ToxTalks

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

Blue Ridge Poison Center | University of Virginia Health | May 2022

Novel NMDA Receptor Antagonists

Similar to other designer drugs, such as "bath salts" or "spice," designer N-Methyl-D-aspartate (NMDA) receptor antagonists, similar to phencyclidine (PCP) and ketamine, are becoming more popular and are easily purchased over the internet. Like the designer amphetamines and cannabinoids, the structures of the novel agents are dissimilar enough from the structures of known illegal substances to skirt current drug laws, making them legal or quasi-legal. However, similar to the abuse of PCP, these agents can have very serious consequences. Just a few of these agents are methoxetamine (MXE), methoxpropamine (MXPr), and methoxphenidine (MXP). Similar to ketamine, they cause an "out of body" experience. Used mostly for recreational purposes, in some cases they are promoted for spiritual use.

What are NMDA receptor antagonists?

NMDA receptor antagonists are a class of drugs that work to antagonize, or inhibit the action of, the NMDA receptor. They are used as anesthetics for animals and for humans; the state of anesthesia they induce is referred to as dissociative anesthesia. A common example is ketamine, an arylcycloalkylamine that is structurally related to PCP. The classic street drug example of an NMDA receptor antagonist is PCP. Ketamine is not only a dissociative anesthetic, but also classified as a hallucinogen. It acts primarily as an antagonist of the NMDA receptor, but also possesses some opioid receptor activity and sympathomimetic properties. Dextromethorphan and its metabolite dextrorphan are NMDA receptor

News and Notes:

June 3, 2022 12pm –1pm
WEBINAR ANNOUNCED:

The Wide World of Cannabinoids: Emerging Products, Legality, and Urine Drug Screen Utility.

Speakers:
Christopher P. Holstege, MD, Professor of Emergency Medicine and Pediatrics, University of Virginia

Avery Michienzi, DO, Medical Toxicology fellow, University of Virginia

Presented by Project Echo
Details and Registration

antagonists that bind in the same location as PCP. Meperidine, methadone, buprenorphine and tramadol are opioid analgesics that antagonize NMDA receptors at therapeutic doses. Ethanol is also a noncompetitive NMDA receptor antagonist.

What are novel NMDA receptor antagonists?

Novel versions are just that, they are new, but slightly altered designer structures that are very similar to their parent compounds. Methoxetamine (MXE) is a known ketamine analogue that has been around since 2010. MXPr is a newer derivative of MXE. Methoxyketamine and methoxphenidine are other examples. Not much is known about these novel substances other than their structures and that they operate inside the human body similar to other NMDA receptor antagonists.

How do NMDA receptor antagonists work?

While the exact mechanism of dissociative anesthesia is not known, NMDA receptor antagonists block the excitatory effects of the neurotransmitter glutamate. Two glutamate receptors, NMDA and alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA), are thought to play a role in the generation and spread of seizures. These receptors are usually found together at neuronal synapses. Normally when activated, calcium and sodium influx through the channel resulting in neuronal depolarization and excitation. Therefore, antagonism at these sites is generally neuroprotective and anti-epileptic. NMDA receptor antagonists also generally have some degree of catecholamine reuptake inhibition, resulting in sympathomimetic affects with use.

What symptoms are expected?

NMDA antagonism produces an acute psychosis and hallucinations that mimics schizophrenia in humans and leads to excess excitatory neurotransmitter release that can cause agitation and seizures. Desired medical effects include dissociation and analgesia without loss of consciousness. Amnesia, palpitations, nystagmus, tachycardia and hypertension may also be witnessed. Similar to ketamine, horizontal, vertical, and/or rotary nystagmus is expected. In overdose, side effects

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include respiratory depression, excessive sedation, muscular hypertonus, and emergence delirium. Rhabdomyolysis could result if the user experiences prolonged agitation. Tolerance can develop with repeated use, as well as withdrawal after cessation of prolonged use or abuse. Death from MXE use has been reported.

How long do effects last?

Novel or designer dugs have limited data available. Therefore using known data about similar structures like ketamine, expected duration of action would be anywhere from 15 minutes to a few hours. This all depends on the dose that was taken, the route it was administered, metabolic factors, and intrinsic sensitivity to a substance an individual has.

How are symptoms treated?

Supportive care is the mainstay of treatment. A quiet environment free from excess stimulation will likely be helpful. Consider intubation and mechanical ventilation for respiratory support if needed; however, with a likely shorter duration of action, these should generally be unnecessary. Monitoring may be required for an hour or two after symptoms resolve to ensure there are no rebound episodes. Hemodialysis is unlikely to be beneficial as ketamine has a known large volume of distribution. There are no antidotes to reverse the effects of NMDA receptor antagonists. Benzodiazepines to treat agitation and butyyrophenones like haloperidol are key to treating any psychosis that may develop. Medical Toxicology consult is available 24/7 from the Blue Ridge Poison Center at 1-800-222-1222, or use our healthcare provider hotline: 1-800-451-1428.

References available upon request.

The Blue Ridge Poison Center receives funding from University of Virginia Health, the Virginia Department of Health, and the U.S. Health Resources Services Administration (HRSA). We are accredited by the American Association of Poison Control Centers. We've been proudly serving the Commonwealth since 1978.