

Flumazenil (Romazicon®)

Benzodiazepines have common therapeutic and recreational uses. While most benzodiazepine overdoses are not serious, benzodiazepine toxic effects can include drowsiness, slurred speech, nystagmus, hypotension, ataxia, coma, respiratory depression and cardio-respiratory arrest.

Mechanism/Indications: Flumazenil (Romazicon®) is used as an antidote for benzodiazepine overdose due to its mechanism as a competitive antagonist at the benzodiazepine site on the GABA_A receptor. Flumazenil is very effective at reversing the CNS depression associated with benzodiazepine overdose in a very select population. Patients previously benzodiazepine naive prior to an acute overdose are appropriate candidates for flumazenil. Flumazenil can be extremely effective in acute benzodiazepine overdoses in children. Likewise, in patients who have not recently taken benzodiazepines chronically, flumazenil can be beneficial for over sedated patients or for excessive drowsiness after benzodiazepines are administered for diagnostic or therapeutic procedures.

Adverse Effects/Contraindications: Despite being extremely effective at blocking the benzodiazepine receptor, its use is extremely limited as the risks may outweigh the benefits. Flumazenil has numerous contraindications including benzodiazepine dependence, coingestion of seizure threshold lowering or arrhythmia causing agents such as tricyclic antidepressants, tachycardia, QRS prolongation, and anticholinergic symptoms (i.e. symptoms that might suggest that a tricyclic antidepressant has been ingested), or seizure history. Because of these contraindications and adverse effects including cardiac effects, seizures, and death, flumazenil is not indicated in most benzodiazepine overdoses. A benzodiazepine dependent patient who is administered flumazenil can go into withdrawal or seizures. In intentional overdoses, it is difficult to ascertain a patient's benzodiazepine history and thus flumazenil is not safe. Likewise it has no role in the management of an unknown overdose, or in patients who are taking pro-convulsives. If flumazenil is given in a mixed benzodiazepine and tricyclic antidepressant overdose, the neuro-protective effects of the benzodiazepine will be removed by flumazenil and can allow the tricyclic antidepressant's pro-convulsive properties to predominate. Treating these seizures becomes complicated as benzodiazepines are first-line anti-convulsives yet cannot be used due to receptor blockade.

Dosing: Flumazenil is available as a clear colorless intravenous solution supplied in 500 mcg/5ml vials. Flumazenil has a rapid onset of within 1-2 minutes at usual doses of 0.2 mg every 1-2 minutes (max 3mg/hour) until the desired effect is achieved. Its short duration of action lends itself to multiple dosing or continuous infusion to prevent recurrent symptoms. Flumazenil is hepatically metabolized to an inactive compound that is excreted in the urine.

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For more on flumazenil:

- *Seeger DL. Flumazenil - Treatment or Toxin. Clin Toxicol 2004; 42:209-216.*
- *Howland MA. Antidotes in Depth: Flumazenil. In: Flomenbaum NE, Goldfrank LR, Hoffman RS et al, eds: Goldfrank's Toxicologic Emergencies. New York NY, 2006;1112-1117.*