

MIDAZOLAM

Alphapharm

Midazolam



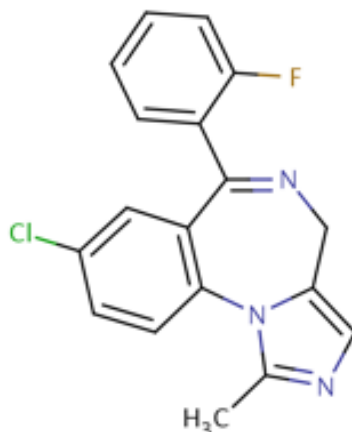
PRODUCT INFORMATION

NAME OF THE MEDICINE

Active ingredient : Midazolam

Chemical name : 8-chloro-6-(2-fluorophenyl)-1-methyl-4H-imidazo [1,5-a][1,4] benzodiazepine

Structural formula :



Molecular formula : C₁₈H₁₃ClFN₃

Molecular weight : 325.8

CAS Registry no. : 59467-70-8

DESCRIPTION

MIDAZOLAM Alphapharm midazolam solution for injection is available as a 5 mg/ 5 mL, 5 mg/ 1 mL, 15 mg/ 3 mL and 50 mg/ 10 mL solution. It also contains the excipients sodium chloride (isotonic agent), hydrochloric acid and sodium hydroxide (for pH adjustment) and water for injections.

MIDAZOLAM Alphapharm solution for injection is a clear, colourless solution. The free base of the active substance of MIDAZOLAM Alphapharm is a lipophilic substance with low solubility in water. The basic nitrogen in position 2 of the imidazobenzodiazepine ring enables the active substance, midazolam to form water-soluble salts with acids. These produce a stable injection solution.

PHARMACOLOGY

MIDAZOLAM Alphapharm belongs to the Benzodiazepine class of drugs.

Midazolam acts as a central nervous system depressant that induces sedation, hypnosis, anaesthesia and amnesia. Like all benzodiazepines, midazolam also induces muscle relaxation. Pharmacokinetic and pharmacodynamic data in chronic intravenous usage are not available beyond 15 days.

Pharmacodynamics

The mode of action of the benzodiazepines is under constant investigation. Benzodiazepines appear to increase the physiological inhibitory mechanisms mediated by gamma-aminobutyric acid (GABA), which is the most common inhibitory neurotransmitter in the brain.

The effects of midazolam on the CNS are dependent on the dose administered, the route of administration and the presence or absence of other premedications. After intramuscular administration, the onset time of sedative effects is 15 minutes. Peak sedation occurs 30 to 60 minutes following administration.

When used intravenously (as a sedative for endoscopic or other short therapeutic or diagnostic procedures), the end point of slurred speech is reached within 2.8 to 4.8 minutes. This end point is dependent on the total dose administered and whether or not it is preceded by opioid premedication. The time to induction of anaesthesia for surgical procedures is variable, occurring in approximately 1.5 minutes (0.3 - 8 minutes) subsequent to the administration of an opioid premedicant and in 2 to 2.5 minutes without premedication or with a sedative premedication.

Approximately two hours are required for full recovery from midazolam-induced anaesthesia. Duration of effect is dependent on the dose and the other drugs used. Induction of anaesthesia after administration of midazolam alone is ineffective in approximately 14% of patients, however, when given with an opioid it is ineffective in about 1% of patients.

At doses sufficient to induce sedation, intravenous midazolam decreases the sensitivity of the ventilatory response to elevated CO₂ tension in normal subjects and in those with chronic obstructive lung disease, who are at special risk of hypoxia. Sedation with midazolam has no adverse effects on pulmonary compliance and does not cause bronchoconstriction or significantly affect functional residual capacity or residual volume.

Midazolam may cause a modest decrease in mean arterial pressure. Baroreceptor response is not affected and decreases in arterial pressure are accompanied by increases in heart rate. Intravenous midazolam at doses of 0.15 to 0.2 mg/kg did not have a harmful effect on cardiac haemodynamics.

Unless the patient is intubated, intravenous administration of midazolam does not alter intracranial pressure. As with thiopentone, the intracranial pressure rises during intubation. Cerebral blood flow may be reduced by up to 35%, which is of the same order as caused by equivalent doses of diazepam. The effect on cerebral metabolism is not clearly established.

Midazolam reduces the intraocular pressure to the same degree as thiopentone and diazepam. However, the increase in intraocular pressure after succinylcholine administration or endotracheal intubation is not prevented by midazolam, thiopentone or diazepam.

Pharmacokinetics

Distribution

The pharmacokinetic profile of midazolam in man is linear over the 0.05 to 0.4 mg/kg dose range. The volume of distribution of midazolam at steady state is 0.6 – 1.9L/kg.

