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Flumazenil Use in Children

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Aim: **To review reversal of benzodiazepine-induced central nervous system depression in children by flumazenil.**

Methods: **A Medline search of original data on flumazenil use, employing the keywords *benzodiazepine, antagonist, flumazenil, paediatric, children, overdose, coma, sedation, reversal, treatment.***

Results: **Our search revealed 36 original studies, case reports or letters involving 413 patients describing flumazenil use in emergency departments, intensive care units, operating theatres or outpatient clinics. Flumazenil use promptly reversed central nervous system depression resulting in full awakening and avoiding the need for artificial ventilation. Intravenous (IV) flumazenil administration in boluses of 5–10 microg/kg reversed midazolam sedation or benzodiazepine overdose within 15 minutes. A second dose was required in a third of the children for complete awakening and continuous infusions ranging from 6 to 24 hours in cases of benzodiazepine intoxication. Intraoperative awakening was achieved using IV boluses of 3–10 microg/kg. Re-sedation after the first bolus occurred in 36% (of 308 specified cases). The rate of adverse effects was between 16 and 17%.**

Conclusions: **Flumazenil is a safe antidote for the prompt diagnosis and reversal of benzodiazepine-induced central nervous system and respiratory depression in children.**

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Keywords: Flumazenil – paediatric – benzodiazepines – overdose – sedation

Introduction

Benzodiazepines are frequently prescribed drugs for the alleviation of anxiety, insomnia or depression[1]. Their widespread availability has led to their frequent use in deliberate self-harm[2-5] with children (<18 years) accounting for ~50% of the cases. Anaesthetists are increasingly using short-acting benzodiazepines for sedation in children outside the operating room[6, 7]. The use of midazolam has become popular in paediatrics due to the ability to administer it in a relatively painless way i.e., orally, rectally, intranasally or sublingually, in addition to the intramuscular (IM) and intravenous (IV) routes[6-10]. Sedation has been used for a variety of medical and dental procedures[8, 11]. Benzodiazepine-induced depressive effects may increase in the paediatric population[5], especially in children suffering from cerebral palsy, cardiorespiratory disturbances or when other central nervous depressants are concomitantly used[12]. Hence, familiarity with the only clinically available antagonist, flumazenil, is mandatory since its administration causes prompt reversal of their effects, thus avoiding life-threatening side effects such as coma and upper airway obstruction[13-16].

In this review, we summarise the clinical data that we retrieved from a Medline literature search in English, French, German, Spanish and Italian on the use of flumazenil in the paediatric population. There were 36 publications (original studies, case reports and letters) which involved 413 patients and which described flumazenil use in emergency departments, intensive care areas, operating theatres and outpatient clinics, and in non-benzodiazepine-mediated unconscious children.

Pharmacology of flumazenil

Benzodiazepines exert their central nervous sedative effect by enhancing gamma-amino butyric acid (GABA) activity at the $GABA_A$ receptor, which controls the chloride ionophore distributed throughout the brain and the spinal cord. When activated by GABA, the $GABA_A$ complex mediates postsynaptic inhibition by facilitating chloride influx into the neurons, resulting in hyperpolarisation leading clinically to phenomena ranging from anxiolysis to hypnosis. Flumazenil has proved effective and safe in reversing all agonistic benzodiazepine effects in humans[1, 4, 12]. Flumazenil has a highly specific and competitive antagonistic activity at the GABA-benzodiazepine receptor[17]. By binding to the benzodiazepine receptor with high affinity, it counteracts the effects of the attached benzodiazepine without exercising any intrinsic activity[17, 18]. The result is the complete reversal of the sedative, implicit and explicit anterograde memory effects of the benzodiazepine, as well as the loss of time-space, orientation-collaboration and psychomotor performances without revoking its tranquillising and amnesic properties[19, 20].

