Dormicum®

Midazolam

Short-acting benzodiazepine for premedication, sedation, induction and maintenance of anesthesia
Ampoules for intravenous, intramuscular and rectal administration

Composition

Active ingredient: midazolam as hydrochloride.

Ampoules 15 mg/3 ml and 5 mg/5 ml for i.v., i.m. and rectal administration.

The content of the vial is a clear liquid, practically free from particles and colourless to yellowish.

Excipients: sodium chloride, hydrochloric acid, sodium hydroxide, water for injection.

Sterile product.

Properties and effects

Dormicum has hypnotic and sedative effects characterized by a rapid onset and short duration. It also exerts anxiolytic, anticonvulsant and muscle-relaxant effects. Dormicum impairs psychomotor function after single and/or multiple doses but causes minimal haemodynamic changes.

The central actions of benzodiazepines are mediated through an enhancement of the GABAergic neurotransmission at inhibitory synapses. In the presence of benzodiazepines the affinity of the GABA receptor for the neurotransmitter is enhanced through positive allosteric modulation resulting in an increased action of released GABA on the postsynaptic transmembrane chloride ion flux.

Chemically, midazolam is a derivative of the imidazobenzodiazepine group. Although the free base is a lipophilic substance with low solubility in water.

The basic nitrogen in position 2 of the imidazobenzodiazepine ring system enables the active ingredient of Dormicum to form water-soluble salts with acids. These produce a stable and well tolerated injection solution.

This together with rapid metabolic transformation are the reasons for rapid onset and, because of rapid metabolic transformation, short duration of effects. Because of its low toxicity, midazolam has a wide therapeutic range.

After parenteral administration anterograde amnesia of short duration occurs (the patient does not recall events that occurred during the peak of activity of the compound).

Pharmacokinetics

Absorption after intramuscular injection
Absorption of midazolam from the muscle tissue is rapid and complete. Maximum plasma concentrations are reached within 30 minutes. Bioavailability is over 90%.

Absorption after rectal administration
Midazolam is absorbed quickly. Maximum plasma concentration is reached within 30 minutes. Bioavailability is about 50%.

Distribution
When midazolam is injected intravenously, the plasma concentration-time curve shows two distinct disposition phases. The volume of distribution calculated under steady-state conditions is 0.7-1.2 l/kg bodyweight. Studies show a protein binding of 96-98%.

In animals and humans, midazolam has been shown to cross the placenta and to enter fetal circulation. Small quantities of midazolam are found in human milk. Midazolam is not a substrate for drug transporters.

Metabolism
Midazolam is metabolized rapidly and completely. The primary metabolite is α-hydroxy-midazolam. The fraction of the dose extracted by liver has been estimated at 40-50%. Many medicaments have been found to inhibit the production of this metabolite in vitro. For some of these drugs, this has been confirmed in vivo (see Interactions).

Elimination
In young healthy volunteers, the elimination half-life of midazolam ranges from 1.5 to 2.5 hours. The elimination half-life of the metabolite is shorter than 1 hour; therefore after midazolam administration of the parent compound and the main metabolite decline in parallel. The metabolites are renally excreted. Plasma clearance of midazolam is in the range of 300-400 ml/min. When midazolam is given by i.v. infusion, its elimination kinetics do not differ from those following bolus injection. Repeated administrations of midazolam do not induce drug-metabolizing enzymes.

Pharmacokinetics in special clinical situations
In adults over 60 years of age, the elimination half-life may be prolonged up to three times and in some intensive-care patients requiring midazolam by i.v. infusion for long-term sedation, up to six times. In these patients infusion at an unchanged rate results in higher plasma levels at steady state.

The elimination half-life may also be prolonged in patients with congestive heart failure and with reduced hepatic function.
In children (3-10 years) the elimination half-life is between 1 and 1.5 hours.

In neonates the half-life of elimination is prolonged with a mean of 6 hours (3-12 hours) due to liver immaturity.

Indications and usage

Conscious sedation before diagnostic or therapeutic procedures with or without local anesthesia (i.v. administration).

Premedication before induction of anesthesia (i.m. or rectal administration in children).