Midazolam is 97% plasma protein bound. The extent of protein binding does not vary in renal failure.

Bioavailability

Absorption of midazolam from the muscle tissue is rapid and virtually complete.

Following intramuscular administration, the mean absolute bioavailability of midazolam is greater than 90%. Following intramuscular dosing, the mean time of maximum midazolam plasma concentrations occurs within 45 minutes post-administration. Peak concentrations of midazolam as well as 1-hydroxymethyl midazolam after intramuscular administration are about one-half of those achieved after equivalent intravenous doses.

Metabolism

Less than 0.03% is excreted in the urine unchanged. The drug is rapidly metabolised to the active metabolite, 1-hydroxymethyl midazolam, which is conjugated with subsequent excretion in the urine. The elimination half-life of the active metabolite is similar to that of parent drug. The concentration of midazolam is 10 to 30 times greater than that of 1-hydroxymethyl midazolam.

Elimination

In normal subjects the mean elimination half-life of midazolam is between 1.4 – 2.4 h and the clearance is in the range of 220 – 470 mL/min. Midazolam is mainly excreted by renal route: 60 – 80% of the administered dose of midazolam is excreted in urine as glucoconjugated α -hydroxymidazolam. The elimination half-life of this metabolite is < 1 h.

Compounds that inhibit or induce cytochrome P450 3A4 (CYP3A) may alter patients' elimination of midazolam, and the dose may need to be adjusted accordingly (see **PRECAUTIONS - Interactions with Other Medicines**).

Pharmacokinetics in Special Populations

Elderly:

In adults over 60 years of age, the elimination half-life of midazolam may be prolonged up to four times.

Renal impairment:

The free fraction of midazolam in chronic renal failure may be significantly higher than normal. After correcting for protein binding the pharmacokinetics of unbound midazolam is similar to that reported in healthy volunteers.

Critically ill:

Midazolam elimination half-life is prolonged in critically ill patients.

Cardiac insufficiency:

Midazolam elimination half-life is prolonged in patients with congestive heart failure.

Obese:

The elimination half-life of midazolam is prolonged in obese patients. The clearance is not altered.

In patient populations with prolonged elimination half-life, midazolam infusion at an unchanged rate resulted in higher plasma levels at steady state. Consequently, the infusion rate should be reduced once a satisfactory clinical response has been obtained.

INDICATIONS

Intravenously as an agent for:

- conscious sedation prior to short surgical, diagnostic, therapeutic or endoscopic procedures such as bronchoscopy, gastroscopy, cystoscopy, coronary angiography and cardiac catheterisation, either alone or in conjunction with an opioid
- induction of anaesthesia preliminary to administration of other anaesthetic agents. With the use of an opioid premedicant, induction of anaesthesia can be obtained with a narrower dose range and in a shorter period of time.

Intermittent intravenous administration or continuous infusion for:

- sedation in intensive care units

Intramuscularly for:

- preoperative sedation (induction of sleepiness or drowsiness and relief of apprehension) and to impair memory of perioperative events

CONTRAINDICATIONS

- Patients with a hypersensitivity to benzodiazepines
- Patients in shock, coma or in acute alcoholic intoxication with depression of vital signs
- Patients with acute narrow angle glaucoma. Benzodiazepines may be used in patients with open angle glaucoma only if they are receiving appropriate therapy. Measurements of intraocular pressure in patients without eye disease show a moderate lowering following induction with midazolam. Patients with glaucoma have not been studied.
- Myasthenia gravis

PRECAUTIONS

Intravenous midazolam should only be used in settings with equipment and skilled personnel for continuous monitoring of cardio-respiratory function and resuscitation procedures.

Midazolam must never be used without individualisation of dosage. Midazolam should not be administered by rapid or single bolus intravenous administration (see DOSAGE AND ADMINISTRATION). Extravasation should also be avoided. The hazards of intra-arterial injection of midazolam solutions into humans are unknown; therefore, precautions against unintended intra-arterial injection should be taken.

Patients should be continuously monitored for early signs of under-ventilation or apnoea. Vital signs should continue to be monitored during the recovery period. During intravenous application of midazolam, respiratory depression, apnoea, respiratory arrest and/or cardiac arrest have occurred. In some cases where this was not recognised promptly and treated, hypoxic encephalopathy or death has resulted. These life-threatening incidents may occur, especially if the injection is given too rapidly or with excessive doses. Particular care must be used in administering the drug, by the intravenous route, to the elderly, to very ill patients, high risk surgical patients and to those with significant hepatic impairment, chronic renal insufficiency, congestive heart failure, or with limited pulmonary reserve because of the possibility that apnoea or respiratory depression may occur. These patients require lower doses whether premedicated or not.

