Flumazenil

A Brief Review for Clinicians

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ABSTRACT

Flumazenil is a specific benzodiazepine antagonist which may be used to promptly reverse or attenuate benzodiazepine-induced sedation or anesthesia, usually postoperatively or in the intensive care unit. Flumazenil is also useful

in the management of the patient presenting a suspected benzodiazepine overdose, has had anecdotal success in the treatment of hepatic encephalopathy, and can be used for intra-operative "wake-up" testing (e.g., to test for neurological intactness during back surgery).

Because of rapid absorption and uptake by the CNS, the drug is effective within minutes. However, its short elimination half-life (about 1 hour) may result in re-sedation in patients, especially when benzodiazepines with a long half-life have been administered or in overdose cases. Consequently monitoring for re-sedation and respiratory depression is essential, and repeated doses of flumazenil may become necessary.

Adverse reactions to flumazenil are rare. Withdrawal symptoms in benzodiazepine-dependent patients, seizures and arrhythmias in tricyclic antidepressant overdose cases, and seizures in epileptic patients using benzodiazepines are the three most important potential adverse reactions.

HISTORY

Flumazenil was synthesized at Hoffmann La Roche Laboratories during the search for a benzodiazepine with a very short duration of action. Animal testing of the new compound revealed no benzodiazepine-like activity despite radio-labeling studies that demonstrated binding to benzodiazepine receptors in the brain. In 1981, flumazenil was identified as the first specific benzodiazepine antagonist. [1]

Flumazenil has been available since 1987 in Europe and was introduced into Canada and the USA in the early 1990s.

PHARMACEUTICAL DESCRIPTION

Flumazenil is a 1,4-imidazobenzodiazepine with empirical formula C15 H13 03 N3 F and a molecular structure quite similar to midazolam. It is supplied commercially as 5 ml or 10 ml vials containing 0.1 mg/ml of active drug, compounded with methylparaben, propylparaben, sodium chloride, edetate disodium and acetic acid, and stored at room temperature. The drug is insoluble in water, but is slightly soluble in acidic aqueous solutions. The pH is adjusted to about 4 with hydrochloric acid and/or sodium hydroxide. Flumazenil is compatible with 5% dextrose in water, lactated Ringer's solution and normal saline. Intravenous solutions with flumazenil are stable at room temperature for up to 24 hours [2].

MECHANISM OF ACTION

Flumazenil competitively antagonizes the actions of benzodiazepines in the CNS, not by displacing the agonist, but rather by occupying the benzodiazepine receptor site on the GABA-benzodiazepine receptor complex, when the agonist dissociates from it [1,3,4]. Flumazenil does not affect the plasma concentration, bioavailability, or mean elimination half-life of benzodiazepines [5,6].

While flumazenil is a weak partial agonist in some animals [7,8], it is essentially free of agonist activity in humans [9,10].

Flumazenil does not antagonize the CNS effects of opioids, ethanol, or, propofol [11,12]. However, there is question surrounding the antagonism of flumazenil with regards to barbiturates and inhalational agents. There have been certain studies conducted implicating administration of flumazenil with a reduction in the duration of thiopentone (a barbiturate) in humans [13], and a decrease in the minimum alveolar concentration of isoflurane (an inhalational anesthetic) in dogs [14]. In the latter cited study, their data indicated that flumazenil potentiated the analgesic effect of isoflurane, which they concluded may be due to the analgesic effect of flumazenil, or perhaps due to its partial agonist activity. While such findings do prove exciting, they contrast, by their own admission, with other similar studies, and hence, provide an avenue for further research and potential discovery.

PHARMACOKINETICS

The pharmacokinetics of flumazenil have been studied in human volunteers [15,16,17]. Oral bioavailability of flumazenil is only 16% due to first-pass metabolism and hepatic clearance [17]; intravenous dosing is therefore the route of choice. Flumazenil has a short plasma elimination half-life (0.7 to 1.3 hours) [15,17], is moderately protein-bound (40 _+ 8%) [15] and has a large apparent volume of distribution (0.63 - 10.061/kg) [15,17]. (Table 1).