Induction and maintenance of anesthesia. As an induction agent in inhalation anesthesia or a sedative component in combined anesthesia, including total intravenous anesthesia (i.v. injection, i.v. infusion).

Ataranalgesia in combination with ketamine in children (i.m. administration).

Long-term sedation in intensive care units (i.v. administration as bolus injection or continuous infusion).

Dosage and administration

Standard dosage
Midazolam is a potent sedative agent which requires slow administration and individualization of dosage.

The dose should be individualized and titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication.

In adults over 60 years of age, debilitated or chronically ill patients the dose should be determined with caution, the special factors relating to each patient being taken into consideration.

a) Intravenous conscious sedation
For basal (conscious) sedation prior to diagnostic or surgical intervention, Dormicum is administered i.v. The dose must be individualized and titrated and should not be administered by rapid or single bolus injection. The onset of sedation may vary individually depending on the physical status of the patient and the detailed circumstances of dosing (e.g. speed of administration, amount of dose). If necessary, subsequent doses may be administered according to the individual need.

The intravenous injection of Dormicum should be given slowly at a rate of approximately 1 mg in 30 seconds. The drug takes effect in about 2 minutes after the injection has been given.

In adults below the age of 60 the initial dose is 2.5 mg given 5 - 10 minutes before the beginning of the procedure.

Further doses of 1 mg may be given as necessary. Mean total doses have been found to range from 3.5-7.5 mg.

A total dose greater than 5 mg is usually not necessary.

In adults over 60 years of age, debilitated or chronically ill patients the initial dose must be reduced to 1-1.5 mg and given 5-10 minutes before the beginning of the procedure.

Further doses of 0.5-1 mg may be given as necessary. Since in these patients the peak effect may be reached less rapidly, additional Dormicum should be titrated very slowly and carefully.

A total dose greater than 3.5 mg is usually not necessary.

b) Anesthesia
Pre-medication: Pre-medication with Dormicum given shortly before a procedure does produce sedation (induction of sleepiness or drowsiness and relief of apprehension) and preoperative impairment of memory.

Dormicum can also be administered in combination with anticholinergics.

The pre-medication is usually administered 20-60 minutes before induction of anesthesia.

Intramuscular administration: In adults below the age of 60 the dose of Dormicum ranges from 0.07-0.1 mg/kg according to the general condition of the patient.

The usual dose is 5 mg.

In adults over 60 years of age, debilitated and chronically ill, the dose ranges from 0.025- 0.05 mg/kg.

The usual dose is 2-3 mg. In patients over 70 years i.m. Dormicum should be administered cautiously, under continuous observation, because excessive drowsiness may occur.

Children
In children between ages of 1 and 15 proportionally higher doses are required than in adults in relation to body weight. The dose range from 0.08-0.2 mg/kg bodyweight has been shown to be effective and safe.

Dormicum should be administered deep into a large muscle mass 30-60 minutes prior to the induction of anesthesia.

Rectal administration in children: The total dose of Dormicum ranging from 0.3-0.5 mg/kg bodyweight should be administered 20-30 minutes before induction of anesthesia.

Rectal administration of the ampoule solution is performed by means of a plastic applicator fixed on the end of the syringe.

If the volume to be administered is too small, water may be added up to a total volume of 10 ml.

Induction: If Dormicum is used for induction of anesthesia before other anesthetic agents have been administered, the individual response is variable. The dose should be titrated to the desired effect according to the patient's age and clinical status. When Dormicum is used before other i.v. agents for induction of anesthesia, the initial dose of each agent may be significantly reduced, at times to as low as 25% of the usual initial dose of the individual agents.

The desired level of anesthesia is reached by stepwise titration.

The intravenous induction dose of Dormicum should be given slowly in increments.

Each increment of not more than 5 mg should be injected over 20 - 30 seconds allowing 2 minutes between successive increments.

In pre-medicated adults below the age of 60 the dose can range from 0.15-0.2 mg/kg but a total dose greater than 15 mg is usually not necessary.

