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"Krokodil": The drug that kills

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Abstract

Psychotropic substances use and abuse have become a real global problem. Up to now, heroin is still one of the most abused drugs, however its consumption is in sharp decline in favor of Krokodil, also called "the poor's heroine". Krokodil originates from codeine that is extracted from antitussive and analgesic drugs, in "improvised" rudimentary laboratories and through artisan synthetic routes. Its low cost and easy procurement have allowed its rapid and dangerous spread.

The objective of this paper was to describe the epidemiology, chemistry, synthesis and toxicology of Krokodil.

Story and evolution

Krokodil's origin is not well defined yet and the literature is rather vague [1]. Currently, there are no reported data on its use and spread, however it has been observed that its diffusion is due to the easy access to drugs containing codeine [2]. Furthermore, heroin deficiency contributed to Krokodil expansion. In fact, several authors have suggested that Krokodil has replaced traditional opioids [2,3]. The name Krokodil is due to the color of the skin of its consumers, scaly and greenish like a crocodile. Krokodil production probably emerged in Siberia and Eastern Russia about 15 years ago [4,5]. In May 2004, it was reported for the first time the description of Krokodil abuse, in the Republic of Komi, and in 2008, 5.000 Krokodil consumers were reported, out of a total estimated population of 20.000-30.000. In addition, the number of Krokodil consumers in Russia has grown reaching about 5% of the population [6], while, according to others, the number of Russians consuming Krokodil would be higher, almost a million [3].

Lately, about 50 Russian cities have reported the use of Krokodil [7]. Epidemiological data are worrisome and show how the use of Krokodil has reached epidemic proportions, in Russia and in Ukraine [6-9]. Russia, Ukraine and other former Soviet countries have an ancient tradition in the production of opioids and stimulant drugs. There are several factors which have contributed to the spread of Krokodil in Russia and Ukraine, in particular the blocked import of heroin and the use of western drugs [5,8]. In Europe, its use was initially reported in Germany and in Northern Norway, while its use is growing in Kazakhstan, Georgia, the Czech Republic, France, Belgium and Sweden [5,10-12]. In 2011, German newspapers reported the first case

of Krokodil abuse, defined as"Krok". In the United States, possible cases of Krokodil abuse were reported between 2012 and 2013, in particular in Illinois, Oklahoma and in Chicago [13].

According to various reports, Krokodil seems to spread throughout the American nation [14]. However, it has been estimated that the use of this drug in the US has spread since 2011, throughout the American nation, and has actually been available for much longer than originally intended. It is plausible that consumers initially were not aware of what they were taking, thinking that it was regular heroin, but then continued to use this substance for its cost 10 times lower and for its action more intense than heroine [13].

Drug use tends to occur during adolescence, especially in the most isolated and poor areas [3]. Factors influencing the dissemination and use of Krokodil and other artisanal drugs are shaped by various psychological, social, economic, and political factors [15,16].

Chemistry and synthesis

Discrepancies between online information around purification and making homemade drugs safer, and the synthesis of the same substances in a proper laboratory environment, exist [17].

Krokodil is synthesized through a very simple chemical process consisting of two successive reactions. The required laboratory equipment is minimal, requires the use of highly toxic substances, but easily available and cheap: strong alkalis, hydrochloric acid, red phosphorus and finally organic solvents such as petrol, ethyl acetate or paint thinner [5]. The starting substance is codeine, derived from antitussive drugs or pain killers, which may also contain paracetamol or ephedrine. Generally, small amounts of this precursor are required, from 80 to 400 mg, and the process lasts about 40-45 minutes [18].

Two steps are required: (i) codeine extraction from the drug and (ii) codeine molecule reduction in what is believed to be desomorphine. This reduction process is known as the Nagai method and is based on a reduction method with hydriodic acid and red phosphorus as reagents, often also used for the synthesis of illegal methamphetamine [19].

(i) Codeine extraction: The first step consists in the extraction of the codeine from tablets or syrup. Initially, it is mixed with strong alkalis, such as sodium hydroxide, with a diluent agent that may contain lead, ferric or ferrous and antimony agents, and other organic solvents, while subsequently a strong acid is added, such as hydrochloric acid obtained from batteries or industrial products. Petrol may be used as organic solvent, although some users have reported the use of paint thinners.

(ii) Reduction of desomorphine codeine: Codeine is mixed with iodine, water and red phosphorus in glasses or glass containers or in enamelled pots. The resulting mixture is heated, producing hydriodic acid, a very strong acid which has been used to reduce carbonyl groups, nitriles, halides and alcohols for more than 100 years [20]. The reduction process is carried out using directly hydriodic acid or iodine and red phosphorus which form the acid in situ. Iodine is extracted from medical solutions or used as crystal, while red phosphorus is usually obtained from match heads.

