

JULY 2008
QUESTION 14

Compare and contrast the pharmacology of midazolam and dexmedetomidine when used for sedation.

	Midazolam	Dexamedetomidine
Intro	benzodiazepine imidazole ring in its structure accounts for its water-solubility and rapid metabolism	central alpha2 agonist greater selectivity for A2 than clonidine
Uses	sedative, amnesic, antiepileptic	sedative - short term mx of intubated pts
Pharmaceutical	Tablet or IV/IM preparation	IV only in Aus (PO overseas) precedex comparatively expensive, D-stereoisomer
Pharmacodynamics		
Mechanism	increases the sensitivity GABA _A receptors which open (via GABA) and allow Cl influx causing hyperpolarisation	acts mainly on alpha 2 adrenoceptors centrally in the locus cerelus, and peripher- ally at higher doses
CNS	Sedative, reduces epileptiform activity, increases confusion and disorientation, amnesic properties more prominent than sedative effects	produces sedation and some analgesia without as much confusion or disorienta- tion as benzos. pts are generally easily roused
Cardio	minor hypotension has been reported	higher doses cause peripheral A2 effects such as vasoconstriction, followed by hypotension and bradycardia (decreased SNS outflow)
Respiratory	causes respiratory depression this effect is synergistic with opioids	minimal respiratory depression
Side effects	Main issues are respiratory depression and excessive sedation with overdosage Same CYP as alfentanil (increases effect)	main concerns are the cardio side effects, as described, plus rebound hypertension on ceasing dose. dry mouth
Pharmacokinetics		
absorption	poor oral bioavailability 45%	IV only in aus
distribution	small-mod Vd = 1-2 L/kg lipid soluble at physiological pH (pKa 6.5) highly protien bound (95%)	large Vd 120 litres (steady state) lipid soluble (rapid distribution) highly protien bound
metabolism	hepatic via CYP3A4, and glucuronidation active metabolite	Hepatic via CYP and glucuronidation
excretion	1-4 hrs prolonged in cirrhosis, CRF, obesity, elderly excreted in urine	half life - initial 6 minutes (redistribution) - terminal 2 hrs excreted in urine