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A REVIEW ARTICLE ON FLUMAZENIL DRUG

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Abstract:-
The main idea of this composition is to give all healthcare professional who are interested in BZD detoxification with an approach and clear practical information on how to administer FLU. Flumazenil is benzodiazepine receptor antagonist. Flumazenil acts as a competitive antagonist at the benzodiazepine receptor to envenom the conduct of benzodiazepines. Flumazenil does not reverse the goods of opioids. After intravenous administration flumazenil is considerably distributed in the extravascular space with an original distribution half-life of 4 to 11 twinkles and a terminal half-life of 40 to 80 twinkles. The major metabolites of flumazenil linked in unine are the de-ethylated free acid and its glucuronide conjugate. The goods of fumazenil on ventilatory response following sedation with a benzodiazepine in combination with an opioid are inconsistent.

Objective: The end of this composition is to give all healthcare professional who are interested in BZD detoxification with an approach and clear practical information on how to administer .

Aim: To review the literature on the safety and efficacy of flumazenil in benzodiazepine use diseases and identify gaps in the literature.

Keywords: Flumazenil; Benzodiazpeine, Antagonist,Conjugate,Half-life etc.

INTRODUCTION:-
Flumazenil Injection, USP is a benzodiazepine receptor antagonist. Chemically, flumazenil is ethyl 8-fluoro-5,6-dihydro-5-methyl-6-oxo-4H-imidazo [1,5-a](1,4) benzodiazepine-3-carboxylate. Flumazenil has an imidazobenzodiazepine structure a adviced molecular weight of 303.3.[13,14,66]

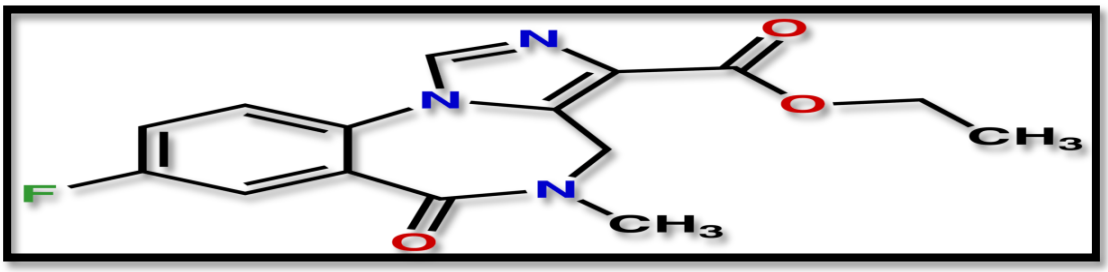

Fig no1- Structure of Flumenzil

and the ensuing structural formula Flumazenil is a white to out-white crystalline compound with an octanol:buffer partition measure of 14 to 1 at pH 7.4. It is undoable in water but slightly answerable in acidic waterless results. Flumazenil is available as a sterile parenteral dosage form for intravenous administration. Each mL contains 0.1 mg of Flumazenil compounded with 1.8 mg of Methylparaben , 0.2 mg of Propylparaben , 0.9% mg Sodium Chloride , 0.01% Edetate Disodium Dihydrate , and 0.1 mg Glacial

Acetic Acid ; the pH is adjusted to 3.4 to 4.6 with Hydrochloric Acid and/or, if necessary, Sodium Hydroxide and Water for Injection q.s. to 1 mL. [4,10]