The role of phosphorus is to reconvert the molecular iodine, formed during the reaction, into hydriodic acid [21]. The reaction involves a cyclic oxidation of iodide anions to iodine and the subsequent reduction of iodide to iodine by the red phosphorus which instead is converted into phosphoric or phosphoric acid [22]. This step allows the cleavage of the methoxyl group of codeine to form a hydroxyl group. The solution is ready when the mixture has changed its color and smell. The final product is a caramel-colored solution with an acrid smell that is injected into the vein [6]. However, there are limitations on possible production methods and it is important to assess how secondary reactions can affect final drug performance. Numerous descriptions of Krokodil production are reported in the literature [17], weak bases such as cigarette ash or bicarbonate are often found after the reaction has been completed [23]. A key question is whether the synthetic way followed actually produces desomorphine. The classical synthesis of desomorphine involves the reaction between codeine and thionyl chloride, leading to the formation of α-chlorocodide, and subsequently a reduction and a final demethylation [24]. However, using gas chromatography, Savchuk and coworkers identify 4 synthetic analogues of desomorphine, such as methyldesomorphine, 3,6-dideoxy-dihydromorphine, morphinan-4,5-epoxy-3-ol, and didehydro desomorphine, as well as traces of codeine and other compounds, with a desomorphine content up to 75% [25-27]. However, there is a variability in desomorphine concentrations on the basis of the different synthesis processes [27,28]. Furthermore, it should be noted that codeine formulations almost always contain other ingredients, such as paracetamol, caffeine etc. It is not perfectly known yet how each of these compounds affects the chemical reactions and the final result. The Krokodil psychoactive effects may therefore depend on the type of medicine, chemical substances, reagents available locally and actual reaction used. Further analysis is needed to define the actual drug constituents [5]. Recently, Soares and collaborators (2017) reported a total of 54 detected morphinans, highlighting the fact that these additional morphinans may contribute to the psychotropic effects of krokodil.

Toxicology

The desomorphine, semi-synthetic opioid, is the pharmacological active molecule of Krokodil that by binding to μ and δ receptors induces euphoria and anxiolytic effect. Desomorphine, like heroin and morphine, activates the μ receptors on GABA-ergic neurons, causing abundant dopamine release in the nucleus accumbens. Furthermore the desomorphine activates the δ receptors in the locus coeruleus interfering with the release of noradrenaline.

The desomorphine induces tolerance, dependence and abstinence syndrome, with an average survival of about 2 years. Tolerance to desomorphine is pharmacodynamics. The μ and δ receptors are rapidly internalized through the classic endocytic pathway (down regulation) [29,30]. The desomorphine, contained in the Krokodil, is able to induce a strong dependence, both psychic and physical, in a short time.

The abstinence syndrome is characterized by anxiety, irritability and insomnia.

However, it is divided into 6 phases:

- Phase I (6 to 14 hours after the last dose): craving, anxiety, irritability, sweating, and dysphoria (mild to moderate).

- Phase II (14 to 18 hours after the last dose): profuse sweating, mild depression, crying, rhinorrhea, dysphoria.

- Phase III (16 to 24 hours after the last dose): rhinorrhoea,

dilated pupils, piloerection, muscle spasms, hot flashes, painful bones and muscles, loss of appetite, start of intestinal cramps.

• Phase IV (24 to 36 hours after the last dose): severe cramps and involuntary leg movements, loose stools, insomnia, increased blood pressure, increased respiration rate, tachycardia, agitation, nausea.

• Phase V (36 to 72 hours after the last dose): increased vomiting, frequent diarrhea, weight loss up to 2-5 kg every 24 hours. The subject takes a fetal position.

• Phase VI (after completion of the previous phases) i: slow recovery of appetite and normal intestinal function, with symptoms mainly of a psychological nature, but may also include greater sensitivity to pain, hypertension, colitis or other gastrointestinal symptoms [3,6,18].

Krokodil shows signs of toxicity not only related to the presence of desomorphine, but also from the high concentration of toxic substances used in its synthesis [2,5,18].

Neurological, endocrine, ulcer and skin rashes have been reported due to the presence of toxic metals (lead and zinc) and corrosive substances such as paint thinner, petrol and even hydrochloric acid, iodine and red phosphorus used for its preparation [31]. This leads to the decay of the skin and muscles around the injection site and, over time, the skin becomes scaly due to the rupture of blood vessels, often exposing the underlying bone [20,32]. Finally, widespread inflammation, abscesses and even decomposition is observed. This explains why Krokodil is nicknamed "carnivorous drug" [2,5].

The recovery of Krokodil addiction is minimal. The initial intervention involves the removal of necrotic tissue and broad-spectrum antibiotic therapy (penicillin G, clindamycin, vancomycin, and gentamicin). Unfortunately, in more severe cases, surgical amputation may be necessary [33] or maxillofacial interventional intervention [34-36]. In Krokodil's consumer, because of his lethality, detoxification is almost impossible. Methadone and buprenorphine represent the replacement drugs used today, both during the weaning phase and in the maintenance phase.

The Krokodil, appeared and spread initially in Russia, is no longer a problem limited to the Eastern European countries, but a global threat, so it is necessary to deepen the studies on its composition and its toxicity, as well as implement the right rules precautionary measures to prevent a dangerous spread.

The consumption of Krokodil fits into a multi-faceted high-risk environment, composed of a multitude of macro and micro risk factors that have favored its spread and lethality. Among these there are: the rudimentary chemical synthesis and the use of corrosive contaminants; the frequency of injection; the artisan production environment; the lack of availability of replacement therapies; poverty, social exclusion; the increase in the price of heroin and its shortage in the markets.

Conclusion

A trans-disciplinary research effort is needed to comprehensively understand all aspects of this recent and alarming drug trend.

From the chemical point of view, it is necessary to understand the qualitative and quantitative composition of the substances that go under the name of Krokodil. The active ingredient of Krokodil is in fact presumed to be desomorphine, but the real solution injected can contain various opioid alkaloids, which could derive from codeine, depending on the available reagents, reaction times and temperatures, and ultimately, from the competences chemicals of the Krokodil producer [5].

Understanding its real composition is essential to provide more information for the development of programs for harm reduction and for potentially safer production processes. Therefore, laboratory analyzes of Krokodil samples are necessary to assess the presence of any contaminants, determine the possible neurological consequences on hospitalized Krokodil consumers, to increase understanding of the effects on the human body and contribute to an effective treatment.

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