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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.

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).

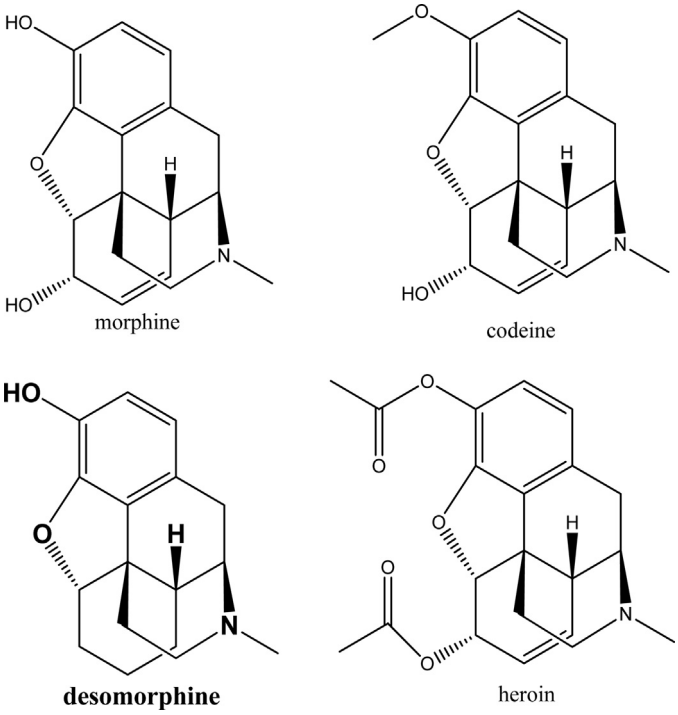

Fig. 1. Structures of morphine, desomorphine, codeine and heroin.

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-

chlorocodide by reaction of codeine with thionyl chloride and then to desocodeine (dihydrodesoxycodeine D) by catalytic reduction. Finally, the removal of a methyl group (demethylation) reduces the intermediate to desomorphine (Small and Morris, 1933; Small, 1934). This catalytic hydrogenation of alkyl halogenates to obtain a derivate of morphine has low yields and requires tedious reaction conditions. Then, Srimurugan et al. (2012) described a convenient and improved pathway for the synthesis of desomorphine from codeine. The method gives highly pure desomorphine without the need for column purification and an acceptable overall yield of 38%, which means that it can be easily applied in common laboratories. In this synthetic pathway, desomorphine is obtained by demethylation of desocodeine with BBr_3 after desocodeine semisynthesis by reduction of the 6-protected-hydrogen group and hydrogenation protection by a hydroxyl group (7,8 double bond reduction) of codeine using H_2 gas and platinum (IV) oxide as catalyst (PtO_2).

According to the balanced chemical equation and the estimated average yield for the synthesis of 1 mg of desomorphine, about 3 mg of codeine salt (sulfate or phosphate) are required (Katselou et al., 2014). In that vein, desomorphine could be synthesized from codeine and differs from morphine only in the lack of a hydroxy group and an extra double bond in its chemical structural (Fig. 1).

5. Pharmacological and clinical properties of desomorphine

Desomorphine has some pharmacological properties, such as analgesic and sedative (Eddy and Howes, 1935), the sedative effect being higher than that presented by morphine (around 15 times) (Duron, 2015). It also presents a faster onset and shorter half-life than morphine (Janssen, 1962; Casy and Parfitt, 1986). Mu-, kappa-, and delta-opioid receptors are located throughout the body in areas such as the brain, spinal cord, and gastrointestinal tract. The opioids produce effects including analgesia, sedation, gastrointestinal dysmotility, and euphoria (Nelson et al., 2011). The analgesic activity is explained because desomorphine binds primarily to mu-opioid receptors (Matiuk, 2014). To a lesser extent, it has some binding activity at kappa and delta receptors (Gahr et al., 2012a).

According to Janssen (1962) (Janssen, 1962), the analgesic effect of desomorphine is around 8–10 times greater than that of morphine. Thus, a person will require less desomorphine than morphine to achieve the desired effect.

As mentioned above, desomorphine has a chemical structure similar to that of morphine, although there are some structural differences (Fig. 1). Accordingly, the higher analgesic action than morphine and even more than that of heroin was attributed to the lack of alcoholic hydroxyl group in desomorphine and its replacement by a hydrogen (Weill and Weiss, 1951; Sargent and May, 1970; Srimurugan et al., 2012). These modifications make the molecule of desomorphine more lipophilic than morphine, promoting its penetration into the brain, which may explain the higher analgesic potency and faster effect (Casy and Parfitt, 1986).

