AH-7921: A review of previously published reports

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ABSTRACT

AH-7921 is a synthetic opioid that was developed in the early 1970s. It has resulted in several fatal and nonfatal intoxications, despite not having approval from the US Food and Drug Administration. To date, AH-7921 is listed as a schedule I drug, and there have been no clinical trials exploring the safety of AH-7921. Herein, we provide an analysis of existing case reports available in the literature regarding AH-7921. We searched PubMed, Scopus, Web of Science, and EBSCO for articles (up until December 2017) using the terms “AH-7921” and “AH7921.” In total, 48 articles were identified, and 5 articles were included in our review. A total of 14 cases were found, of which 13 resulted in fatalities. The oral route of administration was reported in two cases, and most cases reported use of concomitant pharmaceutical agents. Pulmonary edema was the most common finding postmortem among deceased cases, with nine of the cases having heavier lungs. Overall, fatalities occurred with low and high concentrations of AH-7921 in the femoral blood. We strongly encourage toxicology screenings for this novel opioid to be included when an overdose of an opioid of unknown nature is suggested.

KEYWORDS AH-7921; drugs of abuse; opioid poisoning; overdose; pulmonary edema; synthetic opioid

The landscape of the opioid epidemic is changing, with more synthetic opioids being made readily available. AH-7921 is a synthetic mu-opioid receptor agonist developed in 1974 and patented in 1976 by Allen and Hanburys Ltd, where the “AH” stands for Allen and Hanburys.¹ Its structure is shown in *Figure 1*, and its chemical name is 3,4-dichloro-*N*-[1-(dimethylamino)cyclohexylmethyl]benzamide.^{1,2} Initially developed with the intent of being an analgesic, AH-7921 has not been marketed for any medical purposes. AH-7921 is available via the Internet by its street name “doxylam” and is listed as a schedule I drug by the Drug Enforcement Agency. Information made available through anecdotal reports indicates AH-7921 is an opioid with potential for abuse and thus a contributor to hospitalizations and emergency room visits. Herein, we summarize the reported cases related to AH-7921 and describe the clinical and analytical implications associated with this agent.

METHODS

We searched PubMed, Scopus, Web of Science, and EBSCO for articles up to December 2017, using the keywords “AH-7921” or “AH7921.” We examined the reference lists of

each article for additional resources that fit the selection criteria. We utilized the following criteria for article selection: must (1) be full-text articles; (2) involve humans that used AH-7921; (3) be either a randomized controlled trial, prospective trial, retrospective analysis, case series, or case report; and (4) include clinical findings at presentation. The senior author (SKA) identified relevant articles reporting clinical and analytical outcomes of interest. Two authors (ZMA, SF) extracted data independently and blinded to each other from all case reports. Extracted data were cross-reviewed by ZMA and SF; SKA resolved any discrepancies.

RESULTS

Forty-eight articles were initially identified. After applying the inclusion criteria, five relevant articles were included for this review with a total of 14 patients (*Figure 2*).^{3–7} Of the 14 cases found, 13 were fatalities, with the subjects’ ages ranging from 19 to 45 years (*Table 1*).^{3–6} Additionally, 11 of the 13 subjects were male and 12 of the 13 cases occurred in Europe (nine in Sweden, two in Norway, one in Germany); only one case occurred in the United States. Only two cases mentioned the route of exposure, with oral being the route reported in

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Figure 1. Structure of AH-7921.

both cases.⁴ In 11 out of the 13 cases, concomitant use of other pharmaceutical agents occurred.^{4,5} Of note, the cases were reported postmortem and, as such, the duration of toxicity is unknown. Nine of the 13 cases reported postmortem findings of heavy lungs, three reported findings of cerebral edema, three reported findings of pneumonia, two reported internal bleeding, one case reported acute bronchitis, one case reported hepatomegaly, and one case reported splenomegaly.³⁻⁶