In non pre-medicated adults below the age of 60 the dose may be higher (0.3-0.35 mg/kg bodyweight), but a total dose greater than 20 mg is usually not necessary. If needed to complete induction, increments of approximately 25% of the patient's initial dose may be used. Induction may instead be completed with volatile liquid inhalational anesthetics. In resistant cases, a total dose of up to 0.6 mg/kg may be used for induction, but such larger doses may prolong recovery.

In adults over 60 years of age, debilitated and chronically ill patients lower doses will be required.

Dormicum is not recommended for the induction of anesthesia in children, as experience is limited.

Maintenance: The maintenance of the desired level of unconsciousness can be achieved by either further intermittent doses or continuous infusion of intravenous Dormicum typically in combination with analgesics.

The maintenance dose usually ranges from 0.03-0.1 mg/kg/hr when used in combination with narcotics or ketamine.

In adults over 60 years of age, debilitated or chronically ill patients lower maintenance doses will be required.

In children receiving ketamine for anesthesia (ataranalgesia), an intramuscular dose of Dormicum of 0.15 - 0.20 mg/kg is recommended.

A sufficiently deep level of sleep is generally achieved after 2-3 minutes.

c) Intravenous sedation in the intensive care unit
The desired level of sedation is reached by stepwise titration of Dormicum followed by either continuous infusion or intermittent bolus.

The intravenous *loading dose* should be given slowly in increments.

Each increment of 1-2.5 mg should be injected over 20-30 seconds allowing 2 minutes between successive increments.

The intravenous loading dose can range from 0.03-0.3 mg/kg but a total dose greater than 15 mg is usually not necessary.

In hypovolemic, vasoconstricted or hypothermic patients the loading dose should be reduced or omitted.

The *maintenance dose* can range from 0.03-0.2 mg/kg/hr.

The level of sedation should be assessed regularly if permitted by patient's condition.

In hypovolemic, vasoconstricted or hypothermic patients the maintenance dose should be reduced, at times to as low as 25 % of the usual dose.

When Dormicum is given with potent analgesics, the latter should be administered first so that the sedative effects of Dormicum can be safely titrated on top of any sedation caused by the analgesic.

Special dosage instructions
Compatibility with infusion solutions: The Dormicum ampoule solution can be diluted with sodium chloride 0.9 %, dextrose 5 % and 10 %, levulose 5 %, Ringer's solution and Hartmann's solution in a mixing ratio of 15 mg midazolam per 100-1000 ml infusion solution. These solutions remain physically and chemically stable for 24 hours at room temperature, or 3 days at 5 °C (see also Special remarks).

The Dormicum Ampoule solution should not be diluted with Macrodex 6 % in Dextrose or mixed with alkaline injections.

Patients with renal impairment

In patients with severe renal impairment, Dormicum may be accompanied by more pronounced and prolonged sedation possibly including clinically relevant respiratory and cardiovascular depression. Dormicum should therefore be dosed carefully in the patient population and titrated for the desired effect.

Hepatic Impairment

The clinical effects in patients with hepatic impairment may be stronger and prolonged. The dose of midazolam may have to be reduced and vital signs should be monitored.

Contraindications

Dormicum must not be used in patients with known hypersensitivity to benzodiazepines or any of their formulation excipients.

Precautions

Dormicum ampoules should be used only when resuscitation facilities are available.
Benzodiazepines are not recommended for the primary treatment of psychotic illness.

Special caution should be exercised when administering Dormicum parenterally to patients representing a higher risk group:

- adults over 60 years of age
- debilitated or chronically ill patients
- patients with obstructive pulmonary disease
- patients with chronic renal failure
- patients with impaired hepatic function (benzodiazepines may precipitate or exacerbate encephalopathy in patients with severe hepatic impairments)
- patients with congestive heart failure
- pediatric patients with cardiovascular instability

These higher risk patients require lower dosages (see Dosage and administration) and should be continuously monitored for early signs of alterations of vital functions.

Concomitant use of alcohol / CNS depressants
The concomitant use of Dormicum with alcohol or/and CNS depressants should be avoided. Such concomitant use has the potential to increase the clinical effects of Dormicum possibly including severe sedation that could result in coma or death, clinically relevant respiratory and/or cardiovascular depression (see Interactions).

