized by ButyrylChE



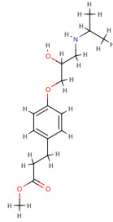
Remifentanyl

- Rapid onset of analgesia
- Metabolized by plasma esterases
- Elimination $t_{1/2} = 8$ min
- No prolongation with repeat doses



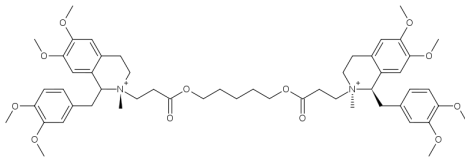
Esmolol

- Rapid onset of β_1 blockade
- Metabolized by rbc esterases
- Elimination $t_{1/2}$ = 8 min
- Slight prolongation with repeat doses



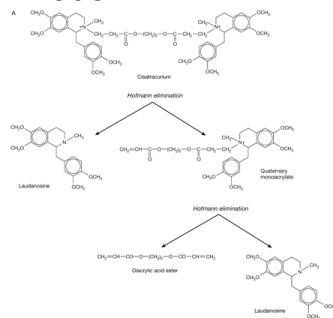
Cisatracurium

- Intermediate onset/duration
- Metabolized by Hofmann and esterases



Hofmann Elimination

- Spontaneous degradation of N-alkyl portion of benzylisoquinoline



Esterase Activity

- Plasma esterases

The diagram illustrates the metabolic pathways of Diacetylmorphine. Diacetylmorphine is hydrolyzed by esterases into Monoacetylmorphine alcohol and Monoacetylmorphine acid. Monoacetylmorphine alcohol can undergo further ester hydrolysis to Morphine or undergo Hofmann elimination to Laudanosine. Monoacetylmorphine acid can be further hydrolyzed to Acetic acid and Morphine.

MOC-Etomidate, Carboetomidate

- Rapid onset
- Ester hydrolysis
- No adrenal suppression

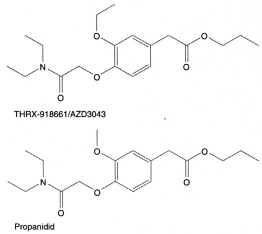
The chemical structure of Etomidate is shown, consisting of a benzene ring attached to a pyrrolidine ring, which is further substituted with an ethyl ester group.

Sugammadex

- Binds NMBAs (steroid-type)
- Makes NMBA "soft"
- Rapid onset of reversal
 - 2.9 minutes

The ball-and-stick model of Sugammadex is shown, illustrating its cyclic heptamethine cage structure with a central cavity.

THR-918661



THR-918661/AZD3043

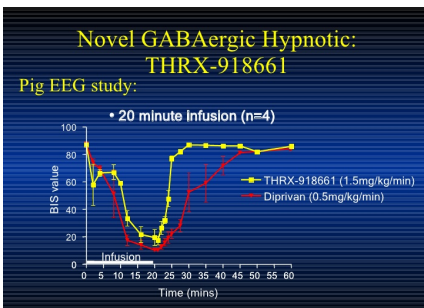
Propofol

THR-918661

Novel GABAergic Hypnotic:
THR-918661

Pig EEG study:

• 20 minute Infusion (n=4)



BIS value

Time (mins)

THR-918661 (1.5mg/kg/min)

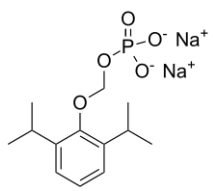
Diprivan (0.5mg/kg/min)

Infusion

Beattie et al. MJA UK, Mar 2003

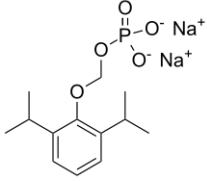
Fos Propofol

- Alkaline phosphatase removes phosphate of prodrug
- 1 mmol results in 1 mmol propofol
- 1.86 mg fospropofol converts to 1 mg propofol



Fos Propofol

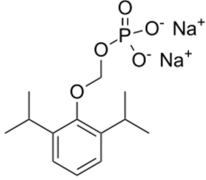
- Longer time to peak effect
- Lower peak concentration
- Less apnea



The chemical structure shows a central benzene ring with two isopropyl groups at the 3 and 5 positions. At the 1 position, there is a methylene group (-CH₂-) attached to an oxygen atom (-O-), which is further attached to a phosphorus atom. The phosphorus atom is double-bonded to an oxygen atom and single-bonded to two negatively charged oxygen atoms, each associated with a sodium ion (Na⁺).

Fos Propofol

- 123 patients
- Initial dose 6.5 mg/kg, followed by 1.6 mg/kg
- Satisfactory MAC
- Adverse Events
 - 63% paresthesias
 - 28% pruritus

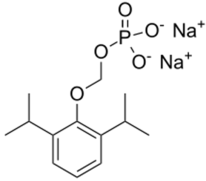


The chemical structure is identical to the one in the first slide, showing the benzene ring with isopropyl groups and the phosphonate group.

Gan et al J Clin Anes 2010; 22: 260-267

Fos Propofol

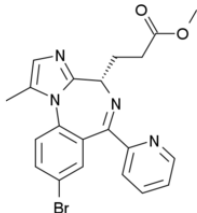
- Paresthesias
 - "Paresthesia genital male; Burning sensation; Genital burning sensation; Vaginal burning sensation"
- Pruritus
 - "Genital pruritus female; Genital pruritus male; Pruritus genital; Pruritus ani"



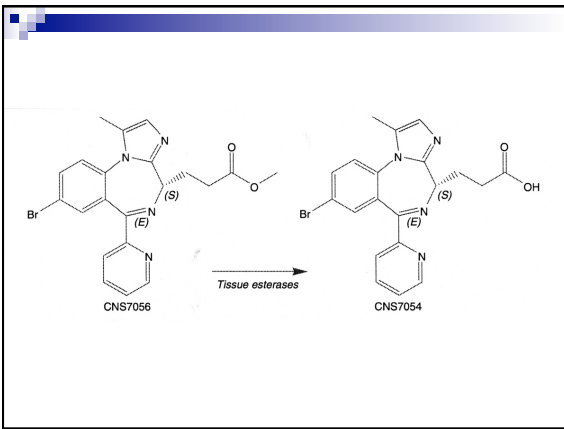
The chemical structure is identical to the ones in the previous slides.