Table 1. Pharmacokinetic Parameters for Flumazenil (for adults) [17]

Elimination half-life	**0.95 + 0.13 h**
Apparent volume of distribution	**1.11 + 0.23 1/kg**
Total plasma clearance	**14.8 + 2.3 ml/min/kg**

Disposition parameters are linear over a wide range of doses. Maximal cerebral flumazenil concentrations are attained 5 to 8 minutes after IV administration as shown by Positron Emission Tomography studies [18,19] which demonstrate high binding affinity in regions of the CNS rich in benzodiazepine receptor sites.

Flumazenil has a high liver extraction ratio (0.6) and undergoes extensive hepatic metabolism by microsomal oxidation to inactive carboxylic acid and glucuronide derivatives [15,16,17]. Less than 1 % of the drug is recovered unchanged in the urine [15,17]. Pharmacokinetics are not significantly

affected by gender, age or renal failure or hemodialysis beginning one hour after drug administration [2] [Product Monograph]. There are no significant pharmacokinetic interactions with concurrently administered benzodiazepines [6,16] or ethanol [23]. Clearance is reduced to about 50% of normal with moderate liver dysfunction, and to about 25% with severe hepatic disease [2,21].

CLINICAL INDICATIONS

Some clinical indications for using flumazenil are given in Table 2.

Table 2. Clinical Indications for Flumazenil

1. Reversal of anesthesia
2. Reversal of conscious sedation
3. Reversal of sedation in the ICU
4. Management of benzodiazepine overdose
5. Treatment of hepatic encephalopathy (?)
6. Intra-operative wake-up testing

1. Reversal of anesthesia

Many studies have reported the use of flumazenil for the antagonism of benzodiazepine-induced general anesthesia [22-31]. Response to flumazenil has been assessed by sedation rating scales, coma scales, duration of amnesia, and degree of orientation, comprehension and collaboration. In placebo-controlled trials [32-34] reporting comparable demographic data, duration of anesthesia, dose of anesthetic agents, and degree of sedation, flumazenil administered intravenously in titrated doses up to 1 mg has been significantly superior to placebo in reversing sedation after benzodiazepine-induced general anesthesia. Differences were significant one to five minutes after flumazenil and persisted for 30 - 120 minutes. Anxiety has been the only significant adverse effect of flumazenil after benzodiazepine-induced general anesthesia, is dose-related and rare at the recommended dosage (< 1 mg). Cardiovascular parameters post-flumazenil have been essentially unaffected, and these studies have not shown flumazenil to be associated with an increase in analgesic requirements, nausea or vomiting.

Prompt reversal of sedation or general anesthesia may facilitate the management of patients during the first 30 to 60 minutes of the recovery period. However, normal monitoring is still required during this time and the routine use of flumazenil is difficult to justify without evidence for increased safety, earlier discharge from outpatient surgical units or a reduction in the

cost of perioperative care.

The midazolam-flumazenil combination invites comparison with propofol which has entered into wide usage for both conscious sedation and general anesthesia. Until recently, sedation with propofol had not been compared directly with midazolam/flumazenil, though it was shown that total intravenous anesthesia with propofol results in better recovery indices when compared with midazolam/fentanyl infusions reversed by flumazenil [35]. However, this may be attributed to the short lasting effect of flumazenil in the presence of high doses of midazolam [32]. It has been shown though, that early recovery from midazolam sedation and flumazenil reversal is similar to recovery after propofol sedation, and is an improvement over propofol sedation when involving total intravenous anesthesia [32,36-37]. Furthermore, studies examining flumazenil use directly with propofol have concluded that there is no significant effect on the reversal of propofol anesthesia [13,38]. In **addition, better recovery of psychomotor function is seen also after propofol-induced general anesthesia, when compared with midazolam-induced general anesthesia reversed by flumazenil [39]. Although, residual psychomotor deficit following reversal of midazolam with flumazenil has been reported [40], this appears to be dose dependent and depends on the dose of the agonist and antagonist. Flumazenil possesses a dose dependent effect on reversing the actions of benzodiazepines, with certain effects being reversed in the presence of low doses of the antagonist, while others requiring higher doses.**

2. **Reversal of conscious sedation**

Flumazenil has been effective in reversing or attenuating benzodiazepine sedation in patients who have undergone a wide variety of medical and surgical procedures without general anesthesia [41-56]. In **these studies, benzodiazepine sedation was used in conjunction with IV regional, epidural, or local anesthesia, or alone. Medical procedures included bronchoscopy, cardioversion, cardiac catheterization, and endoscopy. Surgical procedures included lower abdominal surgery, urologic, orthopedic and dental procedures. These trials have included elderly and high-risk patients [41-43,48] as well as healthy young adults.**

