



DRUG DELIVERY AND MONITORING TECHNOLOGY

- Newer, Safer Anesthesia Drug Development-
“Soft Drugs”
John Pawlowski
- Safe Technology in Drug Delivery
George Blike
- Drug Effect/Safety Monitors using Processed
EEG Technology
Scott Kelley



SOFT DRUGS

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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

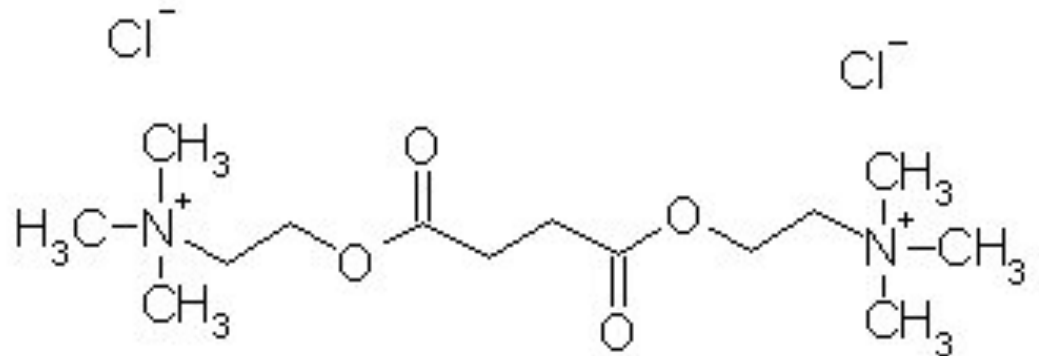
The Problems

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



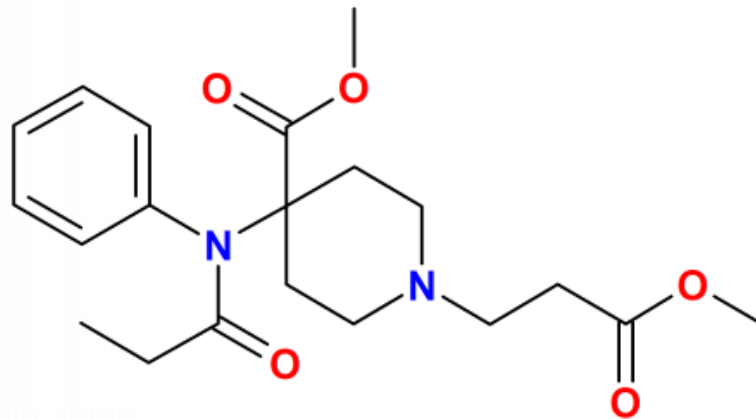
Succinylcholine- A Classic (1951)

