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FORENSIC TOXICOMETRY AND TANATOGENESIS IN ACUTE COMBINED POISONINGS

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Abstract*. The nosology of acute poisoning is extremely diverse and differs significantly in different countries. In Uzbekistan, the bulk of poisoning is accounted for by alcohol and its surrogates, acids (mainly acetic) and alkalis, various medications, mainly hypnotics and sedatives, organophosphorus and other pesticides. The biological activity of chemical compounds is determined by their structure, physical and chemical properties, dose (concentration) and duration of exposure; features of intake and biotransformation in the body; resistance of tissues and organs to poisons and the individual characteristics of a particular victim. In this regard, the forensic medical assessment of concomitant acute poisoning is a very relevant and unresolved problem.*

Keywords*: toxicokinetics, toxicodynamics, resistance of tissues and organs, structural portrait, specific and nonspecific effects of poisons, toxicometry, toxicometric parameters, mean lethal concentration, probit analysis.*

The era of the scientific and technological revolution raised many new problems for mankind. One of them is the accumulation in its habitat of a huge amount of newly synthesized chemicals, most of which are potentially dangerous poisons for humans. According to WHO, at present, the total number of newly created chemical compounds has reached more than 7 million items (92). Acute poisoning mainly occurs as a result of accidents at home and at work, suicidal attempts, overdose of drugs and drugs, alcohol abuse, less often with the intent to kill.

Forensic medical diagnosis of acute poisoning is difficult due to the lack of clinical data and characteristic morphological features in most cases, as well as due to the variety of combinations of poisons and the limitation of the existing methods for determining poisons in the biospheres of the body. If the effect of a poison, under all equal conditions, is primarily determined by its concentration (Frolov et al., 1976), then its quantitative effect can be either indifferent for the body, or have a therapeutic effect, or poison (causes a toxic effect). Consequently, the concept of "Poison" is not so much qualitative as quantitative in nature and the essence of the phenomenon of toxicity is estimated by the quantitative relationship between chemicals and the body (Oxingender, 1982).

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 lethal effects. Identical graphs also have lethal concentrations (CL). In practical forensic medicine, poisoning toxicometry is not actually carried out. There are very conflicting data in the literature

on oral doses of only certain chemicals (Luzhnnikov E.A., 1982; Ludowig Gons, 1983; Mogos, 1984)

In the light of the foregoing, studies of assessing the state of the body in various poisonings from the standpoint of a systematic approach are of particular interest.

The human body is a complex multi-level system and interacting with the environment is called an open system (like any living organism), between the elements of which there are numerous and diverse connections.

To understand the essence of critical disorders in the body with combined acute poisoning, the properties of biological systems, such as stability, the principle of optimality of their reactions and reliability, are also of particular importance. Since stability is a property of the system as a whole, the latter may turn out to be unstable even if its constituent parts are stable. Therefore, many chemical compounds, especially with combined action (for example, dichloroethane and ethyl alcohol), in the course of their biotransformation, may at a certain moment not reduce, but sharply increase their toxicity.

All of the above indicates the urgency of the problem and dictates the urgent need for the study of toxicometry in all manifestations of combined acute poisoning of the body.

The aim of this study was to develop objective quantitative criteria for diagnosing, assessing the severity of chemical injury and determining the main stages of thanatogenesis in acute combined poisonings.

The material for the study was the case histories and the conclusions of forensic medical examinations of 528 victims of acute poisoning and our own observations (expertise) of 62 corpses of persons who died from acute oral poisoning; karbofos, chlorophos, dichloroethane, phenobarbital, acetic acid and ethyl alcohol. Quantitative analysis of dichloroethane and ethyl alcohol in the blood was carried out by the gas chromatographic method (A.A. Koldaev, Sh.A. Lisovik, 1978). The analysis of the qualitative composition and quantitative content of the FOI in the blood was carried out on the chromatograph "Tsvet-100" with a selective detector (Sh.A. Lisovik, 1980). The activity of the cholinesterase enzyme in whole blood was determined by the colorimetric method of H. Hestrin (1969).

Free hemoglobin in blood plasma was studied by a modified hemoglobin cyanide method according to I.N. Nikitenko (1969).