Mechanism Action Of Flumazenil:-

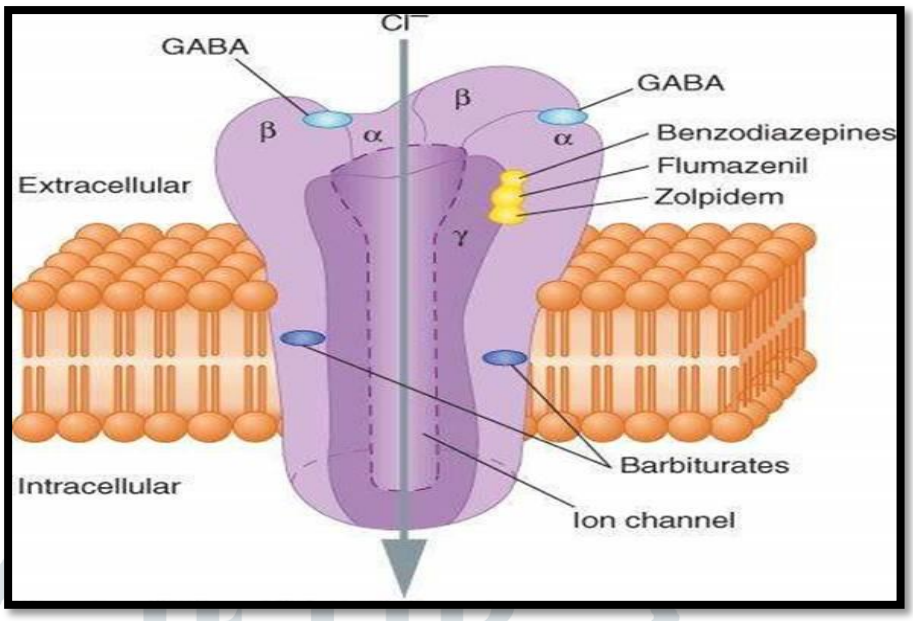

Fig no-2-Mechanism action of Flumazenil

It binds competitively to BDZ binding site and antagonizes the allosteric action of BDZ and other ligands. Flumazenil can antagonizes both behavioral and electrophysiological effects of BDZ. It doesn't block pharmacological effects of GABA or GABA-mimetics.[1,2,3]

It also blocks effects of non-benzodiazepine agonists like zopiclone at BDZ receptor. [6,7,13]

.PHARMACOLOGY:-[1]

Pharmacodynamic:-

With reference literature Data Intravenous flumazenil has been shown to antagonise sedation, impairment of recall, psychomotor impairment and ventilatory depression produced by benzodiazepines in healthy mortal ompositions (still, amnesia is less commonly and less constantly reversed). The duration and degree of reversal of comforting benzodiazepine goods are related to the cure and attention of flumazenil. Flumazenil acts as a competitive antagonist at the benzodiazepine receptor to antagonize the conduct of benzodiazepines. Flumazenil does not reverse the goods of opioids. The following data is from a reported study in normal lieves. Generally, bolus of roughly 0.1 mg to 0.2 mg (corresponding to peak tube situation of 3 to 6 ng/mL) produce partial enmity, where advance boluses of 0.4 to 1 mg (peak tube situation of 1 12 to 28 ng/mL) generally produce complete enmity in cases who have entered the usual sedating bolus of benzodiazepines. The onset of reversal is generally apparent within 1 to 2 twinkles after the injection is completed. Eighty percent response will be reached within 3 twinkles, with the peak effect being at 6 to 10 twinkles. The duration and degree of reversal are related to the tube attention of the sedating benzodiazepine as well as the cure of flumazenil given. Flumazenil is cleared fleetly and the eventually for resedation exists. Resedation is less likely to do when flumazenil is used to reverse effect of midazolam as midazolam has a more rapid fire concurrence than other benzodiazepines[13,27,79].

PHARMACOKINETICS:-

Distribution:-

The pharmacokinetics of flumazenil are cure-commensurable up to 100 mg. After intravenous administration flumazenil is condsiderably distributed in the extravascular space with an original distribution half-life of 4 to 11 twinkles and a terminal half-life of 40 to 80 teinkels. Peak attention of flumazenil are commensurable to cure, with an apparent original volume of distribution of 0.5 L/kg. The volume of distribution at steady-state is 0.9 to 1.1 L/kg Flumazenil is a weak lipophilic base. Protein list is roughly 50% and the medicine shows no preferential partitioning into red blood cells. Albumin accounts for two thirds of tube protein list..[79,81]

Metabolism:-Flumazenil is nearly (99%) metabolized. Veritably little unchanged fumazani (<1%) is set up in the urine. The major metabolites of flumazenil linked in unine are the de-ethylated free acid and its glucuronide conjugate. In preclinical studies there was no substantiation of pharmacologic exertion displayed by the de-ethylated tree acid [13,14,6]

Elimination:-

Elimination of radiolabeled medicine is basically complete within 72 hours, with 90% to 95% of the radicactivity appearing in urine and 5% to 10% in the feces.Occurance of flumazenil occurs primarily by hepatic metabolism and is dependent on hepatic blood

inflow (as per iterature data in pharmacokinetic studies of normal levies, total concurrence ranged from 0.8 to 1.0 U hr kg. [77]Ingestion of food during an intravenous infusion of medicine results in a 50% increase in concurrence (probably due to the increased hepatic blood inflow that accompanies a mess) Pharmacokinetic parameters (mean) following a 5-minute infusion of a total of 1 mg of fumazerat. [13,77,79]