Preoperative sedation: Adequate observation of the patient after preoperative sedation of midazolam is mandatory as individual sensitivity varies and symptoms of overdose may occur.

Patients with chronic obstructive pulmonary disease are unusually sensitive to the respiratory depressant effect of midazolam.

Elderly patients frequently have inefficient function of one or more organ systems and dosage requirements have been shown to be reduced with age. Patients with chronic renal failure and patients with congestive heart failure eliminate midazolam more slowly.

In some intensive care patients, and in some elderly patients given midazolam by intravenous infusion for prolonged sedation, the elimination half-life was found to increase by up to four times (see **PHARMACOLOGY – Pharmacokinetics, Pharmacokinetics in Special Populations**).

Particular care should be exercised in the use of intravenous midazolam in patients with uncompensated acute illnesses, such as severe fluid or electrolyte disturbances.

There have been rare reports of hypotensive episodes requiring treatment during or after diagnostic or surgical manipulations in patients who have received midazolam. In conscious sedation studies, hypotension occurred more frequently in patients premedicated with a narcotic.

After prolonged intravenous administration of midazolam, abrupt discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended.

Reactions such as agitation, involuntary movements (including tonic/clonic movements and muscle tremor), hyperactivity and combativeness have been reported. These reactions may be due to inadequate or excessive dosing or improper administration of midazolam; however, consideration should be given to the possibility of cerebral hypoxia or true paradoxical reactions. If midazolam is the suspected cause, the use of the drug should be discontinued and all other drugs, including local anaesthetics, should be evaluated before proceeding.

Concomitant use of barbiturates, alcohol or other central nervous system depressants increases the risk of under-ventilation or apnoea and/or cardio-ventricular depression and may contribute to a profound and/or prolonged drug effect. When midazolam is used with a narcotic analgesic, the dosage of both agents should be reduced. Narcotic premedication also reduces the ventilatory response to carbon dioxide stimulation.

Midazolam does not protect against the increase in intracranial pressure or against the heart rate rise and/or blood pressure rise associated with endotracheal intubation under light general anaesthesia.

Since an increase in cough reflex and laryngospasm may occur with per oral endoscopic procedures, the use of a topical anaesthetic agent and the availability of necessary counter measures are recommended. The use of a narcotic premedicant is recommended for bronchoscopies.

Administration of a muscle relaxant may sometimes be necessary to overcome midazolam-associated hiccoughs.

As with other benzodiazepines, midazolam may have the potential to cause dependence. Benzodiazepines should be avoided in patients with a history of alcohol or drug abuse. The risk of dependence increases with the duration of treatment; it is also greater in patients with a medical history of alcohol and/or drug abuse.

After parenteral administration of midazolam, patients should not be discharged from hospital for at least 3 hours, and responsibility for medical supervision of discharge shall lie with a physician (preferably the treating physician) and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle must be individualised. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the contribution of these can vary and should also be considered.

Effects on Fertility

A reproduction study in male and female rats did not show any impairment of fertility at dosages up to 10 times the human IV dose of 0.35 mg/kg.

Use in Pregnancy: Category C

Benzodiazepines should be avoided during pregnancy unless there is no safer alternative. Midazolam crosses the placenta and the administration of midazolam in the last weeks of pregnancy or at high doses during labour have resulted in neonatal CNS depression and can be expected to cause irregularities in the foetal heart rate, hypothermia, hypotonia, poor sucking and moderate respiratory depression 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. Midazolam is therefore not recommended for obstetric use.

Teratological studies with midazolam in a number of animal species have not shown association between administration of the drug and disturbances of foetal development, nor has clinical experience so far yielded any evidence of such an association. However, like any other drug, midazolam should not be used in the first three months of pregnancy unless considered absolutely necessary by the physician.

Australian Categorisation Definition of Category C: Drugs 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. Accompanying texts should be consulted for further details.

Use in Lactation

There is evidence that midazolam is excreted in breast milk and its effects on the new born are not known. Therefore midazolam is not recommended or use in nursing mothers.

Paediatric use

The safety and effectiveness of midazolam in children under the age of 8 have not been established. Pharmacokinetics in children have not been established and may differ from adults.

Use in the elderly

The risk for falls and fractures is increased in elderly benzodiazepine users.

Driving, operating machinery and other activities requiring mental alertness

Following administration of midazolam, patients should not be discharged from hospital for at least three hours and then, if possible, only if accompanied by a responsible person. The decision as to when patients may again engage in activities requiring complete mental alertness, operate hazardous machinery or drive a motor vehicle will depend on the individual. Gross tests of recovery from the effects of midazolam cannot be relied upon to predict reaction time under stress. When midazolam is used with other drugs during anaesthesia, the role of these can vary and should be considered accordingly.

