

## Comparison of Routes of Flumazenil Administration to Reverse Midazolam Induced Respiratory Depression in a Canine Model.

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### ■ ABSTRACT

**Objective:** To determine whether flumazenil, a drug used to reverse benzodiazepine-induced respiratory depression and approved only for IV use, is effective by alternative routes.

**Methods:** A randomized, controlled, nonblinded, crossover canine trial was performed to evaluate reversal of midazolam-induced respiratory depression by flumazenil when administered by alternative routes. Mongrel dogs were sedated with thiopental 19 mg/kg IV, then tracheally intubated. With the dogs spontaneously breathing, tidal volume, end-tidal CO<sub>2</sub>, and O<sub>2</sub> saturation were observed until a stable baseline was achieved. Incremental doses of midazolam were administered until respiratory depression (30% decline in tidal volume, 10% decrease in O<sub>2</sub> saturation, and 15% increase in end-tidal CO<sub>2</sub>) occurred. Flumazenil was administered by a randomly selected route [0.2 mg followed 1 minute later by 0.3 mg IV, sublingual (SL) or intramuscular (IM); or 1 mg followed 1 minute later by 1.5 mg per rectum (PR)]. Time to return to baseline respiratory functions was recorded ("time to reversal"). Each of 10 dogs was studied using all 4 routes of flumazenil administration with a washout period of at least 7 days. An additional dog served as a control (no flumazenil).

**Results:** The control time to reversal was 1,620 seconds. The IV route was significantly faster (mean 120 ± 24.5 sec) than the other 3 routes (p < 0.005). The SL route was the second fastest (mean 262 ± 94.5 sec), the IM route was the third fastest (mean 310 ± 133.7 sec), and the PR route was the slowest (mean 342 ± 84.4 sec). The SL, IM, and PR routes did not differ significantly from one another.

**Conclusions:** Flumazenil administered by all 4 routes reversed midazolam-induced respiratory depression in a dog model. For the selected dosages used, the IV route was significantly faster than all 3 other routes, and SL was the second fastest.

**Key words:** flumazenil; injections; intravenous; administration, rectal; midazolam; conscious sedation; animals; laboratory.

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