Cmax	24
V ss (L/Kg)	1
Cpncurrence (L/h/Kg)	1
T 1/2 (min)	54

Special Populations:-

The Elderly The pharmacokinetics of flumazenil are not significantly altered in the senior. Gender The pharmacokinetics of flumazenil are not different in manly and womanish subjects. [84]

Renal Dysfunction:-

The pharmacokinetics of flumazenil are not significantly altered by renal failure or by hemodialysis. [77,]

Liver Dysfunction:-

In cases with moderate liver dysfunction the mean total concurrence is dropped to 40% to 60% and in patients with severe liver dysfunction it is dropped to 25% of normal value as compared with age matched healthy subjects. [43] This results in a extension of the half life to 1.3 hours in cases with moderate hepatic impairment and 2.4 hours in severaly disabled cases. Caution must be exercised with original and/or repeated dosing to cases with liver complaint.[71,73]

Pediatric cases:-

Compared to agrown-up the elimination half-life in pediatric cases is more variable. Concurrence and volume of distribution, regularized for body weight are in the same range as those seen in agrown-ups although further variablility may be seen. (Limited information grounded on literature reports of unbridled studies in pediatric cases).

SUGGESTIONS AND OPERATION:-

To reverse the benzodiazepine goods in

Pediatric cases

Reversal of benzodiazepine goods in cases where benzodiazepine was a part of general anesthesia Reversal of benzodiazepine goods in cases where benzodiazepine was used as part of conscious sedation for individual and remedial procedures operation elderly cases

Benzodiazepine overdose

For the complete or partial reversal of the dreamy goods of benzodiazepines in cases where general anesthesia has been convinced and/or maintained with benzodiazepines where sedation has been produced with benzodiazepines for, and for the operation of benzodiazepine overdose Pediatric cases (progressed 1 to 17): Flumazenil injection is indicated for the reversal of conscious sedation convinced with benzodiazepines [9,31,39,40,52,]

PREVENTIVES:-

Return of Sedation - Flumazanil may be anticipated to ameliorate the alertness of cases recovering from a procedure involving sedation or anesthesia with benzodiazepines, but it is not a cover for an acceptable period of post-procedure monitoring Avilability of fumazenil does not reduce the pitfalls associated with the use of large boluses of benzodiazepines for sedation. [29,96]

Use in Benzodiazepine Overdosage - Flumazanit is intended as an adjunct to, and not as a cover for, proper operation of airway, supported breathing, circulatory access and support, internal decontamination by lavage and charcole (in oral overdose of a benzodiazepine), and acceptable clinical evaluation .

Threat of seizures-Flumarenl is known to precipitate pullout seizures in cases who are physically dependent on benzodiazepines within a few days of sedation in Intensive Care Unit (ICU) surrounding. Flumazenit should be used in similar settings with extreme cauton Possible threat factors include concurrent major opiate-narcotics medicine pullout. Recent remedy with repeated boluse of parenteral benzodiazepines myoclonic jerking or seizure exertion prior to flumazenil adminstration in overdose cases, or concurrent cyclic antidepressant poisoning [1]

Head Injury-Flumazanil should be used with caution in cases with head injury as it may be able of pouring storms or altering cerebral blood inflow in cases entering benzodiazepines. It should be used only by interpreters prepared to manage similar complications should they do.[97]

Use in Respiratory Complaints- The primary treatment of cases with serious lung complaint whowitness serious respiratory depression due to benzodiazepines should be applicable ventilatory support rather than the administration of flumazenil. Although Pumazenil is able of incompletely reverse benzodiazepine convinced differences in ventilatory drive in healthy leives it has not been shown to be clinically effective.

Cardiovascular Disease - Flumazenil did not increase the work of the heart when used to reverse benzodiazepines in cardiac cases when given at a rate of 0.1 mg/min in total doses of lower than 0.5 mg in studies reported in the clinical literature. Flumazani alene had no significant goods on cardiovascular parameters when administered to cases with stable ischemic heart complaints.[84,90,97]

Use in Liver Disease- While the cure of flumazenil used for original reversal of benzodiazepine goods is not affected, repeat boluses of the medicine in liver complaint should be reduced in size or frequency.[

Pain On Injection -To minimize the liability of pain or inflammation at the injection point, fumazanit should be administered through a freely flowing intravenous infusion into a Inge vein. Original reproduction may do following extravasation into perivascular issues.

