

CASES OF ACUTE POISONING BY KETAMINE HYDROCHLORIDE IN FORENSIC CHEMISTRY

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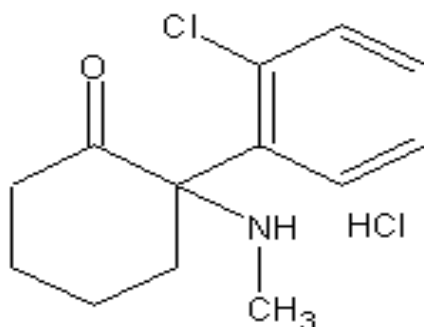
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ABSTRACT

The article presents the results of the study of cases caused by the non-medical use of ketamine hydrochloride, which belongs to the phenylalkylamine group. There are increasing among minors the occurrence of serious crimes due to the use of ketamine hydrochloride for various non-medical purposes, severe poisoning and death in most cases as a result of their abuse. According to statistics, recently, the number of poisonings from ketamine hydrochloride, a representative of the phenylalkylamine group has been sharply increasing worldwide. There were studied information about the illegal consumption of ketamine hydrochloride is given in the literature, and the methods and techniques of the research conducted in connection with the study of cases of poisoning with them.

Key words: psychotropic substances, phenylalkylamines, ketamine hydrochloride, poisonings, illicit trade, international drug control, cases of abuse, trade in social networks.

Introduction. In recent years, the development of various synthetic drugs and their use for various non-medical purposes, the sharp increase in their trade in the black market, has led to a large-scale increase in drug addiction among adolescents [1]. The use of these drugs especially by school-aged children is causing severe poisoning and also death among children. Ketamine hydrochloride is one of the drugs used by adolescents along with synthetic spices, and is used as an anesthetic in medicine [2]. In Latin: Ketaminum hydrochloridum.



(±)-2-(2-Chlorophenyl)-2-(methylamino) cyclohexanone (hydrochloride).

The brutto formula of ketamine hydrochloride is $C_{13}H_{16}ClNO$. Ketamine is a white crystalline powder with a weak characteristic odor. Good in water, methyl alcohol, 96% ethyl alcohol, slightly soluble in chloroform. pH medium in an aqueous solution is 3.5-5.5. Ketamine hydrochloride ampoule contains 10, 50, 100 mg/ml of drug substance and is produced by adding an isotonic solution of sodium chloride as a stabilizer and 0.1 mg/ml benzitonium chloride as a preservative. The toxic amount of the drug is LD_{50} (900 mg/kg) for adults. Currently, ketamine hydrochloride and its analogues are used as drugs for non-medical purposes in the form of "happiness water", "k-dry milk", "tuki", "pink cocaine", "K", "vitamin K", "super K", "special K", "super S", "special Coca-Cola Los Angeles", "jet", "superacid", "zelen", "special K", "revy" are common among teenagers in night clubs, smoking in the form of cigarettes, it is used to smell through the nose or mixed with various drinks for

enjoyment [3]. The effect can last from at least 30 minutes to several hours [4]. The non-medical use of ketamine drugs under these trade names by adolescents creates a negative environment among them, resulting in a sharp increase in mortality. Based on these cases, development of methods of forensic chemical analysis of ketamine hydrochloride is one of the urgent tasks facing forensic chemists.

Materials. There will be collected general information about ketamine based on the information presented in the literature review and improving the methods and methods of their chemical-toxicological analysis.

