Pharmacology of Midazolam

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Objectives

+ Know how to store, order and dispose of midazolam
+ Understand the mechanism of action midazolam
+ Be aware of the clinical effects of midazolam
+ Know the properties of midazolam
+ Understand the pharmacokinetics of midazolam
+ Be aware of the factors determining the effects of midazolam
+ Understand the MOA, properties and effects of Flumazenil
+ Remimazolam – The future of conscious sedation?

Midazolam

- Schedule 3 controlled drug
- Does not have to be stored in a controlled drug cupboard – BUPA policy advises that it should be locked away at the end of the day
- Store away from direct sunlight
- Order using prescription form FP10CD
- Invoices should be retained for 2 years (6yrs for HMRC)
- Should be disposed of correctly
- Disposal should be witnessed



What Neurotransmitter Pathway does Midazolam Activate?

Mechanism of Action of Midazolam

- Agonist - Act on receptors in CNS to enhance the effect of the GABA neurotransmitter pathway – inhibitory
- When midazolam binds to the receptor it is modified and there is an increase in GABA A receptor activity
- Increases the frequency of channel opening events, which leads to an increase in chloride ion conductance and inhibition of the action potential - decreasing excitability
- Sedation, anxiolysis, amnesia, muscle relaxation, anticonvulsant

Can you name any of the clinical effects of midazolam?

Clinical Effects of Midazolam

+ Anxiolysis
+ Anticonvulsant
+ Slight sedation
+ Reduced attention
+ Amnesia (anterograde)
+ Intense sedation
+ Muscle relaxation
+ Anaesthesia

Clinical Effects

- Anxiolysis
  - First effect seen at low doses
  - May require higher doses in acute anxiety states
- Anticonvulsant
  - Prevent and terminate convulsions
  - Status epilepticus

Clinical Effects

- Sedation
  - Slight at low doses
  - Intense at higher doses
  - Decreased response to constant stimulus
  - Reduced attention
  - Increasing dose will lead to sleep
  - Dis-inhibition

Clinical Effects

- Amnesia
  - Anterograde amnesia
  - Intense for 20-30mins
  - Unpredictable duration
  - Most intense with IV drug
  - Midazolam produces good amnesia

Clinical Effects

- Muscle relaxation
  - Central effect
  - Depression of spinal reflex activity
  - Partly responsible for respiratory depression
  - Helps reduce trismus
  - Useful in Cerebral Palsy and Parkinson's
  - Affects standing/walking/balance

Clinical Effects

- Anaesthesia
  - Too large or too rapid (bolus) dose
  - Not analgesic
  - Altered response to pain - wisdom teeth model
    - Longer time to first analgesic
    - Lesser analgesic consumption
    - Lower pain intensity scores 8 hrs post op

What is the Arm to Brain Time of Midazolam?

Midazolam Properties

+ Imadobenzodiazepine
+ Potent BZD
+ Water soluble at PH <4.0 – painless to inject
+ Lipid soluble at physiological PH - crosses BBB
+ Onset in one arm –brain circulation 30sec
+ Used in dentistry as 1mg/1ml preparation - safer



Midazolam Properties

Recovery occurs by 2 processes:

1. Redistribution – initial recovery (alpha-half life)
   + From CNS to body fat
   + 6-15mins
2. Elimination – complete recovery (beta-half life)
   + Metabolism
   + Excretion
   + 1.9 +/-0.9hrs
   + Sedation window 45mins

Midazolam Pharmacokinetics

+ 94-8% protein bound

+ Metabolised by the liver
  + CYP3A4 enzyme
  + Alpha-hydroxymidazolam – half life 1.25+/-0.25hrs
  + No rebound sedation