Quantitative analysis of barbiturates in blood plasma and urine was carried out by spectrophotometric method.

In addition to toxicometric studies, the results of clinical, laboratory and instrumental research methods were analyzed and entered into the database; complete blood count, acid-base state of the blood, blood electrolytes, total protein and protein fractions, bilirubin, urea, creatinine, total activity of LDT, AsAT and AmAT, activity of FMFA, FDFA, basic parameters of the immune system. According to the results of instrumental research methods, hemodynamic parameters determined by the electrical impedance method (SBP, CHOC, IOC, CTC and OPS), the results of electrocardiographic studies and fibrogastroduodenoscopy in chemical burns of the gastrointestinal tract were analyzed.

Sectional studies were carried out no later than 24 hours from the moment of death. After a macroscopic description of the internal organs with the introduction of all changes into the computer database, histological and electron microscopic studies were performed. For histological studies, the material was fixed in 12% formalin and embedded in paraffin blocks. Histological

sections were stained with hematoxylin-eosin, according to van Giesen, Malleri and Weigert. Ultrastructural changes in organs were studied on the materials of early sections (28 observations). For electron microscopic examination, pieces of internal organs (liver, heart, brain, lungs, and kidneys) were fixed in 2.5% glutaoraldehyde solution in phosphate buffer (pH 7.2) or 5% paraform solution in phosphate buffer (pH 7.4), followed by treatment in osmium latch. After dehydration, the pieces were poured into oraldite. Semi-thin and ultra-thin sections were counterstained with Reynold's lead acetate and lead citrate.

The assessment of the general toxicity of the studied poisons was carried out according to the test of the risk of death of victims in the entire range of registered concentrations of poisons in the blood. For this purpose, the method of probit analysis was used. As the initial level of chemical injury, the content of poisons in the blood plasma at the time of admission of patients to the hospital was considered. In a typical case, the probit plot of the poison concentration-effect relationship has a characteristic S-shape; the lower sloping part of the graph corresponds to those concentrations at which the initial value of chemical injury does not exceed the limits of the body's physiological defenses and the outcome of poisoning is always favorable. The next ascending section of the graphic curve corresponds to those concentrations at which the outcome of poisoning is uncertain, and the risk of death increases exponentially as the content of poisons in the blood increases. Within these concentrations, the organism is in critical, i.e. from the point of view of forensic medicine, in a life-threatening condition. When assessing such a state, we used the CL50 value of the average lethal concentration of poisons in the blood as an objective indicator. Having reached a certain limit, regardless of the further increase in the poison in the blood, the probit curve again takes a horizontal position. This section of the curve corresponds to CL100, an absolutely lethal concentration of poisons in the blood or an incompatible level of chemical injury. The results of the tokisimetric evaluation of the studied poisons are presented in Figures 1,2 and Table №1