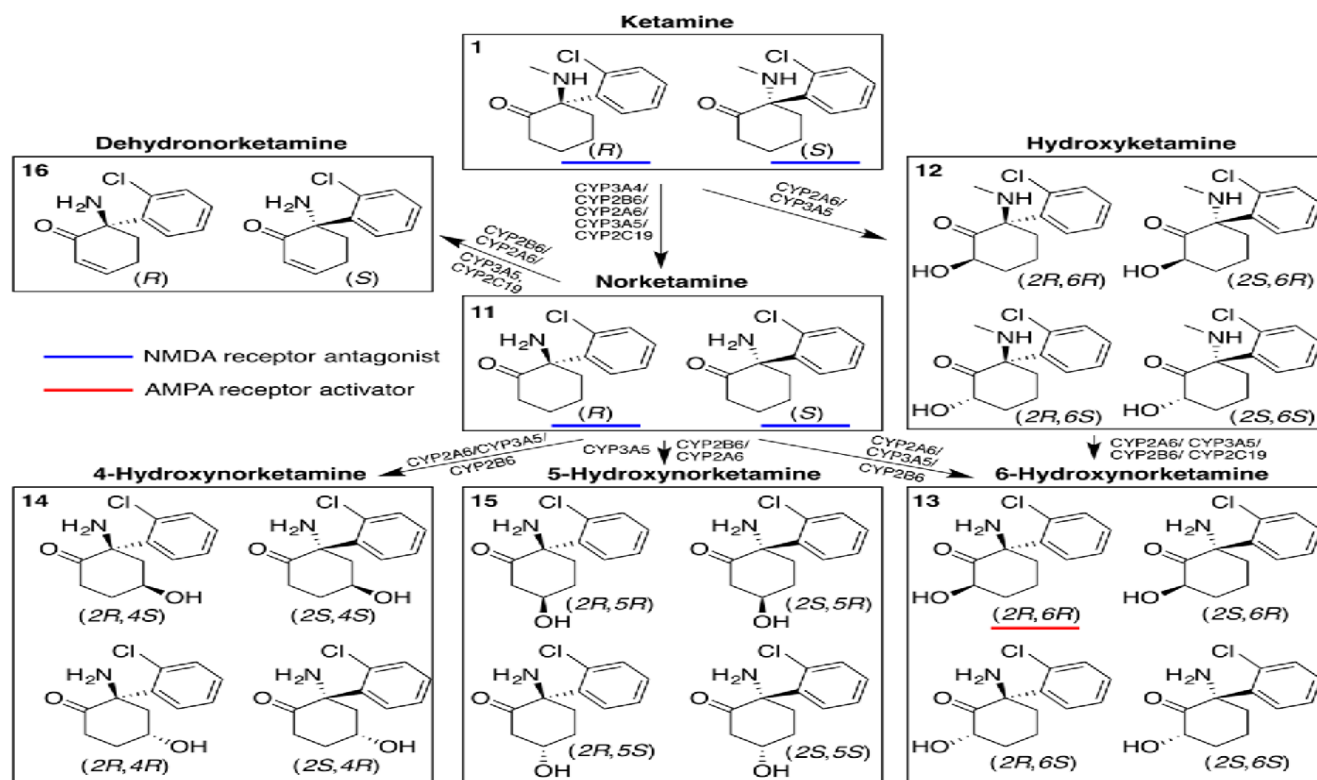
Methods and techniques. Ketamine hydrochloride was first synthesized in 1962 as ketamine "CI-581" (clinical investigation 581) by the American researcher Kelvin Stevens (K. Stevens) [5]. Although ketamine is ten times less potent than CI-581 phencyclidine, it is hallucinogenic in humans and exhibits a strong depressive state [6]. Ketamine hydrochloride was used in clinical trials by the researchers Corssen (Corssen) and Edward Domino in 1965 and showed that this drug has a strong narcotic effect. In 1970-78, a book was published describing scientific research on the psychotropic effects of ketamine hydrochloride. The book Marcia Moore and Howard Alltunian published under the title "Journey to the Bright World" details the authors' research on the drug [7]. Ketamine was used in the Vietnam War as a pain reliever for wounded servicemen and soldiers on the battlefield. It was placed under Schedule III control in the United States in the 1960s and 1970s. However, illicit use of ketamine hydrochloride flourished between 1980 and 1999 [8]. According to the United States Federal Bureau of Investigation, the annual rate of ketamine hydrochloride abuse in the country was 0.033% in 2005 and 0.12% in 2011 (Drug Abuse warning network 2011).

According to the emergency center of the United States of America, the side effects of ketamine combined with other drugs, especially with ethyl alcohol, were 71.5% (Drug Abuse Warning Network, 2011). Between 2002 and 2012, ketamine use decreased from 2.5% to 1.5% among 12th graders and college students, respectively. In the UK ketamine has been classified as a "Ketamine C" form drug since 2006. According to the World Health Organization, the number of adults and adolescents using ketamine for non-medical purposes in the UK fell down from 0.6% to 0.4% in 2011, respectively, and from 1.8% to 0.8% in 2013. Non-medical recreational use of ketamine is becoming increasingly popular in Southeast Asian countries such as Taiwan, Malaysia and China [8]. In Hong Kong, ketamine was included in the 1st list in 2000, but now it is among the most widely used drugs [9]. Observations have shown that the non-medical use of ketamine is concentrated in the southeastern part of China. In 1996-2000, 9% of traffic accidents were caused by citizens addicted to ketamine, ethyl alcohol and opioids [10]. Ketamine abuse often occurs in combination with substances such as alcohol, amphetamine, MDMA, cocaine, and caffeine [11]. In 2015, a report by the World Anti-Drug Society reported that ketamine was used as a recreational drug worldwide, with 58 countries reporting its illegal use. However, in 2014, the United Nations Office on Drugs and Crime reported that 1% of "New Psychoactive Substances" were phencyclidine derivatives [12]. At the same time, it was reported that ketamine has a high therapeutic effect in cases of medical use, but remains one of the psychoactive drugs with a rate of less than 1% of serious complications with other drugs, especially narcotic drugs [13]. Ketamine is a fat-soluble enantiomeric derivative of phencyclidine that has been used as an anesthetic for over 65 years [14].

