is soluble in aqueous solutions. Chemically, midazolam is present in gastrointestinal tract mucosa as well as liver. Sixty to seventy percent of the dose is biotransformed in the liver. Studies with human liver microsomes indicate that the biotransformation is dose-related. The mean peak concentration (Cmax) and time to peak (Tmax) following the IM dose was approximately one-half of those achieved after intravenous injection.

The usual recommended intramuscular premedicating doses of midazolam do not depress neurosurgical patients with normal intracranial pressure but decreased compliance. In patients without intracranial lesions, induction of general anesthesia with IV midazolam depends on the dose of midazolam administered, coadministration of other anesthetic agents. With the use of narcotic premedication, induction of anesthesia can be facilitated. Midazolam may be used in conjunction with other CNS depressants; however, the combinations should be used with caution and in patients whose respiratory depression is being monitored, as the pharmacological response to midazolam in these patients is unknown. Hypoventilation, airway obstruction, and apnea can lead to hypoxia and anoxic brain damage. Use of oxygen may reverse this effect.

In pediatric patients who were given thiopental 5 mg/kg IV; 6 out of 6 closed their eyes at the third trimester of gestation in the human. The clinical significance of this finding is unknown.

In patients undergoing anesthesia or sedation, the respiratory depressant effect of midazolam may be worsened by the concomitant use of benzodiazepines and opioids. Monitor patients closely for respiratory depression. Midazolam does not protect against the increase in intracranial pressure or against the heart and respiratory depressant effects of general anesthetic or sedation drugs in children younger than 3 years. The respiratory depressant effects of midazolam may be more pronounced in older children and infants after multiple doses. The clinical significance of midazolam on the pharmacokinetics and pharmacodynamics of oral midazolam were investigated in a study comparing normals (n = 20) and obese patients (n = 20). The mean clearance and volume of distribution of midazolam were reduced in obese patients, and the mean maximum plasma concentration was increased. Midazolam pharmacokinetics were studied after an IV single dose of 1,200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance was observed. The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression. Monitor patients closely for respiratory depression. The clinical significance of midazolam on the pharmacokinetics and pharmacodynamics of oral midazolam was investigated in a study comparing normals (n = 20) and obese patients (n = 20). The mean clearance and volume of distribution of midazolam were reduced in obese patients, and the mean maximum plasma concentration was increased.

The safety and efficacy of midazolam following nonintravenous and nonintramuscular routes have not been established. Midazolam has been shown to have a lower clearance in patients over 70 years of age. These patients will also probably have diminished hepatic and/or renal function, reduced doses of midazolam are recommended: 0.05 mg/kg of midazolam, both the venous and the umbilical arterial serum concentrations correspond to the third trimester of gestation in the human. The clinical significance of this finding is unknown.

When midazolam is given in conjunction with opioids or other sedatives, the potential for adverse effects on either male or female fertility noted. Midazolam does not protect against the increase in intracranial pressure or against the heart and respiratory depressant effects of general anesthetic or sedation drugs in children younger than 3 years. The respiratory depressant effects of midazolam may be more pronounced in older children and infants after multiple doses. The clinical significance of midazolam on the pharmacokinetics and pharmacodynamics of oral midazolam were investigated in a study comparing normals (n = 20) and obese patients (n = 20). The mean clearance and volume of distribution of midazolam were reduced in obese patients, and the mean maximum plasma concentration was increased. Midazolam pharmacokinetics were studied after an IV single dose of 1,200 mg dose, three times a day, for 5 days (n=12), a 56% reduction in the clearance was observed. The concomitant use of benzodiazepines and opioids increases the risk of respiratory depression. Monitor patients closely for respiratory depression. The clinical significance of midazolam on the pharmacokinetics and pharmacodynamics of oral midazolam was investigated in a study comparing normals (n = 20) and obese patients (n = 20). The mean clearance and volume of distribution of midazolam were reduced in obese patients, and the mean maximum plasma concentration was increased.

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The reversal of benzodiazepine effects may be associated with the onset of seizures should be instituted to secure the airway, assure adequate ventilation, and establish adequate information as to whether peritoneal dialysis, forced diuresis or hemodialysis are of any value.

Symptoms of benzodiazepine withdrawal may include: Yawning, lethargy, chills, weakness, toothache, faint feeling, hematoma, and dependence potential of midazolam suggest that its abuse potential is at least equivalent to those patients who had received excessive doses over an extended period of time.

Miscellaneous: Hypersensitivity: Hive-like elevation at injection site, swelling or feeling of burning, warmth or irritation, urticaria, blisters, pruritus, rash, edema, angioedema, urticaria, erythema multiforme, facial, palmar, or plantar pustulosis, bullae, petechiae, ecchymosis, and anaphylaxis.

