Flumazenil

Introduction

• Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a benzodiazepine antagonist.

Uses

Flumazenil is used in adults for the complete or partial reversal of benzodiazepine-induced sedation when **benzodiazepines** are used for induction or maintenance of general anesthesia or for diagnostic or therapeutic procedures (i.e., conscious sedation) and for the management of benzodiazepine intoxication.1 Flumazenil also is used in children 1-17 years of age for the reversal of benzodiazepine-induced sedation when **benzodiazepines** are used for diagnostic or therapeutic procedures.1 The manufacturer states that the safety and efficacy of flumazenil have *not* been established in pediatric patients for reversal of benzodiazepine-induced sedation when **benzodiazepines** are used for induction of general anesthesia, for the management of benzodiazepine intoxication, nor for the resuscitation of neonates.1 (See Special Populations: Pediatric Use.)

• Reversal of General Anesthesia

Flumazenil has been shown to be effective in reversing sedation and restoring psychomotor function in adults who received midazolam for induction or maintenance of general anesthesia.1 Efficacy was established in 4 clinical studies in adults who received 5-80 mg of midazolam alone or in conjunction with skeletal muscle relaxants, nitrous oxide, regional or local anesthetics, opiates, and/or inhalational anesthetics.1 A 0.2-mg dose of flumazenil was administered, followed by additional 0.2-mg doses as needed to reach a complete response (up to a maximum of 1 mg).1 In these studies, 81% of patients became completely alert or remained only slightly drowsy following total flumazenil doses of 0.4-0.6 mg (36%) or 0.8-1 mg (64%).1 However, resedation occurred in 10-15% of patients who responded to flumazenil.1 (See Warnings: Resedation.) Flumazenil failed to restore memory completely as tested by picture recall.1 In addition, flumazenil was not as effective in the reversal of sedation in patients who received multiple anesthetic agents in addition to **benzodiazepines**.1

• Reversal of Conscious Sedation

Flumazenil has been shown to be effective in reversing the sedative and psychomotor effects of **benzodiazepines** when these drugs are used for diagnostic or therapeutic procedures but was less effective in completely and consistently reversing benzodiazepine-induced amnesia.1 Efficacy was established in 4 clinical studies in adults who received an average of 30 mg of diazepam or 10 mg of midazolam for sedation (with or without an opiate) for both inpatient and outpatient diagnostic or surgical procedures.1 Flumazenil was administered as an initial dose of 0.4 mg (2 doses of 0.2 mg each), with additional 0.2-mg doses administered as needed to achieve complete awakening, up to a maximum of 1 mg.1 In these studies, 78% of patients receiving flumazenil achieved complete consciousness, but approximately 50% of these patients required 2-3 additional doses of the drug in order to achieve this level of consciousness.1 In addition, while most patients remained alert throughout the 3-hour postprocedure observation period, resedation occurred in 3-9% of these patients.1

Pediatric Considerations

The safety and efficacy of flumazenil for the reversal of benzodiazepine-induced conscious sedation have been established in children 1 year of age and older.1 In one uncontrolled clinical trial involving 107 children 1-17 years of age who had received midazolam for conscious sedation, flumazenil was administered at doses of 0.01 mg/kg (maximum of 0.2 mg) up to a maximum of 5 doses or a total dose of 1 mg.1, 3 In this study, 56% of the children achieved complete consciousness within 10 minutes of flumazenil administration, but 51% of them required the maximum number of doses of the drug allowed for initial treatment in order to achieve this level of consciousness.1, 3 In addition, approximately 12% of the patients (all of whom were 1-5 years of age) who achieved complete consciousness following flumazenil administration experienced resedation within 19-50 minutes of initial administration of the drug.1 Episodes of resedation were reversed by additional doses of flumazenil.3 However, the manufacturer states that the safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have *not* been established.1

• Benzodiazepine Overdosage

Flumazenil is used in adults for the management of benzodiazepine overdosage.1, 2, 4 The drug is an adjunct to, not a replacement for, appropriate supportive and symptomatic measures (e.g., ventilatory and circulatory support) in the management of benzodiazepine overdosage.1, 2 Because patients admitted to hospitals for drug overdoses may have ingested multiple substances and/or are being treated for concomitant illnesses (e.g., depression, substance abuse), the presence of contraindications or precautions, which may limit the use of flumazenil therapy, should be considered.1, 4 (See Contraindications under Warnings/Precautions, in Cautions.) Flumazenil has no known benefit other than reversal of benzodiazepine-induced sedation in seriously ill patients with multiple-drug overdosage, and the drug should

not be used in cases where seizures (from any cause) are likely.1 In addition, the manufacturer warns that flumazenil should *not* be used in patients with serious cyclic depressant overdosage.1 (See Drug Interactions: Cyclic Antidepressants.) For information on the pathogenesis, manifestations, and treatment of benzodiazepine overdosage, see Acute Toxicity in the **Benzodiazepines** General Statement 28:24.08.

Efficacy of flumazenil has been established in 2 studies in patients who were presumed to have taken an overdose of a benzodiazepine, either alone or in combination with a variety of other agents.1 In these studies, of patients who were proven to have taken a benzodiazepine, 80% of those who received flumazenil responded with an improvement in level of consciousness.1 Of those who responded to flumazenil, 75% responded to a total dose of 1-3 mg.1 However, reversal of sedation was associated with an increased frequency of symptoms of CNS excitation, and 1-3% of patients who received flumazenil were treated for agitation or anxiety.1

• Other Uses

The manufacturer states that the safety and efficacy of flumazenil for the treatment of benzodiazepine dependence or for the management of protracted benzodiazepine abstinence syndrome have not been established and therefore such use currently is not recommended.1

Dosage and Administration

• General

Flumazenil is administered by rapid (over 15-30 seconds) IV injection through a freely flowing IV infusion into a large vein.1 Because of the risk of local irritation, the drug is recommended for IV use only, and extravasation into perivascular tissues should be avoided.1 Patients should have a secure airway and established IV access prior to administration of the drug.1

While flumazenil dosages exceeding the minimally effective dose may be tolerated by most adults, such dosages can complicate the management of patients who are physically dependent on **benzodiazepines** or in whom the therapeutic benefit of the drugs is needed (e.g., for seizure control in cyclic antidepressant overdosage).1 Therefore, flumazenil dosage should be titrated carefully using the smallest effective dosage.1 Currently recommended flumazenil dosing regimens involve multiple small doses rather than large bolus doses in order to provide better control of sedation reversal while minimizing the risk of adverse effects.1

Reversal of General Anesthesia and Conscious Sedation in Adults

When flumazenil is used to reverse benzodiazepine-induced sedative effects after anesthesia or conscious sedation in adults, the usual initial dose is 0.2 mg given IV over 15 seconds; if the desired consciousness level is not achieved after waiting 45 seconds, additional 0.2-mg doses may be administered at 1-minute intervals until an adequate response is achieved or a maximum of 4 additional doses is administered (i.e., maximum cumulative dose of 1 mg during an initial 5-minute dosing period).1 If resedation occurs, the initial dosing regimen (i.e., up to 1 mg given in divided 0.2-mg doses at 1-minute intervals) may be repeated no more frequently than every 20 minutes up to a maximum of 3 mg in any 1-hour period. In certain high risk patients (consult the manufacturer's labeling), it may be necessary to reduce the dose and/or increase the interval between doses to longer than 1 minute.1 Most patients respond to cumulative flumazenil doses of 0.6-1 mg, but individual requirements may vary considerably depending on the dose and duration of effect of the benzodiazepine administered and patient characteristics.1 In clinical situations where resedation is not yet apparent but must be prevented, the initial dosing regimen can be repeated at 30 and possibly repeated at 60 minutes despite the current absence of manifestations of recurrence.1

Reversal of Conscious Sedation in Children

When flumazenil is used in children to reverse benzodiazepine-induced sedative effects after conscious sedation, the usual initial dose is 0.01 mg/kg (up to 0.2 mg) given IV over 15 seconds; if the desired consciousness level is not achieved after waiting 45 seconds, additional 0.01-mg/kg (up to 0.2 mg) doses may be administered at 1-minute intervals until an adequate response is achieved or a maximum of 4 additional doses is administered (i.e., maximum cumulative dose of 0.05 mg/kg or 1 mg, whichever is lower).1 In the pediatric clinical trial of flumazenil, a mean total dose of 0.65 mg (range: 0.08-1 mg) was administered to children 1-17 years of age with approximately 50% of children requiring the maximum of 5 injections.1 The safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have not been established.1

