

THE FALLACY OF A LIFESAVING SUBLINGUAL INJECTION OF FLUMAZENIL

Flumazenil is a competitive pharmacologic antagonist of benzodiazepine (BZD) agonists at BZD receptor sites. It is approved by the Food and Drug Administration (FDA) for reversal of BZD-associated conscious sedation and BZD overdoses when administered only by the intravenous route. If administered in sufficient dose to overpower the effects of the BZD agonist overdose by competitively displacing the agonist from its BZD receptor sites, and if in an acute emergency sufficient flumazenil reaches those receptor sites quickly enough to reverse the unconsciousness before hypoxic brain damage from hypoventilation, upper airway obstruction, or apnea occurs, the drug can be lifesaving. Typically in emergency departments, multiple small 0.2 mg increments are administered by slow intravenous titration to arouse a known or suspected BZD overdose patient who, if necessary, is being artificially ventilated by skilled medical personnel until the drug awakens them. Since research has shown that up to 100 mg of intravenous flumazenil has produced no serious adverse effects in healthy volunteers, a larger 1 to 3 mg single intravenous bolus dose should be safe to inject in an uncontrolled emergency crisis when a hypoxic BZD-overdosed patient is unconscious, apneic, and cannot be ventilated by the dentist.

Despite its apparent wide margin of safety, flumazenil does have some precautions and contraindications associated with its use. If given to an epileptic patient whose seizures are controlled at least in part with a BZD, flumazenil may precipitate seizure activity. It may precipitate abstinence syndrome including prolonged seizures in patients who regularly use or abuse BZDs. If flumazenil is administered to a patient who has overdosed with a combination of tricyclic antidepressants and BZDs, the neuroprotective effect of the BZD is suddenly lost, and prolonged seizures as well as life-threatening cardiac dysrhythmias caused by the tricyclic toxicity can be unmasked. Flumazenil also has a relatively short duration of efficacy such that after its antagonist effects have diminished in 20 to 45 minutes, any BZD agonist that is still in the body can recapture the receptors, and the sedation can recur. Thus, rather than hasten the recovery of patients to allow them to leave the dental office more quickly, patients who are pharmacologically reversed require a longer period of observation to be certain that when the flumazenil is no longer effective, the level of re-sedation that may develop is not enough to require an even longer recovery period before the patient can be

safely escorted home. Thus, clinicians who administer flumazenil after some or even all sedations involving a BZD not only unnecessarily risk the rare occurrence of possible significant side effects from flumazenil but also risk the redevelopment of sedation in an unmonitored postsedation environment that can be compounded by the additive or potentiated effects of post-operative narcotic-containing analgesics. Flumazenil should be used only for overdose urgencies and emergencies or to perhaps help differentiate a BZD effect from some other cause of prolonged sedation, such as a possible stroke.

The FDA-approved package insert states that for reversing conscious sedation, the starting intravenous dose is 0.2 mg, given at 1-minute intervals if needed, "with most patients responding to doses of 0.6 to 1 mg." It also states that for reversing a BZD overdose, in which presumably the patient is unconscious, "most patients with a BZD overdose respond to a cumulative dose of 1 to 3 mg" of intravenous flumazenil. It is critical to this discussion to note that the small dose of 0.2 mg is merely the initial intravenous starting dose, not the recommended or average total dose for successful reversal of oversedation in most patients.

The rather wide variation in the dose needed to reverse the agonist by a competitive antagonist such as flumazenil is not only a function of individual patient variability but also required because the dose of the agonist to be reversed may range from a very small dose to a very large overdose. Therefore, a patient who is unconscious from 20 mg of midazolam or 2 mg of triazolam will likely need much more than 0.2 mg of flumazenil for reversal, whereas a patient given only 3 mg of midazolam or 0.5 mg triazolam may adequately respond to the initial 0.2 mg flumazenil dose. The mechanism of action of a competitive antagonist such as flumazenil dictates that the dose needed to reverse the agonist depends in large part on the dose of the agonist to be reversed and its strength of binding to its receptors. There is no single dose that is recommended but rather an intravenously titrated dose range.

It is therefore very disturbing that some practitioners believe and even teach that 0.2 mg of flumazenil will somehow, perhaps by magic, be lifesaving when given by sublingual injection for an unconscious patient who has been inadvertently overdosed and is unconscious in the office of a dentist who lacks general anesthesia training and may not be experienced in delivering positive-pressure ventilation. If 0.2 mg of flumazenil given intravenously does not adequately reverse even conscious sedation in most people, much less in un-

conscious overdosed patients, to recommend that a single small dose injected by the much slower and much less researched sublingual route is not only unscientific but also unsafe. Although it is reasonable to suspect that flumazenil would eventually work by sublingual or intramuscular injection if enough drug is injected, a sufficient amount of flumazenil may not be absorbed quickly enough to save a patient from hypoxic brain damage. I suspect that after a procedure under minimal or light-moderate BZD sedation, one can demonstrate a lessening of the sedation following 0.2 mg of flumazenil by sublingual or intramuscular injection. However, any success at that dose by that route cannot be extrapolated to support a recommendation of injecting that small dose by that route in a life-threatening emergency in which brain damage will occur in only a few fleeting minutes for an overdosed, unconscious, hypoxic patient if rapid reversal does not happen.

It makes sense that when an IV cannot be readily established and the BZD-overdosed unconscious patient is in a life-threatening situation, the dentist should attempt to ventilate the patient with oxygen and should consider injecting intramuscularly at least 0.6 to 1 mg of flumazenil, which is at least within the dosage range that reverses most conscious sedation patients if given intravenously. Unfortunately, that is a volume of 6 to 10 mL, which is far too much to safely inject sublingually, and therefore, the intramuscular

injection volume should perhaps be divided between both deltoid muscles as a last-ditch effort to save a life.

In all fairness, perhaps all the research on the intravenous doses of flumazenil for reversal of conscious sedation and overdose that swayed the FDA to accept flumazenil is totally flawed. Perhaps the dose of 0.2 mg totally reverses all levels of sedation and overdose of BZDs, and perhaps the sublingual route is somehow faster and even more effective than the IV route. However, until additional research is done, I'll believe in the massive amount of research already completed that was needed to get flumazenil on the market rather than buy into the widely discussed fallacy of relying on the tiny 0.2 mg sublingual flumazenil injection when a patient's life is at stake. It would most likely be too little and too late.

Sadly, the 0.2 mg sublingual flumazenil injection "lifesaver" for a BZD overdosed unconscious patient who cannot be adequately ventilated (eg, the obese, undiagnosed obstructive sleep apnea patient who has been given a 2 mg cumulative dose of oral triazolam via multiple 0.5 mg increments) is a lifesaver that almost for sure won't float when it is most needed.

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