

Article

TOXICOMETRIC ASSESSMENT OF ACUTE POISONING AND INFORMATION SUPPORT FOR ENVIRONMENTAL AND INDUSTRIAL DISASTERS

Kh. Kh. Yakubov¹, T. K. Nasirov²

^{1,2}Tashkent State Medical University, Tashkent, Uzbekistan

Email: ¹khayotyakubov13@gmail.com, ²tulkinnasirov09@gmail.com

Abstract: Currently, in most countries worldwide, including the Republic of Uzbekistan, chemical pollution poses the greatest threat to human life and the environment. Due to the growing scale of chemical production, the increase in international trade, and the use of chemicals in all areas of economic activity and everyday life, this pollution has acquired a global character. The aim of this study was to develop objective quantitative criteria for the diagnosis, assessment of the severity of chemical injury, and determination of the main stages of thanatogenesis in acute combined poisoning. The material for the study was provided by the case histories and forensic examination reports of victims of acute poisoning and the authors' own observations (examinations) of the corpses of individuals who died from acute oral poisoning with malathion, chlorophos, dichloroethane, phenobarbital, acetic acid, and ethyl alcohol. The study found that the immediate causes of death in victims of acute combined poisoning are respiratory paralysis, toxic shock, and toxic coma, occurring within the first 24 hours after ingestion of the poisons. In more remote periods, death is most often due to pneumonia and acute renal and hepatic failure. The main toxicometric parameters of general toxicity determine the threshold, toxic (critical), and incompatible with life levels of poisons in the blood, making it possible to determine the severity of chemical injury. Toxicokinetic parameters of poisons are recommended as an additional quantitative criterion for assessing the severity of chemical injury and evaluating the effectiveness of therapeutic measures. Modern scientific research in forensic toxicology must, as a prerequisite, take into account the chronology of the pathological process. This is important for understanding the main stages of complex thanatogenesis in acute poisoning.

Keyword: Toxicometry, Acute Poisoning, Industrial Disasters, Information Systems

Introduction

Currently, in most countries, including the Republic of Uzbekistan, chemical pollution poses the greatest threat to human life and the environment. Due to the increasing scale of chemical production, the growth of international trade, and the use of chemicals in all areas of economic activity and everyday life, this pollution has become global in nature. Humanity has synthesized over 7 million new chemicals, while approximately 70,000 different types of chemicals are used in everyday life, and their number continues to increase by 500-1,000 per year. It is difficult to predict all the expected consequences of this chemical aggression, since in relation to neither the human body nor the surrounding environment possesses the genetic memory to effectively counteract newly synthesized poisons. Often, a low-toxicity chemical substance becomes a highly potent poison as a result of metabolic transformations within the body itself. [1,2]Forensic diagnosis of acute poisoning is complicated by the lack of clinical data and characteristic morphological features in most cases, as well as by the variety of poison combinations and the limitations of existing methods for identifying poisons in the body's biospheres. If the effect of a poison, all things being equal, is primarily determined by

its concentration, [3] then its quantitative effect can be either indifferent to the body, have a therapeutic effect, or be a poison (cause a toxic effect). Consequently, the concept of "poison" is quantitative rather than qualitative, and the essence of toxicity is assessed by the quantitative relationship between chemical substances and the body [4]. In experimental toxicology, the degree of toxicity of a substance is determined by determining the lethal dose, expressed by the symbol DL. DL0, DL25, DL50, DL75, and DL100 are commonly used as toxicometric criteria and to assess lethal effects. Lethal concentrations (CL) also have identical graphs. In practical forensic medicine, toxicometry of poisonings is virtually nonexistent. The literature contains highly contradictory data on oral doses of only individual chemicals [5, 6, 7, 8]. In light of the above, studies assessing the body's condition during various poisonings from a systems approach are of particular interest. The human body is a complex, multi-level system, and interacting with the environment is considered an open system (like any living organism), with numerous and diverse relationships between its elements.

To understand the nature of critical disorders in the body during combined acute poisonings, the properties of biological systems, such as stability, the principle of optimal response, and reliability, are also of particular importance. Since stability is a property of the system as a whole, the latter may prove unstable even if its component parts are stable. Therefore, many chemical compounds, especially when combined (for example, dichloroethane and ethyl alcohol), may, at a certain point, sharply increase, rather than decrease, their toxicity during biotransformation.