Patients should be warned to take extra care as a pedestrian and not to drive a vehicle or operate machinery until effects such as drowsiness, have subsided or until the day after anaesthesia and surgery, whichever is longer. The physician should decide when activities such as driving a vehicle or operating a machine may be resumed. The patient's attendants should be made aware that anterograde amnesia may continue longer than the sedation and therefore patients may not carry out instructions even though they appear to acknowledge them.

Carcinogenicity

Midazolam maleate was administered with diet in mice and rats for two years at dosages of 1, 9 and 80mg/kg/day. In female mice in the highest dose group there was a distinct increase in the incidence of hepatic tumours. In high dose male rats there was a small but statistically significant increase in benign thyroid follicular cell tumours. Dosages of 9 mg/kg/day of midazolam maleate do not increase the incidence of tumours. The pathogenesis of induction of these tumours is unknown. These tumours were found after chronic administration, whereas human use will ordinarily be of single dose or of short duration.

Mutagenicity

Midazolam did not have mutagenic activity in five bacterial strains *Salmonella typhimurium*, Chinese hamster lung cells (V79), human lymphocytes, or in the micronucleus test in mice.

Genotoxicity

The effects of midazolam on genotoxicity have not been established.

INTERACTIONS WITH OTHER MEDICINES

Specific Interaction Studies

Midazolam can increase the central sedative effect of neuroleptics, tranquillisers, antidepressants, sleep-inducing drugs, analgesics, anaesthetics, antipsychotics, anxiolytics, antiepileptic drugs and sedative antihistamines. This potentiation of effect can in certain cases be therapeutically advantageous.

There is potentially relevant interaction between midazolam and compounds which inhibit or induce certain hepatic enzymes (particularly cytochrome P450 IIIA). Data clearly indicate that these compounds influence the pharmacokinetics of midazolam and this may lead to prolonged sedation. At present, enzyme induction is known to occur *in vivo* with rifampicin, carbamazepine and phenytoin, and enzyme inhibition occurs with cimetidine, erythromycin, diltiazem, verapamil, ketoconazole, fluconazole, itraconazole, ritonavir and saquinavir.

Therefore patients receiving the above compounds or others which inhibit CYP3A together with midazolam should be monitored carefully for the first few hours after administration of midazolam. During long-term midazolam infusions, a reduction of up to 50% of the initial dose followed by careful titration is recommended. Studies have shown that ranitidine has no influence on the pharmacokinetics of parenterally given midazolam.

In some patients the mutual potentiation of alcohol and midazolam can produce unforeseeable reactions (no alcoholic beverages for at least 12 hours after parenteral administration).

The sedative effect of intravenous midazolam is accentuated by premedication. Consequently, the dosage of midazolam should be adjusted according to the type and amount of premedication administered.

Following oral administration, the plasma concentration of midazolam has been shown to increase when used in combination with erythromycin and this results in a potentiation of midazolam's sedative effect. A much smaller change in plasma concentration with no observed increase of the sedative effects was observed following intravenous administration of midazolam, however, caution is advised.

A moderate reduction in induction dosage requirements of thiopentone (about 15%) has been noted following use of intramuscular midazolam for premedication.

Simultaneous administration of cimetidine (but not ranitidine) has been reported to reduce clearance of midazolam.

Displacement of midazolam from its plasma protein binding sites by sodium valproate may increase the response to midazolam and, therefore, care should be taken to adjust the midazolam dosage in patients with epilepsy.

The intravenous administration of midazolam decreases the minimum alveolar concentration (MAC) of halothane required for general anaesthesia. This decrease correlates with the dose of midazolam administered.

The effects of midazolam can be reversed by the benzodiazepine antagonist flumazenil.

Pharmacokinetic Drug-Drug Interaction (DDI)

Midazolam is almost exclusively metabolized by CYP3A. Inhibitors and inducers of CYP3A have the potential to increase and decrease the plasma concentrations and, subsequently, the pharmacodynamic effects of midazolam. No mechanism other than modulation of CYP3A activity has been proven as a source for a clinically relevant pharmacokinetic DDI with midazolam. However, acute protein displacement from albumin is a theoretical possibility of drug interaction with drugs that have high therapeutic serum concentrations, as has been hypothesized for valproic acid (see below). Midazolam is not known to change the pharmacokinetics of other drugs.

