

MIDAZOLAM



*“Hera Seducing Zeus”, from the “Loves of the Gods” frescos, 1597, Annibale Carracci, Farnese Gallery Rome.*

*Hera flew down from Mount Olympus...till she came to the Isle of Lemnos. There she found Hypnos, the god of Sleep, the brother of Thanatos, the god of death. She took his hand in hers and she said: "Hypnos, Lord of gods and men, you have helped me once before, now please help me again and I shall be grateful to you for the rest of my days. Seal Zeus' eyes in slumber beneath his eyelids as soon as I have seduced him and made him weak. Do this for me and I shall give you a beautiful golden throne, imperishable forever. My son Hephaestus, the crippled god, will make it for you, with a footstool to rest your glistening feet as you drink your nectar".*

*Then Hypnos, god of Sleep said in response, "Queen of goddesses, daughter of mighty Cronus, I would readily grant your request if it were a matter of anyone else among the immortal gods - even Lord Oceanus, the origin of us all. But I dare not come close to Zeus or lull him to slumber unless it is he himself who commands me to do it! I was once before taught a lesson when I agreed to help you out, when Zeus' arrogant son Heracles sailed from Troy after laying it waste. I made Zeus slumber, pouring my sweetness around him while you plotted against his son and stirred up a mighty gale that swept him far from his friends, to the Isle of Cos. Zeus was enraged when he woke up, hurling aside the gods of the palace before he went looking for me. He would have flung me into the abyss of the sea, if my mother Nyx, the goddess of Night, had not saved me".....*

*Then Hera smiled and answered, "Why should you trouble your mind with such silly ideas? Do you think that Zeus is as hell bent on helping the Trojans as on helping his own son...but very well Hypnos, if you do what I ask, I shall give you one of the Graces for you to marry and call your beloved wife!"*

*When he heard this Hypnos was overjoyed, and he answered, "Well then Hera, by the inviolate waters of the Styx swear to me, with one hand on the bountiful Earth and the other hand on the glistening sea - and let all the gods who dwell in the lower depths with old Cronus witness - that you will give me one of the Graces: Pasithea - I have longed for her all of my days".*

*Hera nodded her head in agreement and did what he asked for. She swore invoking the names of those lower gods. After she had completed her oath, the two shrouded themselves in mist and quickly set out....*

*Hera sped on to Gargarus, Ida's summit. And when Zeus saw her, he was overwhelmed with desire...he stood there in a fever of lust and said, "Hera what brings you down from the heights of Olympus?"....*

*Then with cunning deceitfulness Hera said, "Oh I am off to the ends of the Earth, to visit Lord Oceanus, the sire of the gods and Mother Tethys, who received me from Rhea and brought me up in their house. I am going to visit them now and try to resolve their endless quarrel; they are so furious at each other that it's been a very long time since they made love...but to tell the truth, you are really the reason I came down here from Olympus. I wanted to see you so that you wouldn't be angry that I went to Lord Oceanus' house without first letting you know".*

*Then Zeus said, "Hera, visit them later! For now let's go to bed and be joined in pleasure. Never before has desire for goddess or woman so inundated my heart and so overpowered it..."*

*Then with cunning deceitfulness, Hera said, "Dread Lord what do you mean? If we make love on the summit of Mount Ida everyone will see! What if one of the gods were to pass by and spot us sleeping together and go and tell all the others? It would be such a scandal I could never go back to Olympus!"*

*And Zeus said, "Hera, I promise that no god or man will see us. I shall cover us up in a golden cloud so thick that not even Helios could see through it..."*

*After these words, Zeus took Hera in his arms, and beneath them the shining Earth burst forth with spring flowers, dewy clover and crocus and hyacinth, thick and soft, which lifted them off the ground. They lay there, concealed in a beautiful golden cloud and from it dew drops fell glistening all around them.*

*And then as Zeus lay there in peace and contented exhaustion holding Hera in his arms, Hypnos weaved his spell of sleep over him. Hypnos then immediately ran down to the black ships of the Achaeans to bring the news of Zeus' deep slumber to the god Poseidon.... "Go now quickly Poseidon; bring as much help as you can to the Argives, give them a victory, if only for a short time while Zeus lies sleeping. I have sent him into a very deep slumber, after Hera seduced him"....*