Flumazenil is a water soluble 1,4-imidazobenzodiazepine with a molecular weight of 303.3 and a p*Ka* of 7.0. It possesses a two-compartment model of pharmacokinetic behaviour: a rapid and extensive distribution phase with a high volume of distribution and a rapid metabolic and elimination phase[21]. The volumes of distribution of both midazolam and flumazenil are quite similar. The clearance of flumazenil, however, is more rapid and the half-life shorter than that of midazolam[22]. Resedation with benzodiazepine after flumazenil administration is therefore possible. An IV equimolar dose of flumazenil will reverse the clinical effects of midazolam within 1 minute, with the antagonistic effect recognisable for up to 3.5 hours[23]. Flumazenil undergoes a complete and rapid hydroxylation by the hepatic microsomal system resulting in 3 non-active metabolites, which are almost entirely (90–95%) excreted in the urine within 2 hours from its administration[24]. Hence, when administered orally, flumazenil undergoes a high hepatic clearance and its bioavailability averages only 16%[24]. This explains its relatively high therapeutic index[25]. The metabolism of flumazenil is reduced in the presence of liver disease, but remains unaffected in uraemic patients[26] as well as in children[27].

Clinical use of flumazenil

Flumazenil has been shown to successfully reverse symptoms in 77–95% of children who had received excessive benzodiazepines[1, 13, 14]. Reports on flumazenil utilisation in children consist mainly of case reports. The drug has been used: (1) following suspected or known benzodiazepine-related overdose[15, 28-42]; (2) to reverse benzodiazepine-induced anaesthesia or sedation – both within and outside the operating room – during various procedures[43-47] and (3) after the termination of short procedures[6, 48-52]. There are also two large-scale studies each involving more than 100 children[14, 53] and another three double blind, placebo-controlled smaller studies (29, 38 and 40 children, respectively)[13, 54, 55].

Use of flumazenil for accidental overdose (emergency department, perinatal or paediatric ICU) (Table 1)

An overdose of a drug is a medical emergency that necessitates correct diagnosis and prompt

Table 1. Reversal of benzodiazepine overdose by intravenous flumazenil

Age (years)	Initial dose (microg)	Repeated doses	Infusion rate (microg/h)	Awakening (min)	Comments	Reference
1.2	170 kg^{-1}	✓		Prompt		5
8	40 kg^{-1}			Prompt		5
4.5	200			2		15
1.5	100	✓		1		15
3, 5 (2pt)	10 kg^{-1}	✓ (1pt)	10 kg^{-1}	3	Infusion for 6h	32
3	200			10		33
1.7	10 kg^{-1}	✓	5 kg^{-1}	3	Infusion for 24h	34
16	200			Prompt	Seizure	35
2	5 kg^{-1}	✓	5 kg^{-1}	<1		41
4–13 (3pt)	10 kg^{-1}		100–500	<1		42
0.1–14 (12pt)	100	✓ (3pt)		1–2		52
4	200	✓	200	Prompt	Infusion for 12h	56
13	500	✓	500	Prompt	Infusion for 12h	56
Perinatal						
36wk	300			<5		36
1h	10 kg^{-1}		10 kg^{-1}	1	Infusion for 6h	37
1h	20 kg^{-1}		20 kg^{-1}	10	Infusion for 6h	38
10h	10 kg^{-1}		10 → 3.8 kg^{-1}	<1	Infusion for 24h	39

treatment[31]. Mortality from pure benzodiazepine-induced overdose is uncommon. However, when combined with other depressant drugs, morbidity and mortality increase significantly, especially in the paediatric population[31]. There have been numerous case reports documenting the efficacy of flumazenil in reversing the effects of a benzodiazepine overdose[6, 15, 32-35, 41, 42, 56]. Most of the case reports involved a single child and all the children regained consciousness. Artificial ventilation was not required in any of the cases.

In several cases repeated doses of flumazenil were given on the basis of the patient showing a decreased level of consciousness. In some cases this was followed by a continuous infusion of flumazenil with the duration ranging from 6 to 24 hours in children and 6 hours-5 days in neonates (Table 1). In one paper a continuous infusion was used without a repeated bolus of flumazenil. This paper reported three children, one of whom showed a decreased level of consciousness and two of whom showed anxiety[42]. The need for repeated doses highlights the short duration of action of flumazenil in comparison to benzodiazepines.

In one study 39 children were admitted to the paediatric intensive care unit (PICU) because of respiratory depression or dystonia following the use of midazolam as a sedative agent[52]. Twelve children had respiratory depression, which required flumazenil. All awoke promptly but three required a second dose.

Perinatal

A woman, who was 36 weeks pregnant, ingested approximately 300 mg of diazepam[36]. Fetal monitoring showed decreased heart rate variability, absence of accelerations, tendency towards tachycardia and occasional decelerations. The woman received flumazenil and the abnormalities in the fetus resolved within five minutes. The mother remained awake for 3–5 hours, whereas abnormalities in fetal monitoring did not recur until approximately 14 hours after administration of flumazenil. A second dose resulted in disappearance of symptoms in both mother and fetus. Flumazenil has also been shown to be effective in neonates whose mothers had received either a single dose of diazepam or multiple doses prior to delivery[37-39]. A rapid clinical response was seen in each case.

