= Midazolam =

Midazolam , marketed under the trade names Versed among others , is a medication used for anesthesia , procedural sedation , trouble sleeping , and severe agitation . It works by making people sleepy , decreasing anxiety , and causing a loss of ability to create new memories . It is also useful for the treatment of seizures . Midazolam can be given by mouth , intravenously , by injection into a muscle , sprayed into the nose , or in the cheek . When given intravenously it begins working typically within five minutes , when injected into a muscle it can take fifteen minutes to begin working . Effects last for between one and six hours .

Side effects can include a decrease in efforts to breathe , low blood pressure , and sleepiness . Tolerance to its effects and withdrawal syndrome may occur following long term use . Paradoxical effects , such as increased activity , can occur especially in children and older people . There is evidence of risk when used during pregnancy but no evidence of harm with a single dose during breastfeeding . It is of the benzodiazepine class and works through the GABA neurotransmitter .

Midazolam first came into use in 1976 . It is on the WHO Model List of Essential Medicines , the most important medications needed in a basic health system . Midazolam is available as a generic medication and is not very expensive . The wholesale cost in the developing world of a vial is about 0 @.@ 35 USD . In many countries it is a controlled substance .

= = Medical uses = =

= = = Seizures = = =

Midazolam is sometimes used for the acute management of seizures . Long @-@ term use for the management of epilepsy is not recommended , however , due to the significant risk of tolerance (which renders midazolam and other benzodiazepines ineffective) and the significant side effect of sedation . A benefit of midazolam is that in children it can be administered buccally or intranasally at home or at school for emergency control of acute seizures , including status epilepticus . Midazolam is effective for status epilepticus that has not improved following other treatments , and has advantages of being water @-@ soluble , having a rapid onset of action and not causing metabolic acidosis from the propylene glycol vehicle , which occurs with other benzodiazepines . Drawbacks include a high degree of breakthrough seizures ? due to the short half @-@ life of midazolam ? in over 50 % of people treated , as well as treatment failure in 14 ? 18 % of people with refractory status epilepticus . Tolerance develops rapidly to the anticonvulsant effect , and the dose may need to be increased by several times to maintain anticonvulsant therapeutic effects . With prolonged use , tolerance and tachyphylaxis can occur and the elimination half @-@ life may increase , up to days . There is evidence buccal and intranasal midazolam is easier to administer and more effective than rectally administered diazepam in the emergency control of seizures .

= = = Procedural sedation = = =

Intravenous midazolam is indicated for procedural sedation (often in combination with an opioid , such as fentanyl) , for preoperative sedation , for the induction of general anesthesia , and for sedation of people who are ventilated in critical care units . Midazolam is superior to diazepam in impairing memory of endoscopy procedures , but propofol has a quicker recovery time and a better memory @-@ impairing effect . It is the most popular benzodiazepine in the intensive care unit (ICU) because of its short elimination half @-@ life , combined with its water solubility and its suitability for continuous infusion . However , for long @-@ term sedation , lorazepam is preferred due to its long duration of action , and propofol has advantages over midazolam when used in the ICU for sedation , such as shorter weaning time and earlier tracheal extubation .

Midazolam is sometimes used in neonatal intensive care units . When used , additional caution is required in newborns ; midazolam should not be used for longer than 72 hours due to risks of

tachyphylaxis , and the possibility of development of a benzodiazepine withdrawal syndrome , as well as neurological complications . Bolus injections should be avoided due to the increased risk of cardiovascular depression , as well as neurological complications . Midazolam is also sometimes used in newborns who are receiving mechanical ventilation , although morphine is preferred , owing to its better safety profile for this indication .

= = = Problems sleeping = = =

Oral midazolam is indicated for the short @-@ term treatment of moderately severe insomnia in people who have not reacted adequately to other hypnotics , and who have persistent trouble in falling asleep . Because of midazolam 's extremely short duration , it is not used for people who have trouble staying asleep through the night ; moderate- to long @-@ acting benzodiazepines , such as temazepam , nitrazepam , flunitrazepam , and lormetazepam , are used for those purposes . Midazolam and other benzodiazepines may cause a deterioration in sleep quality .

= = = Agitation = = =

Midazolam in combination with an antipsychotic drug is indicated for the acute management of schizophrenia when it is associated with aggressive or out @-@ of @-@ control behaviour .

= = = End of life care = = =

In the final stages of end @-@ of @-@ life care , midazolam is routinely used at low doses via subcutaneous injection to help with agitation , myoclonus , restlessness or anxiety in the last hours or days of life . At higher doses during the last weeks of life , midazolam is considered a first line agent in palliative continuous deep sedation therapy when it is necessary to alleviate intolerable suffering not responsive to other treatments , but the need for this is rare .

