The Toxicologist and Delirium: Flumazenil as a Diagnostic and Therapeutic Tool for Delirium During the Course of Alcohol Withdrawal

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We appreciate the thoughtful comments from Dr Lucyk et al. and the opportunity to clarify and report further details regarding our experience with managing delirium during the course of alcohol withdrawal (AWS). We agree that the treatment of AWS is best managed with symptom-triggered therapy with benzodiazepines, and this is our practice. However, we do not believe that this approach can always limit the occurrence of benzodiazepine-induced delirium, as was demonstrated in our results [1]. In addition, this was not a study of the optimal therapy of alcohol withdrawal, but rather a study of the utility and safety of flumazenil in the delirious patient who has received large doses of benzodiazepines.

Flumazenil can improve mental status for patients with hepatic encephalopathy. However, hepatic encephalopathy was highly unlikely as a confounding factor, except possibly in a very few patients. Of the 85 subjects, 45 (53 %) had ammonia levels evaluated during their hospitalization (mean 37, median 33, and range 13–92 mcg/dl). Only 3 of our 85 patients had a clinical diagnosis of hepatic encephalopathy (ammonia levels 43, 64, and 94 mcg/dl). Another four had cirrhosis, but with no evidence of hepatic encephalopathy (ammonia levels 21, 44, 52, 65 mcg/dl). Another patient without change in delirium after flumazenil had Wernicke's encephalopathy. While alanine transaminase and aspartate transaminase are markers of hepatic inflammation rather than failure, we had transaminase data for every patient, with mean (range) as 66 (10–245 U/L) and 113 (15–665 U/L), respectively.

Respectfully, we disagree that paradoxical reactions to benzodiazepines are rare or that "ICU delirium" or persistent AWS were the more likely cause of delirium. Benzodiazepine

use, as in our cases, may increase the risk of delirium [2–4]. The fact that 73 % of our total patients improved with flumazenil, most of whom (69 %) had agitated delirium or mixed sedation and agitation, further demonstrates that paradoxical benzodiazepine delirium is not a rare event. ICU delirium is multifactorial and usually has a specific cause such as hypoxia, oversedation or other iatrogenic adverse drug reactions, sepsis, and toxic and metabolic encephalopathies [5]. Regarding AWS, it ordinarily was resolving by the time we gave flumazenil in our cases and was the most common differential diagnosis as the reason to utilize flumazenil. Furthermore, delirium associated with AWS would be unusual to persist beyond 4–5 days of abstinence [6–8], which our data supports. Prolonged AWS was ruled out in the majority of our patients by their improvement with flumazenil in the majority of patients (73 % objective improvement). To further demonstrate that benzodiazepine delirium was the diagnosis in the majority of cases, an average of 8 doses of flumazenil was used with success in the 56 patients who required repetitive dosing. In the other cases, it was useful to exclude benzodiazepine delirium as the etiology.

Despite the retrospective and subjective nature of our latest study, the patients were observed at least for the initial flumazenil dose by experienced medical toxicologists, and the result in most cases was unequivocal. Our data could significantly impact the diagnosis and management of patients with delirium during the course of AWS, offering providers an additional diagnostic and therapeutic tool. Further study of the length of stay and costs associated with flumazenil vs placebo (or other therapy) during the course of AWS would be helpful because this could significantly impact patient care and may increase our role as toxicologists in patient care nationwide.

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