*Homer, Book 14, The Iliad 8th Century BCE*

*The great war with Troy had not gotten off to a good start for the Greeks. Achilles had withdrawn to his tent refusing to fight after a fearful argument he had had with Agamemnon. Nothing or no one could entice the hero to take up his arms. To make matters even worse, Zeus himself, had taken an interest in the war, catastrophically sympathizing with the Trojans, even though he had once previously helped his demigod son, Heracles, against the Trojans. This greatly angered the goddess Hera who sympathized with the Greek cause, but she was powerless to assist them in the face of opposition from Zeus. She therefore concocted a devious plan. She sought out the assistance of Hypnos, the god of sleep. She implored him to send Zeus into a deep slumber, so that she could allow the great god of the sea, Poseidon, to assist the Greeks whilst Zeus was asleep. Hypnos was terrified of Zeus, having already once incurred his wrath by putting him into a deep sleep at Hera's request. On that occasion he had been lucky to escape Zeus' wrath, with his life, only being saved by his mother Nyx, the goddess of the Night. Not even the offer of a golden throne and footstool forged by Hephaestus, the god of fire could induce him to help. Hera however, countered this refusal with an offer he could not refuse...the hand of one of the Graces in marriage! Hypnos quite overwhelmed immediately agreed, especially when Hera promised to make his task easier by seducing Zeus and exhausting him with her lovemaking. Hera's plan worked magnificently. Hypnos was not only able to send Zeus into a deep slumber, but by sprinkling him with waters from the Lethe - the stream of forgetfulness - Zeus would have no memory of what had taken place when he awoke. Poseidon led the Greeks to a victory over the Trojans, but the war nonetheless would go on for ten long years.*

*Today the gods no longer take much interest in the affairs of mortals. They sit back and merely watch, astonished at their ingenuity. Today mortals have no need to call on the powers of the god Hypnos, who once helped the Greeks during the Trojan War, by use of the magical waters of the river Lethe. By use of a magic Hypnos potion of their own, known as midazolam, mortals themselves can induce a powerful spell of deep slumber and forgetfulness.*

## MIDAZOLAM

### Introduction

**Midazolam** is a short acting benzodiazepine agent that is very widely used in Emergency Departments and Intensive Care Units

It is primarily used for its useful **sedative-hypnotic, anxiolytic and anticonvulsant** actions.

Midazolam is a very safe drug when used appropriately and has the added advantage of having a specific antidote in the form of **flumazenil**.

**See also separate document for Flumazenil.**

### Chemistry

Midazolam is a benzodiazepine from the imidazobenzodiazepine group.

### Preparation

Preparations include ampoules of:

- 5mg/1mL
- 5mg/5mL
- 15 mg/3 mL.

*And:*

Vials of 50 mg/10 mL

### Mechanism of Action

**Midazolam**, like other benzodiazepines potentiates the inhibitory effects of GABA throughout the CNS.

GABA is the most ubiquitous inhibitory neurotransmitter in the brain.

### Pharmacokinetics

#### Absorption:

Midazolam can be given:

- IV:
  - ♥ As bolus dose or as a continuous infusion.

- IM:
  - ♥ Injected undiluted
  - ♥ Absorption of midazolam from the muscle tissue is rapid and virtually complete.
  - ♥ Onset time of sedative effects after intramuscular (IM) administration is 15 min, with peak sedation occurring 30 to 60 min following injection. <sup>4</sup>
- Orally:
  - ♥ Oral absorption is rapid, although erratic. Maximal effect is generally within 30 - 60 minutes and duration of effect is up to 2 hours
- Rectal:
  - ♥ After rectal administration midazolam is absorbed quickly.
  - ♥ Maximum plasma concentration is reached in about 30 min.
  - ♥ The absolute bioavailability is about 50% (range 40 to 65%).

#### Distribution:

- The volume of distribution of midazolam at steady state is 0.6 to 1.9 L/kg. <sup>4</sup>
- Midazolam is highly protein bound (around 97%).