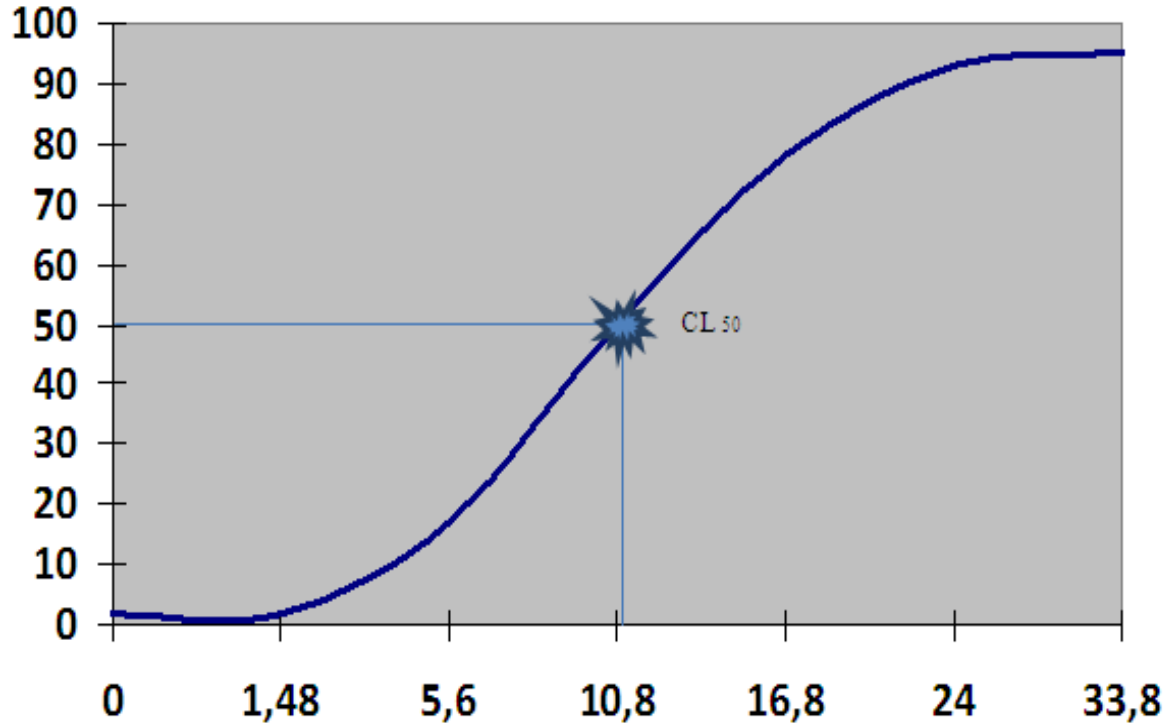

Fig. No. 1. Probit-graph of the dependence "poison concentration-effect" in case of poisoning with acetic acid. The abscissa is the concentration of the poison in the blood (mg / ml), the ordinate is the percentage risk of death.

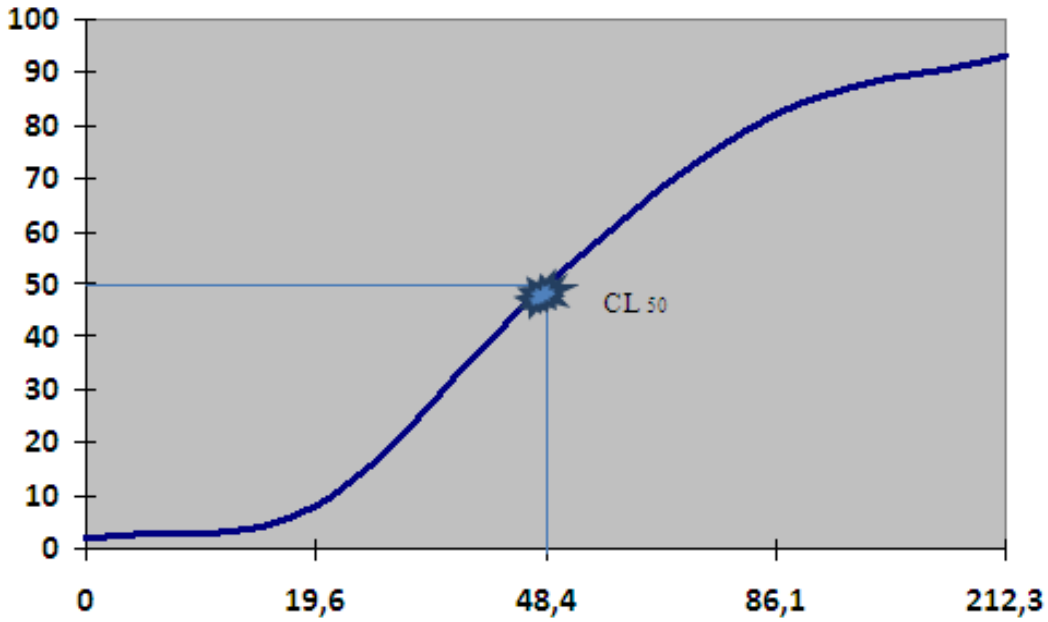

Fig. No. 2. Probit-graph of the dependence "poison concentration-effect" in case of poisoning with dichloroethane. The abscissa is the concentration of the poison in the blood (mkg / ml), the ordinate is the percentage risk of death.

Table № 1.

The results of toxicometry of the "poison concentration-effect" dependence in acute oral poisoning.