Medical history of alcohol or drug abuse
Dormicum should be avoided in patients with a medical history of alcohol or drug abuse.

As with any substance with CNS depressant and/or muscle-relaxant properties, particular care should be taken when administering Dormicum to a patient with myasthenia gravis, owing to pre-existing muscle weakness.

Tolerance
Some loss of efficacy has been reported when Dormicum has been used as long-term sedation in intensive care units (ICU).

Dependence
When Dormicum is used in long-term sedation in ICU, it should be borne in mind that physical dependence on Dormicum may develop. The risk of dependence increases with dose and duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

Withdrawal symptoms
During prolonged treatment with Dormicum ampoules in ICU, physical dependence may develop. Therefore, abrupt termination of the treatment will be accompanied by withdrawal symptoms. The following symptoms may occur: headaches, diarrhea, muscle pain, extreme anxiety, tension, restlessness, confusion, irritability, sleep disturbances, mood changes, hallucinations and convulsions. Since the risk of withdrawal symptoms is greater after abrupt discontinuation of treatment, it is recommended that the dose is decreased gradually. In severe cases, the following symptoms may occur: depersonalization, numbness and tingling of the extremities, hypersensitivity to light, noise and physical contact.

Amnesia
Anterograde amnesia may occur with therapeutic doses, with the risk increasing at higher dosages (frequently this effect is very desirable in situations such as before and during surgical and diagnostic procedures), the duration of which is directly related to the administered dose. Prolonged amnesia can present problems in outpatients, who are scheduled for discharge following intervention. After receiving Dormicum parenterally, patients should be discharged from hospital or consulting room only if accompanied by an attendant.

"Paradoxical" reactions
Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic convulsions and muscle tremor), hyperactivity, hostility, delusion, anger, aggressiveness, anxiety, nightmares, hallucinations, psychoses, inappropriate behaviour and other adverse behavioural effects, paroxysmal excitement and assault, have been reported to occur with Dormicum. The highest incidence of susceptibility to such reactions has been reported among children and the elderly. Should this be so, discontinuation of the drug should be considered.

Should such symptoms suggestive of a paradoxical reaction occur, the response to Dormicum should be evaluated before proceeding.

Drug elimination may be delayed in patients receiving compounds which inhibit certain hepatic enzymes (particularly cytochrome P 450 III A), in patients with liver dysfunction, low cardiac output and in neonates.

Sleep Apnoea

Dormicum ampoules should be used with extreme caution in patients with sleep apnoea syndrome and patients should be regularly monitored.

Adverse hemodynamic events have been reported in pediatric patients with cardiovascular instability; rapid intravenous administration should be avoided in this population.

Preterm infants and neonates
Due to an increased risk of apnea, extreme caution is advised when sedating preterm and former preterm patients whose trachea is not intubated.

Rapid injection should be avoided in the neonatal population.

The neonate also has reduced and/or immature organ function and is also vulnerable to profound and/or prolonged respiratory effects of Dormicum.

Effects on ability to drive or use machines
Sedation, amnesia, impaired concentration and impaired muscular function adversely affect the ability to drive or use machines. Prior to receiving Dormicum, the patient should be warned not to drive a vehicle or operate a machine for at least 12 hours.
If sleep duration is insufficient or alcohol is consumed, the likelihood of impaired alertness may be increased.

Cognitive deficits
Some published studies in children have observed cognitive deficits after repeated or prolonged exposures to anaesthetic/sedative agents early in life. These studies have substantial limitations, and it is not clear if the observed effects are due to the anaesthetic/sedation drug administration or other factors such as the surgery or underlying illness.

Pregnancy, nursing mothers
Insufficient data are available on midazolam to assess its safety during pregnancy. Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. If, exceptionally, it is considered by a physician that administration of the medical product during labour or delivery is essential, effects on the neonate such as hypothermia, hypotonia, poor sucking and moderate respiratory depression can be expected, due to the pharmacological action of the product. Moreover, infants born to mothers who received benzodiazepines chronically during the latter stage of pregnancy may have developed physical dependence and may be at some risk of developing withdrawal symptoms in the postnatal period.