Management of Benzodiazepine Overdosage in Adults

When flumazenil is used for known or suspected benzodiazepine overdosage in adults, the usual initial dose is 0.2 mg given IV over 30 seconds; if the desired consciousness level is not achieved after waiting 30 seconds, an additional 0.3-mg dose may be administered over 30 seconds.1 If an adequate response still is not achieved, further additional 0.5-mg doses may be administered over 30 seconds at 1-minute intervals up to a cumulative dose of 3 mg.1 Most patients respond to cumulative flumazenil doses of 1-3 mg, and cumulative doses exceeding 3 mg have not been shown reproducibly to provide additional benefit.1 However, some patients who exhibit a partial response after a 3-mg

cumulative dose rarely may require additional doses up to a total of 5 mg.1 If no response is observed within 5 minutes after administration of an initial 5-mg cumulative dose of flumazenil, the major cause of sedation may not be a benzodiazepine and additional flumazenil doses likely will provide little if any beneficial effect.1 If resedation occurs, the initial dosing regimen (i.e., up to 1 mg given in divided 0.5-mg doses at 1-minute intervals) may be repeated no more frequently than every 20 minutes up to a maximum dose of 3 mg in any 1-hour period.1

• Special Populations
Patients with hepatic impairment have decreased clearance of flumazenil.1 While the initial dose of flumazenil for reversal of benzodiazepine effects is not affected, repeat doses of the drug should be reduced in size or frequency in patients with hepatic impairment.1

Cautions

• Contraindications
Flumazenil is contraindicated in patients receiving a benzodiazepine for control of a potentially life-threatening condition (e.g., control of intracranial pressure or status epilepticus) and in those exhibiting manifestations of serious cyclic antidepressant overdosage.1 (See Warnings: Seizures.) Flumazenil also is contraindicated in patients with known hypersensitivity to the drug or **benzodiazepines**.1

• Warnings/Precautions
Warnings
Seizures. Use of flumazenil for the reversal of benzodiazepine effects may be associated with the onset of seizures in certain high-risk patients.1 Seizures are most frequent in patients who have been receiving **benzodiazepines** for long-term sedation or in patients with manifestations of serious cyclic antidepressant overdose.1 Other risk factors for seizures following flumazenil administration include major sedative-hypnotic drug withdrawal, recent therapy with repeated doses of parenteral **benzodiazepines**, myoclonic jerking or seizure activity prior to flumazenil administration in overdose cases, or concurrent cyclic antidepressant poisoning.1 Most convulsions associated with flumazenil administration require treatment, and have been successfully managed with anticonvulsants such as phenytoin, barbiturates, or **benzodiazepines**.1 However, if **benzodiazepines** are used to treat flumazenil-associated seizures, higher dosages than usual may be required.1

Hypoventilation. The manufacturer states that the efficacy of flumazenil in reversing benzodiazepine-induced hypoventilation has not been established, and the drug may not fully reverse postoperative airway problems or ventilatory insufficiency associated with benzodiazepine administration.1 In addition, even if initial efficacy is observed, the ventilatory effects of flumazenil may subside prior to those of the benzodiazepine; therefore, facilities and equipment for immediate ventilatory support should be readily available for any patient receiving the drug.1 In patients with serious pulmonary disease who experience serious benzodiazepine-induced respiratory depression, primary therapy should be appropriate ventilatory support rather than flumazenil therapy.1

General Precautions
Return of Sedation. Resedation may occur in patients who have responded to flumazenil.1 Resedation is most likely to occur in cases where a large single or cumulative dose of a benzodiazepine (e.g., midazolam dosages exceeding 10 mg) has been administered in the course of a long procedure (e.g., longer than 60 minutes) along with neuromuscular blocking agents and multiple anesthetic agents and least likely to occur in cases where flumazenil is administered to reverse a low dose of a short-acting benzodiazepine (less than 10 mg of midazolam).1 In clinical studies, resedation was observed in 1-3% of adults and in about 12% of children.1, 3 Therefore, patients should be carefully monitored for an adequate period of time (i.e., up to 2 hours) based on the dose and duration of effect of the benzodiazepine employed for signs of resedation, respiratory depression, or other residual benzodiazepine effects.1 Although the safety and efficacy of repeated flumazenil administration in pediatric patients experiencing resedation have not been established, repeated doses of flumazenil may be administered to adult patients when necessary.1 (See Dosage and Administration: Dosage.)