The name of the poison and the measure of its measurement	Toximetry parameters				
	CL0	CL25	CL50	CL75	CL100
Phenobarbital (mg/ml)	16,0	38,5	66,69	151,34	-
Karbofos (mg/ml)	0,03	0,176	1,04	1,92	3,03
Chlorophos (mkg/ml)	0,21	1,22	3,81	6,41	8,51
Dichloroethane(mkg/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

As follows from the table, the most toxic are organophosphorus compounds - karbofos and chlorophos, in which the average lethal concentration is 1.04 mg / ml and 3.8 mg / ml, respectively, and the least toxic among the studied drugs is phenobarbital (CL50 is 66.69 mg / ml). It should be noted that the use of the probit analysis method is especially appropriate for the forensic medical examination of combined poisonings.

When studying acute poisoning, the question naturally arises; What in the complex clinical symptom complex and in the morphological manifestations of a chemical disease is a direct reflection of the damaging effect of the poison on the body, and what is the body's response to this damage? Within the framework of this general task, we pursued two goals: to determine the clinical and morphological structure of specific and nonspecific reactions and to establish their most important link. The main difficulty in evaluating the reactions of the organism as a whole to chemical injury lies in the systemic nature of its response. It is impossible to localize any part of

the organism of this system with very complex and interdependent functions. In methodological terms, the solution of this problem is most consistent with the method of factor analysis. A factor is a mathematical construction built on the principle of interconnectedness (correlation) of the signs combined in them, that is, on the principle of the generality of their changes in the pathological process. In turn, the factor load of each individual feature characterizes its correlation with the factor and thus reflects the comparative role of the feature in the generalized reaction of all its elements. In addition, the sequence of procedures for this analysis is arranged in such a way that the first factor explains the largest part of the generalized variance of all data, while the second factor explains the largest share of the remaining part of it, and so on. As a result, the number of the factor corresponds to the rank of its significance in the process under study.

In acute poisoning with OPI, according to the above provisions, the most significant features of these poisonings are represented by factor I (Table № 2)

Table 2. Factor structure of the clinical and morphological picture of karbofos poisoning

Feature name	Factor I	Factor II	Factor III	Factor IV	Factor V	Factor VI	Factor VII	Factor VIII	Factor IX
Outcome of poisoning	0.74 (2)								
Age	0.33 (8)	0.43 (3)			0.27 (2)	-0.40 (3)			
Detox method									
Stage of poisoning	0.72 (3)								
The level of poison in the blood	0.58 (1)								
sick day	-0.27 (10)	-0.68 (1)							
Systolic BP	-0.28 (7)		0.83 (2)						
Diastolic BP			0.85 (1)						
Sex							0.51 (2)		
Cholinesterase activity	-0.46 (2)					0.38 (4)			
Respiratory paralysis	0.78 (4)								

Level of consciousness	0.64 (3)	-0.39 (4)							
Time of death	0.62 (5)		-0.39 (3)						
Pneumonia					0.65 (3)				
Myofibrillation		0.62 (2)				0.34 (5)			
Tracheobronchitis					0.64 (1)				
Vomit									0.87 (1)
bronchorrhea				0.60 (2)					
Rigidity of the pectoral muscles								-0.91 (1)	

Note: The numbers in parentheses indicate the comparative significance of factor loadings. Factor loadings less than 0.25 are omitted.

The composition of the elements of this factor reflects both the etiology and the main specific effect of poisoning, as well as its main clinical and morphological manifestations, which play a leading role in the outcome of a chemical disease. Thus, the structure of the considered factor demonstrates that in the zone of critical concentrations of the poison, the response of the organism is not limited only by the effect of selective toxicity (decrease in acetylcholenesterase AChE) or damage to any one physiological system, but is of an integral, systemic nature.

In this integral reaction, the leading element is respiratory paralysis (as evidenced by the value of its factor load - 0.78). On the contrary, other specific manifestations of the anticholinesterase effect of the poison summarized in factor IV (deceleration of myocardial conduction, myofibrillation) do not belong to life-threatening conditions, since they do not have an independent effect on the outcome of poisoning.

Some poisons or their combinations cause the development of not one, but a number of completely independent specific effects. An example of such a compound is dichloroethane, especially in combination with alcohol intoxication.