- **General:** Fumazenil should not be used until goods of neuromuscular lraguer have been completely reversed.In psychiatric cases flumazenil has been reported to provoke fear attacks in parents with a history of panic disorder[54,44]
- Flumazenil may cause benzodiazepine pullout symptoms in individualities dependent on benzodiazepines .Storms associated with flumazenil administration bear treatment and may be successfully managed with benzodiazepines, phenytoin or barbiturates. [93]
- Overdose cases should always be covered for resedation until the cases stable and resedation is doughyful Resedation is most likely in cases where a large single or accretive cure of a benzodiazepine has been given in the course of a long procedure along with neuromuscular blocking agents and multiple anesthetic agents [32,92]
- Pediatric cases who have come completaly awake following treatment with tumazan may witness a rush of sedation. The safety and effectiveness of repeated fumazenil administration in pediatric cases passing resedation have not been established Upon arousal caseas may assay to withdraw endotracheal tubes and/or intravenous lines as a result of confusion and agitation following awakening
- Cases with serious lung complaint should have applicable ventilatory support [9,10,15]
- Flumazenil should be used with caution in cases with drunkenness and other medicine dependence due to the increased frequency of benzodiazepine forbearance.[

- Assume that flumazenil administration may spark cure-dependent pullout runss in cases with physical dependence on benzodiazepines and may complicate the operation of pullout runs for alcohol, barbiturates and cross-tolerant sedatives.[94,95]
- Use with great caution when using flumazenit in cases of mixed medicine overdosage since the poisonous goods (similar as unheal and cardiac dysrhythmias) of other medicine taken in overdose (especially cyclic antidepressants) may crop with the reversal of the benzodiazepine effect by flumazonil.

CONTRAINDICATIONS:-

flumazenil injection is contraindicated:

- patients with a known hypersensitivity to flumazenil or benzodiazepines .[70]
- In patients who have been given a benzodiazepine for control of a potentially life threatening condition (eg, control of intracranial pressure or status epilepticus)
- in patients who are showing signs of serious cyclic antidepressant overdose Flumazeni is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although flumazenil exerts a slight intrinsic anticonvulsant attect, abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients [13]
- Flumazenil is not recommended te diagnose benzodiazepin-induced sedation in theICU [57,58]
- As treatment for benzodiazepine dependenes/ management of benzodiazepine abstinence syndrome [72]

DRUG INTERACTIONS:-

- The pharmacokinetic profile of flumazenil is unaltered in the presence of benzodiazepine agonists and the kinetics of diazepam, flunitrazepam, lormetazepam, and midazolam are not altered by flumazenil. [46,49,67,69]
- Interaction with central nervous system depressants other than benzodiazepines has not been specifically studied, however, no delaterious interactions have been reported when flumazenil was administered after narcotics, inhalational anesthetics, muscle relaxants and muscle relaxant antagonists administered in conjunction with sedation of anesthesia
- The effects of nonbenzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others are also blocked by flumazenil.[88]
- The effects of fumazenil on ventilatory response following sedation with a benzodiazepine in combination with an opioid are inconsistent [89]

Use In Ambulatory Patients:-

The effects of flumazenil may wear off before a long-acting benzodiazepine is completely
cleared from the body. In general, if a patient shows no signs of sedation within 2 hours after a 1 mg dose of flumazenil, serious resedation at a later time is unlikely. An adequate period of observation must be provided for any patient in whom either long-acting benzodiazepines (such as diazepam) or large doses of short-acting benzodiazepines (such as 10 mg of midazolam) have been used.[8] Because of the increased risk of adverse reactions in patients who have been taking benzodiazepines on a regular basis, it is particularly important that physicians query patients or their guardians carefully about benzodiazepine, alcohol and dedative use as part of the history prior to any procedure in which the use of a benzodiazepine and or flumazenil is planned.[8,33,45]

Pregnancy:-

Flumazenil should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery:-

The use of flumazenil to reverse the effects of benzodiazepines used during labor and delivery is not recommended because the effects of the drug in the newborn are unknown.