It is recommended to carefully monitor the clinical effects and vital signs during the use of midazolam; taking into account that the clinical effects of midazolam might be stronger and also last longer after co-administration of a CYP3A-inhibiting drug. Depending on the magnitude of the CYP3A-inhibiting effect, the dose of

midazolam may be largely reduced. Conversely, administration of a CYP3A-inducing drug may require a higher dose of midazolam to achieve the desired effect.

In case of CYP3A induction and irreversible inhibition (so-called mechanism based inhibition), the effect on the pharmacokinetics of midazolam may persist for a period of several days up to few weeks after administration of the CYP3A inhibitor. Examples for mechanism based CYP3A inhibitors include antibacterials (e.g. clarithromycin, erythromycin, isoniazid); anti-HIV agents (e.g. HIV protease inhibitors, delavirdine); antihypertensives (e.g. verapamil, diltiazem); sex steroids and their receptor modulators (e.g. gestodene, raloxifene), and several herbal constituents (e.g. bergamottin (grapefruit)). In contrast to the other mechanism based inhibitors (see listing below), ethinyloestradiol/norgestrel (used for oral contraception) and grapefruit juice (200 mL) did not significantly change the Area Under the plasma concentration / time Curve ($AUC_{0-\infty}$) of (or exposure to) IV midazolam. The range of the inhibiting/inducing potency of drugs is wide. The antifungal ketoconazole, a very potent CYP3A inhibitor, increased the plasma concentration of intravenous midazolam by approximately 5-fold. The tuberculostatic drug, rifampicin, belongs to the strongest inducers of CYP3A and its co-administration resulted in a decrease in the $AUC_{0-\infty}$ of intravenous midazolam by approximately 60%.

The mode of midazolam use also determines the magnitude of change in its pharmacokinetics due to CYP3A modulation:

The change in plasma concentration is expected to be less for intravenous administration compared with oral administration of midazolam. This is because CYP3A modulation not only affects the systemic clearance, but also the bioavailability of oral midazolam.

There are no studies available that have investigated the effect of CYP3A modulation on the pharmacokinetics of midazolam after intramuscular administration. After intramuscular administration, the drug directly enters the systemic circulation. Therefore, it is expected that the effect of CYP3A modulation will be similar to that for intravenous administration of midazolam.

In line with pharmacokinetic principles, clinical studies have shown that after a single intravenous dose of midazolam, in the presence of CYP3A inhibition, the change in maximal clinical effect due to CYP3A modulation will be minor, whereas the duration of effect may be prolonged. However, after prolonged dosing of midazolam, both the magnitude and duration of effect may be increased.

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, either *in vitro* or *in vivo*, has the potential to change the plasma concentration of midazolam, and therefore its effects. The listing includes information from clinical drug-drug interaction studies for oral midazolam. As outlined above, the change in plasma concentration is expected to be less for intravenous compared with oral midazolam.

Drugs that inhibit CYP3A

Patients receiving compounds which inhibit CYP3A should not be administered midazolam whenever possible. Otherwise, the dose of midazolam should be adjusted and the patient kept under careful surveillance. There is a potential interaction with the following:

Azole antifungals

Ketoconazole: Increased the $AUC_{0-\infty}$ of intravenous midazolam 5-fold while the terminal half-life increased by approximately 4-fold.

Fluconazole and itraconazole: Both increased the $AUC_{0-\infty}$ of intravenous midazolam, which was associated with a 2.4-fold and 1.5-fold increase in terminal half-life for itraconazole and fluconazole, respectively. A 100 – 300% increase in plasma midazolam at 48 hours after receiving fluconazole was commonly (3/10) seen in intensive care unit patients with a midazolam infusion. Orally, fluconazole increased C_{max} 1.7-fold and $AUC_{0-\infty}$ 3.6-fold, while for itraconazole they increased 2.5- and 6.6-fold, respectively.

Posaconazole: Increased the $AUC_{(tf)}$ (AUC zero to last measurable concentration) of intravenous midazolam by 1.8-fold.

Macrolide antibiotics

Erythromycin: Resulted in an increase in the AUC_(0-t) of intravenous midazolam and was associated with a 1.4 – 1.8-fold increase in the terminal half-life of midazolam.

Clarithromycin: Increased the AUC of intravenous midazolam by approximately 2.5-fold and was associated with a 2.7-fold increase in terminal half-life.

HIV protease inhibitors

Saquinavir and other HIV protease inhibitors: 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.

Histamine receptor 2 antagonists

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

Calcium-channel blockers

Diltiazem: After pretreatment with lorazepam and a single dose of diltiazem, on cessation of an intravenous infusion of midazolam, the AUC from cessation for 23 h increased approximately 25% and the terminal half-life was prolonged approximately 43%.

HMG-CoA reductase inhibitor

Atorvastatin: Increased the AUC of intravenous midazolam by approximately 1.4-fold compared with control group.

