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AH-7921: From Potential Analgesic Medicine to Recreational Drug

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Dear Editor,

In recent years, there has been a worrying increase in the use of new synthetic opioids worldwide. These substances are sold in specialized stores known as "smart" or "head" shops or online, although they were originally synthesized as potential analgesic medicines. The medicinal use of these substances was abandoned due to their severe adverse effects, including addiction. In particular, since 2012, a new synthetic opioid known as AH-7921 (an opioid analgesic drug selective for the μ-opioid receptor) has become available on the recreational drug market (1). AH-7921, the IUPAC name of which is 3,4-dichloro-N-[[1-(dimethylamino) cyclohexyl]methyl]benzamide, is an N-substituted cyclohexylmethylbenzamide where in the benzamide moiety is dichlorinated at positions 3 and 4 of the ring, while the aminocyclohexane moiety is N,N-dimethylated (1, 2). It was synthesized in the 1970s by Allen and Hanburys Ltd. as a potential medicine, but its development was abandoned due to its addictive properties (1, 2). AH-7921 has never been marketed as a medicine and it has no other known industrial use (1, 2).

Recently, AH-7921 has been associated with several cases of non-fatal and fatal intoxication in Europe and the USA. For instance, five analytically confirmed non-fatal AH-7921 intoxications were registered between December 2012 and March 2013 by the Swedish poison information centre. Furthermore, ten deaths associated with the consumption of AH-7921 in combination with other psychoactive substances occurred between January and September 2013 in Sweden. In two of these cases, the consumption of AH-7921 was considered to be the cause of death. In nine cases, AH-7921 was detected in the femoral blood and its concentration ranged between 0.03 and 0.99 mg/L. In the last case, AH-7921 was detected in hair samples. In Norway, between December 2012 and August 2013 there were two fatalities associated with the consumption of AH-7921. In one case, AH-7921 was detected in the peripheral blood at a concentration of 0.43 mg/L, while in the other, it was found in a syringe used by the deceased. In both cases, other psychotropic substances were detected. In the United Kingdom, three AH-7921-related deaths were reported between January and November 2013. In all cases, AH-7921 (the femoral blood concentration ranged between 0.05 and 4.46 mg/L) was detected in combination with other psychotropic drugs. Finally, a fatality has been reported in the USA. In this case, the presence of AH-7921 was analytically confirmed in the peripheral blood at a concentration of 9.1 mg/L. Other psychotropic substances were also detected in the sample (1-3).

Very little is currently known regarding the pharmacology and toxicology of this synthetic opioid. Studies performed in guinea pig brain preparations have shown that AH-7921 acts as an agonist at the μ and κ opioid receptors with a Ki of 10 and 50 nM, respectively (4). Animal model studies have demonstrated that AH-7921 can produce an analgesic effect that is approximately as potent as morphine (5). Furthermore, it was found to be only slightly less potent than morphine in reducing the respiratory rate, body temperature, and pupil diameter (6). Additionally, the addictive properties of AH-7921 have been tested in rats and rhesus monkeys pre-treated with the opioid. In these animals, the administration of naloxone or nalorphine produced an opioid-like withdrawal syndrome that was alleviated by a single dose of AH-7921 (7). Preclinical studies have identified pharmacological similarities between AH-7921 and morphine, including a narrow therapeutic window between the desired and undesired effects (6). In particular, the two substances are equipotent in inducing analgesia, respiratory depression, hypothermia, and addictive behavior.

In conclusion, the information currently available confirms that AH-7921 is a potent respiratory depressant with a narrow therapeutic window. Additionally, AH-7921 has a high addictive potential. Finally, considering that the human dose is currently unknown, packages of the drug sold online could contain toxic doses. Preliminary evidence

suggests that AH-7921 could become a serious new public health concern. International co-operation will therefore be of great importance in monitoring and preventing its spread among drug users.

Footnotes

Authors' Contribution: Maurizio Coppola and Raffaella Mondola developed the original idea and the study protocol, abstracted and analyzed the data, and wrote the manuscript. They both act as guarantors for the study.

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