The first reported clinical case of desomorphine use was in 1935 as an alternative to morphine in terms of tolerance and addiction and improved side effect profile. In this study, clinicians treated approximately 900 traumatic cases over about a year with satisfactory pre- and postoperative prognostics. Comparatively, 1.0 mg of desomorphine was equivalent to 10 mg of morphine for postoperative pain relief and sleep was produced by 91.8% of desomorphine doses compared with 80.5% of morphine doses. In a similar study performed on cancer patients, 1 mg of desomorphine was equivalent to 10 mg of morphine for pain relief, and a satisfactory effect was obtained in 96.4% of desomorphine doses and in 94.0% of morphine doses, but sleep per dose was less with desomorphine. The pain relief also showed an average of 2 h and 25 min for desomorphine and 3 h and 7 min for morphine (Eddy et al., 1957). Moreover, desomorphine also presented more potent gastrointestinal mobility and general depression than morphine (Eddy and Howes, 1935). In addition to its faster onset than other powerful painkillers drugs such as morphine, desomorphine also initiates less sedative effects and seems to have favorable postoperative results, such as reduced need for catheterization, less dizziness, and decreased vomiting incidence (Gahr et al., 2012a). Medical studies continued to endorse desomorphine for traumatic cases and for premedication for local anesthesia because of its ability to provide a palliative effect on excitement or fear. However, other clinical studies found that desomorphine wore off quicker, a slower and incomplete tolerance, a faster withdrawal and sooner abstinence syndrome, and, sometimes, a greater risk of respiratory depression; it was concluded to have no real overall advantage over morphine (Duron, 2015; Eddy et al., 1957).

Despite controversies, desomorphine (in ampul or suppository form) was first introduced in Switzerland in 1940 by Hoffman-LaRoche under the brand name of Permonid™ for the postoperative treatment of severe pain as an analgesic drug. This drug was withdrawn in 1952, although its production was continued until 1998 (Gahr et al., 2012a). Notably, the production of Permonid™ continued in Switzerland until 1981, when its use was terminated. After that, it was being used due to the idiosyncratic analgesic needs of a single patient in Bern, Switzerland, who suffered from a rare disease (Gahr et al., 2012a). At present, desomorphine is classified as a narcotic drug (DEA code number 9055) in Schedule I of the U.S. Controlled Substances Act and is listed as a controlled substance under the international Single Convention on Narcotic Drugs of 1961 (Erowid, 2013). In Brazil, it is classified as List – F1 (List of Narcotic Substances in Brazil) SVS/MS n° 344/98 and its updates (ANISA, 2016). Therefore, it is subject to annual aggregate manufacturing quotas in the United States, and in 2014, the quota for desomorphine was 5.0 g (DEA, 2014; USFDA, 2015).

6. Toxicology of desomorphine

Because desomorphine is an opiate, its effects include miosis, flushing, and paresthesia, as well as constipation and urinary retention, nausea, and vomiting. In addition, the intoxication by desomorphine can provoke allergic reactions, seizures, and respiratory depression leading to death (Grund et al., 2013). The lack of alcoholic hydroxyl group in desomorphine and its replacement by a hydrogen, with a consequent increase in liposolubility, can also explain the higher toxicity of this drug than morphine. Duron (2015) describes desomorphine as three times more toxic than morphine (Duron, 2015; Eddy et al., 1957). In fact, desomorphine causes a more pronounced convulsive effect than morphine (Sargent and May, 1970). Moreover, the LD_{50} of desomorphine in mice is 27 mg/kg (intravenously) and 104 mg/kg (subcutaneously), while the LD_{50} of morphine in mice is 226–318 mg/kg (intravenously) and 400 mg/kg (subcutaneously) (Lewis, 2004).

In terms of addictive power, although original studies in cats, dogs, and monkeys suggested that the compound had a low addiction liability, those pharmacological reinforcement characteristics of desomorphine such as faster onset and a shorter elimination mentioned above described in human studies also significantly increases the desomorphine addictive power (Himmelsbach, 1939; Nelson et al., 2014). In accordance, repeated administration of this drug can cause complications, which include physical and psychological dependence, tolerance, and withdrawal syndrome (Grund et al., 2013). The dependence reported in desomorphine users seems to be related to its mu-opioid agonist effect (Nelson et al., 2011), while the ability to produce tolerance is related to the ability of opioids to induce the internalization of the mu-opioid recep-

tor (Just et al., 2013). In relation to withdrawal syndrome, a study conducted in human subjects demonstrated that the abrupt withdrawal of desomorphine resulted in typical abstinence syndrome as was experienced by morphine sulfate withdrawal (Eddy and Howes, 1935).

Another effect of desomorphine is the inhibition of cholinesterase from plasma and human brain, which can result in neurological symptoms. In addition, desomorphine seems to be a more potent inhibitor of cholinesterase than codeine and morphine (Wright and Sabine, 1943). Schürch and Brunner (1935) also demonstrated that desomorphine could present greater respiratory depression than morphine. In fact, in a study performed with rhesus monkeys, the authors found that desomorphine showed 10 times more depressant effect than morphine (Duron, 2015).

In contrast to the above observation, Gahr and co-workers (Gahr et al., 2012a) demonstrated that desomorphine tends to cause fewer incidences of nausea than morphine because desomorphine has a fast onset of action. In fact, Eddy et al. (1957)) reported that the effect of desomorphine on intestinal peristalsis, as well as dizziness and vomiting, were lower than those of morphine.