Flumazenil rapidly reversed benzodiazepine-induced sedation in these trials, resulting in improved scores for sedation, orientation, comprehension/collaboration, anterograde amnesia and psychomotor performance. As with patients receiving flumazenil after general anesthesia, anxiety has occurred occasionally. Some patients may prefer to remain drowsy following the procedure. Flumazenil does not affect retrograde amnesia, as benzodiazepines cause only anterograde amnesia, which is a prime reason for using benzodiazepine sedation [44]. Unfortunately, antagonism of respiratory depression is incomplete and does not permit earlier discharge from outpatient facilities. All patients should be monitored for residual sedation (sometimes termed "resedation") [57,58]. Residual sedation is seldom reported after midazolam, as the pharmacokinetics of flumazenil and midazolam are reasonably well matched [59] but may occur after diazepam and flunitrazepam [57]. In cases where residual sedation after midazolam has been reported, the authors were criticized for using rather high

doses of midazolam in elderly patients [59]. Nonetheless, availability of flumazenil should not encourage overuse or overdose of benzodiazepines which in good clinical practice are titrated to effect.

Although somewhat controversial, recent studies have also reported flumazenil to be highly effective in the reversal of benzodiazepine-induced sedation for patients with severe pre-ECT anxiety [60]. Pre-ECT anxiety may normally be reduced to a manageable level by the administration of a benzodiazepine, but a dose that is adequate to sufficiently lower the patient's anxiety may also manifest an anticonvulsant effect which would interfere with the development of an adequate seizure. In being confronted with this problem, attempts to administer flumazenil to reverse the anticonvulsant effect of benzodiazepines in ECT have proven to be effective and potentially useful [60]. However, the many uncontrolled variables in such cases, e.g., different types and doses of benzodiazepines, anesthetic agents, etc., preclude definite conclusions regarding the efficacy and safety of this novel use of a benzodiazepine antagonist. Further investigation to determine the potential benefits from employing flumazenil in such capacity should certainly be pursued, and likely focus on determining in controlled studies whether such use of flumazenil is sufficiently safe (the main concern being the possibility of inducing a spontaneous seizure), and whether the benzodiazepine reversing effect is clinically relevant [60].

Concerning the interactions of midazolam and flumazenil on memory and cognition, previous research has been unable to demonstrate, unequivocally, the ability of flumazenil to reverse completely, partially, or not at all, the memory effects of benzodiazepines. However, a recently conducted study investigated the effects of midazolam on implicit memory, the behavioral effects of flumazenil alone, and the acute reversal of benzodiazepine effects [61]. It was found that midazolam produced marked sedation and pervasive memory (both explicit and implicit) impairment. The latter included impairment of implicit memory, word and picture recall, and picture recognition. The dose-response effects of the drug were more apparent in rates of recovery than in magnitudes of peak effects. Flumazenil alone produced no significant behavioral effects, but produced complete reversal of the memory, cognitive, and sedative effects of midazolam. Finally, the 1 mg dose of flumazenil was found to be just as effective as the 3 mg dose for reversal [61].

3. **Reversal of sedation in** the ICU

When BZDs with long elimination half-lives are used in ICU patients, prolonged sedation may contribute to inability to wean from mechanical-ventilation. Flumazenil has been used as an adjunct to weaning and extubation in these patients [62-64]. Unfortunately, flumazenil has not been shown to reverse all the respiratory depressant effects of benzodiazepines, and, because of resedation, a flumazenil infusion may be required [65,66]. An alternative strategy is to use a very short acting agent, such as propofol, for the last few hours of ventilatory support in patients requiring sedation [66]. Nonetheless, for the most part, depression of ventilatory responsiveness induced by BZDs can be reversed effectively and promptly by flumazenil [67].