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



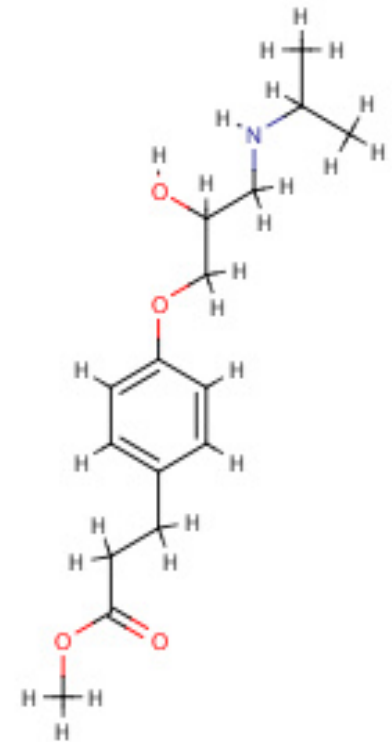
Remifentanyl

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



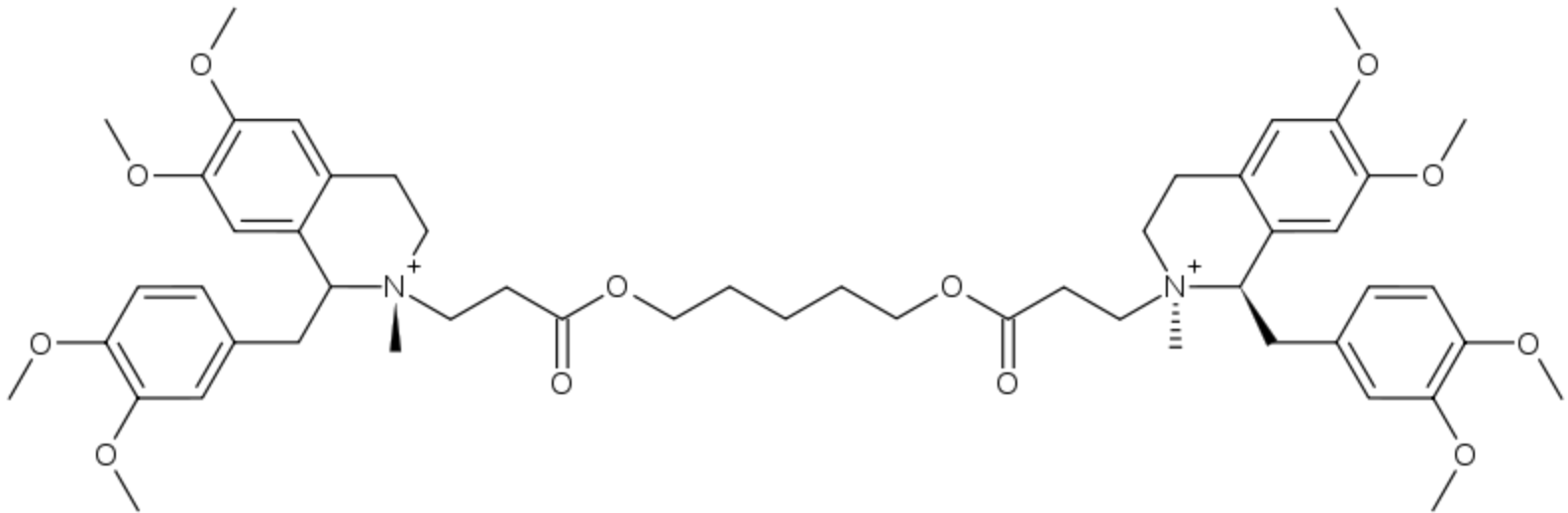
Esmolol

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



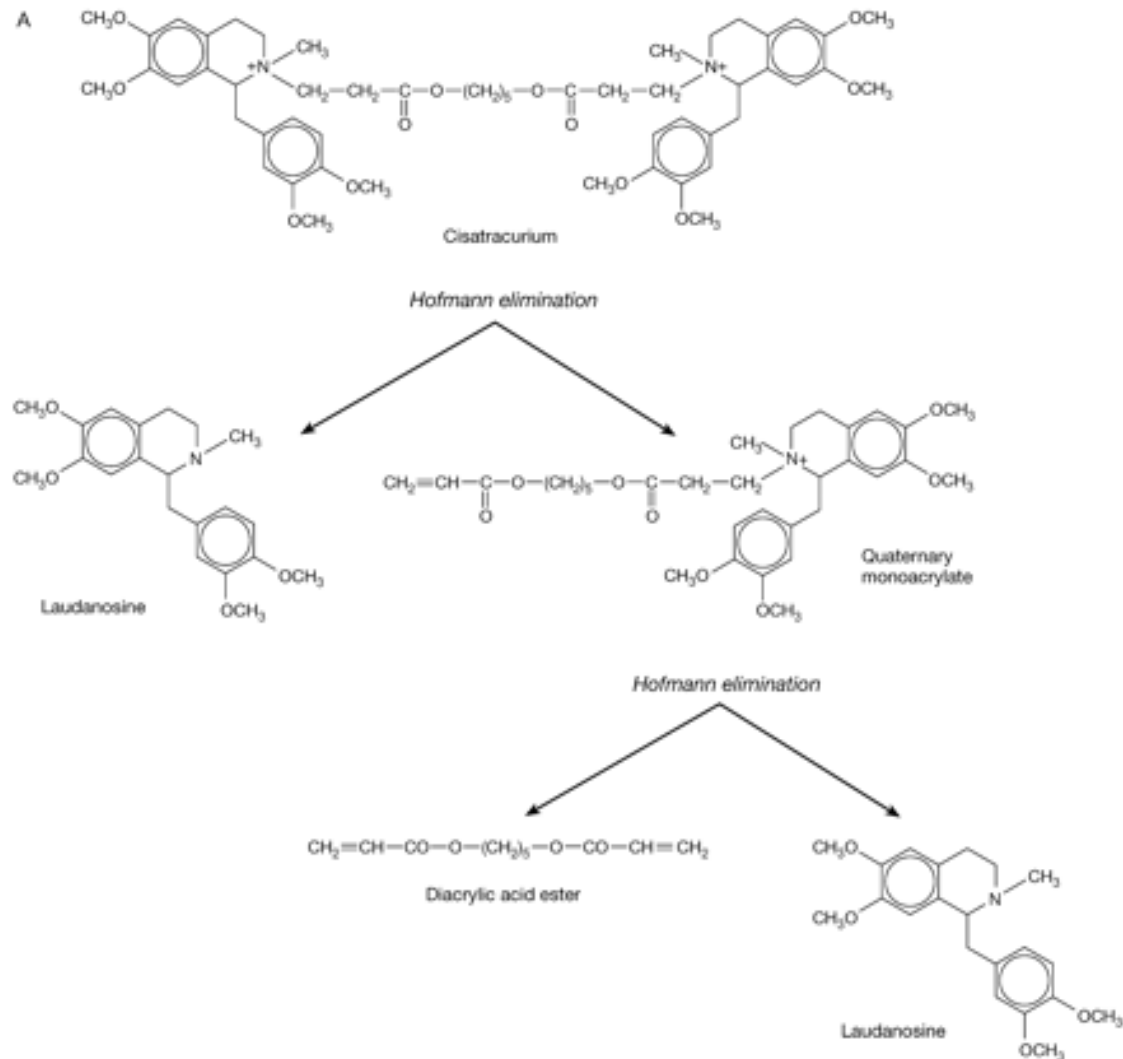
Cisatracurium

- Intermediate onset/duration
- Metabolized by Hofmann and esterases



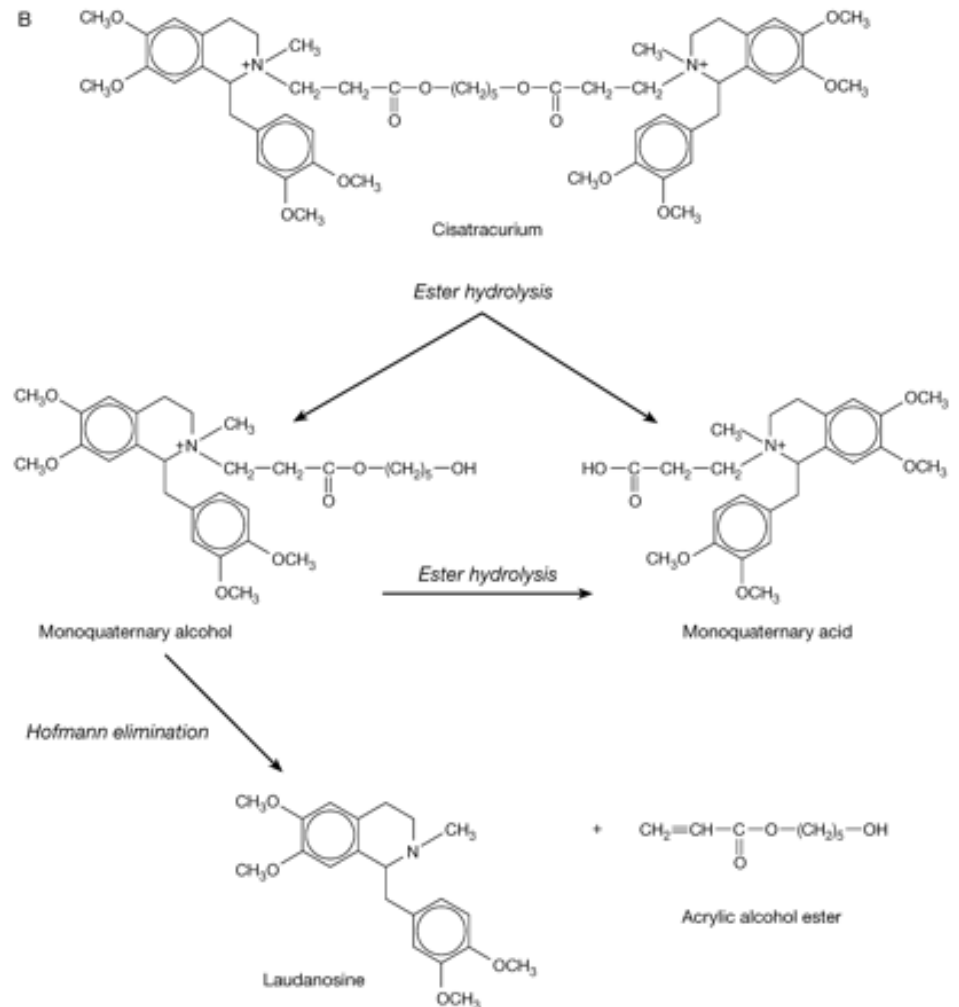
Hofmann Elimination