Nursing Mothers :-

It is not known whether flumazenil is excreted in human milk

Pediatric Use:-

The safety and effectiveness of flumazenil have not been established in pediatric patients younger than 1 year of age. The risks identified in the adult population with flumazenil use also apply to pediatric patients.[40,42,43]

Adverse Reactions:-

Serious Adverse Reactions As per available medical literature, deaths have occurred in patients who received flumazenil in a variety of clinical settings. The majority of deaths occurred in patients with serious underlying disease or in patients who had ingested large amounts of non benzodiazepine drugs (usually cyclic antidepressants), as part of an overdose. Serious adverse events have occurred in all clinical settings, and convulsions are the most common serious adverse events reported Flumazenil administration has been associated with the onset of convulsions in patients with severe hepatic impairment and in patients who are relying on benzodiazepine effects to control seizures, are physically dependent on benzodiazepines, or who have ingested large doses of other drugs (mixed-drug overdose) [19,39]Adverse Events reported in Clinical Studies in literature Adverse events most frequently associated with Flumazenil alone were limited to dizziness, injection site pain, increased sweating, headache, and abnormal or blurred vision (3% to 9%) Body as a Whole fatigue (asthenia, malaise), headache, injection site pain, injection. site reaction (thrombophlebitis, skin abnormality, rash) Cardiovascular System: [46] cutaneous vasodilation (sweating, flushing, hot flushes) Digestive System: nausea, vomiting Nervous System agitation (anxiety, nervousness, dry mouth, tremor, palpitations,

insomnia, dyspnea, hyperventilation), dizziness (vertigo, ataxia), emotional lability (abnormal crying. depersonalization, euphoria, increased tears, depression, dysphoria, paranoia).[39,46]

Additional Adverse Reactions Reported During Post Marketing Experience:-

Literature reports the following events during post-approval use of flumazenil. Fear, panic attacks in patients with a history of panic disorders. Withdrawal symptoms may occur. following rapid injection of flumazenil in patients with long-term exposure to benzodiazepines. [23,24,30,54,55]

OVERDOSAGE:-

There is limited experience of acute overdose with flumazenil. There is no specific antidote for overdose with flumazenil. Treatment of an overdose with Flumazenil should consist of general supportive measures including monitoring of vital signs and observation: of the clinical status of the patient. With reference literature, most adverse reactions to flumazenil were an extension of the pharmacologic effects of the drug in reversing benzodiazepine effects. Reversal with an excessively high dose of flumazenil may produce anxiety, agitation, increased muscle tone, hyperesthesia and possibly convulsions. Convulsions have been treated with barbiturates, benzodiazepines and phenytoin, generally with prompt resolution of the seizures,[31,39,64,87,]

Dosage Individualization:-

Any serious adverse effect of flumazenil is related to the reversal of benzodiazepine effects. Use of more than the minimally effective dose of flumazenil is tolerated by most patients but may complicate the management of patients who are physically dependent on benzodiazepines or patients who are depending on benzodiazepines for therapeutic effect (such as suppression of seizures in cyclic antidepressant overdose).[27] In high-risk patients, it is important to administer the smallest amount of flumazenil that is effective. The 1-minute walt between individual doses in the dose-titration recommended for general clinical populations may be too short for high-risk patients. This is because it takes 6 to 10 minutes for any single dose of flumazenil to reach full effects. Administration of flumazenil should be very slow in high-risk patients. Fiumazenil alone at a rate of 0.1 mg/ min in total doses of less than 0.5 mg is unlikely to have significant effects on cardiovascular parameters when administered to patients with stable ischemic heart disease [27,87]

DOSAGE AND ADMINISTRATION:-

The 1-minute walt between individual bolus in the cure-titration recommended for general clinical populations may be too short for high-threat cases. [10] This is because it takes 6 to 10 teinkles for any single cure of flumazenil to reach full goods. [51,54]

Flumazeni injection, is recommended for intravenous use only. It is compatible with 5% dextrose in water, lactated Ringer's and normal saline results. For optimum sterility fumazenil injection should remain in the vial until just before use. As with all parenteral medicinal products, flumazenil injection should be audited visually for particulate matter and abrasion previous to administration, whenever results and vessels permit. To minimize the liability of pain at the injection point, flumazenil injection should be administered through a freely running intravenous infusion into a large tone.[78,91,94]

Operation of Suspected Benzodiazepine Overdose in Adult cases:-

For original operation of a known or suspected benzodiazepine overdose, the recommended original cure of flumazenil injection is 0.2 mg (2 mL) administered intravenously over 30 seconds.[5] If the asked position of knowledge is not obtained after staying 30 seconds, a further cure of 0.3 mg (3 mL) can be administered over another 30 seconds. Further cure of 0.5 mg (5 ml) can be administered over 30 seconds at 1 minute intervals up to a accretive cure of 3 mg. Do not rush the administration of flumazenil injection. Cases should have a secure airway and intravenous access before administration of the medicine and be awakened gradationally, upmost cases with a benzodiazepine overdose will respond to a accretive cure of 1 mg to 3 mg of flumazenil injection, and bolus beyond 3 mg do not reliably produce fresh effects.[95] On rare occasions, cases with a partial response at 3 mg may bear afresh titration up to a total cure Of 5mg

