Forensic Science International 249 (2015) 207–213

Contents lists available at ScienceDirect

Forensic Science International

journal homepage: www.elsevier.com/locate/forsciint

Review article

The harmful chemistry behind krokodil (desomorphine) synthesis and mechanisms of toxicity

Emanuele Amorim Alves [a,b,c,*], Jean-Paul Cornelis Grund [d,e], Carlos Manuel Afonso [f,g], Annibal Duarte Pereira Netto [h], Félix Carvalho [b], Ricardo Jorge Dinis-Oliveira [a,b,i,*]

[a] Department of Legal Medicine and Forensic Sciences, Faculty of Medicine, University of Porto, Porto, Portugal
[b] REQUIMTE, Laboratory of Toxicology, Department of Biological Sciences, Faculty of Pharmacy, University of Porto, Porto, Portugal
[c] EPSJV—Polythecnical School of Health Joaquim Venâncio, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
[d] DoA-CUNI—Addiction Research Centre, Utrecht, The Netherlands
[e] Department of Addictology, 1st Faculty of Medicine, Charles University in Prague and General University Hospital in Prague, Prague, Czech Republic
[f] Center of Medical Chemistry (CEQUIMED-UP), Faculty of Pharmacy, University of Porto, Porto, Portugal
[g] Interdisciplinary Center of Marine and Environmental Investigation (CIIMAR/CIMAR) , Porto, Portugal
[h] Department of Analytical Chemistry, Chemistry Institute, Fluminense Federal University, Niterói, Brazil
[i] IINFACTS—Institute of Research and Advanced Training in Health Sciences and Technologies, Department of Sciences, Advanced Institute of Health Sciences—North (ISCS-N), CESPU, CRL, Gandra, Portugal

ARTICLE INFO

Article history:
Received 19 September 2014
Received in revised form 30 January 2015
Accepted 2 February 2015
Available online 7 February 2015

Keywords:
Opioids
Desomorphine
Krokodil synthesis
People who inject drugs
Signs and symptoms

ABSTRACT

"Krokodil" is the street name for the homemade injectable mixture that has been used as a cheap substitute for heroin. Its use begun in Russia and Ukraine and nowadays is being spread over several other countries. Desomorphine is the semi-synthetic opioid claimed to be the main component of krokodil and considered to be responsible for its psychoactive characteristics. The starting materials for desomorphine synthesis are codeine tablets, alkali solutions, organic solvent, acidified water, iodine and red phosphorus, all of which are easily available in retail outlets, such as supermarkets, drugstores, etc. The resulting product is a light brown liquid that is called krokodil. People who inject krokodil present a great variety of serious signs and symptoms, including thrombophlebitis, ulcerations, gangrene, and necrosis, quickly evolving to limb amputation and death. These effects are thought to result from the toxic components produced as byproducts during the homemade drug synthesis.

In this work, we reviewed several aspects of krokodil use, including its epidemiology, pharmacology and the chemical properties of the main active ingredient (desomorphine). To enhance our understanding of the clinical and toxic effects and to support the implementation of harm reduction measures, we also describe the "bathtub chemistry" of krokodil and the content of the final solution.

Contents

1. Introduction . . . 208
2. Epidemiology of krokodil use . . . 208
3. Chemical properties of desomorphine . . . 208
4. Synthesis of krokodil . . . 208
5. Quantification of desomorphine . . . 210
6. A mixture of alkaloids . . . 210
7. Pharmacology and toxicology of desomorphine . . . 210
8. Signs and symptoms of krokodil exposure . . . 211
9. Bad chemistry hurts: use of harmful reagents . . . 212
10. Pharmacology and social context . . . 212

* Corresponding authors at: Department of Legal Medicine and Forensic Sciences, Faculty of Medicine, University of Porto, Alameda Prof. Hernâni Monteiro, 4200-319 Porto, Portugal. Tel.: +351 225513600.
E-mail addresses: manuhpa@hotmail.com (E.A. Alves), ricardinis@sapo.pt, ricardinis@med.up.pt (R.J. Dinis-Oliveira).

http://dx.doi.org/10.1016/j.forsciint.2015.02.001
0379-0738/

11. Concluding remarks . . . 212
Acknowledgements . . . 212
References . . . 213

1. Introduction

"Krokodil" is the street name for an injectable drug mixture, which is used as a cheap substitute for heroin and was first observed in Russia and Ukraine around 2002/3. Krokodil is obtained from codeine tablets in a simple bootleg process aimed to synthesize desomorphine. Media reports suggest that krokodil is about five times cheaper than heroin [1,2]. In Russia, krokodil is also known as "Russian magic", "croc" or "krok" [2,3]. The name krokodil is derived from the typical scaly green colored skin injuries associated with continued use, resembling a crocodile (krokodil in Russian) skin [3–5]. Russia, Ukraine and Georgia seem to be the countries most affected by krokodil use.