- Spontaneous degradation of N-alkyl portion of benzyloisoquinoline



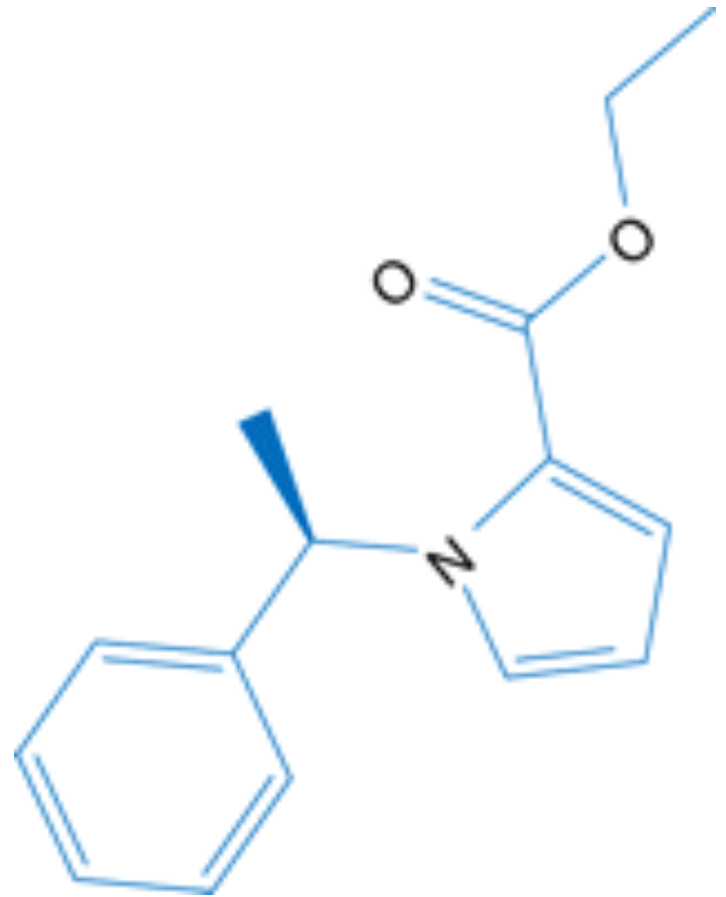
Esterase Activity

■ Plasma esterases



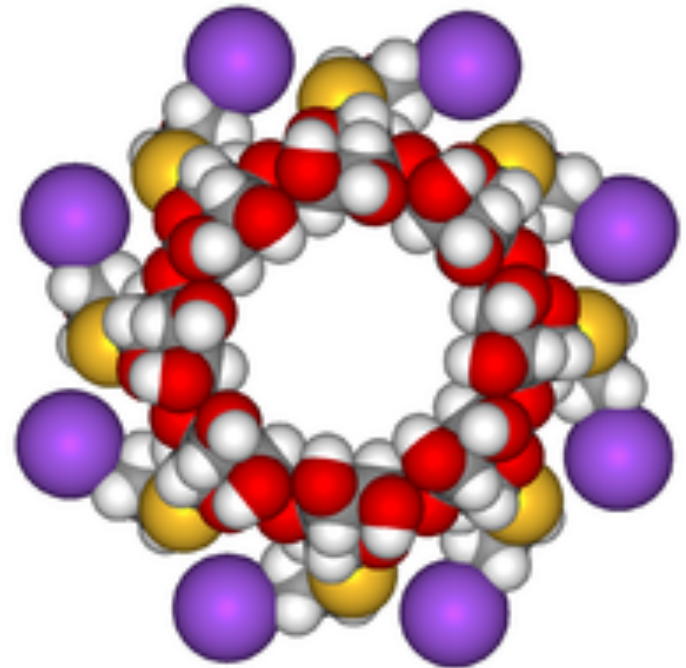
MOC-Etomidate, Carboetomidate

- Rapid onset
- Ester hydrolysis
- No adrenal suppression



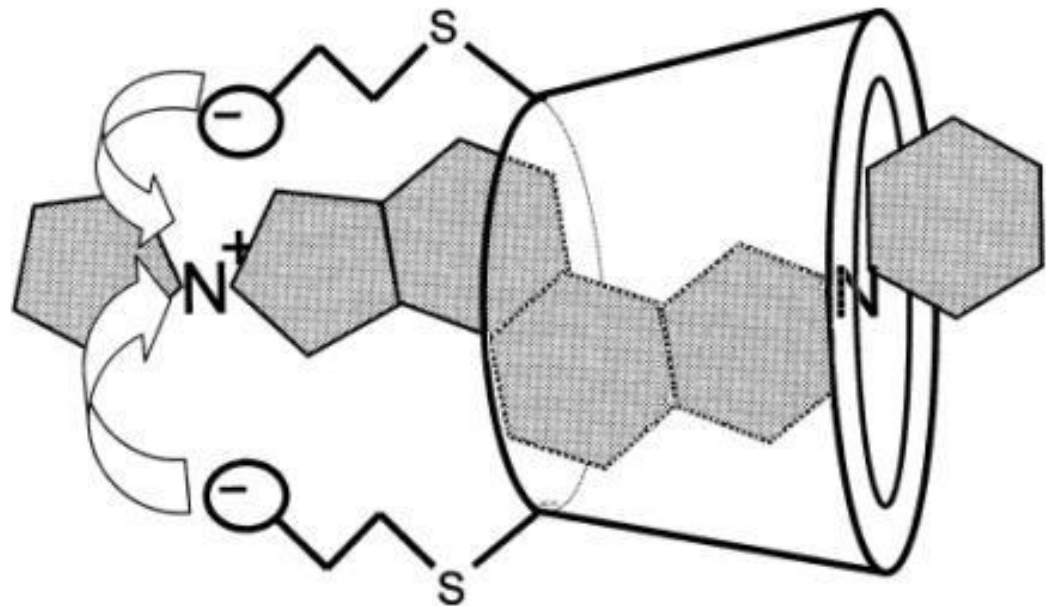
Sugammadex

- Binds NMBA (steroid-type)
- Makes NMBA “soft”
- Rapid onset of reversal
 - 2.9 minutes



Sugammadex surrounds Rocuronium

- Cyclodextrin with lipophilic core
- (-) charged extensions bind ammonium
- NMBA unavailable
- Excreted in urine



New Compounds

- THRX-918661 (sedative/hypnotic)
 - Esterase hydrolysis
 - Propranadid derivative
- CNS-7557, CNS-7056 (benzodiazepine)
 - Esterase hydrolysis
- Fos-propofol
 - Prodrug
 - (Slower onset?- less respiratory depression)
- PF0713
 - Larger side groups than propofol
 - (No pain on injection)

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: Lazarova J Med Chem 2003; 46: 674-6.

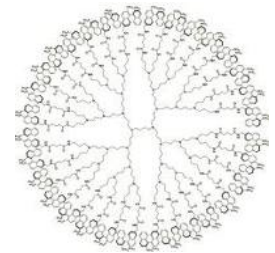
3: Graffner-Nordberg Eur J Pharm Sci 2004; 22: 43-54.

4. Kim NEJM 2010; 363: 2434-43.



Nanotechnology

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



CONCLUSIONS

- Soft Drugs are important to Anesthesia
 - Rapid, dependable biotransformation
- Most Soft Drugs utilize esterases
- Hofmann Elimination offers enzyme-independent degradation
- Scavenging (eg Sugammadex, Digibind^R)



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