7. Metabolism of desomorphine

To date, there is no study on the metabolic fate of desomorphine in the human body and about its detectability in common standard urine screening approaches. However, Richter et al. (2016) investigated the metabolic fate of desomorphine in vivo using rat urine and in vitro using pooled human liver microsomes (pHLM) and pooled human liver cytosol (pHLC). Some metabolites were found and some metabolic steps could be proposed as

N-demethylation, hydroxylation at various positions, *N*-oxidation, glucuronidation and sulfation (see Fig. 2). The cytochrome P450 (CYP) initial activity screening revealed CYP3A4 to be the only CYP involved in all phase I steps. In addition, UDP-glucuronyltransferase (UGT) initial activity screening showed that UGT1A1, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B15 and UGT2B17 formed desomorphine glucuronide. Therefore, desomorphine intake can be detectable by all standard urine screening approaches, mainly via the parent compound and its glucuronide (Richter et al., 2016).

8. Homemade "Krokodil"

Unlike Crystal Meth produced in the USA (Pourmand et al., 2014), Pervitin in the Czech Republic, or Homebake heroin in New Zealand (Skowronek et al., 2012), the homemade production of "Krokodil," as occurs in Russia, does not lead to a powder or crystal-like drug but instead a liquid ready for consumption is obtained. This liquid is frontloaded in syringes used for injection (Skowronek et al., 2012). Then, "Krokodil" consumption is similar to morphine and heroin, being intramuscular or parenteral and, more commonly, intravenously injected (De Boer et al., 2001). These drugs are traditionally prepared by one or more producer members that may assist the cook and inject the home producers' manufactured drug in small groups of friends, where sharing of needles and other injecting equipment is common (Grund and Merkinaite, 2013). In former Soviet Republic countries, injecting drug use is the principal risk factor for transmission of hepatitis C virus (HCV) and an important cause of human immunodeficiency virus (HIV) infection in poor people younger than 25 years. It happens either by sexual transmission or by the inoculant practice of exchanging syringes, lancets, and needles (Jolley et al., 2012). The desirable effects, as described by consumers, are pleasure and excitement, increased sensory perception, and inhibition of patterns that cause physical pain (Jolley et al., 2012).

The street- and homemade "Krokodil" preparation process commonly does not employ standardized technique and it is a crude synthesis product homemade from codeine requiring easily obtainable chemicals and rudimentary laboratory needs. According to Alves et al. (2015a), it resemblances Nagai's route, first used to synthesize methamphetamine from ephedrine or pseudoephedrine (Nagai, 1983), but employs codeine as morphinan starting material. This compound is usually extracted from analgesics and antitussives commercially available as pharmaceutical products in the form of tablets or syrup, which may also contain other substances, such as acetaminophen, acetylsalicylic acid, caffeine, ephedrine, tropicamide, and terpin hydrate (an expectorant). The illegal production requires the use of chemical agents of low cost and easy availability in a retail market or drugstores without government control, as well as rudimentary laboratory conditions with very little equipment and undertaken in unsanitary conditions (De Boer and Bosman, 2004). The similarity in synthesis pathway with desomorphine guarantees sedative and analgesic effects 8–15 times more potent than morphine, and has weaker toxic, convulsant, emetic, and respiratory depressant action. It has a very fast onset of action (2–3 min) and a short duration of effect (2 h). First addiction effect usually appears 5–10 days after intravenous or intramuscular injection and death comes maximally after 2–3 years, but even a single dose may be lethal in cases of idiosyncrasy (Nelson et al., 2014; Schep et al., 2011). Some studies associated the early widespread use of "Krokodil" in former Soviet Republic countries to the higher addictive power of this drug (Skowronek et al., 2012). The availability, easy and economic manufacturing involve a simple extraction and reduction process, in which codeine tablets are boiled in a pot on a stove, often using iodine, red phosphorus, paint thinner, ethyl acetate, gasoline, or some other toxic substance, as diluting agent, and potassium or sodium hydroxide, as strong base. Hydrochloric acid, or some other strong acid, is also used to convert codeine-base into its water-soluble salt. It is believed that desomorphine is the main active opioid of "Krokodil." However, the homemade drug preparation produces an impure and harmful suspension contaminated with a high concentration of toxic and corrosive chemical intermediates, by-products, and residuals (e.g., heavy metals like iron, zinc, lead, and antimony) that is injected intravenously (Alves et al., 2015a; Kunalan et al., 2012; Rohan, 2013). Because of its hazardous properties, contaminants from the final product are considered responsible for the major undesirable effects observed in drug users after repeated injections of "Krokodil." According to Savchuk et al. (2008), "Krokodil" composition varies significantly between dealers (desomorphine concentration ranges from traces to 75% in different seized drugs). In terms of health damage, it is responsible for unpredictable clinical effects observed among heavy users, which makes drug users' treatment even more difficult.

To help to explain signs and symptoms presented by the abuser, recently, Alves et al. (2015b) described a procedure for the synthesis of "Krokodil" mimicking the street conditions used in its preparation as reported by abusers in Georgia. In this study, the authors identify possible by-products in the catalytic reduction from codeine to desomorphine at different conditions that could be associated to the toxicity elucidation of this drug (Alves et al., 2015b; Neves et al., 2016).