Since midazolam passes into breast milk, Dormicum should not be administered to breast-feeding mothers.
An increased risk of congenital malformation associated with the use of benzodiazepines during the first trimester of pregnancy has been suggested.

Undesirable effects
The following undesirable effects have been reported to occur when Dormicum is injected:

Immune System Disorders: generalized hypersensitivity reactions (skin reactions, cardiovascular reactions, bronchospasm), angioedema, anaphylactic shock.

Psychiatric Disorders: Confusional state, disorientation, emotional and mood disturbances. Changes in libido have been reported occasionally.

Paradoxical reactions such as restlessness, agitation, irritability, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity, nervousness, hostility, anger, aggressiveness, anxiety, nightmares, abnormal dreams, hallucinations, psychoses, inappropriate behavior and other adverse behavioural effects, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Dependence
Use of Dormicum - even in therapeutic doses - may lead to the development of physical dependence. After prolonged i.v. administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions.
Abuse has been reported in poly-drug abusers.

Nervous System Disorder: Drowsiness, Prolonged sedation, decreased alertness, headache, dizziness, ataxia, postoperative sedation, anterograde amnesia, the duration of which is directly related to the administered dose. Anterograde amnesia may still be present at the end of the procedure and in isolated cases prolonged amnesia has been reported.

Convulsions have been reported in premature infants and neonates.

Cardiac Disorders: Severe cardiorespiratory adverse events have occurred on rare occasions. These have included cardiac arrest, hypotension, bradycardia, vasodilating effects, slight increase in heart rate. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see Precautions).

Dormicum ampoules should be used only when resuscitation facilities are available.

Respiratory Disorders: Severe cardiorespiratory adverse events have occurred on rare occasions. These have included respiratory depression, apnea, respiratory arrest, dyspnea, laryngospasm. Life-threatening incidents are more likely to occur in adults over 60 years of age and those with pre-existing respiratory insufficiency or impaired cardiac function, particularly when the injection is given too rapidly or when a high dosage is administered (see Precautions). Hiccup.

Dormicum ampoules should be used only when resuscitation facilities are available.

Gastrointestinal System Disorders: Nausea, vomiting, constipation, dry mouth.

Skin and Appendages Disorders: Skin rash, urticaria, pruritus.

General and Application Site Disorders: Fatigue, erythema and pain on injection site, thrombophlebitis, thrombosis.

Injury, poisoning and procedural complications: There have been reports of falls and fractures in benzodiazepine users. The risk is increased in those taking concomitant sedatives (including alcoholic beverages) and in the elderly.

Interactions with other Medicinal Products and other Forms of Interaction
Pharmacokinetic Drug-Drug Interactions (DDI)

Midazolam is almost exclusively metabolized by cytochrome P450 3A4 (CYP3A4, CYP3A5). Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. No other mechanism than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic drug-drug interaction with midazolam. Midazolam is not known to change the pharmacokinetics of other drugs. When co-administered with a CYP3A inhibitor, the clinical effects of midazolam may be stronger and also longer lasting and a lower dose may be required. Conversely the effect of midazolam may be weaker and last shorter when co-administered with a CYP3A inducer and a higher dose may be required.

In case of CYP3A induction and irreversible inhibition (so-called mechanism-based inhibition), the effect on the pharmacokinetics of midazolam may persist for several days up to several weeks after administration of the CYP3A modulator. Examples of mechanism-based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); antiretroviral agents (e.g. HIV protease inhibitors such as ritonavir (including ritonavir-boosted protease inhibitors), delavirdine); calcium channel blockers (e.g., verapamil, diltiazem); tyrosine kinase inhibitors (e.g., imatinib, lapatinib, idelalisib); or the oestrogen receptor modulator raloxifene and several herbal constituents (e.g. bergamottin). In contrast to other mechanism-based inhibitors, ethinyloestradiol combined with norgestrel or gestodene, used for oral contraception and grapefruit juice (200 ml) did not modify exposure to midazolam to a clinically significant degree.

The range of the inhibiting / inducing potency of drugs is wide. The antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentrations of i.v. midazolam by about 5- fold. The tuberculostatic drug rifampicin belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the plasma concentrations of intravenous midazolam by about 60%.

