

22. Designer benzodiazepines etizolam and flubromazolam detected in patients with suspected opioid overdose

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Background: A growing number of novel psychoactive substances, including designer benzodiazepines, have become available on the illicit drug market and over the internet. Etizolam, a thienodiazepine, and flubromazolam, a triazolobenzodiazepine, have recently emerged on the illicit drug market in Europe and the United States in recent years. Reports of non-medical use and detection of etizolam and flubromazolam drugs in counterfeit medications appear to be rising, as is their identification in drug-related deaths, often in combination with opioids and other CNS depressants.

Methods: This case series includes adult ED patients who presented to emergency departments within the American College of Medical Toxicology's Toxicology Investigators Consortium (ToxIC) fentalog study group after a suspected opioid overdose. Toxicological comprehensive testing was performed on residual blood samples via liquid chromatography quadrupole time-of-flight mass spectrometry for the presence of over 900 psychoactive substances and their metabolites. Cases with etizolam and flubromazolam identified in biologic samples were reviewed.

Results: Between 10/6/20 and 3/9/21, 141 biological samples of patients suspected of opioid overdose were analyzed from 5 clinical sites encompassing 4 states (Missouri, Oregon, New York, and Pennsylvania). The median age of subjects was 41.9 years (range: 25-69); 80% were male. Etizolam was detected in 10 samples (7%) and flubromazolam in 2 samples (1.4%). Etizolam was confirmed in all states except Missouri and flubromazolam was detected only in Oregon. Oregon had the most exposures overall (N = 5).

In all 10 cases with confirmed presence of etizolam, at least 1 opioid was also identified in biological samples (methadone (n = 6), Fentanyl (n = 3), heroin (n = 2), buprenorphine (n = 1). Flubromazolam, was detected in 2 samples, both from Oregon. Methamphetamine (n = 4) and amphetamine (n = 3) were also commonly detected. The primary reason for the exposure was intentional in all 10 cases, the most common being misuse/abuse (n = 5). No patients received flumazenil. Naloxone was administered in 7 cases. The most common indications for naloxone administration were depressed level of consciousness (n = 5), respiratory depression clinically (n = 3), decreased oxygenation (n = 1), and decreased expired carbon dioxide (n = 1). In 5 cases, the response to naloxone was known: No response (n = 1), increased respiratory rate (n = 2), improved level of consciousness (n = 4), iatrogenic withdrawal precipitated (n = 1). In 3 cases, 3 or more doses of naloxone was administered. One patient was intubated for acute respiratory failure non-responsive to naloxone. The primary reason for the exposure was intentional in all 10 cases, the most common being misuse/abuse (n = 5). Nine patients were discharged without sequelae and 1 left against medical advice. There were no deaths.

Conclusion: Combined designer benzodiazepine and illicit opioid use can result in synergistic toxicity that may increase the risk of an overdose and/or death. In these preliminary data, etizolam was always identified along with at least 1 opioid, suggesting either addition to the opioid supply or concomitant use.