Factorization of signs divided the symptom complex of this poisoning into seven different groups (factors). Among them, three factors (I, III, VII) are quantitatively associated with the level of poison in the blood and, therefore, can be interpreted as its specific effects. Since in factor I the degree of depression of the CNS function (0.73) and respiratory paralysis (0.74) have the highest factor load, it can be designated as the narcotic effect of dichloroethane or toxic coma, and factor III, in which the maximum load belongs to the levels of diastolic (0 .86) and systolic (0.83) blood pressure, as a reflection of toxic damage to the vascular system. Taking into account the factor loads of those signs that are combined in factor VII (hepatic coma, vomiting, jaundice of the skin, fatty degeneration of the liver), it can be interpreted as a specific hepatotoxic effect of

dichloroethane. On the basis of the presented data, we can state that the toxic coma plays the largest role in the outcome of this poisoning, and the vascular system lesion occupies the next most important place in the pathological process.

Table 3. Factor structure of the clinical and morphological picture in dichloroethane poisoning

Feature names	Factor loadings of features						
	Factor I	Factor II	Factor III	Factor IV	Factor V	Factor VI	Factor VII
Outcome of poisoning	0.80 (1)		-0.45 (5)				
Age (in adults)	0.61 (6)						
The level of poison in the blood	0.72 (4)		0.29 (4)				0.44 (4)
sick day	-0.55 (8)						
Systolic BP	-0.28 (7)		0.83 (2)				
Diastolic BP			0.86 (1)				
Sex		-0.78 (1)					
Respiratory paralysis	0.73 (2)						
Level of consciousness	0.73 (3)	-0.26 (3)				-0.35 (1)	
hepatic colic					-0.81 (1)		0.61 (3)
Yellowness of the skin							
pupil diameter				-0.68 (1)			
Fatty degeneration of the liver							0.80 (1)
Vomit				0.28 (3)	0.58 (2)		0.37 (5)
Dose of poison						0.25 (3)	0.71 (2)
Time of death	0.66 (5)	-0.36 (2)	0.38 (3)		0.36 (3)	0.28 (2)	

Note: The numbers in parentheses indicate the comparative significance of factor loadings. Factor loadings less than 0.25 are omitted.

Conversely, the hepatotoxic effect of dichloroethane is not directly related to the outcome and, therefore, this type of impairment is not the main cause of death in these poisonings. However,

it should be noted that in case of combined poisoning with dichloroethane and ethyl alcohol, factor VII may be among the leading causes of death. If factor analysis made it possible to break down the complex picture of the pathogenesis of various poisonings into their components, then the unification of all elements of the pathological process can be achieved using cluster analysis.

The clustering procedure is performed stepwise, i.e. the two most related features are combined and then treated as one cluster. Further, a similar procedure is repeated at the next, lower level of proximity and can either end at a certain step, or end with the union of all features into a single cluster. Figure 3 shows a dendrogram of the relationship between clinical and laboratory parameters in dichloroethane poisoning. A dendrogram is a way of typological consideration of information and is a generalized graph of the structure of the functional and morphological relationships of an organism in these poisonings. In the figure, the points (top of the graph) indicate clinical, morphological and laboratory parameters. All points are connected by segments of lines (edges of the graph), which characterize the direction and distance of the links between the studied parameters of homeostasis. It should also be borne in mind here that the clustering process begins with the feature that is presented first in their list. In this regard, the examiner should consider it as the main criterion for the classification carried out.