Researchers G.Bokor and P.D. Anderson states that ketamine poisoning occurs from parenteral or intranasal, intravenous or intramuscular administration, infusion (inhalation), smoking, oral abuse [15]

Between 2011 and May 2012, according to the results of a rapid investigation by the United States Federal Service for Drug Control, there were nine criminal cases related to the illegal sale of ketamine, three of which were prosecuted [31]. All of these criminal cases are related to the smuggling or illegal trade of ketamine. According to the information presented in the literature, in European countries, ketamine hydrochloride is used for non-medical purposes under different trade names, in addition to the medicinal form. In particular, analogues of ketamine hydrochloride, generics and synonyms, are produced in many countries under trade names such as velonarcon, calypsol, ketamine in Ukraine, ketal, ketaject in the USA, Japan, Germany, ketamine in France, Panfarma, Diprivan, Propofol-Binergia, Propofol-Lipuro and are used for non-medical purposes. Ketamine hydrochloride (dehydroketamine) belongs to phenylalkylamine derivatives. Phenylalkylamine derivatives make up the majority of drugs affecting the central nervous system. Ketamine hydrochloride is widely used in medicine as a sedative and pain reliever (in stomatology, ophthalmology, middle ear, gynecology and obstetrics practice), as an anesthetic, narcosis agent in rapid surgery in traumatic shocks in emergency medical care. Ketamine hydrochloride in medicine activates the central nervous system and improves cerebral circulation. In addition, it is used as a stimulant of the respiratory center, and as a pain reliever in veterinary practice [16].

When ketamine hydrochloride enters the body, it inhibits the associative area of the brain hypothalamus and subcortical formation. Ketamine is mainly metabolized in the liver by cytochrome enzymes CYP3A4 or CYP2V6 to norketamine, dehydroketamine, hydroxyketamine, 4-hydroxynorketamine, 5-hydroxynorketamine, 6-hydroxynorketamine. Then it leaves the body with urine through the kidneys within 2 hours. A very small amount of the drug can be stored in the body for a day or two, but does not accumulate. The ketamine molecule contains a chiral center that forms two optical isomers [17]. The ketamine molecule has a chiral center and two optical isomers. The S (+) isomer has a greater analgesic effect on muscles, while its pharmacokinetics and pharmacodynamics are similar to the R (-) isomer, but it has fewer side effects and recovers the body faster [18]. The main mechanism of ketamine's pharmacological action is the blocking of N-methyl-d-aspartate (NMDA) receptor ion channels, which are involved in neurotransmission that excite the nervous system [19]. In practice, a racemic mixture of two isomers is more commonly used. Ketamine hydrochloride has low toxicity, but misuse of the drug is fatal in humans. Ketamine hydrochloride 0.5mg/kg intravenously has an onset of action within 1-2 minutes and an analgesic effect lasting 2-3 hours. When injected intramuscularly, the effect begins later, but lasts longer. After entering the body, ketamine hydrochloride is metabolized in several stages. The metabolic process is shown in Figure 1.



According to the data presented in Figure 1, ketamine is mainly broken down in the liver by cytochrome enzymes CYP3A4, CYP2V6 and other enzymes and glucuronides to norketamine, dehydronorketamine, hydroxyketamine, 4-hydroxynorketamine, 5-hydroxynorketamine, 6-hydroxynorketamine. Some derivatives of ketamine act as (S) NMDA receptor antagonists or (R) AMPA activators and are excreted from the kidneys through the urine [18].

According to the results of the research conducted by D. Dj.Tobias, M. Leder and others, now ketamine hydrochloride is widely used mainly in young children in congenital acute heart failure or in heart valve surgery in acquired heart diseases. In these processes, the use of ketamine in combination with various drugs is cited as the reason for the death of children due to the disproportionate use of certain drugs [19].

