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Review Article

Krokodil—Morphine's Deadly Derivative

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Graphically publicized in the media, the use of Krokodil, a heroin-like morphine derivative, has grown in Eastern Europe the last decade. The popularity of the injectable drug has grown in part due to its inexpensive and simple manufacturing process through the use of codeine tablets. Krokodil has a similar mechanism of action to morphine, although it is said to be as much as 10 times more potent and is notorious for plaguing its victims with rotting, scale-like skin lesions. The drug was originally synthesized in hopes of creating a safer, less addictive alternative to morphine; however its impure manufacturing process, toxicity and addiction profile led to abuse and infection among its users. The use of Krokodil is seen most commonly in the Ukraine and Russia, particularly in Siberia, however use has been recorded in Moscow and 27 other Russian cities, Kiev and 24 other Ukrainian cities, Kazakhstan, and other Kazakh regions bordering Russia. Use has not yet been confirmed in the United States despite several reports due to the difficulty in isolating and discerning various metabolites in test samples. Various attempts have been made in Eastern Europe in recent years to halt its production by restricting access to codeine, however without concrete legislation and increased public awareness; it is unclear if the growing Krokodil epidemic will be contained.

History

Krokodil, also known as "Croc" and "Russian Magic," is a highly addictive morphine derivative similar in its mechanism to heroin. Pictures publicized by the media show its devastating effects on its users such as skin necrosis and painful blistering. Its name in Russian translates to "crocodile," referring to the scaly rotten appearance of the user's skin after multiple injections and untreated skin and soft tissue infection. The name, "crocodile" is also thought to be derived from α-chlorocodide, an intermediate in the synthetic pathway of desomorphine, the pure opioid core of Krokodil.[1] Krokodil use is most prevalent in Russia and the Ukraine, although it has not yet become popularized in the United States[2]. Its popularity in the Eastern European region is likely due to the fact that it can be cheaply and quickly synthesized using codeine as a starting substance, which is available over the counter in some countries. The active opioid core of Krokodil is desomorphine, a morphine derivative originally synthesized in the United States and patented in Switzerland[3]. The structural difference between desomorphine and morphine is the absence of a secondary hydroxyl group and a saturated double bond in the desomorphine (Figure 1).

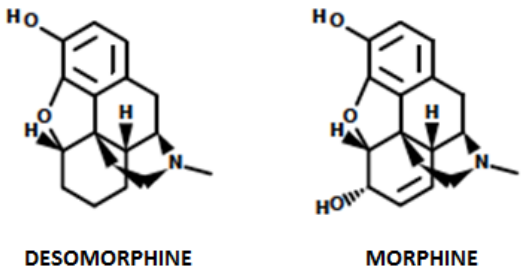

Figure 1: Chemical structure of desomorphine and morphine.

Hoffman-LaRoche introduced desomorphine marketed under the name Permonid to the Swiss market in 1940 as both an ampulla and suppository for the indication of postoperative pain.[4] Desomorphine has a fast onset of action and tends to cause fewer incidences of respiratory depression and nausea. Permonid was withdrawn from the market in 1952, however it was still produced until 1981 for a single Swiss patient who suffered from chronic pain and experienced intolerable nausea from all other opiates available during this time. The patient took a dose of 0.16 g per day, the equivalent of 80 ampules of Permonid, without experiencing dose-limiting side effects such as nausea.[4]

When the structure of morphine was finally published in 1925 by Gulland and Robinson, pioneering studies quickly began in the 1930s to find more potent and less addictive analogues. Dr. N. B. Eddy led the Committee on Drug Addiction to synthesize and evaluate these novel morphine analogues for relative potency and addictive potential[4]. Over 200 novel analogues were synthesized, including dihydrodesoxymorphine, which resulted from the alkylation of the phenolic group of morphine[5]. Dihydrodesoxymorphine, also known as desomorphine, showed a kinetic activity and an addiction profile contrary to expectation with a shorter half-life and higher sedative and addictive potential relative to morphine[6].