Among chemical agents most commonly detected in syringes and biological fluid samples from drug users (Savchuk et al., 2008) or reported by abusers as those used in drug production are sodium hydroxide from pipe cleaner (caustic soda), oil, petrol, kerosene, gasoline, hydrochloric acid, iodine from disinfectants and medical tinctures, petrol, and red phosphorus from matchboxes (Grund et al., 2013).

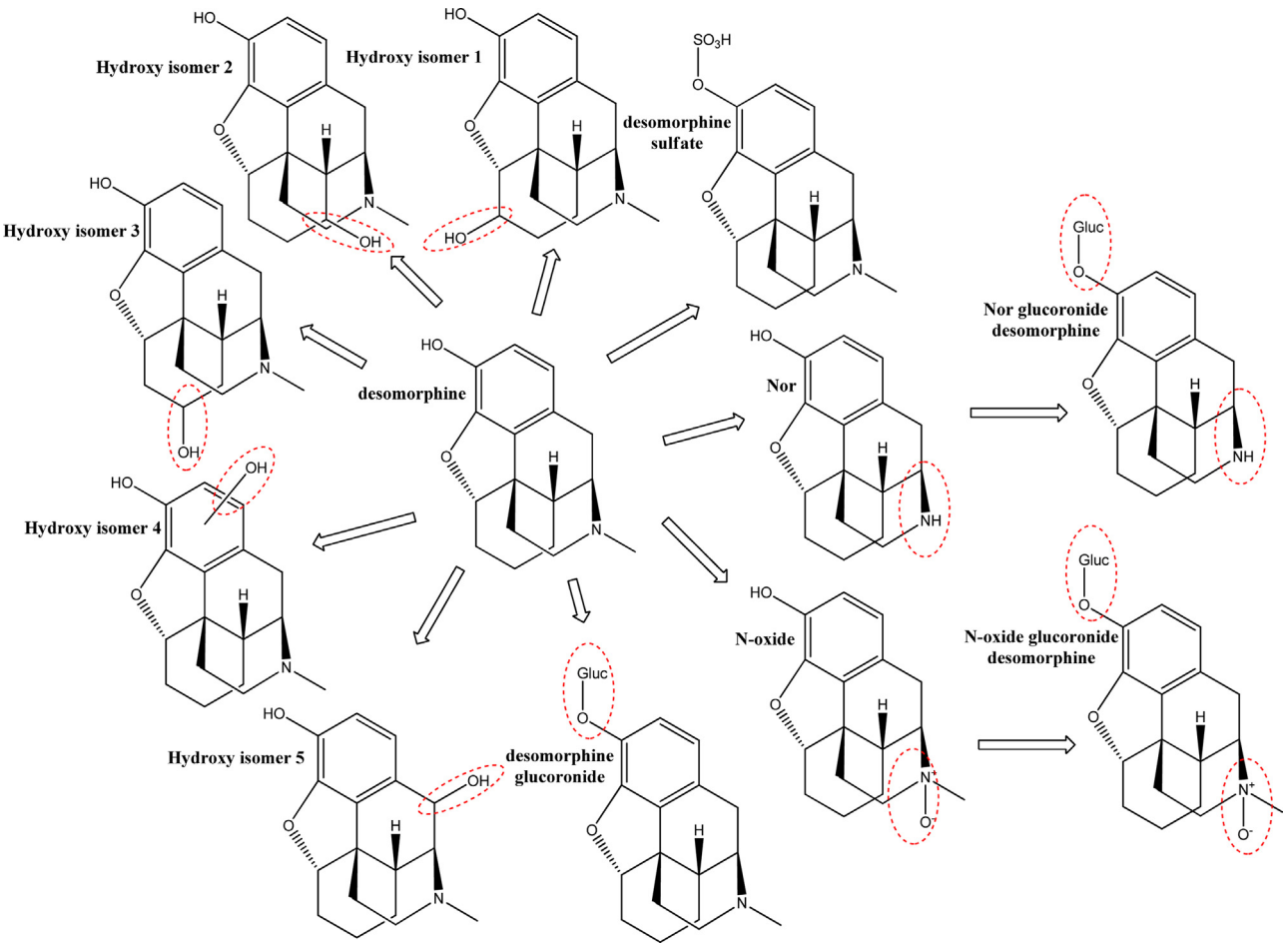

Fig. 2. Metabolic pathways of desomorphine according to the metabolites detected in rat urine, pHLM/pHLC, HepG2, or HepaRG cells by Richter et al., 2016. Hydroxy isomer 1 (HepG2 rat), Hydroxy isomer 2 (pHLM/pHLC, HepG2 rat and HepaRG rat), Hydroxy isomer 3 (HepG2 rat and HepaRG rat), Hydroxy isomer 4 (pHLM/pHLC and HepaRG rat), Hydroxy isomer 5 (pHLM/pHLC), N-oxide desomorphine (pHLM/pHLC, HepG2 rat and HepaRG rat), N-oxide glucuronide desomorphine (HepaRG rat), Nor desomorphine (pHLM/pHLC, HepG2 rat and HepaRG rat), Nor glucuronide desomorphine (HepaRG rat), gluuronide desomorphine (pHLM/pHLC, HepG2 rat and HepaRG rat) and sulfate desomorphine (HepG2 rat and HepaRG rat).

