

## FIVE THINGS TO KNOW ABOUT ...

## Flumazenil in benzodiazepine overdose

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**Isolated benzodiazepine overdoses are rarely fatal**

A population-based retrospective study reported a rate of 3.0–7.9 deaths per million benzodiazepine prescriptions.<sup>1</sup> Sedation is common, but severe respiratory depression and hemodynamic instability are rare.<sup>2</sup> Supportive care is generally sufficient for the management of benzodiazepine overdose.

**Flumazenil should not be used routinely**

Flumazenil is contraindicated in patients with unknown or mixed overdose, benzodiazepine tolerance, seizure disorders or a prolonged QRS interval.<sup>3</sup> In a recent meta-analysis, serious adverse events were significantly more common among patients with suspected benzodiazepine overdose treated with flumazenil than among those in the placebo group (risk ratio 3.81, 95% confidence interval 1.28–11.39; number needed to harm = 50).<sup>2</sup> Seizures and ventricular dysrhythmias can develop, especially if withdrawal is precipitated in benzodiazepine-tolerant individuals or if flumazenil reverses the protective effect of benzodiazepines in patients with unknown or mixed overdose.<sup>3</sup> Seizures may become more difficult to manage and may require the use of propofol or barbiturates. A poison centre should be consulted if the use of flumazenil is being considered.

**Flumazenil antagonizes benzodiazepine activity**

Benzodiazepines promote the binding of  $\gamma$ -aminobutyric acid (GABA) to its receptor. The “Z” drugs (zopiclone, zaleplon and zolpidem) act in a similar manner. Flumazenil is a benzodiazepine analogue with minimal intrinsic activity.<sup>3</sup> It binds to the extracellular surface of GABA<sub>A</sub> receptors and competitively displaces benzodiazepine molecules, preventing further benzodiazepine binding.<sup>3</sup>

**Select patients may benefit from the administration of flumazenil**

Flumazenil can reverse respiratory depression in the rare patient with severe, isolated benzodiazepine or “Z” drug toxicity who does not have contraindications to its use. It is most often considered in accidental pediatric ingestions or reversal of iatrogenic oversedation. Case reports have shown successful flumazenil reversal of paradoxical reactions (agitation) associated with benzodiazepines.<sup>4</sup> Flumazenil does not reverse sedation due to barbiturates, ethanol or opioids.

**References**

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**Flumazenil has a short half-life**

Evidence regarding optimal dosing is limited. The manufacturer recommends an initial dose of 0.2 mg given over 15 seconds.<sup>5</sup> A suggested, more cautious approach would be to administer flumazenil in 0.1-mg doses (or 0.01 mg/kg) each over one minute, to a maximum of 1 mg, or until an effect is achieved or toxicity develops.<sup>2</sup> The half-life of flumazenil is about 50 minutes, which is shorter than that of most benzodiazepines. Therefore, sedation often recurs. Cardiorespiratory monitoring is necessary, and repeat dosing or infusion may be required.<sup>5</sup>

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