= = Contraindications = =

Benzodiazepines require special precaution if used in the elderly , during pregnancy , in children , in alcohol- or other drug @-@ dependent individuals or those with comorbid psychiatric disorders . Additional caution is required in critically ill patients , as accumulation of midazolam and its active metabolites may occur . Kidney or liver impairments may slow down the elimination of midazolam leading to prolonged and enhanced effects . Contraindications include hypersensitivity , acute narrow @-@ angle glaucoma , shock , hypotension or head injury . Most are relative contraindications .

= = Side effects = =

Side effects of midazolam in the elderly are listed above . People experiencing amnesia as a side effect of midazolam are generally unaware their memory is impaired , unless they had previously known it as a side effect .

Long @-@ term use of benzodiazepines has been associated with long @-@ lasting deficits of memory , and show only partial recovery six months after stopping benzodiazepines . It is unclear whether full recovery occurs after longer periods of abstinence . Benzodiazepines can cause or worsen depression . Paradoxical excitement occasionally occurs with benzodiazepines , including a worsening of seizures . Children and elderly individuals or those with a history of alcohol abuse and individuals with a history of aggressive behavior or anger are at increased risk of paradoxical effects . Paradoxical reactions are particularly associated with intravenous administration . After nighttime administration of midazolam , residual ' hangover ' effects , such as sleepiness and impaired psychomotor and cognitive functions , may persist into the next day . This may impair the ability of users to drive safely and may increase the risk of falls and hip fractures . Sedation , respiratory

depression and hypotension due to a reduction in systematic vascular resistance , and an increase in heart rate can occur . If intravenous midazolam is given too quickly , hypotension may occur . A ? midazolam infusion syndrome ? may result from high doses , and is characterised by delayed arousal hours to days after discontinuation of midazolam , and may lead to an increase in the length of ventilatory support needed .

In susceptible individuals , midazolam has been known to cause a paradoxical reaction , a well @-@ documented complication with benzodiazepines . When this occurs , the individual may experience anxiety , involuntary movements , aggressive or violent behavior , uncontrollable crying or verbalization , and other similar effects . This seems to be related to the altered state of consciousness or disinhibition produced by the drug . Paradoxical behavior is often not recalled by the patient due to the amnesia @-@ producing properties of the drug . In extreme situations , flumazenil can be administered to inhibit or reverse the effects of midazolam . Antipsychotic medications , such as haloperidol , have also been used for this purpose .

Midazolam is known to cause respiratory depression . In healthy humans , 0 @.@ 15 mg / kg of midazolam may cause respiratory depression , which is postulated to be a central nervous system (CNS) effect . When midazolam is administered in combination with fentanyl , the incidence of hypoxemia or apnea becomes more likely .

Although the incidence of respiratory depression / arrest is low (0 @.@ 1 @-@ 0 @.@ 5 %) when midazolam is administered alone at normal doses , the concomitant use with CNS acting drugs , mainly analgesic opiates , may increase the possibility of hypotension , respiratory depression , respiratory arrest , and death , even at therapeutics doses . Potential drug interactions involving at least one CNS depressant were observed for 84 % of midazolam users who were subsequently required to receive the benzodiazepine antagonist flumazenil . Therefore , efforts directed toward monitoring drug interactions and preventing injuries from midazolam administration are expected to have a substantial impact on the safe use of this drug .

= = = Pregnancy and breastfeeding = = =

Midazolam , when taken during the third trimester of pregnancy , may cause risk to the neonate , including benzodiazepine withdrawal syndrome , with possible symptoms including hypotonia , apnoeic spells , cyanosis , and impaired metabolic responses to cold stress . Symptoms of hypotonia and the neonatal benzodiazepine withdrawal syndrome have been reported to persist from hours to months after birth . Other neonatal withdrawal symptoms include hyperexcitability , tremor , and gastrointestinal upset (diarrhea or vomiting) . Breastfeeding by mothers using midazolam is not recommended .

= = = Elderly = = =

Additional caution is required in the elderly , as they are more sensitive to the pharmacological effects of benzodiazepines , metabolise them more slowly , and are more prone to adverse effects , including drowsiness , amnesia (especially anterograde amnesia) , ataxia , hangover effects , confusion , and falls .

= = = Tolerance , dependence , and withdrawal = = =

A benzodiazepine dependence occurs in about one @-@ third of individuals who are treated with benzodiazepines for longer than 4 weeks , which typically results in tolerance and benzodiazepine withdrawal syndrome when the dose is reduced too rapidly . Midazolam infusions may induce tolerance and a withdrawal syndrome in a matter of days . The risk factors for dependence include dependent personality , use of a benzodiazepine which is short @-@ acting , high potency and long @-@ term use of benzodiazepines . Withdrawal symptoms from midazolam can range from insomnia and anxiety to seizures and psychosis . Withdrawal symptoms can sometimes resemble a persons underlying condition . Gradual reduction of midazolam after regular use can minimise

withdrawal and rebound effects . Tolerance and the resultant withdrawal syndrome may be due to receptor down @-@ regulation and GABAA receptor alterations in gene expression which results in long @-@ term changes in the function of the GABAergic neuronal system .