Summary
Flumazenil is effective in cases of benzodiazepine overdose. Administration of a second dose is required in a minority of patients. A continuous infusion may be required in certain situations.

Therapeutic (intraoperative or periprocedural) use of flumazenil (Tables 2 and 3)

Intraoperative
Intraoperative awakening is important during scoliosis or spinal fusion surgery in order to assess preservation of motor and sensory functions. In two studies, 30 children were premedicated with midazolam and other anaesthetic agents. Intraoperative administration of flumazenil was effective in fully awakening 27 children[43, 44]. Only one could recall unpleasant intraoperative events during the postoperative interview.

Reversal of paradoxical reactions
Paradoxical reactions to benzodiazepines, ranging from severe behavioural disturbances (e.g. agitation, paranoid reaction and even psychosis) to hostility, aggression and rage have been described with an incidence of 1.4% in children following midazolam administration[46]. The incidence is considerably higher following co-administration with pethidine (11.3%)[45]. In a prospective study of over 2,000 children who received midazolam and pethidine for a variety of endoscopic procedures, 36 children experienced paradoxical behavioural reactions to midazolam, which disappeared within 15 minutes following treatment with flumazenil (10 microg/kg)[46]. There have also been several case reports of the use of flumazenil to reverse paradoxical reactions to midazolam (Table 2)[47, 51, 57-59].

Reversal of sedation
The ability of flumazenil to reverse the sedative effect of benzodiazepines has been used following both sedation and anaesthesia[14, 48-53]. Three double blind clinical trials have compared flumazenil to placebo in a total of 107 children following the use of midazolam and general anaesthesia[13], diazepam and general anaesthesia[55] and diazepam alone[54]. All three studies showed that flumazenil was effective in reversing the sedation. Two large non-randomised studies, each involving 107 children, have confirmed the efficacy of flumazenil in these situations[14, 53]. Repeated injections, however, are often required. There have also been several case reports of small numbers of patients (Table 3).

Summary
In general, intraoperative prompt awakening in children anaesthetised with benzodiazepines results after the administration of 3-5 microg/kg flumazenil IV. In periprocedural occasions, boluses ranging between 5 and 40 microg/kg IV will reverse midazolam-induced sedation within 5 minutes. One third of children may require a second dose.

Other indications for the use of flumazenil

Metabolic coma is sometimes associated with the accumulation of benzodiazepines or endogenous benzodiazepine-like substances in the blood[60]. The effect of flumazenil was evaluated in 18 encephalopathic children (due to renal, hepatic insufficiency or metabolic disorder) in the PICU[16,61]. Repeated boluses of 400 microg flumazenil and a continuous infusion (200–400 microg) for a variable period (from 11 hours to 10 days) resulted in minimal arousal of only 2 children lasting from 30 minutes to a few hours. An improvement in EEG abnormality lasted for only minutes in two patients, indicating probable minimal therapeutic value of flumazenil in children as compared to its reported efficacy in similar encephalopathic adults[60].

Table 2. Periprocedural use of intravenous flumazenil

Number of patients	Age (years)	Initial dose (microg)	Repeated doses	Awakening (min)	Reference
10	16.6±4.9	3 kg^{-1}		Prompt	43
17	17 (5–18)	5 kg^{-1}		<2	44
2	6, 9	10 kg^{-1}		Prompt	45
36	3 (1–17)	10 kg^{-1}		14±12	46
1	11	150		Prompt	51
1	12d	8 kg^{-1}		5	57
1	13	50	✓	20 sec	58
2	15, 19	100			59