In Russia, not only chemical agents used in street- and homemade "Krokodil" production, but also codeine as an analgesic drug for severe pain had no governmental control to commercialization. Russian authorities restricted the sale of drugs containing codeine from June 2012. It contributed to recent widespread "Krokodil" use mentioned above and codeine misuse of OTC drugs in these countries (Grund et al., 2013). In those countries that have a governmental restriction on morphine analogue drug sale (as codeine), the recently reported cases of "Krokodil" use probably will be associated with an increase in prescription of codeine as an analgesic drug reported in the next few years (Region, 2011).

9. Toxicology of "Krokodil"

Addicts more frequently administer "Krokodil" orally, subcutaneously, or intravenously, the intravenous way being the most used by users of this drug (DEA, 2013). The effects are observed very quickly, approximately 15–30 s after the intravenous injection and approximately 3–5 min for the subcutaneous administration (Lyer et al., 2011). As noted above, the active substance of "Krokodil" is desomorphine, and through the intravenous use of "Krokodil," other highly toxic components of this drug can enter the bloodstream along with desomorphine (Gahr et al., 2012b; Lee and Ladizinski, 2014). Then, intravenous injection of homemade and street "Krokodil" can cause several pathologies, such as coronary artery burst, septicemia, and other systemic damage due to infections, such as pneumonia and meningitis (Grund et al., 2013). In addition, infections by HIV and hepatitis A, B, and C are reported in "Krokodil" addicts using contaminated needles (Rohan, 2013). These viruses may cause systemic damage, especially HIV, which causes several complications in the immune system (Grund et al., 2013). The incidence of hepatitis C (HCV) is very high, while HIV prevalence is significantly lower (Nelson et al., 2014). A possible explanation for this fact is that the acidity of the street and homemade drug solutions can render HIV inactive when stored in syringes while such inactivation of HCV would require higher concentrations of acid or longer exposure times (Heimer et al., 2007; Dumchev et al., 2009). Another effect that can be observed in users of "Krokodil" is due to unsanitary conditions in the preparation of this drug; it is common for users to develop infections such as methicillin-resistant *Staphylococcus aureus* (Gahr et al., 2012a).

The manifestations presented by the "Krokodil" consumers are reportedly devastating and bring serious complications to these users. The more visible physical signs of "Krokodil" use involve skin and venous damage, including ulcers and phlebitis around the injection sites. Discoloration and desquamation of the skin can be observed, and repeated or regular use may turn the skin around the injection site scaly and rough, like a crocodile skin (Matiuk, 2014). In addition, gangrene and limb amputations may occur with continued use (Grund et al., 2013; Thekkemuriyi et al., 2014). These effects have been related to by-products and residuals of the manufacturing process of "Krokodil" and not to the opiate effects of

desomorphine (Gahr et al., 2012a). In fact, because "Krokodil" is routinely injected with little or no purification, it can cause immediate skin irritation and ulcers, destruction of skin and severe muscle, and cartilage tissue damage (Gahr et al., 2012b; Lee and Ladizinski, 2014). However, Shuster (2011) demonstrated that the lesions observed after "Krokodil" exposure can include several parts of the body that are not typically used as sites for injecting drugs. This suggests that the ill effects of "Krokodil" are not limited to localized injuries, but spread throughout the body, with neurological, endocrine, and organ damage associated with chemicals common to "Krokodil" production (Shuster, 2011). These alterations consist of motor and speech impairments, memory and personality changes, thyroid abnormalities, and liver and kidney damage (Grund et al., 2013). In addition, Lemon (2013) describes the use of homemade "Krokodil" as a possible cause of hallucinations. Because "Krokodil" presents an analgesic effect, the user often fails to recognize immediately these deleterious consequences (Matiuk, 2014).

In relation to impurities observed in the production of "Krokodil," several toxic effects are observed due to orange-colored liquid contaminated with various toxic and corrosive by-products or residuals like organic solvents (gasoline, ethyl acetate, or paint thinner) (Grund et al., 2013), as well as hydrochloric acid, iodine, and red phosphorus (Savchuk et al., 2008). According to Matiuk (2014), iodine excess is associated with damage to the endocrine system and muscles. Moreover, jaw osteonecrosis develops as a complication in patients who use "Krokodil" (Poghosyan et al., 2014) and one of the main causes of jaw osteonecrosis is exposure to phosphorus compounds (Ruggiero et al., 2004). This pathology is a painful condition characterized by avascular necrosis of bone in the oral cavity that is commonly associated with localized swelling and, sometimes, purulent discharge (Die et al., 2007). The presence of gasoline and hydrochloric acid in the production of "Krokodil" can contribute to the local damage induced by this drug, causing skin irritation, ulcers, and thrombophlebitis (Gahr et al., 2012a). In addition, chronic exposure to gasoline and paint thinner may cause encephalopathy and neurological damage (Tsatsakis et al., 1997). Moreover, it is known that lead exposure induces hematological, renal, and hepatic damage in the human body (Tian et al., 2013). In addition, this heavy metal can affect the hippocampus, causing memory and learning impairment (Liu et al., 2013) and induce reproductive disorders in the human body (Landrigan et al., 2000).