Drugs that induce CYP3A

Rifampicin (600 mg o.d.) decreased the AUC of intravenous midazolam by approximately 60% after 7 days. The terminal half-life decreased by approximately 50 - 60%.

Herbs and food

Echinacea purpurea root extract: Decreased the AUC of intravenous midazolam 20% and was associated with a decrease in half-life approximately 42%.

St John's wort: Decreased the AUC of intravenous midazolam by approximately 20% and AUC of oral midazolam by 50% with C_{max} decreased by 40 – 50%. It was associated with a decrease in terminal half-life by approximately 16 - 19%.

Acute protein displacement

Valproic acid: In one publication, protein displacement of midazolam by valproic acid was discussed as a potential mechanism of DDI. The clinical relevance of this study is considered very limited because of methodological concerns. However, due to the high therapeutic plasma concentration of valproic acid, the protein displacement of midazolam in the acute dose setting, resulting in more apparent clinical effect of midazolam, cannot be excluded.

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 decreased the minimum alveolar concentration (MAC) of Halothane.

Enhanced effects on sedation, respiration and haemodynamics may occur when midazolam is co-administered with any centrally acting depressants including alcohol. Therefore, adequate monitoring of vital signs should be established. Alcohol should be avoided in patients receiving midazolam (see **PRECAUTIONS** and **OVERDOSAGE** for warning of other CNS depressants, including alcohol).

It has been shown that high spinal anaesthesia can increase the sedative effect of intravenous midazolam. The midazolam dose may therefore be reduced. Also, when either lignocaine or bupivacaine were administered intramuscularly, the sedative effect of intravenous midazolam is likely to be potentiated.

Drugs increasing alertness/memory such as the acetylcholinesterase inhibitor physostigmine, reversed the hypnotic effects of midazolam. Similarly, 250 mg of caffeine partly reversed the sedative effects of midazolam.

Effects on Laboratory Tests

Midazolam has not been shown to interfere with results obtained in clinical laboratory tests.

ADVERSE EFFECTS

(See **PRECAUTIONS**)

Fluctuations in vital signs that have been observed following parenteral administration of midazolam include:

- respiratory depression (22.9% following intravenous administration and 10.8% of patients following intramuscular administration)
- apnoea (19% following intravenous administration)
- variations in blood pressure and pulse rate.

These common occurrences during anaesthesia and surgery are affected by the lightening or deepening of anaesthesia, instrumentation, intubation and use of concomitant drugs.

Administration of intramuscular midazolam to elderly and/or higher risk surgical patients has been associated with rare reports of death under circumstances compatible with cardiorespiratory depression. In most of these cases, the patients also received other central nervous system depressants capable of depressing respiration, especially opioid analgesics (see also **DOSAGE AND ADMINISTRATION**).

The following additional adverse reactions were reported after intramuscular administration:

- Local effects at intramuscular injection site: pain (3.7%),
- Headache (1.3%)
- induration (0.5%),
- redness (0.5%),
- muscle stiffness (0.3%)

The following additional adverse reactions were reported following intravenous administration:

- Local effects at the IV site: tenderness (7%)
- pain during injection (6.2%)
- hiccough (5.5%)
- redness (3.8%)

- nausea (3%)
- vomiting (2.9%)
- coughing (1.9%)
- induration (1.9%)
- drowsiness (1.3%)
- oversedation (1%)
- phlebitis (0.5%)

Other adverse experiences, observed mainly following IV injection and occurring at an incidence of less than 1%, are as follows:

- **Respiratory:** laryngospasm, bronchospasm, dyspnoea, hyperventilation, wheezing, shallow respiration, airway obstruction, tachypnoea.
- **Cardiovascular:** bigeminy, premature ventricular contractions, tachycardia, nodal rhythm, cardiovascular collapse, vasovagal episode, cardiac arrest.
- **Gastrointestinal:** acid taste, excessive salivation, retching.
- **CNS/neuromuscular:** anterograde amnesia, headache, euphoria, confusion, argumentativeness, nervousness, agitation, anxiety, grogginess, irritability, restlessness, emergence delirium or agitation, prolonged emergence from anaesthesia, dreaming during emergence, sleep disturbance, insomnia, nightmares, tonic/clonic movements, muscle tremor, involuntary movements, athetoid movements, dizziness, ataxia, dysphoria, slurred speech, dysphonia, paresthesia.
- **Ophthalmic:** blurred vision, diplopia, nystagmus, pinpoint pupils, cyclic movements of eyelids, difficulty in focusing.
- **Integumentary:** hives, hive-like elevation at injection site, swelling or feeling of burning, warmth or coldness at injection site, erythema, rash, pruritus.
- **Hypersensitivity:** in isolated cases, generalised hypersensitivity – including anaphylactic reactions and skin reactions – has been reported.
- **Miscellaneous:** yawning, lethargy, chills, weakness, continued phonation, ears blocked, loss of balance, light-headedness, toothache, faint feeling, haematoma.