All of the above highlights the relevance of the problem and dictates the urgent need for toxicometric studies in all manifestations of combined acute poisoning.

Materials and Methods

The study material consisted of the medical records and forensic examination reports of 78 victims of acute poisoning and our own observations (examinations) of 32 corpses of individuals who died from acute oral poisoning with malathion, chlorophos, dichloroethane, phenobarbital, acetic acid, and ethyl alcohol. Quantitative analysis of dichloroethane and ethyl alcohol in blood was performed using gas chromatography. Qualitative and quantitative analysis of FEI in blood was performed using a Tsvet-100 chromatograph with a selective detector. Cholinesterase activity in whole blood was determined using the colorimetric method of H. Hestrin. Free hemoglobin in blood plasma was determined using the modified hemoglobin cyanide method according to I.N. Nikitenko (1969). Quantitative analysis of barbiturates in blood plasma and urine was performed spectrophotometrically.

In addition to toxicometric studies, the results of clinical, laboratory, and instrumental tests were analyzed and entered into the database: complete blood count, blood acid-base balance, blood electrolyte levels, total protein and protein fractions, bilirubin, urea, and creatinine levels, total LDT, AST, and AMT activity, FMPA and FDP A activity, and key immune system parameters. Based on the results of instrumental research methods, hemodynamic parameters determined by the electrical impedance method (SBP, CHC, IOC, CVC and OPS), the results of electrocardiographic studies and fibrogastroduodenoscopy in chemical burns of the gastrointestinal tract were analyzed.

Autopsy examinations were performed no later than 24 hours after death. After a macroscopic description of the internal organs and the entry of all changes into a computer database, histological examinations were performed. For histological examination, the material was fixed in 10% formalin and embedded in paraffin blocks. Histological sections were stained with hematoxylin and eosin, van Gieson, Mallory, and Weigert stains. Ultrastructural organ changes were studied using material from early autopsies (28 cases).

The overall toxicity of the studied poisons was assessed using a risk-of-death test for victims across the entire range of recorded blood concentrations of the poisons. Probit analysis was used for this purpose. The plasma poison levels at the time of hospital admission were used as the baseline for chemical injury.

Results

The right to monitor the safety of chemical products for the human body belongs exclusively to the Sanitary and Hygienic Service of the Ministry of Health of the Republic of Uzbekistan. This service conducts experimental evaluations of the primary toxic effects of newly developed drugs on laboratory animals, followed by an approximate extrapolation of these results to humans and the development of corresponding MACs (maximum permissible concentrations). Essentially, the sanitary service is responsible only for the safe use of chemicals within the above limits and carries out monitoring at the workplace. The departments of hygienic and preventive toxicology at the relevant research institutes are also primarily focused on studying the preclinical effects of poisons. Meanwhile, in environmental emergencies and industrial disasters, the human body experiences one-time loads hundreds and thousands of times higher than the MAC. These circumstances necessitate the urgent development of "Acute Toxicity Passports for Chemical Compounds." Actual clinical and morphological observations at the Republican Scientific and Practical Center for Forensic Medicine and its branches can serve as the basis for creating these documents.

Below is a methodological rationale and examples of toxicometric assessments of industrial, household, and pharmaceutical products. The use of toxicometric (quantitative) assessment of chemical illness in forensic medicine was first proposed by the author of this study.

The first section of the "Acute Toxicity Passport for Chemical Compounds" assesses the risk of death for victims across the entire range of recorded poison concentrations in the blood. Probit analysis is used for this purpose (Figure 1).

Figure 1. Typically, a probit plot of the "poison concentration-effect" relationship has an S-shape. The lower, flat portion of the graph (or its lower asymptotic point) corresponds to those poison concentrations at which the initial magnitude of chemical injury does not exceed the limits of the body's physiological defenses, and the outcome of poisoning is always favorable. This level is commonly referred to as CL0—the maximum tolerable concentration of the poison. This level is characterized by the appearance of acute clinical symptoms of poisoning and can be referred to as the threshold for acute poisoning. The next, ascending section of the graph corresponds to concentrations at which the outcome of poisoning is uncertain, and the risk of death increases exponentially as the poison concentration in the blood increases. Within these concentrations, the body is in a critical condition, and the outcome of treatment largely depends on the organization of intensive detoxification therapy. When assessing the body's critical condition, the median lethal concentration of poison in the blood (CL50) can be used as an objective criterion. From a forensic perspective, this level of poison in the blood is life-threatening, and these poisonings are considered serious bodily injury (damage to health) that is life-threatening.