Withdrawal Reactions. Flumazenil may precipitate dose-dependent manifestations of withdrawal in patients with established physical dependence on **benzodiazepines**.1 An acute withdrawal syndrome characterized by dizziness, mild confusion, emotional lability, agitation (with signs and symptoms of anxiety), and mild sensory distortions has occurred in adults receiving flumazenil, particularly at doses above 1 mg.1 However, such reactions rarely required treatment other than reassurance and were usually short-lived.1 When treatment was necessary, patients were successfully treated with usual doses of barbiturates, **benzodiazepines**, or other sedative agents.1 Because benzodiazepine tolerance and dependence is frequently observed in patients with alcoholism and other drug dependencies, clinicians should assume that flumazenil administration may complicate the management of withdrawal syndromes for alcohol, barbiturates, and cross-tolerant sedatives.1 Seizures also may occur following flumazenil administration in patients with established physical dependence on **benzodiazepines**.1 (See Warnings: Seizures.)

Intensive Care Setting. The manufacturer states that use of flumazenil in an intensive care setting to define CNS depression as being benzodiazepine induced is *not* recommended because of the risk of precipitating potentially serious manifestations of withdrawal (e.g., seizures) in cases of unrecognized benzodiazepine dependence and because of the prognostic uncertainty of failure to respond to flumazenil in cases confounded by a metabolic disorder, traumatic injury, effects of other drugs, or any other factor not associated with benzodiazepine-receptor occupancy.1

Head Injury. Because flumazenil may precipitate seizures or alter cerebral blood flow in patients receiving **benzodiazepines**, the drug should be used with caution and only by clinicians who are prepared to manage such complications in patients with head injury.1

Panic Disorders. Flumazenil has been reported to provoke panic attacks in patients with a history of panic disorder.1

Pulmonary Disease. Because the efficacy of flumazenil in reversing benzodiazepine-induced alterations in ventilatory drive has not been established, the primary treatment of patients with serious lung disease who experience serious respiratory depression secondary to **benzodiazepines** should be appropriate ventilatory support (see Warnings: Hypoventilation) rather than the administration of flumazenil.1

Cardiovascular Disease. Use of flumazenil alone had no clinically important effects on cardiovascular parameters when administered to patients with stable ischemic heart disease to reverse the effects of **benzodiazepines**.1

Specific Populations
Pregnancy. Category C.1 (See Users Guide.) Use during labor and delivery is not recommended since the effects of flumazenil on the neonate are not known.1

Lactation. It is not known whether flumazenil is distributed in milk.1 Caution is advised if the drug is administered in nursing women.1

Pediatric Use. Safety and efficacy of flumazenil in the reversal of conscious sedation in infants younger than 1 year of age have not been established.1 In addition, the manufacturer states that safety and efficacy of flumazenil, including the potential risks, benefits, and appropriate dosages, have not been established for the management of benzodiazepine overdosage, for neonatal resuscitation, nor for the reversal of sedation when **benzodiazepines** are used for induction of general anesthesia.1 However, published anecdotal reports discussing the use of flumazenil in pediatric patients for these indications have reported similar safety profiles and dosing guidelines to those described for the reversal of conscious sedation.1 The risks associated with flumazenil use in the adult population also apply to pediatric patients.1(See Cautions: Warnings/Precautions.)

Geriatric Use. No substantial differences in safety or efficacy relative to younger adults, but increased sensitivity to flumazenil cannot be ruled out.1

• Common Adverse Effects
Adverse effects occurring in 3-9% of patients receiving flumazenil include dizziness, injection site pain, increased sweating, headache, and abnormal or blurred vision.1 In addition, serious adverse effects such as cardiac arrhythmias (e.g., junctional or ventricular tachycardias), seizures, and deaths have occurred.1 Most deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non-benzodiazepine drugs (usually cyclic antidepressants) as part of an overdose.1 (See Warnings: Seizures in Cautions.)