The intent of a morphine alternative was to produce a drug that was less addictive, caused less dependence, caused less tolerance, and had fewer side effects[5]. A drug's addictive properties determine how likely it is that a drug user will have the urge or need to use the drug. Addiction may be both physical and/or psychological. Behaviors such as drug use, sex, and eating stimulate the reward pathway in the brain, leading to increased dopamine activity in the ventral tegmental area, nucleus accumbens, and the prefrontal cortex. Therefore, a person who is addicted to a drug such as Krokodil experience a sense of "reward" and euphoria upon taking the drug as well as a loss of control in limiting the behavior despite its negative consequences.[7] Dependence, which many times accompanies addiction, develops when a person's neurons adapt to the exposure of the drug and do not function normally in its absence. When a person stops taking the drug, which is acting as a stimulus to the reward pathway, both physiologic and psychological reactions occur such as shaking, nervousness, anxiety, or even seizures. Upon introducing the drug or stimulus back into the body, the user will avoid these withdrawal symptoms, leading to further

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addiction.[7] Finally, tolerance occurs when the user requires a higher dose or more frequent use of a drug to achieve the same sense of reward or response. In the case of drugs like Krokodil, enzymes in the body adapt to the constant level in the body and require more of the drug to produce a stimulus than before. Unfortunately, in the case of desomorphine versus morphine, addiction, dependence, and tolerance were all observed more frequently in human patients who took desomorphine.[7]

Pharmacokinetics/Pharmacodynamics

Although early animal studies seemed to show a low addiction profile and a side effect profile similar to that of morphine, human studies in cancer patients showed more severe withdrawal symptoms[4]. Currently, it is believed that desomorphine has analgesic activity with 10 times greater potency than morphine and that it is up to 15 times more sedating and 3 times more toxic[2]. Analgesic activity is the ability of a drug to relieve pain. A drug that is more potent will require a smaller amount of drug to produce a given effect; a person will require less desomorphine than morphine to achieve its desired effect. It is important to note that a drug that is more potent is not always necessarily more toxic. Observed LD_{50}, the amount of drug that is lethal in 50% of the population, in mice was 27mg/kg given intravenously (IV) or 104 mg/kg given subcutaneously (SQ)[8]. Its mechanism of action is similar to many other opioid analogues. It is an opioid agonist at mu receptors and to a lesser extent has some binding activity at kappa and delta receptors[4]. Mu, kappa, and delta opioid receptors are located throughout the body in areas such as the brain, spinal chord, and gastrointestinal tract. All three receptors bind opioids such as morphine and desomorphine, however depending on the location within the body and the action of each receptor, opioids produce effects including but not limited to analgesia, sedation, gastrointestinal dysmotility, or euphoria. As an agonist, a drug that activates receptors, desomorphine binds primarily to mu opioid receptors, which produce mostly analgesic effects.[9]

The original animal studies conducted by Eddy et al.[5] were observational investigations conducted in dogs, cats, and monkeys. Four dogs were given morphine or desomorphine injections daily, and their behaviors, vital signs, and withdrawal behaviors were observed. Although little tolerance or withdrawal was observed with either drug, the depressant effect of desomorphine at lower doses of 2-5 mg was greater than that of morphine at smaller doses of 10 mg or less[5]. In a similar study with cats, four cats were given intramuscular injections of desomorphine at 0.2 mg/kg while four different cats were given morphine 2 mg/kg. Again, similarities were found between the analgesic effects of both drugs, which attests to the much greater potency of desomorphine. Markedly, the cats given morphine experienced vomiting during the two weeks, and those on desomorphine did not experience any vomiting[5].

Finally, a series of experiments were performed with four rhesus macaque monkeys[5]. The monkeys were injected with either morphine sulfate or desomorphine for a 14-week period and were allowed to run loose in a small room, similarly to the earlier experiments in dogs. The starting dose of desomorphine was 2 mg/kg and was increased to 4 mg/kg per day, and the starting dose of morphine sulfate was 10 mg/kg and increased up to 60 mg/kg. In contrast to findings in the other animal models, desomorphine had 10 times the depressant effect of morphine in the rhesus monkeys. However, the monkeys administered desomorphine again did not experience tolerance or withdrawal as often as did the monkeys in the morphine sulfate group. Physical tolerance was measured by assessing the decrease in temperature, heart rate, and respiratory rate as well as how easily they were aroused. Symptoms of withdrawal were measured by signs of hyperirritability such as pacing or hunching, nausea, weight loss, shivering, and decreases in rectal temperature. In a continued experiment, doses of desomorphine were pushed higher up to 10 mg/kg to observe the possibility of increased tolerance and withdrawal symptoms. Again, monkeys administered the increased doses of desomorphine experienced a more rapid tolerance than in the previous experiment, however its effects were still not comparable to the tolerance seen in the monkeys administered morphine sulfate.