Having reached a certain limit and regardless of further increases in the concentration of the toxic agent, the probit graph curve again assumes a horizontal position. This segment (the upper asymptote) corresponds to CL100 - an absolutely lethal concentration of poison or chemical injury incompatible with life. Thus, the analysis of the "poison concentration-effect" relationship is a very valuable tool for studying the quantitative aspect of the relationship between the absorbed dose of a chemical substance and the nature of the body's overall response. From the perspective of this relationship, a homeostasis crisis should be characterized as an unstable, transitional state between the only two possible polar outcomes of poisoning—recovery and death.

With the help of such standard graphs, it is possible to provide an objective prognosis of the outcome at the very onset of chemical injury and, based on the risk of death, ensure priority treatment for the most seriously injured contingent of victims in mass chemical disasters. The result of a toxicometric assessment of the risk of death

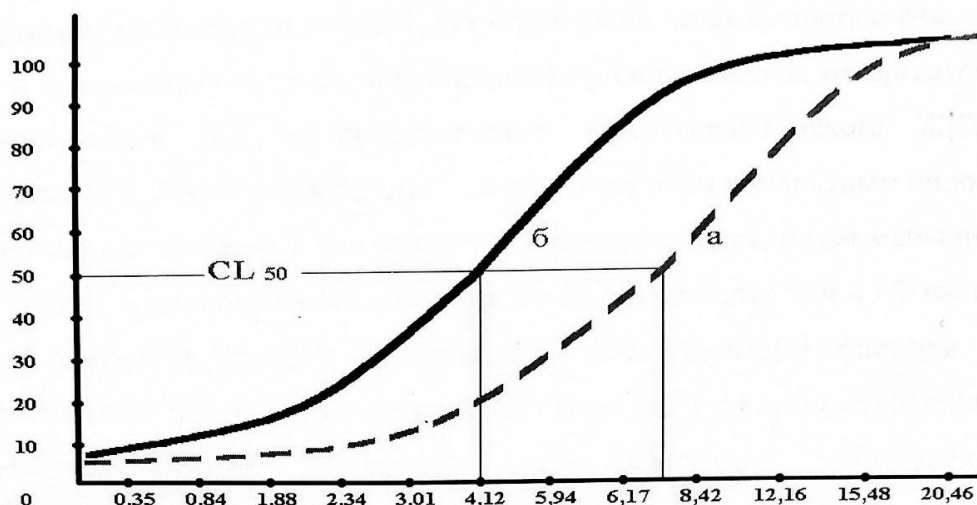


Table No. 1.

A critical condition is not only a specific form of disruption to the body's vital functions, but also a specific phase in the pathological process. Unfortunately, most modern studies do not consider the dynamics of the risk of death from poisoning. However, this indicator is no less important a criterion for the danger of a chemical compound than the level of poison in the blood. Figure No. 2 shows graphs of the survival probabilities of patients at each point in time for unfavorable outcomes of various types of chemical illness. This indicator was obtained computer-generated by determining the reliability function in a special mathematical model developed by D.R. Cox.

Comparing the graphs, we can conclude that the probability of survival from dichloroethane poisoning drops sharply within the first hours of chemical illness; in cases of poisoning with acetic acid or malathion, the decline in homeostasis reliability is less catastrophic, and the dying process can span 120-200 hours. In turn, with phenobarbital poisoning, irreversibility develops relatively late, only after severe pulmonary complications (pneumonia) have developed. Therefore, based on the mortality rate of victims, dichloroethane should be classified as an extremely hazardous toxic substance, phospholipids and acetic acid as highly toxic, and phenobarbital as a moderately toxic poison. This must be taken into account when triaging patients in mass poisonings.

This indicator was obtained by computer-aided determination of the reliability function in a special mathematical model developed by D.R. Cox.