According to the information provided by Dj. E. Morgan and others, in the Altai region of the Russian Federation, in the last five years, 12 people died of poisoning due to the combined use of ketamine hydrochloride with barbituric acid derivatives[21]. Nepal is one of the developing countries of the world. Green S.M., Clark R., conducted a study on the response to ketamine in 679 children treated in the intensive care unit of the eye hospital located in Kathmandu, the capital of this country. The sensitivity (side effects) to ketamine of children treated in the eye hospital was studied. According to the results, none of the children required emergency care after surgery. But in some patients, dysphoria appeared from time to time, and it was difficult for doctors to identify it. Side effects of ketamine resolved on the first day of surgery [22]. In surgery, ketamine is used in combination with 1,4-benzodiazepine derivatives, which has also been reported to reduce the side effects of ketamine during post-operative awakening [27]. The authors report that non-standard sub-anesthetic doses of ketamine are used to prevent acute and chronic pain and to treat sedation and severe depression. In studies which is conducted by P.A Chika. and D. Segers, has been shown that the first aid in cases of poisoning when ketamine is taken in large quantities or used with other drugs is to detoxify the gastrointestinal tract. Activated charcoal can be used as a preliminary treatment for this. It has been

reported that activated charcoal is usually recommended at 1g/kg, and 50g/kg in severe poisoning [23]. According to the information provided by the researchers Alltounian Howard Sunny, Marcia Moore of the United States of America, every licensed physician in this country has the opportunity to purchase the drug ketamine for anesthesia. This also requires strengthening the control of this drug. Ketamine hydrochloride is included in the list of essential medicines of the World Health Organization. The anesthetic effect of the drug on the human body was studied by S.P. Cohen, A. Bhatia In a study was shown that even at therapeutic doses can induce a state of "dissociative anesthesia" that provides analgesia, sedation, and amnesia [24]

One of the global problems observed in the world today is the increase in suicide cases [29]. One of the main causes of suicide is because people fall into depression and try to get rid of this process as soon as possible. Since 1987, science and medicine have not made significant progress in treating depression. Unfortunately, the introduction of the anti-depressant drug under the trade name "Prozac" into the black market has led to an increase in the number of suicides among the population. According to the annual report, suicide cases among people are about 1 million. Axel Griesch /press-service/ According to the observation of professors Alon Hen, Juan Pablo Lopez and others, the press service of the Weizmann Institute, almost 300 million people in the world suffer from chronic depression. More than 700,000 people commit suicide each year due to depression [26].

Results. It was observed that many cases of acute poisoning from the drug Ketamine were recorded not only in European countries, but also in the Republic of Uzbekistan. In the current years, the parts of the internal organs of the corpses who died acutely poisoned by this drug and a sample of ketamine hydrochloride in the form of an ampoule as physical evidence were submitted to the forensic chemistry departments of the Samarkand, Tashkent city and Tashkent regional branches of the Republican Forensic Scientific and Practical Center for forensic chemical analysis. . First, the medical records of the corpses were introduced based on the referrals submitted for forensic chemistry analysis. According to the details of the incident, in 1956 "M.T" was operated on due to gallstones. Ketamine hydrochloride drug was used as anesthesia. As a result, death from this drug was observed.

At the same time, it is known that various levels of poisoning are observed as a result of improper use of this drug and illegal consumption of people, and in most cases these poisonings end in death [28]. It should also be noted that methods of rapid chemical-toxicological investigations of cases of poisoning with this drug has not been developed. This requires special scientific research.

Conclusion: In order to study the cases of poisoning with drugs containing phenylalkylamine derivatives, the statistical data recorded chronically by the World Society against Narcotics was studied. The data showed that the abuse of ketamine hydrochloride has been increasing in numbers in many countries of the world for several years. Taking into account that psychotropic drugs used for non-medical purposes can lead to poisoning, it is important to analyze them in various biological fluids in a fast and accurate way. This requires the development of methods for the express identification of the studied ketamine hydrochloride. In this regard, one of the urgent problems is to improve the methodological support of the forensic-chemical expertise departments of the Republican Forensic-Medical Expertise Scientific-Practical Center. In order to solve the problems, it is considered appropriate to develop modern and rapid analysis methods based on the physico-chemical properties of ketamine hydrochloride, which belongs to the phenylalkylamine group and existing analysis methods and to prepare and implement a methodological recommendation based on them.

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