Chronic users of benzodiazepine medication who are given midazolam experience reduced therapeutic effects of midazolam , due to tolerance to benzodiazepines . Prolonged infusions with midazolam results in the development of tolerance ; if midazolam is given for a few days or more a withdrawal syndrome can occur . Therefore , in order to prevent a withdrawal syndrome a prolonged infusion needs to be gradually withdrawn and sometimes if necessary continued tapering of dose with an oral long @-@ acting benzodiazepine such as clorazepate dipotassium . When signs of tolerance to midazolam occur during intensive care unit sedation the addition of an opioid or propofol is recommended . Withdrawal symptoms can include irritability , abnormal reflexes , tremors , clonus , hypertonicity , delirium and seizures , nausea , vomiting , diarrhea , tachycardia , hypertension , and tachypnea .

= = = Overdose = = =

A midazolam overdose is considered a medical emergency and generally requires the immediate attention of medical personnel . Benzodiazepine overdose in healthy individuals is rarely life @-@ threatening with proper medical support ; however , the toxicity of benzodiazepines increases when they are combined with other CNS depressants such as alcohol , opioids , or tricyclic antidepressants . The toxicity of benzodiazepine overdose and risk of death is also increased in the elderly and those with obstructive pulmonary disease or when used intravenously . Treatment is supportive ; activated charcoal can be used within an hour of the overdose . The antidote for an overdose of midazolam (or any other benzodiazepine) is flumazenil . While effective in reversing the effects of benzodiazepines it is not used in most cases as it may trigger seizures in mixed overdoses and benzodiazepine dependent individuals .

Symptoms of midazolam overdose can include :

= = = Detection in body fluids = = =

The concentrations of midazolam and / or its major metabolite , 1 @-@ hydroxymidazolam glucuronide , may be quantified in plasma , serum or whole blood in order to monitor for safety in those receiving the drug therapeutically , to confirm a diagnosis of poisoning in hospitalized patients or to assist in a forensic investigation of a case of fatal overdosage . Patients with renal dysfunction may exhibit prolongation of elimination half @-@ life for both the parent drug and its active metabolite , with accumulation of these two substances in the bloodstream and the appearance of adverse depressant effects .

= = = Interactions = = =

Protease inhibitors , nefazodone , sertraline , grapefruit , fluoxetine , erythromycin , diltiazem , clarithromycin inhibit the metabolism of midazolam , leading to a prolonged action . St John 's wort , rifapentine , rifampin , rifabutin , phenytoin enhance the metabolism of midazolam leading to a reduced action . Sedating antidepressants , antiepileptic drugs such as phenobarbital , phenytoin and carbamazepine , sedative antihistamines , opioids , antipsychotics and alcohol enhance the sedative effects of midazolam . Midazolam is metabolized almost completely by cytochrome P450 @-@ 3A4 . Atorvastatin administration along with midazolam results in a reduced elimination rate of midazolam . St John 's wort decreases the blood levels of midazolam . Grapefruit juice reduces intestinal 3A4 and results in less metabolism and higher plasma concentrations .

= = Pharmacokinetics = =

Midazolam is a short @-@ acting benzodiazepine in adults with an elimination half @-@ life of 1

@.@ 5 @-@ 2 @.@ 5 hours . In the elderly , as well as young children and adolescents , the elimination half @-@ life is longer . Midazolam is metabolised into an active metabolite alpha1 @-@ hydroxymidazolam . Age @-@ related deficits , renal and liver status affect the pharmacokinetic factors of midazolam as well as its active metabolite . However , the active metabolite of midazolam is minor and contributes to only 10 percent of biological activity of midazolam . Midazolam is poorly absorbed orally , with only 50 percent of the drug reaching the bloodstream . Midazolam is metabolised by cytochrome P450 (CYP) enzymes and by glucuronide conjugation . The therapeutic as well as adverse effects of midazolam are due to its effects on the GABAA receptors ; midazolam does not activate GABAA receptors directly but , as with other benzodiazepines , it enhances the effect of the neurotransmitter GABA on the GABAA receptors (? frequency of Cl ? channel opening) resulting in neural inhibition . Almost all of the properties can be explained by the actions of benzodiazepines on GABAA receptors . This results in the following pharmacological properties being produced : sedation , hypnotic , anxiolytic , anterograde amnesia , muscle relaxation and anti @-@ convulsant .

