

BENZODIAZEPINES

DEVELOPMENT

Librium	1955
Diazepam	1959
Oxazepam	1961
Lorazepam	1971
Midazolam	1976

BNZ RECEPTORS

Discovered in 1977

Enhance the effects of GABA in numerous regions of the CNS
Almost exclusively in the CNS with some in autonomic ganglia

Greatest concentration in the

Basal ganglia

Hippocampus –↓ GABA receptors seen in panic disorders

Cerebellum

Hypothalamus

Substantia gelatinosa in spinal cord

Retina

Act at interneurons—inhibitory

Increase in chloride conductance

Pre and post synaptic effects

Cause presynaptic inhibition by hyperpolarization of afferent terminals

Can vary with menstrual cycle – ↑ progesterone ↑ GABA receptors → may be related to premenstrual dysphoric disorder

Functions

1. Induction of sleep
2. Control of neuronal excitability including epilepsy, memory, hypnosis

Other agents interact with GABA receptors

Halothane

Propofol

Barbiturates – can act indirectly or directly on GABA sites → don't require presence of gamma subunit

Progesterone

Pregnenalone

Prevention of epilepsy

Sodium valproate- reduces GABA metabolism

Vigabatrin – GABA analogue

Antianxiety

Decrease aggression and increase social behaviour

Modifies 5-HT

Social stress increases GABA_A receptor subunit mRNA

Memory retention and storage

GABA and GABA_B receptors – baclofen, which acts at B type, impairs memory

Increase GABA leads to decreased memory → Amnesic effect

3 subtypes

GABA_B presynaptically on nerve terminals postsynaptically in brain and dorsal horn in spinal cord/ esp. near small diameter afferent fibres

Diminish release of amines, neuropeptides hormones and excitatory amino acids

Baclofen binds to control spasticity

May be useful in treatment of pain and reduce craving in addiction

GABA_A

Group of different receptors

7 subunits described alpha, beta delta, and gamma, etc.

include a chloride channel

multiple variants

pentameric form – 2 alpha 1, 2 beta2, 1 gamma 2

presence of gamma subunit confers benzo sensitivity

not all GABA receptors bind benzos

2 benzo subtypes 4 protein subunits +/- gamma

Benz 1 found in brain and cerebellum

Anxiolysis and contains alpha subunit

Benz 2 found in cortex and spinal cord

Contain alpha 2 and alpha 3 subunits

Sedation and muscle relaxant

Benzos bind at interface between alpha and gamma subunits

GABA binds at interface between α and β

GABA C-2 subtypes – little understood – retina

Endogenous Benzos

Beta carbolines act as inverse agonists → cause anxiety and convulsions

Diazepam binding inhibitor – DBI – naturally occurring

Natural Antagonist – production of DBI is influenced by genetic and early conditioning experiences

Injected into humans leads to sweating, nausea, palpitations, chest pain and feelings of worry and impending doom

Endozepines

Agonist substances

Increase mitochondrial synthesis of pregnenolone

Endozepine –4 is elevated in Idiopathic Recurring

Stupor during attacks and is reversible with flumazenil

Benzo like substances are found in many foodstuffs ESP fruits and vegetables

Conclusions

Ligand gated chloride ion channels

5 subunits

span the lipid membrane

joined by chains which can be phosphorylated thus modulates actions

allows interaction with agents that modulate cAMP i.e. Opioids

PHYSIOCHEMICAL CHARACTERISTICS

Small, lipid soluble at physiologic pH

Midazolam is most lipid soluble

Nonirritating -pH in bottle is 3.5, making it water soluble, but once injected the imidazole ring opens at physiologic pH making it fat soluble

Metabolism

2 pathways

Hepatic microsomal oxidation

-susceptible to outside influences i.e. Age, disease (cirrhosis) or coadministration of other drugs i.e. Cimetidine, erythromycin

- smoking increases clearance of diazepam
- Midazolam is less affected by liver because the ring opens easily
- ethanol increases the clearance of Midazolam
- Midazolam and diazepam metabolized by this pathways

Or

Glucoronide conjugation

- less susceptible
- lorazepam

Metabolites are important

Diazepam has two active metabolites

Oxazepam and desmethyldiazepam

terminal 1/2 life 20-40 hours

Extensively bound with small free fraction

if factors alter the binding there is significant prolongation of effect
hepatic/ renal clearance

Elderly – change distribution and binding

Renal disease

less but binding, so more effect but cleared faster by the liver

Lorazepam is resistant to age/gender and renal disease

Obesity

Affects all types due to an increased elimination half-life because of delayed return to plasma from fat stores

PHARMACOLOGY

Order of receptor affinity and thus potency

Lorazepam > Midazolam > diazepam

5x 3-4x

Effects may be due to the degree of receptor occupancy

20% - anxiolysis

30-50 – sedation

>60 - unconsciousness

CNS EFFECTS

- decrease CMRO₂ and CBF and maintain ratio
- 0.15 mg/kg diazepam causes sleep and reduces CBF 34% and increases paCO₂ from 34-39
- all increase seizure threshold
- dose related protective effect against cerebral hypoxia
- pentobarb > midazolam > diazepam

