B. 1 Sedative-hypnotic drugs

a. Define and distinguish: sedation, hypnosis, anxiolysis, tolerance, REM and non-REM sleep, physical and psychological dependence.

b. Identify the major chemical classes of sedatives, hypnotics and anxiolytics.

c. Describe the pharmacodynamics of the barbiturate and non-barbiturate sedatives.

d. Describe the pharmacokinetics of commonly used barbiturates and benzodiazepines and indicate how differences between them may be applied clinically.

e. Describe individual sedative-hypnotic agents.

ethanol

- clear colourless liquid, miscible with water
- usually given orally, can be administered IV
- some is metabolized by gastric alcohol dehydrogenase (more in men)
- small Vₐ = 0.7 l/kg
- metabolized in the liver to acetaldehyde and acetic acid
  - alcohol dehydrogenase active at low BAC (< 0.10)
  - microsomal oxidation at high BAC
  - limited by NAD⁺, NADP⁺ availability
  - zero-order kinetics (~8 g/h)
- dissolves in membranes decreasing viscosity and affecting many receptors and ion channels
  - CNS depression (many complex actions)
  - ↓ cardiac contractility, smooth muscle tone, uterine contraction, platelet aggregation
  - teratogenic
- long term effects are difficult to separate from confounding variables (nutrition, smoking, social status, premorbid problems)
- interacts with other drugs acutely by reducing hepatic metabolism and with chronic use by inducing hepatic metabolism
- tolerance mainly results from cellular adaption, not increased metabolism
- cross-tolerance with other sedatives
- little therapeutic use: acute methanol poisoning, prevention of withdrawal
- dose: 10g per standard drink
  - dependent users 100-750 g/day

thiopentone

- 0.5 g in 20 ml glass ampoule
- yellow powder, sodium salt
- stabilized with anhydrous sodium carbonate 60 mg/g
- prepared with water or saline to 25 mg/ml solution
- pH 11-12. Precipitates in neutral or acid solution
- administered IV
- rapid onset of effect in CNS followed by redistribution
- hepatic metabolism
- binds GABA receptors, increasing the duration of Cl⁻ channel opening

methohexitone

- 500 mg in 50 ml glass ampoule
- white/yellow powder, sodium salt
- stabilized with anhydrous sodium carbonate
mostly αL and αD isomers. β isomers increase involuntary movement. 
prepared with water or saline 
ph 10.6-11.6 
pharmacokinetics and actions similar to thiopentone 

phenobarbitone 
200 mg in 1ml ampoule 
30 mg tablets 
the oldest anticonvulsant 
pKa = 7.4 
undergoes hepatic oxidation of the C5 functional groups and conjugation with renal 
clearance. 25% is excreted unchanged. 
t1/2β = 4 days 
binds GABA receptors increasing Cl- conductance, AMPA receptors blocking 
glutamate transmission 

sedative and anticonvulsant

propofol 
10 mg/ml in 20, 50 and 100 ml ampoules 
white aqueous isotonic emulsion 
solubilized with 2.25% glycerol, 1% soybean oil, 1% purified egg phospholipid 
previously solubilized in Cremaphor EL → anaphylaxis 
pH 6.0 to 8.5 
administered IV 
rapid onset of effect in CNS followed by redistribution 
rapid metabolism in liver (t1/2β 0.5-1.5 h)

diazepam 
Diazemuls 
1 ml of 5 mg/ml glass ampoule 
solubilized in soybean oil 
Diazepam USP 
2 ml of 5 mg/ml brown glass ampoule 
clear yellow solution 
dissolved in 40% propylene glycol, 10% ethyl alcohol, 5% Na benzoate

midazolam 
5 ml of 1 mg/ml or 1, 3 or 10 ml of 5 mg/ml glass ampoules 
clear aqueous solution 
buffered to pH 3.3 
precipitates in strongly alkaline solutions

clonazepam 
1 mg in 1 ml glass ampoule 
2.5 mg/ml oral solution 
0.5 mg and 2 mg tablets 
long t1/2β ~36 h

zopiclone 
7.5 mg tablets 
structurally unrelated to benzodiazepines, but binds at the same site on the GABA 
receptor

chloral hydrate 
no longer on the Australian market 
prodrug metabolized to trichloroethanol 
non-specific membrane stabilizer 
hepatic metabolism produces trichloroacetic acid which accumulates 
possibly carcinogenic 
dose 0.5-1.0 g (of 100 mg/ml solution)

chlmethiazole 
8 mg/ml oral solution 
192 mg capsules

Sedatives, hypnotics 

James Mitchell (December 24, 2003)
5-20% bioavailability
65% protein bound
pKa 3.2
related to vitamin B,
?GABAergic, unknown mechanism

agents affecting CMR and CBF

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**f. Describe the anticonvulsant and proconvulsant properties of the agents.**