Comparing the graphs reveals that the survival rate for dichloroethane poisoning drops sharply within the first hours of chemical illness. In cases of acetic acid or malathion poisoning, the decline in homeostasis is less catastrophic, and the death process can last 120-200 hours. In contrast, with phenobarbital poisoning, irreversibility develops relatively late, only after the onset of severe pulmonary complications (pneumonia). Therefore, based on the severity of death among victims, dichloroethane should be classified as an extremely hazardous toxic substance, phospholipids and acetic acid as highly toxic, and phenobarbital as a moderately toxic poison. This must be taken into account when triaging patients in mass poisonings. When studying acute poisonings, researchers naturally face the question: what in the complex symptom complex of chemical illness directly reflects the damaging effect of the poison on the body, and what is the body's response to this damage?

According to S.N. Golikov et al., the selective action of chemicals (at the point of poison application) merely acts as a trigger for its overall toxicity. The full spectrum of subsequent clinical symptoms and morphological changes, in terms of the specificity or non-specificity of the effects, has remained virtually unexplored in

medical practice. Answering this question is not only of educational value but also of great practical importance for conducting informed pathogenetic treatment, expert assessment of the severity of chemical illness, and postmortem diagnosis.

The main difficulty in assessing the body's response to chemical injury as a whole lies in the systemic nature of its response. It is virtually impossible to localize any one part of this system of highly complex and interdependent functions. Methodologically, factor analysis is the most appropriate method for solving this problem. It should be noted here that factors are mathematical constructs built on the principle of the interrelationship (correction) of the features they combine, i.e., from a biological perspective, on the principle of the commonality of their changes in the pathological process.

In turn, the factor loading of each individual feature characterizes its correlation with the factor and thus reflects the comparative role of the feature in the overall response of all its elements. Furthermore, the sequence of procedures in this analysis is structured such that the first factor explains the largest portion of the overall variance of all data, while the second factor explains the largest share of the remaining portion, and so on. As a result, the factor number corresponds to its rank of significance in the process under study. As an example, let us consider the factor structure of the clinical and morphological picture of acute poisoning with FOI.

Table No. 2.

It is known that chemical substances affect tissue cells and organs only if their concentration exceeds a threshold. Thus, if we arrange the clinical and morphological signs of poisoning in accordance with the value of their concentration thresholds, using the example of poisoning with malathion, then they will be grouped based on the resistance of each tissue to a given toxic substance.

Poison name and unit of measurement	Toximetry parameters				
	CL ₀	CL ₂₅	CL ₅₀	CL ₇₅	CL ₁₀₀
Phenobarbital (mcg/ml)	16,0	38,5	66,69	151,34	215,72
Karbofos (mcg/ml)	0,03	0,176	1,04	1,92	3,03
Chlorophos (mcg/ml)	0,21	1,22	3,81	6,41	8,51
Dichloroethane (mcg/ml)	1,8	19,64	48,37	86,13	212,29
Acetic acid: free hemoglobin in blood plasma (mg/ml)	1,48	5,62	10,84	16,80	33,88

It's always advisable to examine the course of chemical poisoning from two perspectives: what the poison does to the body and how the body itself influences the poison's biotransformation. Our research has shown that toxic coma, exotic shock, and a number of other critical conditions can significantly increase the duration of poison circulation in the blood. This circumstance must be taken into account by forensic experts when removing organs from corpses for forensic chemical analysis. The body's response to injury is not a one-time reaction, but a process that occurs over time through specific phases of interacting factors. In chemical poisoning, where the sequence of toxic effects is, to a certain extent, a consequence of the distribution and biotransformation of poisons in the body, analysis of this process is particularly relevant. The pathogenetic relationship that effectively exists between different types of toxic effects is expressed in their sequence. In terms of the dynamics of poisoning, each preceding stage of chemical poisoning prepares and shapes the subsequent one. Thus, all preceding toxic effects and syndromes, primarily bronchial congestion and chest rigidity, should be considered as risk factors for bronchopneumonia in this type of poisoning. Unfortunately, our country's environmental programs pay extremely little attention to protecting public health from chemical

pollution. Meanwhile, humans are not only the culprit but also the primary victim of environmental disasters. A biological test for acute human poisoning is the earliest and most easily detectable symptom of an unfavorable environmental situation. Based on this, it would be possible to obtain a fairly reliable map of the country's environmental status and study its changes in real time. However, despite the obvious need for such biomonitoring, the country currently lacks not only a comprehensive assessment of the structure but also basic measures for a multi-agency approach to the prevention of acute chemical diseases.

