FLUNEXATE®

Flumazenil

ACTION

Flumazenil, an imidazobenzodiazepine, is a benzodiazepine antagonist which, by competitive inhibition, specifically blocks the central nervous effects of agents acting through benzodiazepine receptors. This antagonistic effect was documented in studies involving 17 different benzodiazepine derivatives. In animal experiments the effects of compounds showing no affinity for benzodiazepine receptors, e.g. barbiturates, ethanol, meprobamate, GABA mimetics, adenosine receptor agonists, were not affected by Flumazenil, but those of nonbenzodiazepine agonists of benzodiazepine receptors, such as cyclopyrrolones (e.g. zopiclone) and triazolopyridazines, were blocked. The hypnotic-sedative benzodiazepine effects are rapidly reversed by Flumazenil after its intravenous injection (within 30-60 seconds) and may reappear gradually within the next few hours, depending on the half-life and dose ratio of the agonist and antagonist. In animal toxicity studies, Flumazenil proved to be of low toxicity and devoid of mutagenic activity. Flumazenil may possess some weak intrinsic agonistic, e.g. anticonvulsant, activity. In animals pretreated with high doses of benzodiazepines over several weeks, Flumazenil elicited symptoms of withdrawal.

PHARMACOKINETICS

Distribution

Flumazenil, a weak lipophilic base, is about 50% bound to plasma proteins. Albumin accounts for two thirds of the plasma protein binding. The mean volume of distribution at steady state (Vss= 0.95 l/kg) is similar to that of structurally related benzodiazepines.

Metabolism

The carboxylic acid in free and conjugated form is the main metabolite in human urine. In pharmacological tests, this main metabolite was inactive as a benzodiazepine agonist or antagonist.

Elimination

Flumazenil is almost completely (99%) nonrenally eliminated. The mean total plasma clearance of flumazenil is 1 l/min and can be attributed almost entirely to hepatic clearance. The low renal clearance rate suggests effective reabsorption of the drug after glomerular filtration. The average elimination half-life of the drug is 50-60 minutes.

INDICATIONS

Flunexate is indicated for reversal of the centrally sedative effects of benzodiazepines. It is therefore used in anesthesia and intensive care in the following indications:

In anesthesia

Termination of general anesthesia induced and maintained with benzodiazepines in inpatients. Reversal of benzodiazepine sedation in short diagnostic and therapeutic procedures in both inpatients and outpatients.

In intensive care

Flunexate provides diagnostic indications of intoxication with benzodiazepines or rules such intoxication out.

As a diagnostic measure in unconsciousness of unknown origin to differentiate between involvement of benzodiazopines, other drugs or brain damage. As specific reversal of the central effects of benzodiazepines in drug overdose (return to spontaneous respiration and consciousness in order to render intubation unnecessary or allow extubation)

DOSAGE AND ADMINISTRATION

Standard dosage

Flunexate should be administered i.v. by an anesthesiologist or experienced physician.

For infusion, Flunexate may be diluted with dextrose 5% or sodium chloride 0.9%; it may also be used concurrently with other resuscitative procedures.

In anesthesia

The recommended initial dose is 0.2 mg administered i.v. over 15 seconds. If the desired degree of consciousness is not obtained within 60 seconds, a second dose (0.1 mg) can be injected, and this may be repeated at 60-second intervals where necessary, up to a total dose of 1 mg. The usual dose is 0.3-0.6 mg.

In the intensive care unit

The recommended initial dose is 0.3 mg i.v. If the desired degree of consciousness is not obtained within 6. seconds, Flunexate may be injected repeatedly until the patient awakes or up to a total dose of 2 mg. If drowsiness recurs, an i.v. infusion of 0.1-0.4 mg per hour has been shown to be useful. The rate of infusion should be individually adjusted up to the desired level of arousal.

In the intensive care unit, in patients treated for a long time with high doses of benzodiazepines, the individually titrated injections of Flunexate, slowly administered, should not produce withdrawal syndromes. If unexpected signs of overstimulation occur 5 mg diazepam or 5 mg midazolam should be given intravenously.

If a significant improvement in consciousness or respiratory function is not obtained after repeated doses of Flunexate, a nonbenzodiazepine etiology must be assumed.