Regarding the remaining patient who lived after using AH-7921, Bernius et al reported on a 22-year-old male from Germany who ingested an unspecified dose of AH-7921 orally twice a day for approximately 1.5 to 2 weeks before deciding to double the dose because of increasing tolerance.⁷ The patient had a history of using tramadol regularly for a headache prior to utilizing AH-7921. The patient had also utilized laxatives to overcome the effects of constipation.⁷ It was reported that approximately 4 g of AH-7921 was purchased and used over an estimated 3 months. The patient later presented to the emergency department where he described constipation, left upper abdominal pain, appetite reduction, and vomiting over 2 weeks prior to presentation.⁷ Following admission, the patient was treated with an enema as well as intravenous pantoprazole. The following day, the patient experienced a tonic-clonic seizure as well as withdrawal symptoms including fear and anxiety. He became bradycardic (heart rate of 44 beats per minute) while remaining normotensive 1.5 days later. Due to

the patient's panic attacks, he received diazepam, piritramide, clonidine, clomethiazole, and pipamperone.⁷ All urine drug screens were negative, but serum/urine mass spectrometry measurements showed AH-7921 in both matrices. Continuing panic attacks, muscle spasms, and tachycardia led to the psychiatric team initiating buprenorphine (initial dose of 2 mg) that minimized the patient's withdrawal symptoms.⁷

With regard to analytical findings, the matrices typically recovered for testing were blood samples.³⁻⁷ In the only case where the patient survived using AH-7921, an immunoassay could not detect AH-7921.⁷ A targeted approach using the patient's blood and urine detected AH-7921 by gas chromatography/mass spectrometry (GC/MS). In patients where samples were taken postmortem, untargeted GC/MS or GC/MS with liquid chromatography/quadrupole time-of-flight detected AH-7921 in two cases.^{3,6} Each targeted approach detected AH-7921 accordingly in all cases postmortem.³⁻⁶ Interestingly, in the case of Fels and coworkers, analysis of the patient's hair detected AH-7921 in all segments of the hair analysis.³

DISCUSSION

Given that AH-7921 is a synthetic opioid, it can be postulated that in sufficient doses, it may mimic opioid overdose symptoms, which include, but are not limited to, respiratory depression and decreased level of consciousness.⁸ Most cases contained herein reported postmortem findings and, as such, could not confirm whether these patients experienced any of those symptoms. Bernius and colleagues reported on a patient who utilized a "kick" dose of AH-7921 that resulted in hospitalization where the patient experienced a tonic-clonic seizure, which is typically uncharacteristic of opioid withdrawal symptoms.^{7,9} Literature indicates that AH-7921 has no effect on gamma-aminobutyric acid receptors and thus the seizure reported by Bernius et al may have been due to the additive effects of other drugs the patient might have utilized or there could have been a contaminant or cutting agent in the batch of AH-7921 that the patient purchased. In the first case reported by Karinen and colleagues, they stated that the patient had to lie down after ingesting his prescribed codeine and acetaminophen as well as AH-7921.⁴ It was further mentioned he started snoring 5 minutes later and was unarousable. This finding is consistent with central sleep apnea in patients receiving high doses of opioids.¹⁰

Though only two cases reported the route of consumption/administration to be oral, several autopsy findings included

Figure 2. Search flow diagram.

