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Review

Desomorphine (Krokodil): An overview of its chemistry, pharmacology, metabolism, toxicology and analysis

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ABSTRACT

Background: "Krokodil" or "Crocodile" is an illegal homemade desomorphine drug obtained from chemical reactions of commercial codeine drugs with several other powerful and highly toxic chemical agents increasing its addiction and hallucinogenic effects when compared with other morphine analogues.
Methods: This paper summarizes a complete review about an old drug called desomorphine (Krokodil), presenting its chemistry, pharmacology, metabolism, toxicology and analysis.
Results: It is of particular interest and concern because this cheaper injectable semisynthetic opioid drug has been largely used in recent years for recreational purposes in several Eastern European as well as North and South American countries, despite known damage to health that continuous use might induce. These injuries are much stronger and more aggressive than morphine's, infecting and rotting skin and soft tissue to the bone of addicts at the point of injection in less than three years, which, in most cases, evolves to death. On this basis, it is imperative that literature reviews focus on the chemistry, pharmacology, toxicology and analysis of dangerous Krokodil to find strategies for rapid and effective determination to mitigate its adverse effects on addicts and prevent consumption.
Conclusions: It is crucial to know the symptoms and consequences of the use of Krokodil, as well as *Methods:* for identification and quantification of desomorphine, contaminants and metabolites, which can help the forensic work of diagnosis and propose actions to control and eradicate this great danger to public health around the world.

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1. Introduction

Nowadays, new drugs or the reappearance of older ones have emerged on the clandestine drug market, either by restriction of classic ones or by addicts looking for novel experiences (Thekkemuriyi et al., 2014). Moreover, novel psychoactive substances (NPS), which are also known as "designer drugs," "herbal highs," "synthetic drugs," "research chemicals" and "legal highs" are a relatively new phenomenon and they often are marketed and purchased online as legal substitutes for more common illicit drugs (Davey et al., 2012; Deluca et al., 2012; EMCDDA, 2011a, 2011b).

The spread of NPS, together with misuse, diversion, rape, home manufacturing, the use of injection of over-the-counter (OTC) and prescription pharmaceuticals has become an important concern around the world (Azbel et al., 2013; Bersani et al., 2013; Van Hout, 2014). Allied to this, alterations in the route of administration, consumption exceeding the recommended dosage, extraction of active pharmaceutical ingredients and tampering with formulations has been undertaken to enhance the desired psychoactive effect. In 2011, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA, 2011c) reported on trend increases in the misuse of opioids other than heroin. In this context, desomorphine is

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an old drug that reappeared in the illicit markets as a novel one. "Krokodil" or "Crocodile" or even "Croc" or "Krok" is the street name for the homemade injectable semisynthetic opioid analogue desomorphine. Its nickname refers to the discolored (green, black) and flaking skin of its users, resembling that of a crocodile (Russian: "Крокодил") (Grund et al., 2013). The street name "Krokodil" also derived from α-chlorocodide, the first intermediate of codeine in the homemade production of desomorphine (Katselou et al., 2014). Media describe "Krokodil" emphasizing its skin damage at the point of injection, commonly using terms such as "Flesh-eating heroin" or "Flesh-rotting drug." In Russian, it is also called "Russian Magic," referring to its potential for short-lasting opioid intoxication or "drug of the poor," referring to its use as a cheap substitute for more expensive heroin (Priymak, 2011). "Krokodil" is about five times cheaper than heroin (Nelson et al., 2014). In 2011, Russian reports suggest that 10 tablets of OTC codeine with acetaminophen could be purchased for 120 Russian Rubles or $3.71 USD, but since 2012, codeine is no longer an OTC medication in Russia. These tablets could produce desomorphine in an equivalent quantity to 500 Rubles or $15.46 USD of heroin. Although there are reports of "Krokodil" in the United States, the authors do not have reliable price information (Grund et al., 2013).

It is of particular interest and concern because this cheaper injectable semisynthetic opioid drug has been largely used in the last few years for recreational purposes in several European and North and South American countries, regardless of known damage to health that continuous use might induce (Hearne et al., 2016). On the basis of this, it is imperative that literature reviews focus on the pharmacology, toxicology, and analysis of dangerous desomorphine to find strategies for rapid and effective determination to mitigate its adverse effects on addicts and prevent consumption.

2. Background

The use of "Krokodil" was first reported in Siberia, a North-East European region of Russia also known as North Asia, in the mid–21 st century (2002) (Grund et al., 2013). After that, the use quickly spread throughout urban centers and remote areas of Russia and some of the former Soviet Republic countries such as Ukraine (Grund et al., 2013), Georgia (Piralishvili et al., 2013), Uzbekistan, and Kazakhstan (Jolley et al., 2012). In 2012, it was estimated that the use of "Krokodil" surpassed 30,000 individuals in Ukraine, 100,000 in Russia and 500,000 are scattered among Georgia, Kazakhstan and Uzbekistan (De Boer et al., 2001; Grund et al., 2013). In addition, all of the former Soviet Republic countries share a long history of injectable drug use; Russia, Ukraine, and Georgia seem to be the countries most affected by "Krokodil" use. In 2012, about 30,000 people died per year in Russia (Skowronek et al., 2012).