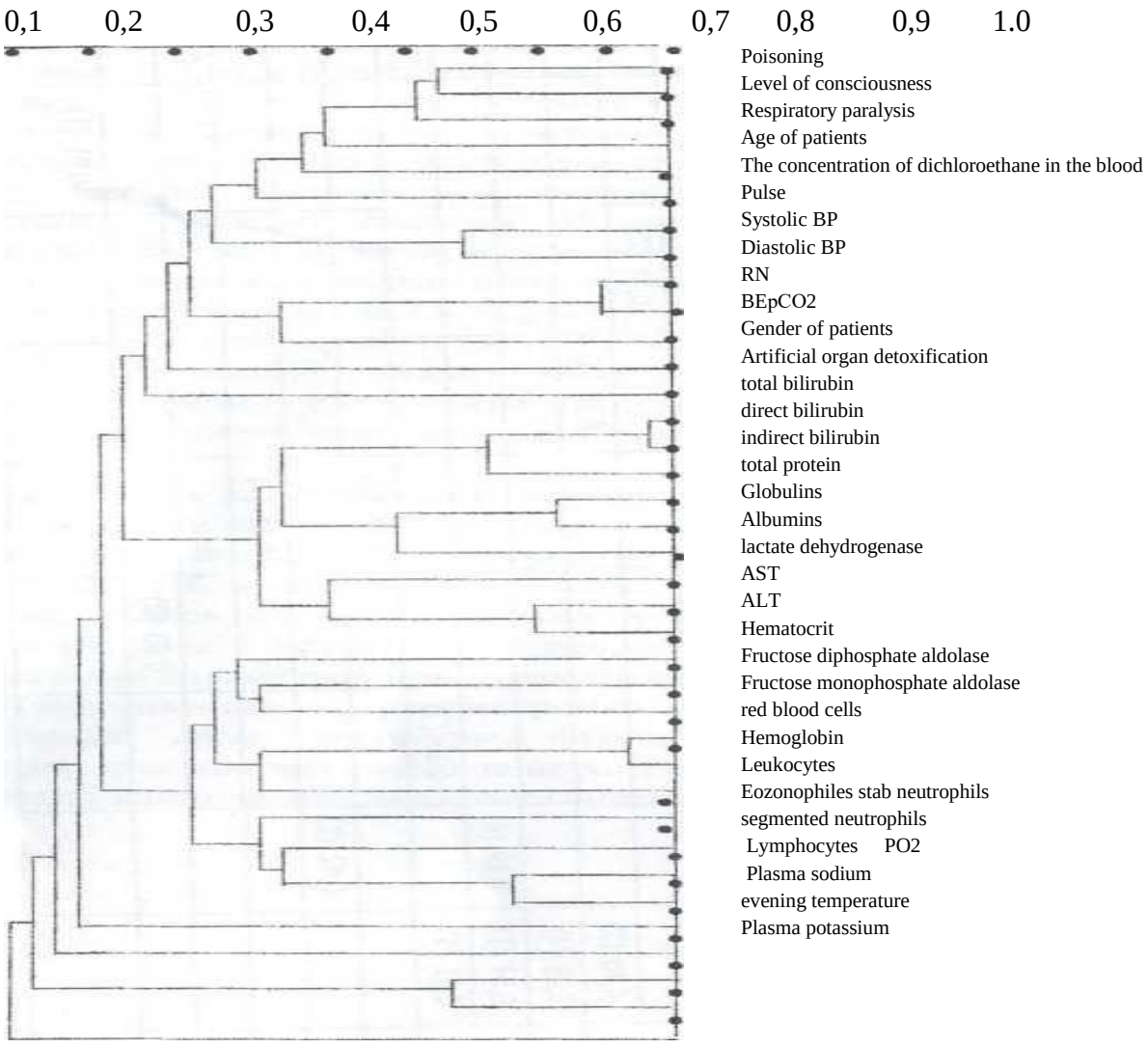

Fig No. 3. Dendrogram of intersystem functional relationships in dichloroethane poisoning.

The presented dendrogram demonstrates not only the complexity of relationships, but also, at the same time, a certain hierarchical ordering of the morphofunctional relationships of the organism. There are two levels of homeostatic regulation in their structure: intrasystemic (ie, between the elements of the physiological system) and intersystemic (for example, between the respiratory and hemodynamic systems). At the first level of regulation, the elements of homeostasis interact at a much higher level of proximity than at the second, intersystem level. Moreover, on the dendrogram, intrasystem connections are oriented in space in a certain way. In particular, on the example of the acid-base state system (ANS) in case of poisoning with dichloroethane, we see that pH most of all depends on the value of BE and only at a close level of 0.44 does the CO2 index also affect the total acidity. The ambiguity of this dependence is explained by the fact that the bicarbonate buffer is the fastest acting, while the lungs (as a relatively inert system) change the pCO2 level with a certain delay.

Characteristically, regardless of the type of toxic substance, the magnitude and spatial orientation of intrasystemic bonds does not change. This indicates that during the crisis of homeostasis, regulation at this level does not suffer significantly.

