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**

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

- **GABA** (Gamma-aminobutyric acid)
- **BZD** (Benzodiazepine)
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
    - E.g. ketoconazole or erythromycin and midazolam
    - St johns wort and grapefruit juice
  - 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**
  - 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

- 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