Pharmacology of Benzodiazepines Used for Conscious Sedation in Dentistry

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Ideal Sedative Agent

• Anxiolysis
• Analgesic
• No effect on CVS
• No effect on respiratory system
• Not metabolised
• Easy and quick to change level of sedation
• Reversible
• No interactions with other drugs
• Long shelf life
• Cheap

Benzodiazepines

• Discovered in 1955
• Librium marketed in 1960
• Diazepam discovered 1959
  – First used in anaesthesia 1966
Pharmacokinetics

• What the **body** does to the **drug**
  
  • Half life
  • Metabolism
  • Excretion

Pharmacodynamics

• This is what the **drug** does to the **body**
  
  • Sedation
  • Analgesia
  • Anxiolysis etc.

Clinical Effects of Benzodiazepines

• Pharmacodynamically the same

• Differences
  – Affinity for receptors (potency)
  – Pharmacokinetic properties
    • Half life
    • Presence active metabolites
Benzodiazepines Actions

- Anxiolysis
- Anticonvulsion
- Slight Sedation
  - reduced attention
- Amnesia
- Intense sedation
- Muscle relaxation
- Anaesthesia

Increasing Dose

Clinical Effects of Benzodiazepines

- Anxiolysis (relief from anxiety)
  - First effect at low dose
  - High anxiety requires higher dose
- Sedation
  - Decreased response to constant stimulus

Clinical Effects of Benzodiazepines

- Anticonvulsion (Prevent epileptic fits)
  - Benzodiazepines terminate or prevent fits
  - Emergency drug for epilepsy
- Amnesia
  - IV give anterograde amnesia
  - Most intense for 20-30 minutes
  - Unpredictable
Clinical Effects of Benzodiazepines

- Effect on Pain experience
- BZD are NOT analgesic
- Respond to pain/stimulus
- Patients may move more during administration of Local.

Benzodiazepine Mechanism of Action

- Principles.
  - GABA (Gamma-aminobutyric acid)
    1. GABA causes sedation to CNS
    2. BZD bind to BZD receptors
    3. When bound will increase GABA effect.
  - Glycine
    1. Glycine causes anxiolysis and muscle relaxation
    2. Midazolam (BZD) mimics Glycine

At the Synapse
Peripheral Benzodiazepine Receptors

- Found in myocardium, kidney and adrenals
  - Role unknown
  - Maybe implicated in cardiovascular effects

Side effects of Benzodiazepines

- Depression of Respiration (breathing)
  - Central nervous system depression and muscle relaxation
  - Decrease cerebral response to CO₂ (carbon dioxide)
  - Synergistic interaction with opioids
  - Enhanced in patients with chronic bronchitis
Side effects of Benzodiazepines

• Cardiovascular effects
  – Reduce blood pressure by decrease in vascular resistance
  – Heart rate increases via baroreceptor reflex
  – Cardiac output unaffected

Side effects of Benzodiazepines

• Drug interactions
  – Enhanced respiratory depression with CNS depressants
  – Synergistic reaction with opioids
  – Pharmacokinetic interactions
    • Eg ketoconazole or erythromycin and midazolam
      – St johns wart and grapefruit juice

Side effects of Benzodiazepines

• Sexual fantasy
  • Reported in both male and female patients
  • Usually patient and dentist opposite sex
  • Dose related (midazolam >0.1mg/kg)
Unwanted effects of benzodiazepines

• Tolerance
  – Patients taking oral BZDs become tolerant to some effects

• Dependence
  – Long term oral administration will cause addiction and will experience withdrawal reactions if cease
  – Dependence can be activated by acute administration
  – Acute withdrawl can be caused by BZD antagonist

Midazolam

• Water soluble
  – Water soluble pH <4.0
  – Lipid soluble at physiological pH
    • Lipid soluble means it can cross blood brain barrier

• No rebound sedation
Midazolam

- Metabolised
  - Liver
  - Significant extra hepatic metabolism
  - Less effected by liver disease
- In acute administration pharmacokinetics not effected by renal (kidney) disease

Temazepam

- Formulation
  - 10mg 20mg tablets
  - 10mg/5ml solution
- Dose
  - 10mg to 40mg 60min prior to surgery
- Elimination half life
  - 20 hours

Flumazenil - Anexate

- Reversal agent
- Antagonist
  - IV injection
  - 500microgram/ml
  - 5ml ampoule
- **High** receptor affinity
- **Low** intrinsic action
Flumazenil - Anexate

- Mode of action
  - Competitively displaces active benzodiazepine from receptor site.
- Elimination half life
  - 53 minutes

Uses of Flumazenil

- Not used as a routine
- Essential emergency drug
  - Should present but not used

Residual Sedation after Flumazenil

When flumazenil runs out the patient is still sedated.
Residual Sedation after Flumazenil

- Due to the different half life's flumazenil is metabolised before midazolam has been made inactive

Contraindications to flumazenil

- Suspected allergy to benzodiazepines
  - Never use for anaphylaxis
- Patients taking benzodiazepines to treat epilepsy
- Patient dependent on BZDs