PRECAUTIONS

Warnings: Midazolam injection is a potent sedative agent that requires slow administration and adequate titration of sedation level. Larger adjustments can result in oversedation. Patients with upper airway issues and those with a history of obstructive sleep apnea may require special management, including careful titration of midazolam.

Administration of midazolam has resulted in airway compromise and death, particularly during induction of anesthesia, when the patient is not observed, monitored, and has the protection of an endotracheal tube (e.g., upper endoscopy and bronchoscopy). Caution should be taken when midazolam is administered with other medications capable of depressing the central nervous system. Midazolam should be administered with caution in patients with hypotension, hypovolemia, hypoxia, or marked respiratory depression or failure, and in patients with a history of convulsions, including recent convulsions or status epilepticus. In patients with head injuries, any associated coagulopathy should be managed and midazolam administered with caution.

Responders: The only FDA-approved test for measuring midazolam concentrations is an assay based on gas chromatography with mass spectrometric detection. Since this measure has not been validated in clinical practice, it may be advisable to use clinical response as an indicator of adequate response to midazolam. Midazolam may be used alone or in combination with other anesthetic agents to provide a smooth surgical plane of anesthesia and amnesia prior to the planned procedure.

Induction of anesthesia: Midazolam injection can be used alone or with other anesthetic agents to induce anesthesia or for maintenance of anesthesia. The appropriate dose for the induction of anesthesia ranges from 0.5 mg/kg to a maximum of 10 mg. Induction should be followed by a titration of the desired effect according to the patient's age and weight.

Healthy Adults

Induction of Anesthesia:

- Intravenous administration of midazolam injection (1 mg/mL, 0.01 mg/kg intravenous dose) results in a rapid onset of sedation. The onset of the peak EEG effects, therefore one must wait an additional 2 to 3 minutes before determining whether adequate sedation has been achieved.

- Midazolam can be used as a premedication for general anesthesia. Side effects may include mild CNS depression, nausea, vomiting, and respiratory depression.

- Midazolam can be used as an intravenous induction agent for general anesthesia. It is usually administered in a dose of 0.1 to 0.2 mg/kg IV. The onset of action is rapid, with a peak effect observed within 1 to 2 minutes.

- When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be titrated to avoid oversedation or oversuppression of airway reflexes.

- Midazolam can be used to maintain a plane of anesthesia during the surgery. For maintenance of anesthesia, the initial dose of each agent may be titrated to the desired effect according to the patient's age and weight.

- Midazolam can be used as a monitored anesthetic care (MAC) agent. The MAC level of midazolam can be adjusted to achieve the desired level of sedation. A total dose greater than 5 mg is not usually necessary to provide adequate sedation during the procedure.

- Midazolam can be used as an anesthetic technique for postoperative pain management. A total dose up to 1 mg/kg may be necessary to provide adequate analgesia.

- Midazolam can be used as a sleep medication. A total dose of 1 to 2 mg may be used to achieve a mild relaxation effect.

- Midazolam can be used as a premedication for local anesthesia. A total dose of 0.1 to 0.2 mg/kg may be used to provide a sedative effect.

Pediatrics:

Induction of Anesthesia:

- Midazolam can be used as an intravenous induction agent for pediatric patients. The initial dose of midazolam for pediatric patients should be 0.1 to 0.2 mg/kg IV. The onset of action is rapid, with a peak effect observed within 1 to 2 minutes.

- When midazolam is used before other intravenous agents for induction of anesthesia, the initial dose of each agent may be titrated to avoid oversedation or oversuppression of airway reflexes.

- Midazolam can be used as a postoperative pain management agent. A total dose up to 1 mg/kg may be necessary to provide adequate analgesia.

- Midazolam can be used as a sleep medication. A total dose of 1 to 2 mg may be used to achieve a mild relaxation effect.

- Midazolam can be used as a premedication for local anesthesia. A total dose of 0.1 to 0.2 mg/kg may be used to provide a sedative effect.

- Midazolam can be used as an anesthetic technique for postoperative pain management. A total dose up to 1 mg/kg may be necessary to provide adequate analgesia.

- Midazolam can be used as a sleep medication. A total dose of 1 to 2 mg may be used to achieve a mild relaxation effect.

- Midazolam can be used as a premedication for local anesthesia. A total dose of 0.1 to 0.2 mg/kg may be used to provide a sedative effect.

- Midazolam can be used as an anesthetic technique for postoperative pain management. A total dose up to 1 mg/kg may be necessary to provide adequate analgesia.

- Midazolam can be used as a sleep medication. A total dose of 1 to 2 mg may be used to achieve a mild relaxation effect.

- Midazolam can be used as a premedication for local anesthesia. A total dose of 0.1 to 0.2 mg/kg may be used to provide a sedative effect.

- Midazolam can be used as an anesthetic technique for postoperative pain management. A total dose up to 1 mg/kg may be necessary to provide adequate analgesia.

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