Letter

Clin Ter 2020; 171 (5):e412-413. doi: 10.7417/CT.2020.2250

Fentanyl analogues potency: what should be known

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Abstract

Fentanyl is a full synthetic opioid acting as a strong μ-opioids receptor agonist. As other opioids, it exerts effects on central nervous systems like euphoria, sedation, anesthesia and respiratory depression at high dosage. It is the parent compound of the high potent opioids class, characterized by a potency up to 10,000 fold higher than mor- phine, currently prescribed as anesthetic and pain killers. Anyway, the diversion of fentanyl analogues has been reported since their appear- ance on the market, rising until alarming rate. Every year, new synthetic alternatives to the controlled fentanyl are proposed on the black market causing an increasing number of fatalities all over the World. Due to the high potency of this class of substances, it may be difficult to ana- lytically detect the molecules in biological matrices and find the actual cause of the deaths. Moreover, an additional analytical challenge is represented by the emergence of newly synthesized derivatives. In this concern, the harmonization of international guidelines, the adoption of common legal responses and the enforcement of international collaboration is desirable to face this alarming public health threat. ***Clin Ter 2020; 171 (5):e412-413. doi: 10.7417/CT.2020.2250***

Key words: *New Psychoactive Substances, opioids, fentanyl, fetanyl analogues*

Dear Editor,

Fentanyl is a full synthetic opioid developed from meperidine, in 1959 by Janssen. It is the prototype of 4-anilinopiperidine class of synthetic opioids (1). It acts on μ-opioid receptors as agonist, exerting the typical opioids effects on central nervous system like sedation, bradycardia, unconsciousness and anesthesia, fatigue, dizziness and respiratory depressions. Since 1968, it has been approved by FDA as anesthetic and pain killer (2). Comparing to other opioids, it is characterized by a fast onset of analgesia and short duration of action. In fact, it crosses the emato-encephalic barrier with a transfer half-life of 4.7-6.6 minutes due to its high lipophilicity (3). Moreover, the 50-100 fold higher potency than morphine is at the base of its success as a prescription opioid over the last decades.

Following the fentanyl discovery, several structural analogues have been designed by pharmaceutical companies to improve the pharmacological profile of these drugs. Structural modification may be theoretically performed on the piperidine ring, the anilinophenyl ring, the 2-phenethyl moiety and the carboxamide group, resulting in a large numbers of new molecules (1). It seems that the fentanyl analogues potency is mainly influenced by steric properties of substituent moieties, especially for substituents on 3- and 4-piperidino substituted analogues (4) or 4 of the piperidine ring. Pharmacological results show that the groups in position 3 of the piperidine ring, which are larger than methyl, severely reduce the analgesic potency compared to fentanyl. It is likely that in regard to the steric factor alone (i.e. voluminosity of the group and cis/trans isomerism), to date the most potent fentanyl analogue legally commercialized, is the veterinary drug carfentanyl, with a potency 10,000-fold higher than morphine. Other fentanyl derivatives currently used as anesthetic for humans are sufentanil (10 times more potent than fentanyl), remifentanil (as potent as fentanyl) and alfentanil (1/3 as potent as fentanyl) (1).

Soon after their appearance on the market, diversion of fentanyl analogues from therapeutic use has been reported, linked to misuse and illicit use by clinicians. In fact, the binding with μ-opioids receptors produces the typical euphoric effect of others opioids. Whereas the popularity among opioids abusers has increased, fentanyl and its analogues appeared also on the illicit market as a cheaper and more potent alternative to heroin, or as a cutting agent (5). According to data reported by European Monitoring Centre for Drugs and Drugs Abuse (EMCDDA), 940 fentanyl derivatives seizures has been registered for a total of 14,3 tons in 13 Countries of European Union in 2017 (6).

In the last few years, a wave of designer fentanyls was reported to the international Early Warning Advisory (EWA) systems. About 50 new synthetic opioids have been reported to the EMCDDA EWA system on new psychoactive substances (NPS) in 2018. (6,7). Designer fentanyls are easily produced in clandestine laboratories in form of powder or tablets to be injected, ingested, snorted or smoked.(8) Furthermore, these molecules have recently been detected as cut-

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ISSN 1972-6007

ting agents in heroin samples or ready-to-use nasal spray and many users are unknowingly consuming these compounds as adulterants in products sold as heroin, or as pain killers. Due to their potency, even a small quantity is sufficient to cause fatal respiratory depression (5). Recently, a dramatic increase of fentanyl related fatalities and acute intoxications has been reported in north America, Canada, Japan as well as in Europe, being a concerning public health threats (6,9). However, the real number of fatalities is underestimated due to the lack of effective analytical assays to detect these substances in biological matrices, especially where consumed in association to more common illicit opioids like heroin (10). As a confirmation, it is interesting to report that the doubling of the number of fentanyl deaths registered in Sweden was related to the introduction of comprehensive screening and more sensitive tests in toxicology laboratories (6). Moreover, it has to be considered that these strictly related molecules often undergo the same metabolic pathways, resulting in the production of the same metabolites. Thus, it may be difficult to figure out the real cause of fatal intoxication (1). Although several methodologies for fentanyl derivatives and related metabolites detection in both classical and alternative matrices have been proposed (5,11–15), an important challenge for toxicological laboratories is the identification of newly introduced molecules that requires an untargeted analysis approach performed with expensive instrument and high specialized personnel. Alongside the scientific advances and technical aspects, an important role is played by the international network of institutions which proposes and promotes common treaties, guidelines and shares clinical and toxicological information. Since the phenomenon of NPS was born to circumvent the narcotic laws, the legal aspect is fundamental. To date, the most important interna- tional treaties are the Single Convention on Narcotic Drugs of 1961 and the Single convention on Psychotropic substances of 1971, signed by the United Nations Organization members. However, every country issued specific law based on different principles to face the growing issue of drug of abuse market (16). Although the national diversities in the illicit market, the fentanyl analogues misuse is a concerning public health issue involving several countries all over the World. In this frame, the harmonization of legal responses, the adoption of common guidelines in toxicological labora- tories and the promotion of an international control systems like the EWA play a fundamental role, not only in the fight against fentanyl derivatives illicit use, but also in case of other health threats caused by replacing controlled psychotropic drugs with cheaper and more easily obtainable ones (17-20).

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