Table 1. Case reports identified in which use of AH-7921 resulted in death

Reference	Country	Age (years)	Sex	Femoral blood concentration of AH-7921	Route of administration	Presence of another opioid	Presence of a benzodiazepine	Presence of ethanol	Presence of another illicit drug	Presence of other drug(s)	Lung weight (g)	Autopsy findings
Fels et al ³	Germany	22	F	450 ng/mL	—	—	—	—	—	+	—	Cerebral edema; pneumonia; internal bleeding
Karinen et al ⁴	Norway	20s	M	330 ng/mL	Oral	+	—	—	+	—	2080	"Bluish" lips
Karinen et al ⁴	Norway	—	F	430 ng/mL	Oral	—	+	—	—	—	—	Needle marks on right cubital fossa
Kronstrand et al ⁵	Sweden	27	M	810 ng/g	—	—	—	—	—	+	1211	Needle marks found on right arm
Kronstrand et al ⁵	Sweden	26	M	990 ng/g	—	—	—	—	+	+	1712	Signs of aspiration pneumonia
Kronstrand et al ⁵	Sweden	24	M	30 ng/g	—	—	—	+	—	+	—	Portine hemorrhage; anoxic brain injury
Kronstrand et al ⁵	Sweden	45	M	200 ng/g	—	+	+	—	—	+	1167	Autopsy unremarkable
Kronstrand et al ⁵	Sweden	26	M	300 ng/g	—	—	+	—	—	+	1254	Pulmonary congestion
Kronstrand et al ⁵	Sweden	34	M	80 ng/g	—	—	—	+	+	—	792	Autopsy unremarkable
Kronstrand et al ⁵	Sweden	27	M	160 ng/g	—	—	—	—	+	—	2146	Extended lungs; bronchopneumonia
Kronstrand et al ⁵	Sweden	25	M	350 ng/g	—	—	—	—	+	—	1256	Acute bronchitis; pneumonia; cerebral edema
Kronstrand et al ⁵	Sweden	22	M	430 ng/g	—	—	+	—	—	+	1590	Needle marks on both arms; cerebral edema
Vorce et al ⁶	United States	19	M	3900 ng/mL	—	—	—	—	—	+	1750	Foaming at the mouth; hepatomegaly; splenomegaly

needle marks, thus leading to the theory that AH-7921 may have been injected. Theoretically, the intravenous route would result in a more marked effect and presentation with a faster onset of action when compared with ingestion. However, because there is no way to ascertain whether this did indeed occur, practitioners should keep this in mind when treating these patients. The femoral blood concentration was similar in the studies of Fels et al³ (450 ng/mL) and Karinen et al⁴ (430 ng/mL) but was not as high as reported by Vorce et al⁶ (3900 ng/mL) and Kronstrand et al⁵ (810–990 ng/g). It should be noted that though therapeutic and toxic ranges for AH-7921 are a gray area, the drug exhibits potency comparable to that of morphine; toxicity for morphine begins at approximately 120 ng/mL.^{11,12} Moreover, several autopsy findings included pulmonary edema and heavy weighted lungs, which is common in deaths resulting from opioid overdose.¹³ When lung weight was reported in autopsy findings, it was higher than the normal weight of 1142 g. It should be noted that though the lungs were heavier, that is not a sole indicator for AH-7921 intoxication.¹⁴

This clinical review is based on case reports, which are not without limitations. The information herein should be considered with due caution because the majority of case reports, albeit a small number, were reported in countries outside of the United States and as such may not generalize to the entire population exposed to AH-7921. Moreover, given the concomitant administration of various pharmaceutical agents in these patients, not only is the presenting clinical picture a gray area but causality cannot be inferred to be solely due to AH-7921. Additionally, the cumulative dose administered/consumed is not provided, which can also impact the presentation of the patient. Of note, the inability to test for novel substances such as AH-7921 is a major limitation, because the stability of the drug in different matrices and storage conditions, among other information, is still unknown.

Regarding an approach to treat a patient with a suspected AH-7921 overdose, a physician would need to look for signs of an opioid toxidrome such as respiratory depression, central nervous system depression, and pinpoint pupils. Ventilatory support may be needed in cases with severe hypoventilation.¹⁵ Reversal of the effects of AH-7921 mu-opioid receptor agonism would necessitate the use of naloxone that would be titrated accordingly, because there is no formal dosing for AH-7921 reversal.¹⁵ AH-7921 is not part of standard urine drug screenings, and the result would be negative. In turn, targeted spectrometry testing would need to be performed to identify AH-7921.

In conclusion, more synthetic opioids are emerging and readily available via the Internet, thus leading to fatal and nonfatal intoxications. Our clinical review shows that deaths can occur at both low and high concentrations of AH-7921. The most common route reported was oral, though autopsy reports also indicated needle marks. Moreover, it is our opinion that synthetic opioids should be included in routine

toxicology screening until a targeted approach to identifying AH-7921 is available.

CONFLICTS OF INTEREST

S.W.F., L.C., and S.K.A. declare employment from Gulfstream Diagnostics, LLC.

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