The administration route of midazolam also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation: (i) The change in plasma concentrations is expected to be less for intravenous compared to oral administration of midazolam because CYP3A modulation is not confined to the liver but also occurs in the intestinal wall and hence not only affects the systemic clearance, but also the bioavailability of oral midazolam. (ii) There are no studies investigating the effect of CYP3A modulation on the pharmacokinetics of midazolam after rectal and intramuscular administration, respectively. As after rectal administration the drug partly bypasses the liver and the expression of CYP3A in the colon is less compared to the upper gastro-intestinal tract, it is expected that the change in midazolam plasma concentrations due to CYP3A modulation will be less for the rectal than for the oral route of administration. As after intramuscular administration the drug directly enters systemic circulation, it is expected that the effects of CYP3A modulation will be similar to those for intravenous midazolam. (iii) In line with pharmacokinetic principles, clinical studies have shown that after i.v. single dose of midazolam the change in the maximum clinical effect due to CYP3A modulation will be minor while the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect will be increased in the presence of CYP3A inhibition.

The following listing gives examples of clinical pharmacokinetic drug-drug interactions with midazolam after intravenous administration. Importantly, any drug shown to possess CYP3A modulating effects in vitro and in vivo, respectively, has the potential to change the plasma concentrations of midazolam and therefore its effects. The listing includes information from clinical drug-drug interaction studies for oral midazolam in case that for the co-administered drug in question no information on intravenous midazolam is available. However, as outlined above the change in plasma concentrations is expected to be less for intravenous compared to oral midazolam.

Azole antifungals

• Ketoconazole and voriconazole increased the plasma concentrations of intravenous midazolam by 5-fold and by 3-4-fold respectively, while the terminal half-life increased by about 3-fold. If parenteral midazolam is co-administered with these strong CYP3A inhibitors, it should be done in an intensive care unit (ICU) or similar setting which ensures close clinical monitoring and appropriate medical management in case of respiratory depression and/or prolonged sedation. Staggered dosing and dosage adjustment should be considered, especially if more than a single i.v. dose of midazolam is administered.

• Fluconazole and itraconazole both increased the plasma concentrations of intravenous midazolam by 2 – 3-fold associated with an increase in terminal half-life by 2.4-fold for itraconazole and 1.5-fold for fluconazole, respectively.

• Posaconazole increased the plasma concentrations of intravenous midazolam by about 2-fold.

Macrolide antibiotics

• Erythromycin resulted in an increase in the plasma concentrations of intravenous midazolam by about 1.6 – 2-fold associated with an increase in midazolam's terminal half-life by 1.5 – 1.8-fold.

• Clarithromycin increased midazolam's plasma concentrations by up to 2.5-fold associated with an increase in terminal half-life by 1.5 – 2-fold.

Additional information from oral midazolam

• Telithromycin increased the plasma levels of oral midazolam 6-fold.

• Roxithromycin: The roxithromycin effects on midazolam's pharmacokinetics are less compared to erythromycin and clarithromycin. After oral administration, the plasma concentrations of midazolam were increased by about 50% compared to a 4.4- and 2.6- fold increase caused by erythromycin and clarithromycin, respectively. The mild effect on the terminal half-life of midazolam by about 30% indicates that the effects of roxithromycin on intravenous midazolam may be minor.

Intravenous anesthetics

• Disposition of intravenous midazolam was also changed by intravenous propofol (AUC and half-life increased by 1.6-fold).

Protease inhibitors

• Saquinavir and other HIV protease inhibitors: Upon co-administration with ritonavir-boosted lopinavir, the plasma concentrations of intravenous midazolam increased by 5.4-fold, associated with a similar increase in terminal half-life. If parenteral midazolam is co-administered with HIV protease inhibitors, treatment setting should follow the description in the section above for ketoconazole within azole antifungals.

• HCV protease inhibitors: Boceprevir and telaprevir reduce midazolam clearance. This effect resulted in a 3.4-fold increase of midazolam AUC after i.v. administration and prolonged its elimination half-life 4-fold.

