ToxTalks

A Bulletin for Healthcare Professionals Who Manage Poisoned Patients

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Sedation and Management of Agitation in the Overdose Patient

Background

Sedation and management of agitation are very frequently required in the overdose patient and can be more difficult to manage than in patients who present with other pathologies. Substance use/misuse, particularly sympathomimetic agents such as cocaine or amphetamines, are a common cause of severe agitation, and failure to control agitation can result in harm to the caring medical providers and harm to the patient with resultant increased morbidity and mortality. The selection of a sedating agent requires careful consideration of mechanism, pharmacokinetics, and safety profile. Poisoned patients on mechanical ventilation also require sedation and the selection of an agent can be based, in part, on attentive monitoring of the mentation, vital signs, and perceived pain during critical illness.

Toxidromes commonly requiring sedation or management of agitation

Sympathomimetic toxicity refers to a toxidrome characterized by excessive release of catecholamines activating the sympathetic nervous system, typically manifesting with hypertension, tachycardia, hyperthermia, mydriasis, diaphoresis, anxiety, and can progress to psychomotor agitation, seizures, rhabdomyolysis, and multi-organ dysfunction. Cocaine and amphetamines are among the most common causes. The use of sedation in these patients is not only necessary for management of agitation, but is critical for prevention of worsening end organ damage. An agitated patient should never be left to fight against physical restraints, as this can result in worsening hyperthermia, acidosis, rhabdomyolysis, and can result in significant morbidity and mortality.

Other toxidromes that may require sedation or management of agitation include anticholinergic poisoning, serotonin neurotoxicity (formerly known as serotonin syndrome) and hallucinogenic toxicity. According to the National Poison Data System, anticholinergic poisoning most commonly results after ingestion of diphenhydramine; however, a wide variety of other medications and even toxic plants can result in anticholinergic poisoning. These patients are often hyperthermic and delirious but characteristically less

agitated. Serotonin neurotoxicity can also result in a presentation similar to sympathomimetic toxicity but can be distinguished by the presence of marked clonus. Finally, hallucinogens can result in significant agitation; this is particularly true of phencyclidine (PCP), which has prominent sympathomimetic effects.

Preferred agents for agitated patients

The typical first line agent for the agitated overdose patient, including those with sympathomimetic, serotonin, anticholinergic, or hallucinogen toxicity, is benzodiazepines. In those patients with marked agitation and failure to comply with direction, the intravenous (IV) or intramuscular (IM) route is necessary. Diazepam and midazolam have the fastest onset of action among the commonly available benzodiazepines when administered IV. If IV access is not available, midazolam and lorazepam can be given IM, but diazepam should be avoided by this route due to its unpredictable pharmacokinetics.

Antipsychotic drugs, such as haloperidol, olanzapine, or risperidone can be used as an adjunct in the agitated patient. For example, patients with a sympathomimetic overdose have excess dopamine release mediated by substances such as amphetamines or cocaine; the addition of an antipsychotic with dopamine-receptor blockade can help reduce psychomotor agitation. The FDA warns against co-administration of IM olanzapine and IV benzodiazepines due to risk of provoking hypotension, bradycardia, and respiratory or central nervous system depression.

Dexmedetomidine is another potential adjunct for management of agitation. Typically administered via IV bolus followed by infusion, dexmedetomidine is a centrally acting alpha-2 receptor antagonist resulting in decreasing sympathetic outflow. Downsides include longer time to onset and potential for hypotension and/or bradycardia, but can be particularly useful for titrating sedation in patients who may have prolonged sympathomimetic or serotonergic toxicity.

In cases of severe combative agitation, rapid control can be obtained using IM or IV ketamine. A noncompetitive NMDA receptor antagonist, ketamine is a dissociative drug with rapid onset but shorter duration than the above agents. Adverse effects include nausea and vomiting, prolonged emergence reaction, and rarely, laryngospasm.

Preferred agents for mechanically ventilated patients

A variety of medications can be used to keep patients comfortably sedated while mechanically ventilated. For the overdose patient, an agent with GABA receptor agonism such as propofol and/or benzodiazepines is preferred. The addition of an opioid either by intermittent bolus dosing or infusion can be useful to help manage pain while also providing sedation, but fentanyl should be avoided in patients who may have taken serotonergic medications or other substances, as the addition of fentanyl can result in iatrogenic serotonin toxicity. Because the exact cause of the patient's overdose or their routine use of prescription medications is not known, our service avoids fentanyl in all suspected overdose patients. A hydromorphone infusion is usually preferred and can be similarly titrated. A dexmedetomidine infusion can be added to the above as an adjunctive agent if needed. Paralytics should be avoided in the majority of cases and instead the above agents utilized to assure adequate sedation and prevention of seizures

Summary

A variety of toxidromes can necessitate rapid control of agitation, and failure to control this agitation can result in progressive hyperthermia, acidosis, seizures, and multi-organ dysfunction. An agent with GABA receptor agonism is the preferred first-line agent in most agitated overdose patients, but adjuncts such as antipsychotics, centrally acting alpha-2 agonists, or dissociative agents may also be necessary. When opioid infusions are used in the mechanically ventilated patient, fentanyl should be avoided due to the risk of iatrogenic serotonin toxicity. Agitated patients should not be restrained for long time periods and allowed to struggle against restraints, as this can result in significant morbidity and mortality. If overdose or toxicity is encountered, please contact the University of Virginia Health's Blue Ridge Poison Center at 1-800-451-1428. Our center can help with management questions.

Suggested reading:

Gosselin S, Hoffman RS. The Management of Agitated Toxidromes. Emerg Med Clin North Am. 2022 May;40 (2):223-235. doi: 10.1016/j.emc.2022.01.009. Epub 2022 Apr 5. PMID: 35461620.

Holstege CP, Borek HA. Toxidromes. Crit Care Clin. 2012 Oct;28(4):479-98. doi: 10.1016/j.ccc.2012.07.008. Epub 2012 Aug 27. PMID: 22998986.

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