Drug Interactions

• Cyclic Antidepressants
Potential pharmacodynamic interactions.1 (See Warnings: Seizures.) Flumazenil should *not* be used in patients exhibiting manifestations of serious concurrent cyclic antidepressant overdosage, such as motor abnormalities (e.g., twitching, rigidity, focal seizures), arrhythmias (e.g., wide QRS complexes, ventricular arrhythmias, heart block), anticholinergic effects (e.g., mydriasis, dry mucosa, hypoperistalsis), or cardiovascular collapse.1 In such cases, the patient should be managed with ventilatory and circulatory supportive measures as needed until the signs of antidepressant toxicity have subsided.1 For information on the pathogenesis, manifestations, and treatment of cyclic antidepressant overdosage, see Acute Toxicity in the Tricyclic Antidepressants General Statement 28:16.04.28.

• Benzodiazepines
Pharmacokinetic interaction unlikely.1 However, flumazenil may precipitate dose-dependent manifestations of withdrawal in patients with established physical dependence on **benzodiazepines**.1

• **Other Drugs**

Interactions of flumazenil with CNS depressants other than **benzodiazepines** have not been studied.1 However, no deleterious interactions have been observed when flumazenil was administered after opiates, inhalational anesthetics, skeletal muscle relaxants, or muscle relaxant antagonists administered in conjunction with sedation or anesthesia.1 Flumazenil should not be administered until the effects of neuromuscular blockade have been fully reversed.1

Description

Flumazenil, a 1,4-imidazobenzodiazepine derivative, is a benzodiazepine antagonist. 1 Flumazenil antagonizes the CNS effects (e.g., sedation, impaired recall, psychomotor impairment, respiratory depression) of **benzodiazepines** by competitively inhibiting the activity of the drugs at the benzodiazepine recognition site on the γ-aminobutyric acid (GABA)/benzodiazepine receptor complex.1 Reversal of benzodiazepine-induced effects usually is evident within 1-2 minutes following completion of IV injection of flumazenil, with an 80% response occurring within 3 minutes, and the peak effect occurring at 6-10 minutes.1 The duration and degree of reversal of benzodiazepine-induced effects appear to be related to the dose and plasma concentrations of flumazenil.1 However, because the elimination half-life of flumazenil (0.7-1.3 hours) is shorter than that of **benzodiazepines**, repeat doses of the drug may be needed to prevent resedation.1, 2 The half-life of flumazenil appears to be shorter (averaging 40 minutes; range: 20-75 minutes) and more variable in children 1-17 years of age compared with that of adults.1

Flumazenil is extensively metabolized in the liver with less than 1% of an administered dose excreted unchanged in urine.1 Ingestion of food during an IV infusion of the drug results in a 50% increase in clearance, most likely because of the increased hepatic blood flow that accompanies a meal.1

Advice to Patients

Impairment of memory and judgment may occur.1 Importance of avoiding activities that require complete alertness, and not operating hazardous machinery or a motor vehicle until at least 18-24 hours after discharge and it is certain that no residual sedative effects of the benzodiazepine remain.1 Importance of avoiding alcohol or nonprescription drugs for 18-24 hours following flumazenil administration or in the presence of persistent benzodiazepine effects.1

Importance of informing clinicians of existing or contemplated concomitant therapy, including prescription and OTC drugs.1

Importance of women informing clinicians if they are or plan to become pregnant or to breast-feed.1

Additional Information

Overview® (see Users Guide). For additional information on this drug until a more detailed monograph is developed and published, the manufacturer's labeling should be consulted. Is is *essential* that the manufacturer's labeling be consulted for more detailed information on usual uses, cautions, precautions, contraindications, potential drug interactions, laboratory test interferences, and acute toxicity.

Preparations

Flumazenil

Routes	Dosage Forms	Strengths	Brand Names	Manufacturer
Parenteral	Injection, for IV use	0.1 mg/mL	**Romazicon®** (with parabens)	Roche

References

Only references cited for selected revisions after 1984 are available electronically.

1. Roche Laboratories, Inc. Romazicon® (flumazenil) prescribing information. Nutley, NJ; 2000 May.

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3. Shannon M, Albers G, Burkhart K et al for the Flumazenil Pediatric Study Group. Safety and efficacy of flumazenil in the reversal of benzodiazepine-induced conscious sedation. *J Pediatr.* 1997; 131:582-6. [IDIS 397529] [PubMed

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4. Mathieu-Nolf M, Babe MA, Coquelle-Couplet V et al. Flumazenil use in an emergency department: a survey. *J Toxicol Clin Toxicol.* 2001; 39:15-20. [PubMed 11327221]