Because of its recent emergence, and, in particular, the dramatic consequences associated with this drug concoction, it is important to understand the epidemiology of krokodil use, the pharmacology of the main active substance (desomorphine) and the synthesis method of krokodil. Such information is highly relevant for the implementation of preventive measures for reducing krokodil use and the reported toxic effects. The present review highlights these different aspects of this harmful drug. To achieve our goals, articles written in English, French and Germany were searched in the National Library of Medicine's PubMed MedLine database and Web of Knowledge using key words such as "croc", krokodil, "home-made drug", "flesh eating drug" and "desomorphine". Web sites and YouTube videos related to krokodil use were also reviewed.

2. Epidemiology of krokodil use

According to the European Drug Report [6], 0.41% of the European population is addicted to opioids, mainly heroin. In Asia, this prevalence is not so different, especially in Asian parts of Russia, Laos, Afghanistan and Myanmar [7]. Russia, Ukraine and all other former Soviet Republics share a long history of injectable drug use [2]. In Russia, 2.3% of the population is injecting drugs, especially opioid derivatives. This percentage reflects the proximity to Afghanistan, the major world opium producer. The Russian government recognizes that it is very difficult to control all the borders due to their extension. Afghan heroin usually crosses the Russian borders inside trucks passing through cities and smaller communities; finally the drug is sold in clandestine street markets.

Heroin is not easily available in Ukraine and therefore home drug production remains a common source for injectable opioids [8]. In Eastern Europe countries, especially Georgia and Ukraine, drug users switched to homemade drugs such as krokodil, due to the cost of heroin. Indeed, media reports suggest that 5% or more of Russian drug users may be injecting krokodil [2]. The homemade krokodil is prepared almost the same way as methamphetamine [2] making this transition not unexpected once methamphetamine seems to be spreading through Russia Federation and Poland [7].

The first case of krokodil use was reported on the North-East of European part of Russia in 2002, and since then it spread over Russia and some of the neighboring former Soviet Republics. Krokodil appeared in the Russian drug market in 2003, associated with the decreased availability of Afghan heroin in local drug markets [2,9]. In 2012, it was estimated that around 100,000 people used krokodil in Russia and around 20,000 in Ukraine [2]. At this time point, Russia and Ukraine seem to be the most affected countries by the use of this drug, but several cases were also reported in Georgia [10] and Kazakhstan [11]. Russia banned over-the-counter codeine sales on June 1, 2012 and that legislative document sharply reduced the use of krokodil, but codeine has been reportedly moved onto the black market [12].

Krokodil was firstly described in USA (Chicago) in 2011 [13]. According to the physician responsible for the case, patients were not aware of being using krokodil. Thekkemuriyi et al. [5] reported a case of a 30-year-old heroin addicted man was treated in a hospital in St. Louis for a painful necrotic ulcer and auto-imputed fingers after 6–7 months of krokodil use. He admitted a unique exposure because he had not enough money to buy his regular diary dose of heroin. A possible case was described in German in 2011 by Gahr et al. [3]. Dermatological lesions, typical for krokodil use, were observed in four heroin users. It was assumed that they were using heroin contaminated with krokodil. Lemon [14] described the first UK case, when a girl from Romania was hospitalized with krokodil symptoms. It is believed that the use of krokodil spread to Poland, Czech Republic, France, Belgium, Sweden, Norway and other European countries with Russian immigration [15].

3. Chemical properties of desomorphine

The main active substance of krokodil is referred to be a semi-synthetic opioid derivative from morphine, called desomorphine ($C_{17}H_{21}NO_2$, dihydrodesoxymorphine) (Fig. 1). Chemically, desomorphine is a white to light beige solid at room temperature, with a molecular weight of 271.35 g/mol and a melting point of 189 °C. It is a stable powder when stored under adequate conditions and an organic base, like other opioids. The protonated form has a p*Ka* value of 9.69 and it is therefore ionized in a biological environment. Desomorphine is only partly soluble in water (1.425 g/L at 25 °C) as a free base, while in salt form, is highly water soluble [16]. Desomorphine was first synthesized in the USA in 1932 by Small et al. [17] as a demonstration of a process of catalytic hydrogenation of halogenocodides to obtain morphine derivatives [3]. Desomorphine may be synthesized from codeine and it differs from morphine only by the lack of a hydroxy group and a double bound (Fig. 1). This structural difference allows an increased activity of desomorphine when compared to codeine and even morphine [18,19]. The elimination of the alcoholic hydroxyl group gives desomorphine the same toxicity and increased analgesic action compared to morphine [17].

4. Synthesis of krokodil

The process of krokodil synthesis is almost identical to that of methamphetamine synthesis from ephedrine [20,21] consisting of a simple extraction and reduction to obtain the opioid derivative. This reduction process is known as the Nagai route and is based on a reduction method using hydriodic acid (HI) and red phosphorus as reagents [21]. This synthetic route is preferred in the Asian and South Asian regions and in Australia in commercial illicit methamphetamine production [21–23]. Krokodil is obtained using codeine as a starting material, which is usually sold in the pharmaceutical market in the form of tablets, mixed with other substances such as paracetamol, acetylsalicylic acid and, in some cases, caffeine. The process needs very little equipment and involves two steps (Fig. 2):