= = History = =

Midazolam is among about 35 benzodiazepines which are currently used medically , and was synthesised in 1975 by Walser and Fryer at Hoffmann @-@ LaRoche , Inc in the United States . Owing to its water solubility , it was found to be less likely to cause thrombophlebitis than similar drugs . The anticonvulsant properties of midazolam were studied in the late 1970s , but not until the 1990s did it emerge as an effective treatment for convulsive status epilepticus . As of 2010 , it is the most commonly used benzodiazepine in anesthetic medicine . In acute medicine , midazolam has become more popular than other benzodiazepines , such as lorazepam and diazepam , because it is shorter lasting , is more potent , and causes less pain at the injection site . Midazolam is also becoming increasingly popular in veterinary medicine due to its water solubility .

= = Society and culture = =

= = = Cost = = =

Midazolam is available as a generic medication and is not very expensive . Wholesale a vial is about 0 @.@ 35 USD .

= = = Availability = = =

Midazolam is available in the United States as a syrup or as an injectable solution . Outside of the United States , midazolam is available in tablet form for oral administration .
Dormicum brand midazolam is marketed by Roche as white , oval , 7 @.@ 5 @-@ mg tablets in boxes of two or three blister strips of 10 tablets , and as blue , oval , 15 @-@ mg tablets in boxes of two (Dormonid 3x) blister strips of 10 tablets . The tablets are imprinted with " Roche " on one side and the dose of the tablet on the other side . Dormicum is also available as 1- , 3- , and 10 @-@ ml ampoules at a concentration of 5 mg / ml . Another manufacturer , Novell Pharmaceutical Laboratories , makes it available as Miloz in 3- and 5 @-@ ml ampoules . Midazolam is the only water @-@ soluble benzodiazepine available . Another maker is Roxanne Laboratories ; the product in an oral solution , Midazolam HCl Syrup , 2 mg / ml clear , in a red to purplish @-@ red syrup , cherry in flavor . It becomes soluble when the injectable solution is buffered to a pH of 2 @.@ 9 ? 3 @.@ 7 . Midazolam is also available in liquid form . It can be administered intramuscularly , intravenously , intrathecally , intranasally , buccally , or orally .

= = = Legal status = = =

In the Netherlands , midazolam is a List II drug of the Opium Law . Midazolam is a Schedule IV drug under the Convention on Psychotropic Substances . In the United Kingdom , midazolam is a Class C controlled drug . In the United States , midazolam (DEA number 2884) is on the Schedule IV list of the Controlled Substances Act as a non @-@ narcotic agent with low potential for abuse .

= = = Marketing authorization = = =

In 2011 , the European Medicines Agency granted a marketing authorisation for a buccal application form of midazolam , sold under the trade name Buccolam . Buccolam was approved for the treatment of prolonged , acute , convulsive seizures in people from three months to less than 18 years of age . This was the first application of a paediatric @-@ use marketing authorisation .

= = = Use in executions = = =

The drug has been introduced for use in executions by lethal injection in certain jurisdictions in United States in combination with other drugs . It was introduced to replace pentobarbital after the latter 's manufacturer disallowed that drug 's use .

Midazolam has been used as part of a three @-@ drug cocktail , with vecuronium bromide and potassium chloride in Florida and Oklahoma prisons . Midazolam has also been used along with hydromorphone in a two @-@ drug protocol in Ohio and Arizona . Ohio used midazolam to execute Dennis McGuire in January 2014 .

Midazolam acts as a sedative to render the condemned prisoner unconscious , at which time the vecuronium bromide and potassium chloride are administered , stopping the prisoner 's breathing and heart , respectively . Florida used midazolam to execute William Happ in October 2013 . The usage of midazolam in executions has become controversial after condemned inmate Clayton Lockett apparently regained consciousness and started speaking midway through his execution when the state of Oklahoma attempted to execute him with an untested three @-@ drug lethal injection cocktail using 100 mg of midazolam . Prison officials reportedly discussed taking him to a hospital before he was pronounced dead of a heart attack 40 minutes after the execution began . An observing doctor stated that Lockett 's vein had ruptured . It is not clear which drug or drugs caused his death or what quantities of vecuronium bromide and potassium chloride were released before the execution was cancelled .

In Glossip v. Gross , three Oklahoma inmates argued that midazolam could not achieve the level of unconsciousness required for surgery , meaning severe pain and suffering was likely . They argued that midazolam was cruel and unusual punishment and thus contrary to the Eighth Amendment to the United States Constitution . In June 2015 , the U.S. Supreme Court ruled they failed to prove that midazolam was cruel and unusual when compared to known alternatives .