Table 3. Reversal of sedation with intravenous flumazenil						
Number of patients	**Age (years)**	**Initial dose (microg)**	**Repeated doses**	**Awakening (min)**	**Comments**	**Reference**
1	2	10 kg^{-1}	✓	5		6
20	7.2 (3.5–11.5)	10 kg^{-1}	✓	17±12	Double blind study	13
107	6 (1–17)	10 kg^{-1} max 50 kg^{1}	✓	Prompt	Resedation (7pt); 56 side effects (43pt)	14
2	5, 8	200		2		48
6	1mo–9	10–30 kg^{1}		5–15	Rectal administration	49
6	1.5–15	20–40 kg^{-1}		8–15	Rectal administration	50
107	3.5 (4mo–14)	100–200 kg^{1}	✓	<1	Resedation (89pt); 17 crying, 4 upset	53
15	11.8 (6.5–16)	10 kg^{-1}		1 (2pt) 10 (7pt) 30-60 (6pt)	Double blind study	54
19	0.5–1	100		<10	Double blind study	55

Summary
Despite isolated case reports, there is no evidence suggesting that flumazenil should be used in children when benzodiazepines have not been administered.

Evaluation of flumazenil efficacy

The efficacy of flumazenil as compared to placebo was clearly proven in all the children cited in the three double blind, placebo-controlled trials[13, 54, 55]. Full consciousness, orientation, comprehension and normal respiration were attained within a short time (usually <15 minutes) regardless of the initial depth of coma. Although resedation occurred in one third of the reported children, no respiratory assistance was required in any case. Benzodiazepine-induced amnesia was maintained in all paediatric patients who were treated with flumazenil with one exception of an intraoperative case[44].

Modes of administration and dosage of flumazenil (Tables 1–3)

Intravenous administration of 10 microg/kg flumazenil was shown to be an effective and safe dose for eliciting optimal arousal in paediatric patients following overdose. Intra- and postoperative usage employed boluses of 3–10 microg/kg. Repeated boluses are often required and on occasions continuous infusions have been used. Most studies report intravenous administration of flumazenil but other routes may be equally as effective[7, 49, 50].

Summary
Overall, the clinical effectiveness of flumazenil among the various paediatric ages is strictly weight-dependent. Doses of 3–10 microg/kg IV are usually required.

Flumazenil-related adverse effects (Tables 1–3)

The incidence of side effects following the use of flumazenil in children has been reported by two different groups[14, 62] to be 16–17%. Resedation is not considered a side effect but rather a result of the shorter effect of flumazenil compared to benzodiazepines. In two large studies[14, 53] it has been described in rates that have varied from 6 to 83%. Resedation occurred in 50% of the intranasally treated children[7]. Flumazenil was also associated with increased systolic arterial

pressure[13]. This, however, may relate to the normal haemodynamic response upon awakening.

Seizures have been reported as a possible side effect of flumazenil. In one report in adults, there were 43 cases of seizures that had been reported to the manufacturers between the years 1987 and 1991[63]. It has been suggested that flumazenil per se does not induce seizures. Repeated seizure activity following the administration of flumazenil may be due to its blocking the anticonvulsant effects of diazepam or midazolam[40, 63].

Summary

Resedation may be frequent in the paediatric population after the first bolus, even though no respiratory assistance is usually required at that time; additional treatment prevents resedation. The incidence of side effects is thought to be between 16 and 17%. The side effects are all relatively minor although recurrence of seizure activity is a possible side effect, which is of significant clinical concern.

Practical notes

The value of flumazenil is as a prompt therapeutic agent for all age groups. Despite the remarkable level of patient tolerance to flumazenil, rational use of this antagonist requires the recognition of several precautions and risks:

- Flumazenil is an *adjunct* drug and, therefore, should not replace appropriate primary care. Facing a comatose child, life-saving protocol should be exercised and possible metabolic disarray (e.g., hypoglycaemia, acidosis, high fever, hypocarbia, hypercarbia, hypothermia, hyponatremia) should be excluded before flumazenil administration is considered.
- When flumazenil is administered, blood pressure, pulse oximetry and respiratory rate should be monitored. Oxygen and resuscitation drugs and equipment should be available.
- Slow incremental titration using weight-related doses and individual response monitoring is essential if anxiety and agitation is to be minimised upon awakening, especially in neonates and infants. The only existing rule of thumb for its use in children is careful weight-based flumazenil titration to the desired end-point.
- Close observation for up to 6 hours is recommended following a satisfactory awakening response.
- Flumazenil should not be used in cases of increased intracranial pressure or brain trauma.
- Flumazenil should not be administered to children with a history or the presence of seizure disorder or clinical findings suggestive of seizure tendency (e.g., high fever).
- If withdrawal symptoms appear, flumazenil administration should be immediately stopped. If resedation is then required, it is preferable not to use a benzodiazepine.

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