CONTRAINDICATIONS

Flumazenil is contraindicated in patients with known hypersensitivity to the drug.

In mixed intoxications with benzodiazepines and cyclic antidepressants, the toxicity of the antidepressants can be masked by protective benzodiazepine effects. In the presence of autonomic (anticholinergic), neurological (motor abnormalities) or cardiovascular symptoms of severe intoxication with tricyclics/tetracyclics, Flumazenil should not be used to reverse benzodiazepine effects.

PRECAUTIONS

The use of Flumazenil is not recommended in epileptic patients who have been receiving benzodiazepine treatment for a prolonged period. Although Flumazenil exerts a slight intrinsic anticonvulsant effect, its abrupt suppression of the protective effect of a benzodiazepine agonist can give rise to convulsions in epileptic patients.

Patients with severe head injury (and/or unstable intracranial pressure) treated with Flumazenil to reverse the effects of benzodiazepines may develop raised intracranial pressure.

Effect on driving and other psychomotor skills in outpatients

Although after intravenous administration of Flumazenil the patients are awake and conscious, they should be warned against engaging in hazardous activities requiring complete mental alertness (such as operating dangerous machinery or driving a motor vehicle) during the first 24 hours after administration since the effect of the originally ingested or administered benzodiazepine may return.

Pregnancy, nursing mothers

Although studies in animals given high doses of Flumazenil have not shown evidence of embryotoxicity or teratogenicity, no controlled studies involving pregnant women have been conducted. Attention is therefore drawn to the general medical principle that no drugs should be administered in the early stages of pregnancy except where absolutely necessary.

Parenteral administration of Flumazenil in emergencies is not contraindicated during lactation.

Special remarks

Please note

When used in anesthesiology at the end of an operation, Flumazenil should not be injected until the effect of peripheral muscle relaxants has subsided.

Drug Interactions

Flumazenil blocks the central effects of benzodiazepines by competitive interaction at the receptor level. The effects of nonbenzodiazepine agonists at benzodiazepine receptors, such as zopiclone, triazolopyridazines and others, are also blocked by Flumazenil. Particular caution is necessary when using Flumazenil in cases of mixed drug overdose since the toxic effects (such as convulsions and cardiac dysrhythmias) of other drugs taken in overdose (especially cyclic antidepressants) may emerge with the reversal of the benzodiazepine effects by Flumazenil. The pharmacokinetics of benzodiazepine agonists are unaltered in the presence of Flumazenil and vice versa.

SIDE EFFECTS

Flumazenil was well tolerated even at high parenteral doses of up to 100 mg.

In rare cases during use in anesthesia, flush, nausea and/or vomiting have been reported. Complaints such as a feeling of anxiety, palpitations and fear have been infrequently observed after rapid injection of Flumazenil. These undesirable effects usually did not necessitate special treatment.

Very rarely, seizures have been reported, particularly in patients known to suffer from epilepsy.

Rapid injection of Flumazenil in patients with long-term exposure to benzodiazepines ending at any time within the weeks preceding Flumazenil administration may produce withdrawal symptoms and should therefore be avoided. If such symptoms arise, a slow i.v. injection of 5 mg diazepam or 5 mg midazolam should be given.

OVERDOSAGE

Even when given at a dosage of 100 mg i.v., no symptoms of overdosage were observed. For withdrawal symptoms attributable to the agonist, see under Standard dosage.

STORAGE

Store between 15 - 30°C. Protect from freezing.

PRESENTATIONS

Ampoules

FLUNEXATE 0.5 mg: Flumazenil 0.5 mg/5 ml

FLUNEXATE 1 mg: Flumazenil 1 mg/10 ml

Excipients: Edetate disodium, Sodium chloride, Glacial acetic acid, NaOH/ HCl (for pH adjustment), Water for injection.

THIS IS A MEDICAMENT

- A medicament is a product which affects your health, and its consumption contrary to instructions is dangerous.
- Follow the doctor's prescription strictly, the method of use and the instructions of the pharmacist who sold the medicament.
- The doctor and the pharmacist are experts in medicine, its benefits and risks.
- Do not by yourself interrupt the period of treatment prescribed for you.
- Do not repeat the same prescription without consulting your doctor.

HIKMA Pharmaceuticals, Amman-Jordan

Keep medicament out of the reach of children

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