Two of Eddy et al.'s experiments were conducted in human subjects, which ultimately lead to the DEA's decision to classify desomorphine as a schedule I substance[5]. Five male morphine addicts were given up to four doses of morphine sulfate daily and were then switched to desomorphine doses equal to those of the morphine sulfate. At between 8 and 21 days, the desomorphine was withdrawn, and patients were observed for symptoms of withdrawal. It was concluded that the abrupt withdrawal of desomorphine in the five individuals resulted in typical abstinence syndrome as was experienced by morphine sulfate withdrawal. Therefore, it is concluded that desomorphine is not an effective substitute to morphine sulfate in patients with opioid addiction.

In the final human study, Eddy et al. evaluated whether or not cancer patients with chronic pain would experience addiction with clinical administration of desomorphine[5]. Six cancer patients were randomized to receive either 1 mg of desomorphine sulfate or 10 mg of morphine sulfate a mean of 8 times daily as needed for pain. It was found that the analgesic effect of morphine lasted between 3 and 4 hours while the desomorphine only lasted up to 3 hours, many times less. In conclusion, desomorphine given continuously for relief of chronic pain produced very rapid dependence and addiction as compared to morphine, although it is arguable that size of the starting dose and its short half-life is responsible for this observation.

Epidemiology

The use of Krokodil is seen most commonly in the Ukraine and Russia, particularly in Siberia, however use has been recorded in Moscow and 27 other Russian cities, Kiev and 24 other Ukrainian cities, Kazakhstan, and other Kazakh regions bordering Russia[4,10].

Figure 2: Map of Russia. World Atlas. Russia Map. http://www.worldatlas.com/webimage/countrys/asia/ru.htm (Accessed July 22, 2014).

Many drug users in the region prefer to inject Afghan heroin or inexpensive opiates such as poppy straw that is easily grown within surrounding countries. Poppy straw is grown in the region year round, however it is much more scarce in the winter months, leading drug users to seek other drugs or ways to traffic poppy straw across borders. Poppy straw, also known as the poppy capsule, refers to the entire dried poppy plant other than the stem. Nearly all of the opium contained in poppy plant is contained in the straw, which includes the seeds.[11] Opium may be extracted from the plant for purposes of smoking, injecting, or manufacture into heroin.

During the Soviet occupation in Ukraine, a strict police presence blocked the traffic of heroin and poppy straw. In December of 1991, the Soviet Union withdrew, and resulting corruption allowed for an influx of drugs across the Russian borders. With the withdrawal of the Soviet Union in Ukraine, state supported healthcare services for addicts was reduced and even discontinued in some areas of the country. Slowly, border control again strengthened leading the popularity of homemade heroin substitutes such as Krokodil that could be manufactured from over-the-counter codeine[10,12,13]. To combat the trafficking of poppy straw across borders, Ukraine has since followed recommendations from the International Narcotics Control Board following a mission conducted in May 2008. The government has since increased funding for the National Narcotics Control Committee and has limited the amount of poppy straw cultivated to amounts deemed sufficient for culinary purposes. Preventative operations such as breeding plants with low opiate content have also been undertaken.[14]

It is estimated that approximately 100,000 people in Russia and 20,000 people in Ukraine use Krokodil.[15] Although Krokodil usage has thus far only been reported in Europe, a case report published in March 2014 suggests the need for physicians and other healthcare providers to be cognizant of the possibility that Krokodil or other homemade heroin substitutes are likely making their way into the United States.[16] The report describes a 30 year-old male who presented to a hospital in St. Louis, Missouri with pain, swelling, and ulceration of the left thigh. He reports that he's been using Krokodil for the past 6-7 months and initially noticed blisters which rapidly turned necrotic and reports auto-amputation of his left little finger.

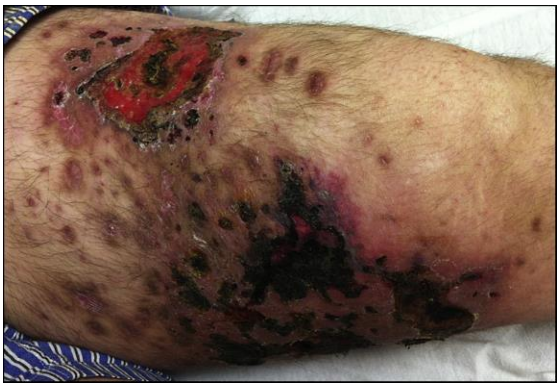

Figure 3: Necrotic ulceration of left thigh. Image originally reported in[17] and reproduced with permission of Elsevier.