4. Management of benzodiazepine overdose

The use of flumazenil in acute benzodiazepine overdose has been recently reviewed [68,69]. With proper supportive care, mortality from pure benzodiazepine overdose, accidental or intentional, should be extremely rare. Flumazenil can quickly restore consciousness and may prevent the need for ICU admission, gastric lavage, endotracheal intubation and mechanical ventilation. Double-blind, placebo-controlled [70-73] have shown that patients intoxicated with benzodiazepines alone can be fully awakened within minutes of flumazenil injection. The duration of antagonism of benzodiazepine effects lasts from one to five hours. Intensive monitoring is necessary to detect resedation, which is common following initial awakening; and further bolus doses and/or continuous infusion of flumazenil may be required. In unstable patients, the correction of severe hemodynamic or respiratory abnormalities should precede the administration of flumazenil. In coma of unknown origin the slow administration of 1 - 2 mg of flumazenil will permit immediate diagnosis of significant BZD overdose [74].

The effectiveness of flumazenil in mixed overdose is dependent on the relative contribution of the benzodiazepine to the intoxication. Flumazenil should not be given to patients in whom tricyclic antidepressant overdose is known or suspected (as manifested by motor abnormalities, ECG disturbances, anticholinergic signs or cardiovascular collapse); the protective effect of the benzodiazepine will be removed and convulsions may occur [75] (see section on Precautions). Flumazenil does not antagonize the CNS effects of alcohol [12,20].

5. Treatment of hepatic encephalopathy (?)

Endogenous substances with BZD-like properties may contribute to the neuropsychiatric manifestations of hepatic encephalopathy [32]. BZD-like substances have been identified in the brain and cerebrospinal fluid of both patients and experimental animals with hepatic encephalopathy and liver failure [32,76]. Anecdotal reports [32,77,78] and uncontrolled studies [32,79,80] have documented both clinical and EEG improvement in patients given flumazenil, but controlled studies have so far failed to show any therapeutic benefit relative to standard treatment [81-83]. The first randomized controlled trial was recently published, showing a 46% clinical response rate to 2 mg of flumazenil [32,84].

Idiopathic recurrent stupor is an interesting, rare syndrome of spontaneous stupor or coma that is not associated with known metabolic, toxic, or structural abnormalities [73]. Recent reports have documented a remarkable return to normal consciousness after the administration of flumazenil. During episodes of stupor there is a large increase of endozepine-4 content in the serum and cerebrospinal fluid of these patients [74].

6. Intra-operative wake-up testing

Flumazenil has been successfully used to induce intraoperative arousal

("wake-up test") for spinal cord function monitoring during midazolam-narcotic anesthesia in patients undergoing spinal fusion [75]. Control of the timing of arousal was achieved more easily compared with halothane-nitrous oxide anesthesia and with no adverse reactions.

ADMINISTRATION & DOSAGE

Flumazenil antagonizes the effects of prior benzodiazepine administration (sedation, impaired recall, psychomotor slowing) but the degree and duration of this effect depends on the dose of benzodiazepine given. To achieve a controlled reversal, the recommended initial dose is 0.2 mg (2.0 ml) given IV over 15 seconds [88]. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, injections can be repeated at 60 second intervals to a maximum dose of 1.0 mg. The titration method is recommended to control patient wakening to the endpoint desired. The administration of a single large bolus dose can result in confusion and agitation upon wakening.

For management of known or suspected benzodiazepine overdose, administration of flumazenil should be titrated in the same manner. In the absence of a response to the initial 0.2 mg, larger increments (0.3 - 0.5 mg) can be injected slowly and at 1 minute intervals. Most patients with benzodiazepine overdose will respond to a cumulative dose of 1.0 - 3.0 mg of flumazenil. Doses beyond 3.0 mg do not reliably produce additional effects and failure to respond at these dosages suggests other etiologies of impaired consciousness.

No clinical studies have been performed in children. Dosage requirements are not altered in renal failure patients and the elderly. Although the usual initial dose of flumazenil may be used in patients with liver dysfunction, subsequent doses should be reduced in amount or frequency [21].

ADVERSE EFFECT

In animal studies flumazenil has extremely low toxicity with a therapeutic index almost 30 times higher than thiopentone or propofol. Adverse effects were reviewed in more than 1700 patients [89] and were uncommon. The incidence of the most commonly reported side effects (nausea, dizziness and headache) did not differ significantly from placebo, and occurred primarily in the post-anesthesia population. There have been occasional reports of anxiety, dysphoria and agitation, and mild pain may occur on injection; these side-effects are reduced by using the minimum required dosage of flumazenil and by slow intravenous administration.

