Coma cocktail: a role for flumazenil?

A common clinical scenario in the emergency department is a patient with a presumed drug overdose. Patients are often unresponsive with respiratory depression and hence unable to give a clear history. When the culprit toxin is known, rapid reversal with administration of the relevant antidote may be life saving. The empirical administration of a 'coma cocktail' consisting of naloxone, glucose and thiamine is common in many emergency departments. It is tempting to add flumazenil to this cocktail if there is a suspicion of benzodiazepine misuse; however, the possibility of mixed overdose or any suggestion of long-term benzodiazepine use should influence management choices.

Only 37% of self-poisonings presenting to hospital involve a single category of drug (National Poisons Information Service, 2006). Benzodiazepine overdose is not commonly fatal when taken in isolation, and the majority of patients recover with minimal intervention. There is, however, increased morbidity associated with the combination of benzodiazepine overdose and other CNS depressants, especially in the elderly or debilitated patient. Mixed overdose with benzodiazepines accounted for 158 deaths in 2004 (Great Britain Office for National Statistics, 2006).

Flumazenil

Flumazenil is sometimes used to reverse benzodiazepine-induced sedation in clinical practice. In the emergency department, flumazenil use in the treatment of benzodiazepine overdose may potentially reduce the need for endotracheal intubation and intensive care unit admission. However, it is not licensed for this indication in the UK and administration is not without risk. Seizure, supraventricular and ventricular arrhythmias and death, resulting from administration of flumazenil in the context of a mixed overdose including tricyclic antidepressants are well reported. A history of epilepsy or benzodiazepine dependence contraindicates flumazenil use, as does overdose where pro-convulsant drugs may be implicated. Often no clear history is obtainable in the emergency department.

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Flumazenil is indicated for the reversal of benzodiazepine sedation in anaesthesia, and during diagnostic procedures in monitored hospital environments. There is some evidence that flumazenil is safe if pure benzodiazepine overdose can be confirmed and there are no contraindications to its use. It should not be used in cases of deliberate self-harm, particularly if there is a history of epilepsy and benzodiazepine dependence. Flumazenil opposes the anticonvulsant effect of benzodiazepine in this group lowering the seizure threshold especially when co-ingested with pro-convulsant drugs.

Flumazenil has an imidazobenzodiazepine structure and competitively inhibits activity at the benzodiazepine recognition site on the GABA (gamma aminobutyric acid)/benzodiazepine receptor complex. It is administered intravenously, at a dose of 200 μg over 15 seconds, with 100 μg increments at 60-second intervals if required. The dose range of 300–600 μg is often effective with a maximum total dose of 1 mg (2 mg in intensive care) recommended. Clinical effect is usually evident 1–2 minutes after injection, with peak effect in 6–10 minutes. The duration and degree of reversal are related to the plasma concentration of the sedating benzodiazepine and the dose of flumazenil given. Flumazenil has a half-life much shorter than that of most commonly abused benzodiazepines (flumazenil $t1_{/2}$ = 40–80 minutes and diazepam $t1_{/2}$>100 hours). When flumazenil is used, careful monitoring post-administration is essential to prevent re-sedation. Common side effects include nausea, vomiting, flushing, agitation and anxiety. Transient increases in blood pressure and heart rate have been reported as have hypersensitivity reactions including anaphylaxis.

Evidence base for use of flumazenil

The National Poisons Information Service states that flumazenil may be used to reverse the sedative effects of benzodiazepines in anaesthetic procedures but should rarely be used in benzodiazepine overdose. Current National Institute for Clinical Excellence (NICE) guidelines (NICE, 2004) for the management of self-harm sanction flumazenil's limited use, but offer no advice regarding the use of flumazenil in the emergency department.

Suggested management

A comprehensive patient assessment is mandatory with particular attention to airway, breathing and circulation. Any reduction in Glasgow Coma Scale presents a potential risk of aspiration and a Glasgow Coma Scale of 8/15 or less is an indication for endotracheal intubation. Risk factors for seizure should be assessed in patients in whom flumazenil use is considered. If risk factors exist, the potential benefits of using flumazenil are outweighed by the possible harm, in accordance with NICE guidelines. Flumazenil should be avoided if tricyclic antidepressants have been ingested.

Conclusions

The current medical literature does not support the addition of flumazenil to the 'overdose cocktail', and it should not be used empirically. The lack of accurate available history in many overdose cases, and hence the inability to assess risk factors, contraindicates its use. Where flumazenil has been used in overdoses, sustained recovery must be ensured before stepping down the level of patient monitoring. **BJHM**

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