#### Metabolism and excretion:

- Midazolam is rapidly metabolised to the active metabolite, **1-hydroxymethyl midazolam**, which is conjugated by the liver Cytochrome P450 isoenzymes with subsequent excretion in the urine.
- Less than 0.03% is excreted in the urine as unchanged midazolam.
- In normal subjects the mean elimination half-life of midazolam is between 1.4 to 2.4 hours.

#### Pharmacodynamics

Actions include:

1. Anxiolysis
2. Sedative - hypnotic

3. Amnesic effects (anterograde)
4. Anticonvulsant
5. Skeletal muscle relaxing effects

Midazolam has **no** significant analgesic properties.

### Indications

1. As an anxiolytic agent
2. Sedative/ hypnotic agent, as a **pre-anaesthetic** medication
3. Anticonvulsant
4. Adjunct to short procedural sedation
5. Adjunctive to induction of aesthesia
6. In toxicology:
  - In particular for seizures and/ or for situations of hyper-sympathomimetic reactions
7. For the control of seizures
8. Sedation in acute behavioural emergencies.

### Contraindications/ Precautions

Precautions include:

- Should be used with close continuous monitoring of cardiorespiratory function and resuscitation equipment on hand.
- The elderly are more susceptible to the effects of benzodiazepines in general
- Caution in hypovolemic patients
- Pre-existing compromised respiratory drive may result in aggravation of hypoventilation and hypoxemia
- Myasthenia gravis, muscular dystrophies and myotonias - respiratory depression prolonged or potentiated; reduce dose.

## Pregnancy

Midazolam is classed as a category C drug in pregnancy.

Class C Drugs are ones in which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. Specialised texts should be consulted for further details.

## Lactation

Midazolam is safe as one off doses

## Adverse Effects

These may include:

1. Excessive depression of conscious state, with consequent airway compromise.
2. Respiratory depression
3. Hypotension, (usually only mild).
4. Synergistic action with all CNS depressants, including alcohol.
5. Following prolonged oral use, or prolonged intravenous infusion a benzodiazepine withdrawal syndrome is possible.

## Dosing

### Acute sedation for procedures in adults:

- 2.5 - 10 mg IV / IM
- If **elderly or debilitated**, use smaller doses; 1-1.5 mg IV initially.

### For acute behavioural emergencies:

Midazolam **2.5 to 5 mg IV**, repeated every 3 to 4 minutes, titrated to clinical response, up to a maximum of **30 mg**.<sup>1</sup>

If **elderly or debilitated**, use smaller doses; 1-1.5 mg IV initially.<sup>1</sup>

**IM** doses of **2.5 - 10 mg** can also be used if IV access is problematic, but effects will take longer to occur.

If adequate control is not achieved after 30 mg has been given, the patient may be unable to be sedated with benzodiazepines, (either because of extreme agitation or prior habituation from chronic abuse).<sup>1</sup> Alternative agents may then be required.

For seizures:

- IV 0.1 mg/Kg, (range 5-10 mg)

Note that if IV access is impossible, options include:

- IM 0.2 mg/Kg ( maximum 15 mg)
- PR diazepam (0.5 mg/kg) may be given.<sup>2</sup>

Premedication in adults:

Premedication in adults: **7.5-15 mg orally**

For procedural sedation in children:

Oral dosing:

Using the injection formulation; for procedural sedation in children give:

- 0.5 mg/kg (to a maximum of 15 mg).

Nasal dosing:

Using 5 mg/mL injection preparation give: 0.2-0.4 mg/kg (max 10 mg)

Infusions:

- Infusion rates are usually given at **0.03 mg/kg/hr - 0.2mg/kg/hr**
- **Generally 1-20 mg hour for adults**

Reversal:

Flumazenil is a specific benzodiazepine antagonist and will rapidly reverse the effects of benzodiazepines including respiratory depression and conscious state.



References

1. eTG - July 2013
2. Australian Medicines Handbook, October 2013
3. RCH Pharmacopoeia October 2103.
4. MIMs October 2013.

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