(administered sluggishly in the same manner). If a case has not responded 5 minutes after receiving a accretive cure of 5 mg of Flumazenil injection, the major cause of sedation is likely not to be due to benzodiazepines, and additional flumazenil is likely to have no effect. In the event of resedation, repeated bolus may be given at 20-minute intervals if demanded. For reprise treatment, no further 1 mg (given as 0.5 mg/min) should be given at any one time and no more than 3 mg should be given in any one hour.[3,5,95,91]

Reversal of Conscious Sedation:-

Adult cases

For the reversal of the dreamy goods of benzodiazepines administered for conscious sedation, the recommended original cure of flumazenil injection is 0.2 mg (2 mL) administered intravenously over 15 seconds. If the asked position of knowledge is not attained after staying an fresh 45 seconds, a second dose of 0.2 mg (2 mL) can be fitted and repeated at 60 second Intervals where necessary (up to a outside of 4 fresh times) to a maximum total cure of 1 mg (10 mL). The dosage should be personalised grounded on the cases response, with upmost cases responding to boluses of 0.6 mg to 1 mg. In the event of resedation, repeated boluses may be administered at 20 minute intervals as demanded. For repaire treatment, no further 1 mg (given as 0.2 mg/min) should be: administered at any one time, and no further 3 mg should be given in any one hour. It is recommended that flumazenil be

administered as the series of small injections as described (and not as a single bolus injection) to allow the practitioner to control the reversal of sedation to the approximate endpoint asked and to minimize the possibility of adverse goods.[82,101,93]

Pediatric cases

For the reversal of the dreamy goods of benzodiazepines administered for conscious sedation in pediatric cases greater than 1 year of age, the recommended initial dose is 0.01 mg/kg (up to 0.2 mg) administered intravenously over 15 seconds.[40] If the desired level of consciousness is not obtained after waiting an additional 45 seconds, further Injections of 0.01 mg/kg (up to 0.2 mg) can be administered and repeated at 60 second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 0.05 mg/kg or 1 mg, whichever is lower.[42,43] The dose should be individualized based on the patient's response. The reported mean total dese administered in the pediatrie clinical trial of fiumazenit was 0.65 mg trange: 0.08 mg to 100 mg). Approximately one half of patients required the maximum of five injections Resedation occurred in 7 of 60 pediatric patients who were fulty alort 10 minutes after the start of fumazenil injection administration. The safety and efficacy of repeated flumazenit administration in pediatric patients experiencing resedation have not been established. The safely and efficacy of flumazenil injection in the reversal of conscious sedation in pediatric patients below the age of 1 year have not been established.[40,43]

Reversal of Benzodiazeoine effects when it was a part of General Anesthesia:-

For the reversal of the sedative effects of benzodiazepines administered during general anesthesia, the recommended initial dose of flumazenil is 0.2 mg (2 ml) administered intravenously over 15 seconds. If the desired level of consciousness is not obtained after waiting an additional 45 seconds, a further dose of 0.2 mg (2 ml) can be injected and s repeated at 60-second intervals where necessary (up to a maximum of 4 additional times) to a maximum total dose of 1 mg (10 mL). [80] The dosage should be individualized based on the patient's response, with most patients responding to doses of 0.0 mg to 1 mg in the event of resedation, repeated doses may be administered at 20-minute intervals as needed. For repeat treatment, no more than 1 mg (given as 0.2 mg/min) should be administered at any one time, and no further 3 mg should be given in any one.[10,71,75,]

Therapeutic Uses of Flumazenil

- Reversal of Benzodiazepine (BDZ) Anesthesia - A patient anesthetized with BDZ can wake up and regain motor control within 1 minute when 0.3-1 mg of flumazenil is administered. It is therefore used in the early discharge of patients after diagnosis or surgery and is useful in post-anesthesia care. [10.71]
- For BDZ poisoning or overdose - used in suspected BDZ overdose. It can help quickly regain consciousness within 5-15 minutes after the injection. In most cases of BDZ overdose, patients respond to a cumulative dose of 1-3 mg. In rare cases, an additional dose of up to 5 mg may be required. If no response is achieved after a 5 mg cumulative dose over 5 minutes, benzodiazepines may not be the primary cause of sedation..[5,31,39]
- Some of its non-FDA approved uses are-
    - Alcohol withdrawal syndrome
    - In reversing drug action of Baclofen
    - In toxicity of drug cannabis

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