Post-Marketing Experience

The following adverse effects have been reported and are not listed above.

Psychiatric Disorders: hallucinations.

Paradoxical reactions: hyperactivity, hostility, rage reaction, aggressiveness, tension, mood changes, paroxysmal excitement and assault, have been reported, particularly among children and the elderly.

Dependence: Use of midazolam, even in therapeutic doses, may lead to the development of physical dependence. After prolonged intravenous administration, discontinuation, especially abrupt discontinuation of the product, may be accompanied by withdrawal symptoms including withdrawal convulsions.

Nervous System Disorder: decreased alertness, convulsions have been reported in premature infants and neonates.

Cardiac Disorders: hypotension, bradycardia, vasodilating effects. 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**).

Respiratory Disorders: respiratory depression, apnoea, respiratory arrest. 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**).

Gastrointestinal System Disorders: constipation, dry mouth.

Skin and Appendages Disorders: urticaria.

General and Application Site Disorders: thrombophlebitis, thrombosis.

Injury, Poisoning and Procedural Complications: An increased risk for falls and fractures has been recorded in elderly benzodiazepine users.

DOSAGE AND ADMINISTRATION

Dosage should be specific to the patient and the medicine should be administered slowly.

Lower doses may be required in elderly or debilitated patients or in patients with hepatic or renal insufficiency. Because serious and life-threatening cardiorespiratory adverse events have been reported, provision for monitoring, detection and correction of these reactions must be made for every patient to whom midazolam is administered, regardless of health status or age. The dosage of midazolam administered should be modified according to the type and amount of premedication used.

This product is for single patient use only. Use once and discard any residue. The solution should be visually inspected prior to use. Only clear solutions without particles should be used.

Intravenous administration:

Midazolam should be administered slowly.

Endoscopic or cardiovascular procedures:

For conscious sedation, midazolam can be used either alone or together with an opioid immediately prior to the procedure with supplemental doses to maintain the desired level of sedation throughout the procedure.

Peroral procedures:

The use of an appropriate topical anaesthetic is recommended. For bronchoscopic procedures, the use of an opioid premedicant is recommended. Individual response will vary with age, physical status and concomitant medications, but may also vary independent of these factors.

Titrate dosage to desired sedative end point, such as slurring of speech, with slow administration immediately prior to the procedure. The initial dose should be given over a period of at least 2 minutes. Wait an additional 2 or more minutes to fully evaluate the sedative effect. When titrating the dose, 2 or more minutes should be allowed after each increment.

In healthy adults the initial dose is approximately 2.5 mg. Some patients may respond to as little as 1 mg. Further doses of 1 mg may be given if necessary. A total dose greater than 5 mg is not usually necessary to reach the desired end point.

In cases of severe illness and in elderly patients the initial dose must be reduced to 1 to 1.5 mg. Total doses greater than 3.5 mg are usually not required. Special caution is required for the indication of conscious sedation in patients with impaired respiratory function (see **PRECAUTIONS**).

If an opioid premedicant or other CNS depressant is used the dose of midazolam should be lowered by 25% to 30%.

Induction of anaesthesia

The dosage of midazolam should be determined by the response of the individual patient.

Administration should be by slow intravenous injection until the patient loses consciousness using approximately 0.15-0.2 mg/kg (10-15 mg) administered at a rate of approximately 2.5 mg per 10 seconds. Maximum sedation is usually reached after 2-3 minutes, however, if required a further dose up to a total of 0.35 mg/kg may be administered. The onset of sedation has not been found to be dose-dependent but the time to recovery is related to the amount of drug administered.

Midazolam should be used with opioid analgesics as it does not have analgesic properties and opioid analgesics increases its anaesthetic-inducing properties.

Intravenous sedation in Intensive Care Units (ICU)

For sedation in ICU, the recommended infusion rate is 0.03-0.2 mg/kg/hour. The dosage should be individualised and midazolam titrated to the desired state of sedation according to the clinical need, physical status, age and concomitant medication. It may be possible to reduce the dose (infusion rate) once the therapeutic effect has been obtained.

The dosage should be reduced in vasoconstricted, hypovolemic and hypothermic patients.

After prolonged intravenous administration of midazolam, sudden discontinuation of the product may be accompanied by withdrawal symptoms. Therefore, a gradual reduction of midazolam is recommended. Midazolam can be used in neurosurgical patients with increased intracranial pressure.