The patient has a history of daily heroin use for the past 7-8 years which he reports was costing approximately $300 per day, leading him to seek the cheaper heroin substitute. While receiving antibiotic treatment as well as wound care and precautions for opiate and benzodiazepine withdrawal, the patient left against medical advice and was lost to follow up. Unfortunately, it is not yet possible to detect the difference between heroin and Krokodil due to the similarity between the drugs and the impure methods in which the drugs are synthesized. Patients who have injected themselves with Krokodil will more than likely test positive for heroin, making it hearsay as to whether or not the user received Krokodil, heroin, or another homemade derivative.[8]

Methods & Patterns of Use

Synthesis of Krokodil was first documented in Siberia in 2002[4]. Its production process is similar to that of methamphetamine in that store bought chemicals such as red phosphorous, iodine, and codeine can be combined with corrosive and toxic reagents such as paint thinner, lighter fluid, gasoline, and lead to produce the final heroin-like product[4]. It is unknown which of these production products stays active and a part of the final product at the end of the production process, leading to the increased concern of toxicity. The production process takes as little as 10-45 minutes but must be completed continuously throughout the day due to the drug's 2-hour half life[10]. Until June 1, 2012, codeine was sold over the counter in Russia and is still sold today over the counter in Ukraine in restricted quantities. A package of 5-10 codeine tablets costs approximately 300 Rubles, equivalent to $9.00 USD.[4]

The production process results in an injectable opioid liquid ready for frontloading into needles and can be injected intravenously or subcutaneously[10]. The practice of frontloading syringes means to pull directly from the product through the needle. As multiple users pull from the product with unclean needles, this leads to an increased risk of contracting blood borne pathogens such HIV and hepatitis B or C.[10] Some laboratory replications have demonstrated that the high acidity of homemade injectable opiates such as Krokodil may inactivate the HIV virus if stored in syringes. However, people with hepatitis C (HCV) tend to carry higher levels of the virus in their bodies than those with HIV, which would mean that the virus would need to be exposed to a very acidic environment for a longer period of time to be

inactivated.[15] However, the environment that Krokodil is prepared and injected in is conducive to the potential spread of viruses through the sharing of needles and contamination. Impaired judgment and irrational behaviors of the users increase the risk for disease transmission and the potential for overdose.[15]

Due to the unsanitary cooking conditions and materials utilized, it is common for users to develop infections such as methicillin resistant *staphylococcus aureus*, gangrene, and necrosis leading to rotting flesh, exposed bone, and amputations, the drug's hallmark effects[4]. Reported localized harms from injection include: thrombosis, open ulcers, phlebitis, gangrene, skin and soft tissue infections, and limb amputations[10]. Other systemic damage includes: pneumonia, blood poisoning, coronary artery burst, meningitis, rotting gums, bone infection, rotting nose, ears, lips, liver and kidney problems[10]. Neurological damage has also been observed from heavy use including: speech impediments, motor skill impairments, hallucination, and personality changes[10]. One of the first complications reported from the usage of this drug was seen in 1876 in the *Lancet.*[11,18] A woman injected herself with "morphia," presumably a homemade opium derivative, to alleviate nausea and vomiting associated with her pregnancy. She reports experiencing "tetanus," which is an infection caused *Clostridium tetani*, typically through a wound or puncture infection. Tetanus is characterized by symptoms such as muscle twitching, jaw pain, and pain surrounding the wound or puncture.

In Eastern Europe, increased punishment and sales restrictions on codeine since the late 2000's have been implemented to combat the use and manufacture of Krokodil[10]. Some funding has allowed for the mobile medical centers, wound care clinics, and needle exchange programs, however Russia has faced criticism for its prejudice against providing accessible medical care to addicts[13]. A recovering addict states, "I was taken to a hospital when I was fever sick with a fever and couldn't walk, and they refused to treat me. They told me to go buy syringes, bandages, and medications. They asked me for money, and when I didn't have any I was asked to leave the clinic by the doctors[12]."

Although Krokodil use has yet to be documented in the United States, its use continues to be a major epidemic in Eastern Europe. Desomorphine use has been reported as 13.6% of all drug use in Eastern Europe, trailing only marijuana and heroin in popularity[12]. It is thought that this number may be even higher since it is difficult to test for the true identity of homemade heroin derivatives in its users[13]. Various attempts have been made in Eastern Europe in recent years to halt its production by restricting access to codeine, however without concrete legislation and increased public awareness, it is unclear if the growing Krokodil epidemic will be contained.

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