Histamine receptor 2 antagonists

• Cimetidine increased the steady state plasma concentrations of midazolam by 26%.

Calcium-channel blockers

• Diltiazem: A single dose of diltiazem given to patients undergoing coronary artery bypass grafting increased the plasma concentrations of intravenous midazolam by about 25% and the terminal half-life was prolonged by about 43%. This was less than the 4-fold increase seen after oral administration of midazolam.

Additional information from oral midazolam

• Verapamil increased the plasma concentrations of oral midazolam by 3-fold. The terminal half-life of midazolam was increased by 41%.

Various drugs/Herbs

• Atorvastatin resulted in a 1.4-fold increase in plasma concentrations of i.v. midazolam compared to control group.

• Intravenous fentanyl is a weak inhibitor of midazolam's elimination: AUC and half-life of i.v. midazolam were increased by 1.5-fold in presence of fentanyl.

Additional information from oral midazolam

• Fluvoxamine resulted in a mild increase in plasma concentrations of oral midazolam (28%) while the terminal half-life doubled.

Nefazodone increased the plasma concentrations of oral midazolam by 4.6-fold with an increase in terminal half-life by 1.6-fold.

• Tyrosine kinase inhibitors have been shown either in vitro (imatinib, lapatinib or after oral administration in vivo (idelalisib) to be potent inhibitors of CYP3A4. After concomitant administration of idelalisib, oral midazolam exposure was increased on average 5.4-fold.

• NK1 receptor antagonists (aprepitant, netupitant, casoprepitant) dose dependently increased the plasma concentrations of oral midazolam up to about 2.5-3.5-fold and increased terminal half-life by approximately 1.5-2-fold.

• Chlorzoxazone decreased the ratio of the CYP3A generated metabolite 1'- hydroxymidazolam (also known as α-hydroxymidazolam) to midazolam indicating a CYP3A inhibiting effect.

• For a number of drugs or herbal medicines, a weak interaction with midazolam's elimination was observed with concomitant changes in its exposure (< 2-fold change in AUC) (bicalutamide, everolimus, cyclosporine, simeprevir, propiverine, berberine as also contained in goldenseal). These weak interactions are expected to be further attenuated after i.v. administration.

Drugs that induce CYP3A

• Rifampicin decreased the plasma concentrations of intravenous midazolam by about 60% after 7 days of rifampicin 600 mg o.d. The terminal half-life decreased by about 50-60%.

• Ticagrelor is a weak CYP3A inducer but has only small effects on intravenously administered midazolam (-12%) and 4-hydoxy-midazolam (-23%) exposures.

Additional information from oral midazolam

• Carbamazepine / phenytoin: Repeat dosages of carbamezepine or phenytoin resulted in a decrease in plasma concentrations of oral midazolam by up to 90% and a shortening of the terminal half-life by about 60%.

• The very strong CYP3A4 induction seen after mitotane or enzalutamide resulted in a profound and long-lasting decrease of midazolam levels in cancer patients. AUC of orally administered midazolam was reduced to 5% and 14% of normal values respectively.

• Clobazam and Efavirenz are weak inducers of midazolam metabolism and reduce the AUC of the parent compound by approximately 30%. There is a resulting 4-5-fold increase in the ratio of the active metabolite (α-hydroxy-midazolam) to the parent compound but the clinical significance of this is unknown.

• Vemurafenib modulates CYP isozymes and inhibits CYP3A4 mildly: Repeat-dose administration resulted in a mean decrease of oral midazolam exposure of 32% (up to 80% in individuals).

Herbs and food

• Echinacea purpurea root extract decreased plasma concentrations (AUC) of i.v. midazolam by 20% associated with a decrease in half-life of about 42%.

• St John's wort decreased plasma concentrations of midazolam by about 20 - 40 % associated with a decrease in terminal half-life of about 15 - 17%.

Additional information from oral midazolam

• Quercetin (also contained in Gingko biloba) and Panax ginseng both have weak enzyme inducing effects and reduced exposure to midazolam after its oral administration to the extent of 20-30%.

