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What's the Deal with Flumazenil?

How often do you see an altered or obtunded patient in the emergency department? How thorough of a work-up is required to determine the cause of these patients' statuses? If there was one drug that you could give to prevent this work-up, would you use it?

Self-induced poisonings are a big cause of altered metal status and ED visits. In these patients, benzodiazepines are one of the most commonly used drugs. Flumazenil is a drug that (rightly- or wrongly-so) has developed a reputation, especially in the emergency department. It is an **imidazole-benzodiazepine that acts on the central benzodiazepine receptors**. Flumazenil has such a **high affinity** for the benzodiazepine receptors that it acts essentially as a **competitive antagonist** on these receptors. Flumazenil's role in the emergency department has been muddied as it is thought that it can cause withdrawal symptoms, including seizures in chronic benzodiazepine users. But does it?

This question was looked at by a group out of Singapore in 2006 in a paper entitled "Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department?" This paper was a meta-analysis of 7 randomized control trials in which flumazenil was given to emergency department or ICU patients who presented with isolated GCS changes. All patients were 17-83 years old and had a GCS of 9-13. In each of the trials, the patients were either given flumazenil (1-10 mg) or a placebo. The results were reported as either waking up from coma or on a continuous GCS improvement scale. The other outcomes reported were major side effects (seizures) and minor side effects (anxiety and vomiting). Overall, the pooled studies showed that there was a **relative benefit (4.99) of "waking up from coma" after receiving flumazenil**. 133 of the 242 total patients receiving flumazenil "woke up from coma." Although this term is not explained well in the paper, it is safe to assume that waking up from coma has to mean that the patients had some type of improvement in their GCS score. But what about the adverse events that flumazenil causes? The study reports that in all 7 trials **only one seizure occurred**. Out of all the patients receiving the controversial drug, only one had a withdrawal seizure. What about other side effects? It was reported that the flumazenil did cause **more anxiety and vomiting**, although vomiting was not statistically significant.

So why is flumazenil seen as such an evil drug to use in the emergency department? **At its core, the argument is that giving flumazenil does not change the management of patients that present to the ED with an altered mental status, and it could potentially cause a patient to have life-threatening adverse events from withdrawal; however, the study above provides evidence that this is not necessarily the case and maybe flumazenil has received an unwarranted poor reputation**. Flumazenil itself is a relatively cheap drug at around $15 per milligram according to UpToDate. It could potentially save the patient and the hospital thousands of dollars in an expensive workup. Does this mean that any patient presenting to the ED with AMS or a decreased GCS should be given flumazenil? Most likely not, but know that the drug is in your arsenal for those patients with access to benzodiazepines or those with a known history of suicidal ideation or depression. These patients should be prime candidates to receive a trial of flumazenil.

References

- Ngo, et. al. “Should a benzodiazepine antagonist be used in unconscious patients presenting to the emergency department?” Resuscitation. 2007.
- “Flumazenil: Drug Information.” UpToDate. 2014

Expert Commentary

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We have no idea what is meant by “waking up.” Since this is THE major outcome of the study… this is a huge problem.

It was a retrospective chart review…likely…if folks seized…that info would have made the chart. Seizures count as BIG. Thus, I believe the data that seizures are uncommon. Conversely, the minor adverse events…like anxiety and nausea…these subtle outcomes are going to be poorly caught and even more poorly documented in the chart. Thus, a retrospective review for these outcomes is close to useless.

This agent, like naloxone, has one indication – make people breath again. It is NOT for awakening the unconscious; there are no data that it is a good diagnostic aid that could obviate the need for a workup. Naloxone…an agent that does the same with opioids…that is much better understood…was demonstrated by Hoffman to be a poor DIAGNOSTIC agent (Jerome Hoffman, “The Empiric Use of Naloxone in Patients with Altered Mental Status: A Reappraisal, Annals of EM, 1991).

I think flumazenil has overall received too much of a bad rap…and I will certainly use it on patients who have CNS depression with questionable ventilation.
I do NOT use it as a diagnostic agent. Of note, I have used in pts who I know are benzo dependent. As with all we do, this is a risk/benefit analysis.