Medetomidine in the US Illegal Fentanyl Supply: An Emerging Threat Requiring Physician Awareness

To the Editor:

Medetomidine has recently emerged as an adulterant in the US illicit drug supply, prompting the Centers for Disease Control and Prevention to issue clinical advisories identifying it as a growing public health concern, particularly in urban areas. It is a veterinary sedative and α2-adrenergic agonist, pharmacologically related to xylazine and dexmedetomidine, and is traditionally used in animal medicine for sedation and analgesia. It is not approved for human use. Compared with xylazine, medetomidine may be up to 300 times more potent, potentially contributing to more profound sedation and greater clinical toxicity.[1] Since it is metabolized hepatically, plasma concentrations generally peak within 10 to 30 minutes after exposure. Its effects may last several hours, with concurrent opioid exposure prolonging sedation and clinical toxicity.[1,2]

Unlike opioids, medetomidine does not respond to naloxone; nevertheless, naloxone should be administered in all suspected overdose cases given the frequent co-ingestion of fentanyl.[2,3] Studies have demonstrated rapidly increasing detection of medetomidine in drug samples and overdose deaths across several US regions.[3,4] Its presence alongside fentanyl and other illicit substances has contributed to increasingly complex and potentially life-threatening overdose presentations.[4,5] Patients exposed to medetomidine may present with sedation, decreased responsiveness, respiratory depression, bradycardia, hypotension, and miosis. Medetomidine may also contribute to recurrent hypoxia, prolonged central nervous system depression, and increased airway management requirements.[3,5]

Diagnosis is challenging because medetomidine is not typically included in hospital rapid drug screens. Physicians should maintain a high index of suspicion when altered mental status or cardiovascular instability persists despite naloxone administration following a suspected fentanyl overdose.[2,3] When exposure is suspected, comprehensive screening should include medetomidine in blood or 3-hydroxy medetomidine with deconjugation in urine, recognizing that rapid metabolism may limit detection once withdrawal symptoms develop.

Beyond acute toxicity, abrupt cessation following regular exposure can precipitate a profound hyperadrenergic withdrawal syndrome that parallels severe clonidine withdrawal and, in some cases, surpasses it in severity. Withdrawal symptoms may begin within hours after cessation, peaking 18 to 36 hours after the last exposure. Clinical manifestations include severe tachycardia, hypertension, altered mental status, tremor, chest pain, and intractable nausea and vomiting. Vital signs may fluctuate rapidly as patients transition from α2-agonist intoxication with hypotension and bradycardia to hyperadrenergic withdrawal. Severe cases have been associated with end-organ complications, including non-ST elevation myocardial infarction (NSTEMI) and posterior reversible encephalopathy syndrome (PRES), underscoring the potential for rapid clinical deterioration.[2,3]

Management is primarily supportive, emphasizing airway protection, oxygenation, and cardiovascular monitoring, with naloxone continued when opioid co-exposure is suspected.[2] Increases in emergency department visits for nonalcohol, non-nicotine, and non-cannabis-related substance withdrawal have been temporally correlated with medetomidine detection in the regional drug supply, with sustained prevalence linked to substantial emergency department and intensive care unit utilization.[5] Treatment of medetomidine withdrawal includes α2-agonist therapy, such as clonidine, guanfacine, tizanidine, or intravenous dexmedetomidine in severe cases, with some patients requiring intensive care monitoring during dexmedetomidine administration.

Heightened clinical awareness is essential for early diagnosis and reducing mortality among patients exposed to medetomidine. Although medetomidine does not respond to naloxone, opioid overdose reversal agents should remain a treatment priority given the frequent co-ingestion of fentanyl. Prompt recognition of acute toxicity and of the potentially life-threatening hyperadrenergic withdrawal syndrome, including complications such as NSTEMI and PRES, facilitates timely escalation of care, improves outcomes, and strengthens public health surveillance efforts aimed at reducing overdose deaths.

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