- antiemetic properties by affecting the CTZ resulting in decreased release and thus effect of dopamine
- intrathecal and epidural effects – acts at the cord level
 - dose related response to visceral distention
 - antinociceptive effects
 - flumazenil given epidurally or intrathecally reduces these effects but not when given IV
 - antinociceptive property depends of type of noxious stimuli
 - in bunnies 20x more potent than morphine against intestinal distention pain
 - dose dependent muscle weakness 6x the antinociceptive dose
 - synergism with fentanyl for the tail flick test
 - additive or competitive depending of route with morphine
 - M.S. is 15x more potent for hot plate test
 - Differential action on A delta and c fibres
 - Differential pathways for noxious Vs somatic afferents
 - Local Vs central effects differ
 - Benzo in brain act to counter antinociception i.e. Increase in brain turns off inhibition

RESPIRATORY SYSTEM

Midazolam > resp. depression than diazepam though no comparative studies

Flattens the CO₂ response curve without a right shift as seen with opioids

Looking at this, Midazolam is 5-9x more potent
Peak at 3 minutes and lasts 15 minutes

- worse in COPD
- greater than an equivalent dose of thiopental
- supradadditive with narcotics
- relax airway smooth muscle by direct activity

CVS

Produce vasodilation by endothelium dependent factors, mediated by release of NO from endothelium

Independent vasodilation seems linked to inhibition of voltage gated Ca channels

Results in decreased SVR but maintains homeostatic reflexes

Similar to STP but safe in aortic stenosis due to a plateau of the drug effect like ketamine

If increased LVEDP they exert a NTG like effect by decreasing filling pressures and increased output

Does not block the stresses of intubation

If give narcotics and benzos results in increased hemodynamic effects

USES

Sedation – disparity in sedation Vs amnesia

- Midazolam Vs diazepam for gastroscopy
- similar early kinetics BUT

Old folks – gastroscopy

Midazolam is a better amnestic

Diazepam increased side effects at 7-10 hours suggests enterohepatic recirculation with diazepam – persisted for 30 hours

In studies the usual dose of Midazolam is usually higher than true equivalence and still diazepam is worse

Mid Vs Propofol for cardioversion

- both acceptable
- similar hemodynamically
- mid approx .16mg/kg
- propofol 1.7 +/- 0.4 mg/ kg

Mid Vs propofol for bronchoscopy

- about same during procedure hemodynamically or O2 Sat
- memory and motor reaction time at 60 minutes baseline for propofol and significant ↓ for Midazolam

Mid Vs mid + flumazenil Vs propofol

- for spinal sedation
- group two good but incomplete antagonism of effects of mid
- propofol best

Induction and Maintenance

-Midazolam is the only reasonable choice for induction

- dose approx. 0.2 mg/kg in healthy adult
- wide variation – onset 30 seconds
- decrease 25% in elderly
- awakening in 15 minutes

Co-induction Techniques

- mid and STP
- synergism allows 50% of STP dose
- ED 50 0.16 mg/kg and ST P 3.6 mg /kg
- Use 25% of midazolam and 50% of STP
- Reverse benzo leads to rapid recovery

Mid and halothane

- decrease 60% with 0.5 mg / kg
- - decrease 34% with 0.2% mg/kg

Mid and propofol

- 2 ugm / kg fent
- 25% ED50 of mid + 50% ED50 prop
- little difference in emergence and a 40% saving in drug costs

Amnestic period anaesthetic dose approx 1-2 hours

Relatively free of allergic reactions

High margin of safety

FLUMAZENIL

Minimal intrinsic activity

Very weak agonist

Competitive antagonist – occupies receptor once agonist has abandoned the site

Rapidly cleared, therefore potential for re sedation

Can precipitate withdrawal in BNZ dependent

Can be used to BNZ anaesthesia

Reversal should be gradual 0.1 mg increments up to 3.0 mg

Metabolized in the liver

For prolonged reversal use a continuous infusion 30-60 ugm / minute

Rapid onset 1-3 minutes

No cardioresp. Effects

Cost 13.00 per 0.5 mg

Aminophylline for reversal acts as a nonspecific CNS stimulant and also reverse opioid depression

Competitive inhibitor of the depressant action of endogenous adenosine

NOT AS EFFECTIVE AS FLUMAZENIL AND LESS PREDICTABLE,
MORE SIDE EFFECTS

Amnesia

Only antegrade amnesia

Reliable only if given IV except for lorazepam

Duration is dose dependent

Need 5 mg midazolam- provides 5-15 minutes dense amnesia then
a variable period

Flumazenil does not cause retrograde antagonism of amnesia

Sexual Fantasies

Dentists – 41 cases reported, 4 lost license

- no opioids in 37 of 41
- 37 fantasies or hallucination
 - 29 female
 - 8 male
 - 23 during sedation 6 slow induction
 - 25 sexual content
 - 20 unpleasant
 - in 16 the details were verified with 13 impossible due to presence of other of physical impossibility
 - difficult to persuade patients otherwise
 - most frequent during dental sedation or oral endoscopy
 - slow induction was described as pleasurable with no trespass reported
 - all cases occurred with large doses 0.1 mg / kg
 - no incidents in 1000 cases given smaller doses