The outcome of any chemical poisoning depends, first of all, on how quickly the body is able to eliminate the absorbed dose of the poison. Therefore, an obligatory stage of toxicological research should be the study of the toxicokinetics of poisons. For this purpose, we determined the main parameters of the kinetics of the studied poisons by the method of nonlinear regression analysis. Comparative toxicokinetics of poisons are presented in Table 3.

Table 3. Comparative characteristics of the toxicokinetics of phenobarbital, karbofos, chlorophos, dichloroethane and free hemoglobin

Name of toxic substances	Baseline poison level in blood (mkg/ml)	Excretion rate constant (Ke)	Half-life of the poison in the blood (T1/2)h	Maximum duration of the toxicogenic phase (H)
Фенобарбитал	34,45+3.18	0.008	82,62	148
Карбафос	0,85+0.06	0,035	19,8	72
Хлорофос	1,70+0.25	0,039	17,76	53
Дихлорэтан	103,91+16.54	0,108	6,41	38
Уксусная кислота (свободный гемоглобин)	12,30+0.73	0,042	16,5	55

The rate of elimination of poisons was judged by the constant Ke. The physical meaning of this constant is as follows: it shows what proportion of the toxic substance present in the blood is given for each individual period of time. If the rate of release of dichloroethane from the blood can be assessed as relatively high (0.108), the rate of elimination of free hemoglobin (0.042) as moderate, then the rate of excretion of phenobarbital from the blood (0.008) should be assessed as low.

The next task was to determine the half-life of poisons in the blood, i.e. the time required to reduce their concentration in the blood by half. This indicator, widely used in theoretical toxicology, is of great importance in the practice of forensic medicine.

At the last stage of our research, the toxicodynamics of the clinical and morphological picture was studied in acute combined poisonings.

Figure 4 shows a diagram of the chronology of clinical and morphological signs in OPI poisoning.

From the presented diagram, it follows that, even in FOI similar in pathogenesis (karbofos and chlorophos), the time of manifestation of clinical and morphological signs differs significantly. Charting based on recording based clinical symptoms and morphological features on autopsies is of value to forensic experts in assessing the severity of chemical injury, as well as in determining the timing of poison intake. As an important result of this stage of the study, it should be noted that with a threshold or irreversible magnitude of chemical injury, the entire symptom complex of the pathological process, as a rule, ends already in the toxicogenic phase, while the somatogenic phase is a distinctive feature of poisoning that occurs in the zone of critical concentrations of the poison. It goes without saying that the risk of death of victims in different phases of the course of poisoning is far from ambiguous. (Table No. 4).

Table No. 4. Timing of death in acute poisoning

Name poison	Time from the moment of taking the poison (h)			Percentage of deaths affected	
	Min	Max	TL50	Toxigenic phase	Self-generating phase
Phenobarbital	16	257	76,0	87,5	12,5
Chlorophos	2	216	32,0	61,1	38,9
Karbofos	2	381	28,5	80,7	19,3
Dichloroethane	4	395	17,3	91,2	8,8
Sirka acid	2	622	19,7	73,7	26,3

The average time of death of the victims (TL50) for all types of poisoning analyzed by us falls on the toxicogenic phase, i.e. for the period of active circulation of poisons in the blood.

Thus, it can be stated that time in acute poisoning is just as important as an objective indicator of the toxic process as the initial value of chemical injury.

CONCLUSIONS

1. The immediate causes of death of those affected by acute combined poisoning are respiratory paralysis, toxic shock, toxic coma that occurs on the first day after taking poisons. In more distant periods, death is most often due to pneumonia, acute renal and hepatic failure.

2. The main toxicometric parameters of general toxicity determine the threshold, toxic (critical) and life-incompatible levels of poisons in the blood, and make it possible to establish the severity of chemical injury.

3. As an additional quantitative criterion for assessing the severity of chemical injury and assessing the effectiveness of therapeutic measures, it is recommended to use indicators of the toxicokinetics of poisons, in particular, the half-life of the poison in the blood (T1 / 2). This indicator is also of great expert significance for substantiating the main cause of death.

4. Modern scientific research on forensic toxicology, as an indispensable condition, must 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.

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