+ Excreted by the kidney



Factors Determining the Effects of Midazolam

+Age

+Hepatic/Renal function

+Cardiovascular function

+Respiratory function

+High BMI/obesity

+Sleep Apnea

+Drug interactions

Age

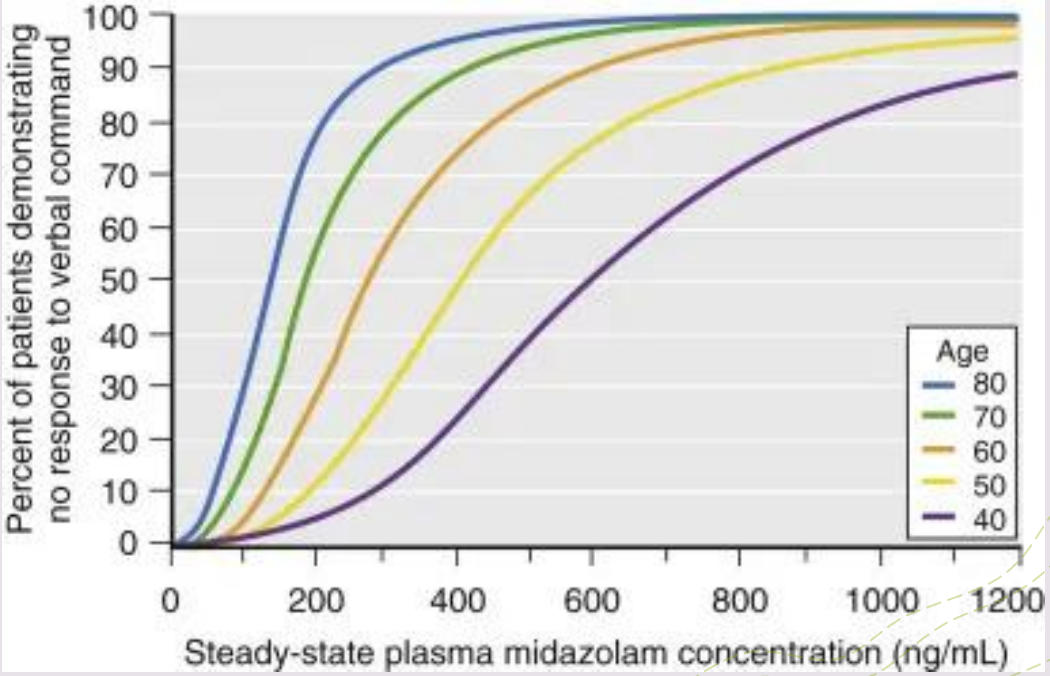
+Aging increases a person’s sensitivity to midazolam

+Greater risk of oversedation in the over 60’s

+In those under 16 years potential for paradoxical reactions

Age

- As an example at 400nanograms/ml no response to verbal command may be seen in approx:
  - 20% - 40year olds
  - 45% -50 year olds
  - 75% -60 year olds
  - 90% - 70 year olds
  - 98% - 80 year olds



What is the Maximum Dose of Midazolam that you can Administer to a Patient Over 70 years old?

Age

- In patients over 60 yo
  - Slow titration
  - Consider maximum 5mg (over 70’s 3.5mg max)

- In patients under 16
  - Consider level of maturity
  - Slow titration
  - Consider a maximum of 5mg

Hepatic and Renal Function

- Ensure hepatic and renal health before sedation
- Affects metabolism and excretion of midazolam
- Variable/unpredictable response
  - Oversedation
  - Prolonged recovery

Cardiovascular Function

+Haemodynamic effect is minimal

+Parasympathetic activity = decreased vascular resistance

+Lowering of blood pressure

+Slight increase in heart rate to maintain cardiac output

+Importance of monitoring BP during treatment and recovery

Respiratory Function

- Midazolam causes respiratory depression due to:
  - CNS depression and muscle relaxation
  - Decreases cerebral response to rise in CO_2
  - Peak respiratory depression 3mins can persist up to 120mins
- Increased risk
  - Rapid administration/bolus dose = apnea
  - Synergistic effect with other CNS depressants e.g. opiates
  - Patients with respiratory disease
    - COPD
    - Emphysema
  - Patient with sleep apnea
- Monitor – Respiratory rate, depth, colour, O_2 sats

What is the Highest BMI we are Allowed to Provide Sedation for in Primary Care?

Body Mass Index

+BMI = weight kg/height m^2

BMI	
Underweight	<18.5
Normal	18.5-24.9
Overweight	25.0-29.9
Obesity	>30.0

Obesity

- What are the issues:
  - Incidence of other systemic comorbidities is higher
  - Compromised cardio-respiratory function
  - Compromised airway
  - Drug dosing
  - Sleep apnea
- Treatment in primary care:
  - BMI <35 – acceptable for primary care
  - BMI 35-40 – needs careful consideration
  - BMI >40 – secondary care

Is flumazenil a controlled drug?

Flumazenil

+ Not a controlled drug
+ Record of flumazenil use should be kept and audited
+ Should not be used for routine reversal
+ Keep 2 vials at the ready whenever you are administering midazolam
+ Check dates regularly

Flumazenil

+ BZD antagonist – displaces active BZD from receptor
+ 40% protein binding
+ It is also a BZD, lacks the benzine ring
+ **Rapid onset 1-3mins**
+ Reverses the anxiolytic, sedative and respiratory depressant effects
+ Does not affect amnesia
+ No sedative or stimulant effects
+ Higher affinity for the receptor than midazolam
+ Short half life – 53mins {+/-13mins
+ Metabolised by liver
+ Excreted by kidney



The Future of IV Sedation……

Remimazolam

+ Combines the properties of two unique drugs already established in anaesthesia – Midazolam and Remifentanil
+ Found to be both faster acting and shorter lasting than midazolam
+ Faster recovery time
+ Indicated for the induction and maintenance of procedural sedation in adults lasting 30 minutes or less
+ It acts on GABA A receptors

Remimazolam

+Metabolism by non-specific tissue esterases in the blood

+Can be safely used in patients with hepatic or renal impairment

+Age-related deterioration of hepato-renal drug handling is less likely to have impact