The toxic effects presented by "Krokodil" are, frequently, confused with heroin abuse, because the impurities and complications of these drugs have a similar profile (Gahr et al., 2012a,b). The withdrawal symptoms of "Krokodil," for example, are similar to heroin and may last up to a month (Katselou et al., 2014). However, differences between heroin and "Krokodil" abuse are reported in the literature. The euphoria in "Krokodil" addicts seems to last one hour and a half, while the effects of heroin use can last four to eight hours. The euphoria reported in "Krokodil" users, as cited above, seems to be related to the mu-opioid agonist effect of this drug (DEA, 2013). Moreover, the use of "Krokodil" leads to a mean survival time of one or two years, while the respective time for heroin could be up to 20 years (Katselou et al., 2014).

10. Determination of the active ingredients and contaminants of "Krokodil"

Because of attention given to increasing reports of cases of health injuries in "Krokodil" users, there is an increasing interest in analytical methods for desomorphine determination in biological and nonbiological samples for clinical and forensic purposes (Celinski et al., 2010; Gibbons, 2012). According to Hayashi et al. (2013), desomorphine and its metabolites may be determined in blood samples within a couple of hours and in a urine sample up to 2–3 days after use of desomorphine.

Although it is an old drug, detailed descriptions of analytical procedures of desomorphine determination are scarce. According to a DEA publication, the National Forensic Laboratory Information System reported that only two exhibits submitted to and analyzed by state and local USA forensic laboratories were identified as desomorphine in 2004 (DEA, 2013).

Gas chromatography–mass spectrometry (GC–MS) using selected-ion monitoring (SIM) or tandem mass spectrometry (MS–MS) is the most frequently adopted technique for an efficient analysis of desomorphine, but methods using other analytical techniques, such as liquid chromatography (LC), have also been reported. According to our research, detection and quantification of desomorphine are cited in different articles about synthesis (Small and Morris, 1933; Small et al., 1933; Eddy and Howes, 1935; Mosettig et al., 1935), clinical (Canales et al., 2015) or forensic purposes, but only a few methods reported the complete analytical procedure.

Toxicological analysis of femoral venous blood of a young man in a coma after brain abscess complications, and admitted to a hospital for treatment with methadone for illicit drugs withdrawal revealed 0.04 μg/mL of free morphine, 0.1 μg/mL of morphine-3-glucuronide, 0.4 μg/mL of methadone, 0.2 μg/mL of trimipramine and 0.2 μg/mL of

N-desmethyltrimipramine. According to the police investigation, the patient was addicted to "Krokodil" and to heroin, but desomorphine was not detected in the blood or urine sample. Although all blood levels were within therapeutic ranges that do not cause severe or life-threatening complications, the authors suggest that morphine and methadone may have led to hypoxic brain swelling due to respiratory depressant effects. Then, although there is no information about the analytical procedure employed, the method proved to be able to determine traces of drugs in postmortem biological samples taken from a suspect in death by illegal drug misuse, and establish a causal relationship with clinical brain injuries (Hayashi et al., 2013).

Srimurugan et al. (2012) reported a simple method of desomorphine synthesis and its deuterium-labeled analogue, using GC–MS as a confirmatory technique. All reaction products were shown to be over 99% pure and the overall yield of the process was 38%, but no column purification was required at any stage.

Some recent studies describe the preparation of "Krokodil" in a street-like fashion, to obtain samples as similar to reality as possible, together with a validated method for quantification of desomorphine and identification of by-products by GC–MS with electron impact ionization. The detection limit and quantification limit of the method for desomorphine were 0.150 μg/mL and 0.490 μg/mL, respectively (Alves et al., 2015a,b; Neves et al., 2016).

The complexity of the analytical methods often described lies in the pretreatment of target compounds, often at trace levels in complex samples such as a biological matrix, which is a significantly time-consuming and laborious process. Therefore, extraction procedures showing simplicity, saving time, sample clean-up, and preconcentration efficiency are worth mentioning. Desomorphine has been determined in biological and nonbiological fluids employing different pretreatment procedures prior to analysis as described above (Thevis et al., 2013).

Savchuk et al. (2008) quantified codeine and synthetic analogues of codeine, including desomorphine, in expert-forensic materials and biological fluids by GC–MS using different derivatization reagents such as trifluoroacetic anhydride (TFAA),

N,*O*-bistrimethylsilyltrifluoroacetamide (BSTFA) and *N*-methyl-bistrifluoroacetamide (MBTFA); mass spectra were obtained for all codeine derivatives. The analogues of morphine were also determined by LC with ultraviolet detection (HPLC–UV) after sample

purification with thin-layer chromatography (TLC). Expert-forensic samples were washouts from cotton wool tampons (through which persons consuming narcotics filtered synthesis products before intravenous introduction), washouts from used syringes and residues of liquids in syringes; expert samples were washed with acidified solution. Biological fluids were urine samples taken from desomorphine users from different regions of Russia, in particular, the cities of Kemerovo and Lipetsk. Opioid derivatives from alkalized expert material washouts and urine samples (hydrolyzed and nonhydrolyzed) were extracted using a mixture of chloroform:isopropanol (9:1, v/v), and analyzed by TLC and GC–MS.