Intramuscular administration:

Preoperative sedation

Induction of sleepiness or drowsiness and relief of apprehension and to impair memory of preoperative events.

For intramuscular use, midazolam should be injected deep in a large muscle mass.

The recommended premedication dose of midazolam for good risk adult patients below the age of 60 years is 0.07 to 0.08 mg/kg intramuscularly (approximately 5 mg intramuscularly) administered approximately one hour prior to surgery.

The dose must be individualised and reduced when intramuscular midazolam is administered to patients with chronic obstructive pulmonary disease, other higher risk surgical patients, patients 60 or more years of age, and patients who have received concomitant opioids or other CNS depressants (see **ADVERSE EFFECTS**). In a study of patients 60 years or older who did not receive concomitant administration of opioids, 2 to 3 mg (0.02 to 0.05 mg/kg) of midazolam produced adequate sedation during the preoperative period. In approximately 25% of patients, 1 mg provided satisfactory sedation. As with any potential respiratory depressant, these patients require special observation for signs of cardio-respiratory depression after receiving midazolam intramuscularly.

Onset is within 15 minutes, peaking at 30 to 60 minutes. It can be administered concurrently with atropine sulfate or hyoscine hydrobromide and reduced doses of opioids.

Dilution and admixture

Midazolam may be mixed in the same syringe with frequently used premedicants: morphine sulfate, pethidine, atropine sulfate or hyoscine. Midazolam is compatible with normal saline, glucose 5% and 10% in water, fructose intravenous infusion (levulose 5%), potassium chloride, sodium chloride and calcium chloride intravenous infusion (Ringer's solution) and compound sodium lactate intravenous infusion (Hartmann's solution).

To avoid potential incompatibility with other solutions, midazolam must not be mixed with any solution except those listed above.

The 15 mg/3 mL, 5 mg/1 mL and 5 mg/5 mL formulations may be diluted to facilitate slow injection.

The 50 mg/10 mL ampoules may be added to the infusion solutions in a mixing ratio of 15 mg midazolam per 100-1000 mL infusion solution.

To reduce microbiological hazard, it is recommended that the infusion commence as soon as possible after preparation and in any case within 24 h. Storage of prepared infusion should be at 2°C – 8°C.

OVERDOSAGE

Symptoms

Overdosage of benzodiazepines is usually manifested by degrees of central nervous system depression ranging from drowsiness to coma. Overdose of midazolam is seldom life-threatening if the medicine is taken alone, but in mild cases, may lead to symptoms including drowsiness, mental confusion and lethargy. In more serious cases, symptoms may include ataxia, areflexia, apnoea, hypotonia, hypotension, respiratory depression, coma and very rarely death. Coma 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. When combined with other CNS depressants, the effects of overdosage are likely to be severe and may prove fatal.

Treatment

Treatment of overdose is symptomatic; institute supportive measures as indicated by the patient's clinical state. If the overdosage is known to be small, observation of the patient and monitoring of their vital signs only may be appropriate. In adults or children who have taken an overdose of benzodiazepines within 1 - 2 hours, consider activated charcoal with airway protection if indicated.

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 may precipitate seizures and is contraindicated in the presence of medicines that reduce seizure threshold (e.g. tricyclic antidepressants) and epileptic patients who have been treated with benzodiazepines. Refer to the prescribing information for flumazenil (Anexate), for further information on the correct use of this medicine.

Haemoperfusion and haemodialysis are not useful in benzodiazepine intoxication.

Contact the Poisons Information Centre on 131126 (Australia) for advice on the management of overdosage.

PRESENTATION AND STORAGE CONDITIONS

Midazolam Injection 5mg in 1mL (sterile) type I glass Ampoule (5 pack*, 10 pack)

Midazolam Injection 5mg in 5mL (sterile) type I glass Ampoule (5 pack*, 10 pack)

Midazolam Injection 15mg in 3mL (sterile) type I glass Ampoule (5 pack)

Midazolam Injection 50mg in 10mL (sterile) type I glass Ampoule (5 pack)

Ready for injection.

Store in the original package below 25°C.

Protect from light. Protect packaging against any physical damage.

* Not marketed in Australia.

NAME AND ADDRESS OF THE SPONSOR

Alphapharm Pty Limited

Level 1, 30 The Bond

30 – 34 Hickson Road

Millers Point NSW 2000

ABN 93 002 359 739

www.alphapharm.com.au

POISON SCHEDULE OF THE MEDICINE

Schedule 4 (Prescription Only Medicine)

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG)

01/04/2011

DATE OF MOST RECENT AMENDMENT

01/06/2015

Midazolam Alphapharm_pi\jun15/00