According to the Russian Federal Drug Control Service, the amount of "Krokodil" seized in Russia increased 23 times between 2009 and 2011, while in some provinces it has replaced traditional opiates. In this perspective, homemade manufacturing of the drug by anyone using only simple equipment contributes to "Krokodil" epidemic use in Russia and Ukraine (Schmidt et al., 2011). In Georgia, "Krokodil" is actually the most widely used opiate (Skowronek et al., 2012). Some authors suggest that immigration of "Krokodil" users from these countries has been responsible for reported cases of "Krokodil" use in other European countries such as Romania, Germany, Poland, Czech Republic, France, Belgium, Sweden, Norway, and Spain (Van Hout, 2014; Escribano et al., 2016). Consequently, medical centers from more than 50 European cities have reported an increase in health injuries associated with "Krokodil' use. In 2012, main cities associated with the drug's use are Moscow and 27 other Russian cities (Schmidt et al., 2011; Gahr et al., 2012a), Kiev and 24 other Ukrainian cities (UNODC, 2012), Aktobe and several other regions of Kazakhstan sharing borders with Russia (Nickolai, 2009). More recently, there was a case of a woman who had extensive ulcerations after a single use of 'Krokodil' (Haskin et al., 2016).

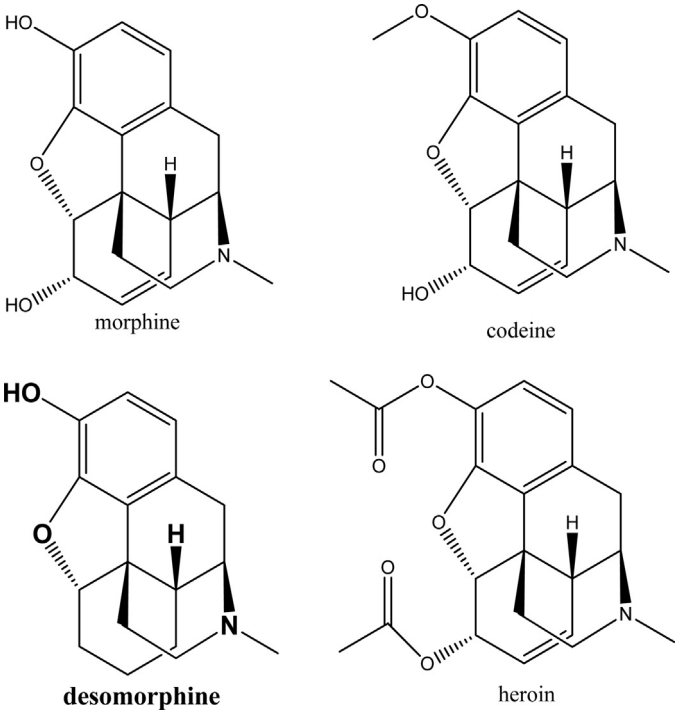

Fig. 1. Structures of morphine, desomorphine, codeine and heroin.

Although only a few, cases of drug users admitted to emergency departments in the United States and in Mexico City with lacerations or rapidly progressing necrotic ulcers have been reported recently, suggesting that intravenous abuse of this homemade heroin has been spreading also to North (Biesk, 2013; Thekkemuriyi et al., 2014) and Latin America (Moran, 2013).

3. Physicochemical properties

Desomorphine is the common name for 4,5-α-epoxy-17-methylmorphinan-3-ol or dihydrodesoxymorphine-D. It is an opioid analogue and morphine derivative in which the 6-hydroxyl group and the double bond at carbons 7 and 8 of morphine are reduced (Small and Morris, 1933). Chemically, desomorphine ($C_{17}H_{21}NO_2$) is a colorless, well-crystallized organic base such as morphine and other alkaloids (Fig. 1). It has a molar mass of 271.35 g/mol, melting point of 189 °C and p K_a value of 9.69 (O'Neil, 2006). Desomorphine can cross the blood–brain barrier, binding to opioid receptors, similar to the pharmacokinetic distribution of all phenanthrene-structured alkaloids (Gahr et al., 2012a). Furthermore, desomorphine, as a free base, is not highly soluble in water at room temperature (solubility of 1.425 mg/L). On the other hand, in allotropic forms, specifically salts that are the most commonly injected form, desomorphine is significantly soluble in water. In addition, it is also soluble in organic polar solvents such as acetone, ethyl acetate and alcohol (Mosettig et al., 1935).

4. Synthesis pathway

Desomorphine was first synthesized in the USA in 1932 by Small and Morris (1933) and patented in 1934 (Small, 1934). The classic synthesis pathway of desomorphine includes the production of α-

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