Conventional liquid–liquid extraction (LLE) has been one of the most commonly used techniques for the preconcentration and matrix isolation of organic compounds from aqueous matrices because it is useful for separating compounds from interferences by partitioning the sample between two immiscible liquids or phases. Because extraction is an equilibrium process, changes in pH, ion pairing, complexation, and so on, can be used to enhance target compounds' mass transfer (or recovery) and/or the elimination of interferences. However, LLE requires large amounts of toxic organic solvents and is time-consuming and tedious (He and Lee, 1997). Under these conditions, Savchuk et al. (2008) identified the main codeine derivatives, caffeine, phenobarbital, dimedrol, analgin, and its decomposition products; emphasizing substantial differences in sample compositions analyzed. This is due to the specific features of the synthesis, its steps, the technique of drug preparation, and the purification degree of products. The concentration of desomorphine in both sample matrices ranged from 70 to 80% to trace amounts (Savchuk et al., 2008).

Alternative solid-phase microextraction (SPME) was developed by Pawliszyn and co-workers in 1990 (Arthur and Pawliszyn, 1990) as an attractive and effective procedure combining sample extraction and concentration with sample introduction in GC and HPLC. It is based on the partitioning of target compounds between a liquid or gaseous sample matrix and an immobilized sorbent as the preconcentration matrix. However, almost all commercially available SPME fibers are prepared with fused silica fiber, which is fragile and should be handled with care. To overcome this problem, researchers have developed a series of metal oxides, achieving a wiresupport metal coating with different coating techniques. These techniques include direct binding coating, electrodeposition, chemical oxidation, and sol–gel techniques. Then, recently, Su et al. (2011) developed a solid-phase dynamic extraction–gas chromatography–mass spectrometry (SPDE–GC–MS) method using sol–gel titanium film-coated needles for the detection and determination of desocodeine and desomorphine at trace levels in urine samples. SPDE is a recent modification of SPME using a sorbent coating on the inner wall of a stainless-steel needle instead of the usual coated fiber, which reduces the fragility of the fiber and increases the extraction capacity of the technique (Lipinski, 2001). This sensitive assay showed a low limit of quantitation (LOQ) ranging from 1.0 to 5.0 ng/g and a wide range of linearity

(5–5000 ppb). Therefore, the authors concluded that the high thermal stability of titania film permitted efficient extraction and analysis of opiate drugs from urine samples. In addition, Su and co-workers suggest that the method provides a rather simple and inexpensive approach for less volatile opiate drugs with sufficient sensitivity and reproducibility. Comparing with SPME, it proved effective with similar extraction time and higher recovery (93%) than the SPME method employed (89%) for desomorphine analysis.

In 2015, a highly sensitive and specific LC–MS–MS method using electrospray ionization in positive ionization mode was developed and validated by Eckart and co-workers (Eckart et al., 2015) for the simultaneous detection of 35 multiple opioid-type drugs, including their metabolites, in plasma. The determined drugs were alfentanil, buprenorphine, codeine, desomorphine, dextromethorphan, dextrorphan, dihydrocodeine, dihydromorphine, ethylmorphine, fentanyl, hydrocodone, hydromorphone, methadone, morphine, naloxone, naltrexone, oxycodone, oxymorphone, pentazocine, pethidine, pholcodine, piritramide, remifentanil, sufentanil, and tramadol as well as the metabolites 6-monoacetylmorphine, bisnortilidine, morphine-3-glucuronide, morphine-6-glucuronide, naltrexol, norbuprenorphine, norfentanyl, norpethidine, nortilidine, and

O-desmethyltramadol. Biological fluids were pretreated by solid-phase extraction (SPE). SPE using cartridge and disk devices is today the most popular sample preparation method in analytical chemistry for isolation, concentration, clean-up, and medium exchange. In this technique, the target compounds, usually from a mobile phase (gas, fluid, or liquid), are transferred to the solid phase where they are retained for the duration of the sampling process. The solid phase is then isolated from the sample and the analytes recovered by elution using a liquid or fluid, or by thermal desorption into the gas phase (Poole, 2003). SPE can be applied to extract hydrophobic, but also more hydrophilic compounds, which is an advantage over LLE. The major advantages of SPE are trace enrichment (preconcentration), sample clean-up and medium exchange (transfer from the sample matrix to a different solvent or to the gas phase). However, SPE disadvantages are the use of an off-line procedure: compounds are desorbed from the sorbent with a small volume of organic solvent and an aliquot of the final extract is subsequently analyzed, with a persistent risk of sorbent material contamination (Brinkman et al., 1994; Borges et al., 2009; Borges et al., 2015). Furthermore, SPE can even lead to a low breakthrough volume for more hydrophilic compounds and could need prefiltering for real-life sample analysis to avoid clogging and subsequent compound loss, and the possibility of interferences such as plasticizers present in the sorbent material (Barceló et al., 1994). Under the conditions mentioned above, the method was applied successfully to authentic blood, serum, urine, and other body fluid samples in routine analysis in forensic toxicology with limits of detection ranging from 0.02 to 0.6 ng/mL and the lower LOQ ranged from 0.1 to 2.0 ng/mL. Recovery rates ranged between 51 and 88% for all compounds except alfentanil, bisnortilidine, pethidine, and morphine-3-glucuronide. In addition, the matrix effect ranged from 86% for ethylmorphine to 105% for desomorphine. The method was also applied to 206 samples provided by palliative and intensive care units and by the police authorities in clinical toxicology and pharmacokinetic studies. Furthermore, a suspected fatal intoxication is demonstrated by an analysis of the sufentanil in postmortem body fluids and tissues.

In addition, some companies have also sought a method for desomorphine quantification. Agilent has developed and presented a method for determination of desomorphine, along with heroin, methadone, buprenorphine, and their metabolites in urine (Stone, 2014), with LOQ below 50 ng/mL in a biological matrix. The company Flir provides, together with their mobile GC/MS system, a method and compound library that enable desomorphine identification and quantification (Flir, 2014).

More recently, Richter et al. (2016) employed an LC-HR–MS/MS with gradient elution on a Phenyl Hexyl column (100 mm × 2.1 mm, 2.6 μm) and mobile phase consisting of 2 mM aqueous ammonium formate containing formic acid (0.1%, v/v) and acetonitrile (1%, v/v) (pH 3, eluent A) and ammonium formate solution with acetonitrile:methanol (1:1, v/v) containing formic acid (0.1%, v/v) and water (1%, v/v; eluent B) for determination of metabolites that include nor, oxo or hydroxyl metabolites, combinations of them, sulfation and glucuronidation of the parent compound and corresponding phase I metabolites.

11. Conclusions and future trends

From the public health point of view, old drug desomorphine named "Krokodil" is an epidemic that recently invaded Russia and other countries of the former Soviet Republic, and later, illicit drug markets in Europe and the Americas. It is a powerful drug of choice for opioid addicts when heroin is unavailable or off-budget because the drug could be easily prepared at home or in the street and it is much cheaper than morphine. Clandestine production of "Krokodil" employs medicines containing codeine and higher toxicity chemicals freely on sale in some markets. The poor performance of its homemade chemical synthesis, the absence of appropriate purification methods before consumption, and the frequently intravenous injection of an extremely dangerous mixture of compounds having desomorphine as its main psychoactive ingredient are often responsible for serious adverse health outcomes and even premature death. Among the main consequences of "Krokodil" exposure are ulcers and phlebitis around the injection sites, in addition to discoloration and desquamation of skin. Neurological damage, such as speech impediments, motor skill impairments, reduced memory and concentration, and hallucinations are also reported in "Krokodil" addicts. Moreover, jaw osteonecrosis can develop in the maxillofacial region in patients who have used "Krokodil." On the other hand, the potent analgesic effect of desomorphine may contribute to a delayed search for medical care in regular consumers.

Although there are increasing reports of cases of health injuries in "Krokodil" users around the world, analytical procedures describing desomorphine and constituents (from synthesis and preparation) determination are very scarce. From a chemical perspective, "Krokodil" analysis should give the active ingredients and contaminants in home- and streetmade production, necessary information for clinical and forensic purposes. In addition, confirmation and laboratory quantification of active ingredients and contaminants in biological samples are very important because they can help in the knowledge of their pharmacokinetics with information about toxic or lethal doses. Desomorphine metabolism has been very little studied, it is very important for the knowledge of human metabolites in cases where desomorphine can no longer be found.

It was observed in this review that the main extraction techniques used were LLE and SPE. Several miniaturized extraction techniques, faster and consuming smaller amounts of solvent could be applied to these analyses, with the advantage that they can be easily automated. Another point to be explored is the use of selective solid phases, with sorbents especially developed for one or more compounds of this class, the novel sorbents such as molecularly imprinted polymers or restricted access material that minimize the interfering matrix, being highly selective for groups of structurally analogous substances such as desomorphine. Finally, it is necessary to develop rapid, robust, sensitive and selective methods for identification and quantification of desomorphine and contaminants, thus helping forensic work to diagnose and propose actions to control and eradicate this great danger to public health around the world.

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The authors declare no conflict of interest, particularly no financial and personal relationships with other people or organizations that could inappropriately influence (bias) this work.

Authors contribution

D.H.Â. Florez and A.M.S. Moreira drafted the review. P.R. da Silva, R. Brandão, M.M.C. Borges also contributed to the drafting of the manuscript and proof reading. F.J.M. de Santana and K.B. Borges supervised the work and provided guidance during manuscript preparation and revisions. All authors have read and approved the final version of the manuscript.

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