Acute protein displacement

• Valproic acid: Increased concentrations of free midazolam due to displacement from plasma protein binding sites by valproic acid cannot be excluded although the clinical relevance of such an interaction is not known.

Pharmacodynamic Drug-Drug Interactions (DDI)

The co-administration of midazolam with other sedative / hypnotic agents, including alcohol, is likely to result in increased sedative / hypnotic effects. Examples include opiates / opioids (when they are used as analgesics, antitussives or substitutive treatments), antipsychotics, other benzodiazepines used as anxiolytics or hypnotics, barbiturates, propofol, ketamine, etomidate; sedative antidepressants, antihistaminics and centrally acting antihypertensive drugs. Midazolam decreases the minimum alveolar concentration (MAC) of inhalational anaesthetics.

Enhanced side effects such as sedation and cardio-respiratory depression may also occur when midazolam is co-administered with any centrally acting depressants including alcohol. Alcohol should be avoided in patients receiving midazolam.

See section Overdose for warning of other central nervous system depressants, including alcohol.

It has been shown that spinal anaesthesia can increase the sedative effect of i.v. midazolam. The midazolam dose may therefore have to be reduced. When lidocaine or bupivacaine, were administered intramuscularly, the dose of i.v. midazolam required for sedation was reduced.

Drugs increasing alertness / memory, e.g. physostigmine, reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effects of midazolam.

Non-clinical studies/Animal toxicology

Published animal studies of some anaesthetic/sedation drugs have reported adverse effects on brain development in early life and late pregnancy. These studies have demonstrated that anaesthetic and sedation drugs that block N-methyl-D-aspartate (NMDA) receptors and/or potentiate gamma-aminobutyric acid (GABA) activity during the period of rapid brain growth or synaptogenesis may result in neuronal and oligodendrocyte cell loss in the developing brain and alterations in synaptic morphology and neurogenesis when used for longer than 3 hours. The clinical significance of these non-clinical findings is yet to be determined. However, based on comparisons across species, the window of vulnerability to these changes is believed to correlate with exposures in the third trimester through the first several months of life, but may extend out to approximately 3 years of age in humans.

Overdosage

Symptoms

Benzodiazepines commonly cause drowsiness, ataxia, dysarthria and nystagmus. Overdose of Dormicum is seldom life-threatening if the drug is taken alone, but may lead to areflexia, apnea, hypotension, cardiorespiratory depression and in rare cases to coma. Coma, if it occurs, usually lasts a few hours but it may be more protracted and cyclical, particularly in elderly patients. Benzodiazepine respiratory depressant effects are more serious in patients with respiratory disease. Benzodiazepines increase the effects of other central nervous system depressants, including alcohol.

Treatment

Monitor the patient's vital signs and institute supportive measures as indicated by the patient's clinical state. In particular, patients may require symptomatic treatment for cardiorespiratory effects or central nervous system effects.

If taken orally further absorption should be prevented using an appropriate method e.g. treatment within 1-2 hours with activated charcoal. If activated charcoal is used airway protection is imperative for drowsy patients. In case of mixed ingestion gastric lavage may be considered, however not as a routine measure.

If CNS depression is severe consider the use of flumazenil (Anexate®), a benzodiazepine antagonist. This should only be administered under closely monitored conditions. It has a short half-life (about an hour), therefore patients administered flumazenil will require monitoring after its effects have worn off. Flumazenil is to be used with extreme caution in the presence of drugs that reduce seizure threshold (e.g. tricyclic antidepressants). Refer to the prescribing information for flumazenil (Anexate®), for further information on the correct use of this drug.

Special remarks

Incompatibilities

Do not dilute Dormicum ampoule solutions with 6% Dextran 70 in dextrose.

Do not mix Dormicum ampoule solutions in alkaline injections. Midazolam precipitates in sodium bicarbonate.

Storage

Dormicum ampoules should not be frozen because they can burst. Furthermore, precipitation can occur which dissolves on shaking at room temperature.

Stability

This medicine should not be used after the expiry date (EXP) shown on the pack.

Packs

Ampoules 15 mg in 3 ml	5
Ampoules 5 mg in 5 ml	10

Medicine: Keep out of reach of children

Current at May 2020

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