Flumazenil is devoid of significant hemodynamic effects when administered to patients with coronary artery disease who have been sedated with a BZD [31,48,90]. In studies of healthy subjects flumazenil administered alone and in high doses has had no serious adverse effects, no effect on intraocular pressure and no intrinsic effect on minute ventilation or inspiratory drive [91].

PRECAUTION

Resedation following reversal of the effects of benzodiazepines is due to the short plasma half-life of flumazenil (approximately 1 h compared with over 2 h for midazolam, which is the shortest for an agonist BZD). Resedation is easily treated with further doses of flumazenil but may occur after the patient has been transferred to an unmonitored environment where satisfactory observation and further access to flumazenil are not available. This has not been a clinical problem in patients sedated with single low doses of midazolam (5 to 11 mg) but tends to be more evident after sedation with the longer acting BZDs, e.g., diazepam. It has been recommended that all patients be observed for an appropriate period based on the dose and duration of the effect of the benzodiazepine used [57].

Although flumazenil reliably reverses benzodiazepine-induced sedation, its ability to fully antagonize the respiratory depressant effects of these agents has not been fully established. Flumazenil improves resting ventilation in patients who have received midazolam but the slope of the ventilatory response to C02 remains depressed [92]. In a double-blind, placebo-controlled study [93], 1 mg flumazenil fully reversed midazolam-induced depression of hypoxic ventilatory drive, but [47] was only partially effective against diazepam. Incomplete action probably relates to the short elimination half-life of flumazenil. These findings emphasize that the appropriate management of hypoxemia and ventilatory depression after BZD administration is delivery of supplemental oxygen, the maintenance of an adequate airway, and assisted ventilation where necessary, before, (or concurrent with) the administration of intravenous flumazenil. Nevertheless, flumazenil should be available in all facilities where intravenous BZDs are used for sedation or general anesthesia.

Flumazenil may cause seizures in patients who have been on long-term benzodiazepine therapy for a seizure disorder or in combined benzodiazepine-cyclic antidepressant overdose cases [94]. Seizures are not dose-related and are not a toxic effect of flumazenil, but represent a reversal of the anticonvulsant effect of the benzodiazepine. Other patient categories considered at risk for seizures include those undergoing concurrent major sedative-hypnotic drug withdrawal, overdose patients with myoclonic jerks or seizures prior to flumazenil administration, patients who have undergone recent therapy with repeated doses of parenteral BZDs, head-injured patients and those who have ingested other drugs (e.g., cyclic antidepressants, cocaine, lithium, methylxanthines) that may themselves precipitate convulsions. If seizures occur they may be treated with BZDs, phenytoin, or a barbiturate. It is however recommended that flumazenil be avoided in patients who are predisposed to seizures (i.e., a history of epilepsy, intracranial pathology, chronic BZD use, preconvulsant ingestion, etc.) [32].

Case reports have described serious arrhythmias, including ventricular tachycardia and refractory bradycardia in patients who have ingested overdoses of a tricyclic antidepressant [71,75,95].

Concerns have been raised about the potential for precipitation of an acute withdrawal syndrome when flumazenil is administered to patients who are chronic users of benzodiazepines. However, placebo-controlled studies have documented the safety of flumazeni10.2 mg IV given to volunteers taking triazolam or diazepam for up to 2 weeks [96]. Doses greater than 1 mg were associated with hot flushes, agitation and tremor. Carefully measured doses of flumazenil may, paradoxically, prevent the anxiogenic component of benzodiazepine withdrawal and reverse tolerance to the anticonvulsant effects of diazepam [97].

Caution is also appropriate when administering flumazenil to psychiatric patients, in whom there is an increased theoretical risk of provoking a panic attack

SUMMARY AND CONCLUSION

The use of flumazenil, in the benzodiazepine agonism-antagonism scheme, has been shown to be of great value and significance for physicians dealing with sedation and general anesthesia. It provides a safe means of effectively attenuating or reversing the CNS-depressant effects of BZDs, in a quick and reliable manner. However, the availability of flumazenil should not be construed as a license to administer an overdose of benzodiazepine [32]. The many studies demonstrating and documenting the clinical efficacy and safety of flumazenil should be now supplemented with studies demonstrating the cost effectiveness and enhancement of patient safety. As well, further research into new applications, such as in the treatment of hepatic encephalopathy, benzodiazepine addiction and withdrawal from chronic alcohol use [32], offer potentially new clinical avenues for the use of this drug.

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