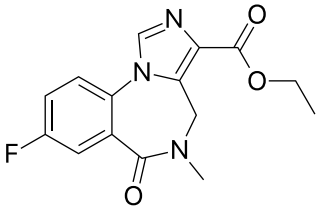
Clinical Pharmacology & Toxicology Pearl of the Week

~ Flumazenil ~

- ✓ First characterized in 1981, flumazenil is a 1,4-imidazobenzodiazepine that functions as a selective $GABA_A$ receptor antagonist. It is used in the treatment of benzodiazepine overdose
- ✓ Dose-dependent reversal begins within 1-2 minutes, with peak effects at 6-10 minutes
- ✓ Elimination half-life is 54 minutes
- ✓ The duration of action of flumazenil depends on the dose and elimination of the benzodiazepine, the dose of flumazenil, and hepatic function



- ✓ **Use in Benzodiazepine Overdose:**
  - Initially, flumazenil was considered a safe antidote and was not only recommended to reverse sedation in benzodiazepine overdoses, but also as a diagnostic tool in comatose patients
  - However, over the years, serious adverse events such as seizures and cardiac dysrhythmias have been reported with several cases of deaths
  - While single-drug overdoses with benzodiazepines often cause sedation, the overall mortality is low as death mainly occurs in the setting of co-ingesting other CNS depressants, which makes the benefits of using flumazenil generally lower than the associated risks

Indications:	**Contraindications:**
✓ Isolated benzodiazepine overdoses in a non-tolerant patient who has: ○ CNS depression ○ Normal vitals (including spO2) ○ Normal ECG ○ Otherwise normal neurologic exam	✓ History: ○ Seizure history ○ Ingestion of drug capable of provoking seizures or dysrhythmias ○ Chronic benzodiazepine use ✓ Clinical: ○ ECG evidence of TCA ingestion ○ Hypoxia or hypoventilation ○ Hypotension ○ Head trauma

- ✓ **Other Uses:**
  - Flumazenil has been used safely in reversal of procedural sedation, as well as in the management of hepatic encephalopathy. The hypothesis is that increased

GABAergic tone is implicated in hepatic encephalopathy, leading to short-term clinical improvement in some patients but no known survival benefit.

- ✓ **Dosing:**
  - Adult dose:
    - 0.2 mg, given at rate of 0.1 mg/min
    - Can repeat the above to a maximum dose of 1 mg IV
  - Pediatric dose:
    - 0.01 mg/kg IV
    - Maximum of 0.2 mg
  - Slow infusions minimize the symptoms associated with rapid arousal (confusion, agitation, emotional lability)
  - The duration of flumazenil is shorter than most benzodiazepines, so vigilance for recurrent toxicity and repeat doses may be required after 20-120 minutes

- ✓ **Risk of Seizures:**
  - Flumazenil administration has been associated with seizures, which can occur for several potential reasons:
    - If the patient has taken a mixed overdose of a benzodiazepine and a pro-convulsant, flumazenil will antagonize the anti-convulsant effect of the benzodiazepine
    - Flumazenil can precipitate benzodiazepine withdrawal, including seizures, in patients who are benzodiazepine dependent
    - If the patient has an underlying seizure disorder and relies on benzodiazepines for seizure control, flumazenil use can precipitate a seizure

- ✓ **Risk of Dysrhythmias:**
  - The most common dysrhythmias reported with flumazenil use are supraventricular arrhythmias, however rare cases of ventricular tachycardia and asystole have also been reported
  - The cause of dysrhythmia in these cases were presumed to be associated with presence of a TCA

References:

1. Nelson L, Lewin N, Howland M, Hoffman R, Goldfrank L, Flomenbaum N. Goldfrank's Toxicologic Emergencies. 11th ed. New York: McGraw Hill Medical; 2019
2. Penninga EI, Graudal N, Ladekarl MB, Jürgens G. Adverse Events Associated with Flumazenil Treatment for the Management of Suspected Benzodiazepine Intoxication--A Systematic Review with Meta-Analyses of Randomised Trials. Basic Clin Pharmacol Toxicol. 2016 Jan;118(1):37-44. doi: 10.1111/bcpt.12434. Epub 2015 Jul 28. PMID: 26096314.
3. Sharbaf Shoar N, Bistas KG, Saadabadi A. Flumazenil. [Updated 2022 Aug 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; Jan 2022.

The Calgary Clinical Pharmacology physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA. Clinical Pharmacology consultations are also available through the Netcare e-referral process and through Calgary Zone Specialist Link. Click HERE for more details.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK).