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Extended Abstract

A New Danger in Our Midst: Krokodil (Desomorphine) Addiction*

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Abstract

The use of addictive synthetic substances is ever-increasing both in Turkey and throughout the world, and new substances are emerging over time. Just as these substances can be re-synthesized, they can also be in the form of known illicit and home-produced substances. Having the active ingredient of desomorphine, krokodil has been known for many years as an addictive synthetic substance whose illegal production and use has increased in recent years. As cases of krokodil use have been reported from many places in the world, especially from regions geographically close to Turkey, this substance must be viewed as a potential threat to the country. The aim of this study is to examine desomorphine in detail and to raise awareness of this substance among healthcare professionals, primarily those working in the area of addiction.

Keywords

Addiction • Desomorphine • Krokodil • Morphine • Codeine

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The production of new substances or the re-launch of old substances in the market by making changes to the production or usage methods are often seen in the field of addiction (European Monitoring Center for Drugs and Drug Addictions [EMCDDA], 2011). Alongside the emergence of illicit home-produced substances in the last 15 years has been the increased spread of the use of these substances, one of which being desomorphine (Grund, Latypov & Harris, 2013; Thekkemuriyi, Gheevarghese, & Unnikrishnan, 2014). The name given to this substance among users is Krokodil, or Krok (Grund et al., 2013; Katselou, Papoutsis, Nikolaou, Spiliopoulou, & Athanaselis, 2014). This name is thought to have been given to the substance because of the green or black color alterations and scaling of users' skin, similar to that of crocodile skin or because of the emergence of α-Chlorocodide as an intermediary byproduct during production (Grund et al., 2013, Katselou et al., 2014). The severe skin lesions that form are generally caused by this flesh-eating heroin / flesh-rotting drug (Florez et al., 2017). It is also called poor man's heroin, as it is cheaper than and has a similar structure to heroin, or Russian magic, as usage started in Russia (Florez et al., 2017).

In 2017, krokodil came to the attention of the treatment team in the Sivas Alcohol and Substance Treatment and Education Centre (AMATEM) when a patient undergoing treatment for opiate addiction stated that he had been in places in Russia where this substance was used but that he had not taken it himself. The literature has case reports related to this substance from several countries with one study in Turkey by Sayar and Nurmedov (2014) drawing attention to this subject.

The aim of the current study is to examine this substance in detail, which has yet to become a severe threat in Turkey, and to draw the attention of all healthcare personnel to this substance, primarily those working in the field of addiction.

Extent of Use

After this substance was first used by certain individuals, reports primarily came from Siberia and other eastern Russian regions from 2002 onwards (Gahr et al., 2013). After a short time, reports emerged of its use in other rural areas of Russia and its neighboring countries (Ukraine, Georgia, Uzbekistan, and Kazakhstan; Grund et al., 2013; Piralishvili et al., 2013). The number of desomorphine users has shown a sharp increase since 2011 (Gahr et al., 2013). Of the 2.5 million substance addicts in Russia in 2011, 100,000 are estimated to be addicted to desomorphine. Approximately 30,000 are estimated to have died from desomorphine addiction in Russia in 2012 (Florez et al., 2017; Piralishvili et al., 2013).

Following these developments, Russia banned in 2012 the sale of drugs containing codeine, which are used in the production of desomorphine, from anywhere other than pharmacies (Gahr et al., 2013). Following the reports coming from Russia

and its neighboring countries, reports related to the use of this substance emerged in European countries such as Romania, Germany, Poland, the Czech Republic, France, Belgium, Switzerland, Norway and Spain (Escribano et al., 2016; Van Hout, 2014). Lately, cases have also been reported of its use in North and Latin America (Thekkemuriyi et al., 2014).

Chemical Structure and Properties

Desomorphine was first synthesized in 1932 in the USA, with a patent for production being obtained in 1934 (Small & Morris, 1933). The classic synthesis pathway of desomorphine is the formation of *α-Chlorocodide* after the reaction of *codeine* with *thionyl chloride,* followed by the transformation of *α-Chlorocodide* to *desocodeine (dihydrodesoxycodeine D)*. Afterward, desocodeine transforms to desomorphine through demethylation (Eddy & Howes, 1935; Small & Morris, 1933) (See Figure 1) .

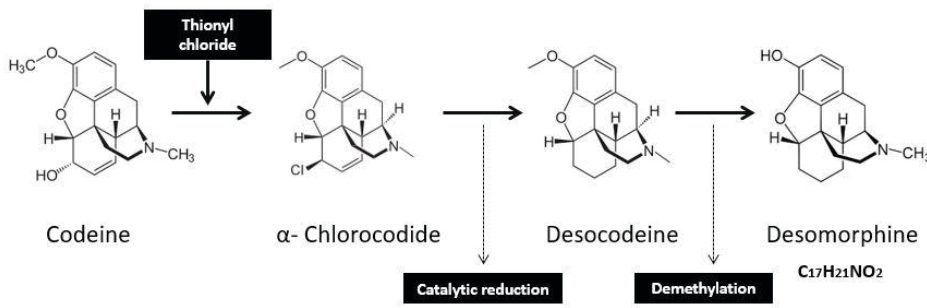

Figure 1. Synthesis of desomorphine from codeine

Desomorphine ($C_{17}H_{21}NO_2$) is the name commonly used for *4,5-α-Epoxy-17-methylmorphinan-3-ol,* or *dihydrodesoxymorphine-D.* It is an opioid analogue and morphine derivative (reduction of the 6-hydroxyl group and 7th-8th carbons of morphine (Small & Morris, 1933) (see Figure 2). Like morphine and other alkaloids, desomorphine is a colorless organic base that can be easily crystallized. It has a stub of 271.35 g/mol, a melting point of 189°C, and a pKa value of 9.69 (Small & Morris, 1933). It can pass the blood-brain barrier and binds to opioid receptors in a way similar to the structure of other alkaloids in the phenanthrene structure (Gahr et al., 2013). Because of its free base, it has low water solubility (1.425 mg/L) at room temperature and dissolves rapidly in organic solvents such as acetone, ethyl acetate, and alcohol (Mosettig, Cohen, & Small, 1935).

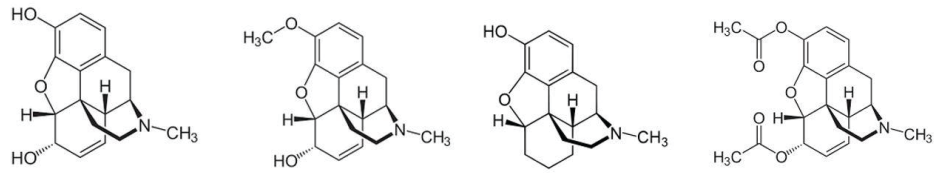

Figure 2. The structure of morphine, codeine, desomorphine and heroin

Street Production and Use

Krokodil is a substance easily produced from tablets containing codeine, generally in homes or illegal laboratories (Gahr et al., 2013). A total of 5-10 tablets containing codeine are boiled together with thinners such as paint thinner or petrol (generally containing zinc, lead, iron, and antimony), hydrochloric acid, iodine, and red phosphorus (obtained from the sides of matchboxes) (Florez at al., 2017). After this process, codeine transforms into two intermediary substances then into desomorphine (see Figure 1; Eddy & Howes, 1935; Florez et al., 2017). The substance produced at the end of this process what is known as krokodil (Gahr et al., 2013). In fact, the name krokodil is given to the mixture that contains iodine, phosphorus, and several heavy metals in addition to the main psychoactive agent, desomorphine (Gahr et al., 2013). As the above-mentioned processes are applied without any hygienic regulations, this mixture becomes dangerous as a chemical and high-risk in terms of infection. Without any filtration, this substance, together with all the foreign substances and heavy metals, is injected intravenously into the body (Florez et al., 2017; Gahr et al., 2013).

The Effects of Desomorphine

Desomorphine is a synthetic opiate that has been developed in the context of searching for a substance that has fewer side-effects like nausea, that is less addictive, and that develops lower tolerance as an alternative to morphine (Small, 1934). Like several other opiates, desomorphine has analgesic and sedative effects (Small, 1934). The sedative effect is approximately 15 times and the analgesic effect approximately 8-10 times greater than morphine (Duron, 2015). The effect has a rapid onset, but the half-life is shorter (Janssen, 1962).

Although the structure of desomorphine is similar to that of morphine, desomorphine is more lipophilic because of some differences in the chemical structure. This property facilitates passage through the blood-brain barrier and provides a rapid

effect (Janssen, 1962). Like other opioids, the effect is shown the on the mu, kappa, and delta opioid receptors located throughout the whole body, which are especially dense in the brain, spinal cord, and gastrointestinal tract. In addition to its analgesic and sedative effect, other effects are created, such as muscle relaxation, changes in gastrointestinal movements, and euphoria, just as with other opioids (Duron, 2015). The reduced gastrointestinal motility and associated effect of creating constipation is greater than from morphine (Eddy & Howes, 1935). It has a greater toxic and much greater epileptogenic effect than that of morphine (Grund et al., 2013). Compared to morphine, the side effects of dizziness, nausea, and vomiting are less (Eddy & Howes, 1935; Gahr et al., 2013). When evaluated overall, the effect of desomorphine is rapidly lost, withdrawal symptoms and withdrawal syndrome form more rapidly, and greater respiratory depression is seen to form; thus, this drug is not considered to provide any advantage over morphine (Duron, 2015; Mosettig et al., 1935).

Despite these findings, preparates containing desomorphine were launched on the market as Permonid ™ in Switzerland in 1940. Although it was withdrawn from the market in 1952, production continued until 1998. Currently, desomorphine is one of the substances under controlled production in several countries (Gahr et al., 2013).

The Toxic Effects of Desomorphine

Desomorphine is an opiate with the toxic effects of myosis, flushing, paresthesia, constipation, urinary retention, nausea, and vomiting, similar to the toxic effects of other opiates (Florez et al., 2017). Furthermore, allergic reactions, seizures, and respiratory depression are often seen in desomorphine toxicity, with death being associated with these effects (Grund et al., 2013). Desomorphine has been reported to be three times more toxic than morphine, and this is explained by its high fat solubility (Duron, 2015; Sargent & May, 1970). The respiratory depression effect is 10 times that of morphine (Duron, 2015), and the convulsant effect is more evident than in morphine (Sargent & May, 1970). Another effect of desomorphine is the inhibition of the cholinesterase enzyme in the plasma and the brain. Desomorphine is a stronger cholinesterase enzyme inhibitor than codeine and morphine, and this effect can cause the formation of severe neurological symptoms (Wright & Sabine, 1943).

The Addictive Effect of Desomorphine

Psychological and physical addiction, tolerance, and withdrawal syndrome develop as a result of repeated desomorphine use (Grund et al., 2013). The addiction is related to the mu opioid receptor's agonist effect (Nelson et al., 2010). Desomorphine's withdrawal symptoms and withdrawal syndrome are similar to those of morphine (Eddy & Howes, 1935). Although krokodil produced at home or on the streets is taken

orally, subcutaneously, or intramuscularly, the most common method is intravenously (De Boer, 2001). The onset of the effect is 15 seconds with intravenous use and 2-3 minutes with subcutaneous use; the duration of the effect is extremely short at 2-3 hours (Florez et al., 2017). Due to the short half-life, it is used at more frequent intervals in comparison with heroin, and this is an important factor increasing the expected risks (Gahr et al., 2013). The withdrawal effects from desomorphine are similar to those of heroin and can last for up to a month (Katselou et al., 2014). The euphoria effect that continues for 4-8 hours with heroin lasts for up to 1.5 hours with desomorphine. Heroin addicts have a mean life expectancy of 20 years, and this falls by 1-2 years for those addicted to desomorphine (Katselou et al., 2014).

The Effects on the Skin and Other Organs

Although the targeted substance in krokodil is desomorphine, several toxic substances and heavy metals are found in the prepared mixture, as well as the several polluting agents it contains. When injected into the body, all these particles and infectious agents, together with desomorphine, are mixed with the blood (Gahr et al., 2012b). This causes coronary artery damage systemic infections such as septicaemia, pneumonia. and meningitis and distant organ damage (Gahr et al., 2012b). These conditions facilitate the spread of hepatitis A, B, and C as well as HIV (Grund et al., 2013).

Due to the heavy metals contained in krokodil, skin and vascular problems develop around the injection area. These local lesions, which may be accompanied by ulcers and phlebitis, are observed as desquamation and color changes in the skin. With the progression of the lesion over time, the skin takes on a rough, scabbed appearance, suggestive of crocodile skin (Matiuk, 2014). Continuous use can cause the lesions to progress to muscle, cartilage, and bone damage, which can even result in gangrene and amputations (Grund et al., 2013; Thekkemuriyi et al., 2014). These effects are not side-effects of desomorphine but develop because of the by-products emerging from the production and residues, especially heavy metals (Gahr et al., 2012b; Gahr et al., 2013) (see Figure 3).

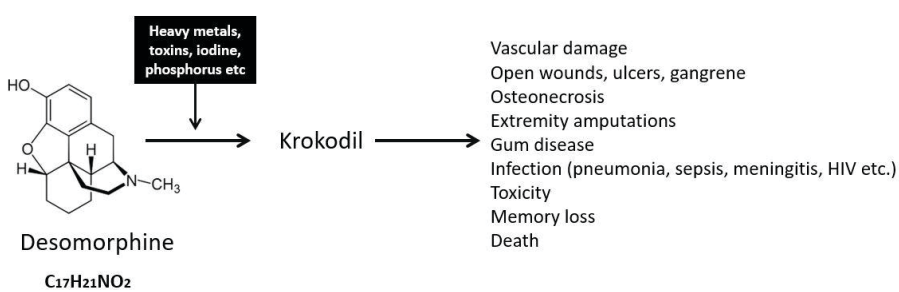

Figure 3. The Effects of Krokodil

In addition to local damage at the injection area, the chemicals contained in krokodil cause neurological, endocrinal, and distant organ damage (Gahr et al., 2012b). These effects are generally seen as motor and speech impairments, memory loss, personality changes, thyroid disorders, and liver and kidney damage (Grund et al., 2013). Widespread itching can be seen associated with krokodil use because of the generally toxic and corrosive by-products (Grund et al., 2013). Osteonecrosis of the jaw can be seen because of the phosphorus content and thyroid disorders associated with the iodine content (Poghosyan et al., 2014; Ruggiero et al., 2014). Exposure to lead can cause hematological, liver and kidney damage (Tian et al., 2013). Continuous exposure to petrol and paint thinners is known to lead to encephalopathy and neurological damage (Tsatsakis et al., 1997). Hallucinations and some psychotic symptoms associated with krokodil use may also occur (Lemon, 2013) (Figure 3).

Conclusion

The increase in the number of cases related to krokodil use in several parts of the world, especially in some countries geographically close to Turkey, suggests that this substance could be a significant threat to Turkey. Desomorphine is a strong substance that could be a potential alternative for heroin users who cannot access heroin or do not have the finances to do so. Availability is increased as home and street production is simple and cheap. Turkey currently has an increase in the heroin use, and the widespread use of heroin in economically poor regions increases the risks associated with this substance.

Another factor increasing its availability is the legal sale of certain drugs containing codeine, which is used in producing this substance. Therefore, many countries throughout the world have brought new restrictions related to the regulation of drugs containing codeine.

Nevertheless, regulations on the sale of preparates containing codeine vary from country to country (Eddy & Howes, 1935; Gahr et al., 2013). For many years, preparates containing codeine have been subject to different controls in Turkey depending on the amount of codeine. If the codeine content is under 15mg, the drug is sold by a prescription that is retained by the pharmacist and must be recorded (the normal monitoring process for prescription drugs). If the amount of codeine is over 20mg or even below this amount and the drug includes substances such as dionine or phenobarbitol, the sale is made with a duplicate green prescription (Asicioglu, 2013). The strict implementation of these regulations can be said to have protected Turkey from the spread of desomorphine addiction, and maintaining these rules without flexibility and rapidly implementing the necessary changes in accordance with the latest developments will be a significant protection against the danger of the spread of desomorphine.

Certain significant skin changes are created in the area where krokodil is injected, such as color changes and desquamation, and this area takes on an appearance resembling crocodile skin. Phlebitis, ulcers and gangrene can develop in this area when the lesions progress. That all physicians, primarily the clinicians dealing with substance addiction and dermatology specialists are able to recognize these skin findings is extremely important in respect of early substance diagnosis and treatment referral for the patient.

Although various studies have been conducted related to determining krokodil's contents, one can still state analyses made on this substance to be at an insufficient level (Richter et al., 2016). To prevent the spread of this substance and to be able to make effective interventions, the need exists for rapid, sensitive, selective and low-cost tests for being able to measure and confirm the active content and contaminants in the biological material to be used for clinical and forensic purposes.

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