Thus, toxicometric assessment of acute chemical illness allows us to determine the direction of the toxic substance's primary impact on homeostasis, thereby enabling differentiated resuscitation measures and a scientifically based expert assessment of the severity of chemical illness and its postmortem diagnosis.

It should be noted that a significant increase in the effectiveness of medical care for acute poisonings, and especially during mass disasters, can be achieved through the development and implementation of intelligent computer systems. There is no alternative to this program, as training physicians in the pathogenesis, clinical presentation, and treatment of the many hundreds of types of chemical illnesses is virtually impossible. The Republican Scientific and Practical Center for Forensic Medicine is currently working on developing an intelligent computer system to advise toxicologists and forensic experts.

Conclusion

1. The immediate causes of death in victims of acute combined poisonings are respiratory paralysis, toxic shock, and toxic coma, which occur within the first 24 hours after ingestion. In later stages, death is most often caused by pneumonia and acute renal and hepatic failure.
2. The main toxicometric parameters of general toxicity determine the threshold, toxic (critical), and incompatible with life levels of poisons in the blood, making it possible to determine the severity of chemical injury.
3. Toxicokinetic parameters of poisons, particularly the half-life of the poison in the blood ($T_{1/2}$), are recommended as an additional quantitative criterion for assessing the severity of chemical injury and evaluating the effectiveness of therapeutic measures. This indicator is also of significant expert value for establishing the underlying cause of death.
4. Modern scientific research in forensic toxicology must, as a prerequisite, take into account the chronology of the pathological process. This is important for understanding the main stages of complex thanatogenesis in acute poisoning, as well as for establishing the morphological equivalent of the clinical signs of these intoxications.

REFERENCES

- Abdurakhmanov, M. M. Systemic inflammatory response in patients with acute acetic acid poisoning / M. M. Abdurakhmanov, Z. Kh. Kuvatov // *Journal of Theoretical and Clinical Medicine*. - 2021. - No. 4. - P. 49-51.
- Akalaev, R. N. Systemic inflammatory response in patients with acute acetic acid poisoning / R. N. Akalaev, V. A. Rozanov, A. N. Lodyagin, G. A. Prokopovich, L. V. Luchsheva, A. A. Stopnitsky, R. Kh. Khonbabaeva, A. A. Akalaeva, Kh. Sh. Khoziev // *Bulletin of Emergency Medicine*. – 2019. – Vol. 12, No. 6. – P. 81–87.
- Alishev A.Zh., Khasanov R.M., Kuralbaev T.Kh., Baisadykov M.M. Forensic classification of poisonings and poisons // *Science and Healthcare*. 2013. No. 4. P. 64–66.
- Anatskaya, A.S. Diagnostics of acute poisoning with alimemazine by GC/MS during chemical-toxicological Barsegyan S.S., Tuchik E.S. Features of posthumous forensic diagnostics of organophosphorus nerve agents // In the collection: *Milestones in the history of the Russian Center for Forensic Medical Examination. On the 90th anniversary of its foundation*. Moscow, 2021. Pp. 11-17.
- Anuchina A.V. Toxic effects of pesticides on humans and animals // *International Student Scientific Bulletin*. - 2019.-№1. URL: <https://eduherald.ru/ru/article/view?id=19454>

- Vorobyova V. V., Zarubina I. V., Shabanov P. D.. Improving the methods of treating poisoning with organophosphorus compounds by using the metabolic protectors metaprot and etomerzol // Bulletin of the Smolensk State Medical Academy. - 2017. - Vol. 16 / - No. 4. - Pp. 5-11
- Frolov A. V., Nikitin G. P., Frolkis V. V., Aging and the biological capacity of the organism. M. Medicine, 1976. Pp. 37-39.
- G. N. Oksengendler. Poisons and Antidotes. - Leningrad: Nauka, 1982. - Page 192
- Luzhnikov E. A. Clinical Toxicology. Moscow: Meditsina, 1999. - 416 p.
- Zabrodsky P. F. Immunotoxicology of Organophosphorus Compounds. - Saratov. Publishing House "Saratovskiy Istochnik". - 2016. - 289 p.
- Mogos G. Acute Poisoning with Chlorinated Solvents Methyl Bromine and Methyl Chloride. - In the book: Acute Poisoning, Diagnosis and Treatment (Study Manual, translated from English). - Bucharest, 1984. - P. 492-493.