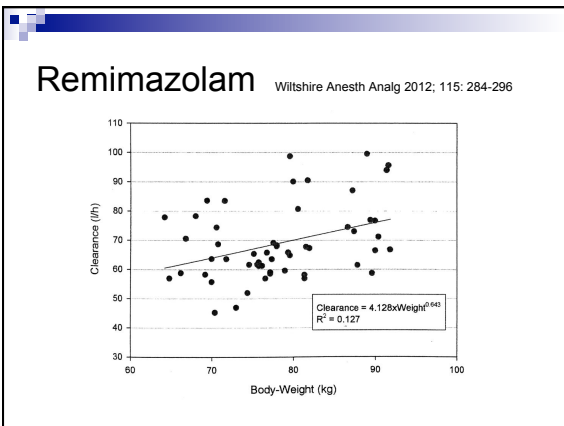
Remimazolam

- Hydrolysis by tissue esterases
- High clearance, low volume of distribution
- Faster onset than midazolam



The chemical structure of Remimazolam is shown, featuring a benzodiazepine core with a methyl group at the 5-position, a bromine atom at the 7-position, and a pyridine ring at the 2-position. The 1-position is substituted with a propyl chain ending in a methyl ester group.





Remimazolam Wiltshire Anesth Analg 2012; 115: 284-296

Table 1. Context-Sensitive Half-Times (in Minutes) for Selected Sedative Hypnotics and Opioids for Continuous Infusions from 2 to 8 Hours^a

Drug	Infusion duration			
	2 h	4 h	6 h	8 h
Remimazolam	6 min	6.5 min	7 min	7 min
Etomidate	5 min	11 min	17 min	22 min
Propofol	8 min	9 min	11 min	12 min
Midazolam	27 min	27 min	27 min	27 min
Dexmedetomidine	133 min	242 min	267 min	273 min
Fentanyl	35 min	131 min	217 min	256 min
Sufentanil	26 min	37 min	41 min	42 min
Remifentanyl	3 min	3 min	3 min	3 min

Remimazolam Wiltshire Anesth Analg 2012; 115: 284-296

The graph plots the Observed BIS Score (Y-axis, 60-100) against Time in Hours (X-axis, 0.00-1.00). The observed data points (open circles) show a rapid initial drop from 100 to approximately 70 within the first 0.1 hours, followed by a steady recovery towards 95. The predicted BIS score (solid line) and individual predicted BIS score (dashed line) closely follow the observed data, indicating high predictive accuracy of the model.

What about the rest of the World?

- Scopolamine esters¹
 - Metab by esterase
 - Only 2% effect on other eye
- Cyclosporine A analogs²
 - Reduced chronic toxicity
 - Higher Therapeutic Index
 - Use: Autoimmune
- Antibiotics- DHFR inhibitors³
 - Preference for Pneumocystis
 - Less human toxicity
- Nanotechnology⁴
 - 1. Kumar. Drug Des Discov. 1993; 10:11-21.
 - 2. Lazarini. J Med Chem 2003; 46: 674-65.
 - 3. Graefter-Norberg. Eur J Pharm Sci 2004; 22: 43-54.
 - 4. Kim. NANO 2010; 3(3): 2424-43.

Nanotechnology

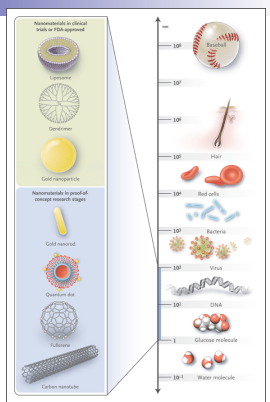
- Drug Delivery
 - Aurimmune
 - Genexol-PM
 - Dendrimer antivirals
- Contrast Agents
- Diagnostic Devices

Nanomaterials

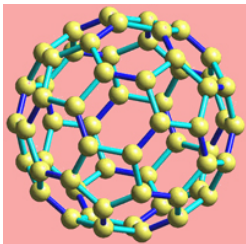


NEJM

- Kim *et al*
- NEJM 363(25):2434-2443

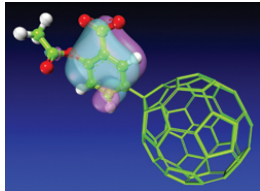


Buckyball

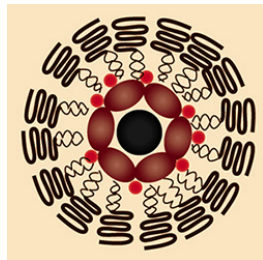


Buckyball attached to drug

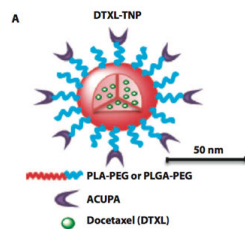
- Slows absorption



Doxorubicin as nanocargo



Docetaxel as nanocargo



CONCLUSIONS

- Soft Drugs are important to Anesthesia
 - Rapid, dependable biotransformation
- Most Soft Drugs utilize esterases
- Hofmann Elimination offers enzyme-independent degradation
- Nanotechnology
 - Scavenging (eg Sugammadex, Digibind[®])
 - Targeted therapy
