

Clinical Picture and Pathogenesis of Delayed Neuroendocrinal Toxicity of VX to be Destructed in Russia

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INTRODUCTION

In the last few years there is widely discussed a problem concerning ultra-low concentrations, i.e. a capability of some chemical substances to cause pathologic changes in organisms of human and animals in doses that are lower than maximum allowable ones.

This phenomenon was extended to highly toxic chemical agents as well. These agents should be destructed in a large scale within the next few years both in Russia and in other countries. Naturally, it has negative public response including the opinion that chemical weapon should not be destructed at all because it may be resulted in national ecological disaster.

As a confirmation of such version there was presented, as an example, the data about tragic consequences of the exposure of 100 000 American solders to ultra low concentrations in Persian Gulf. Among them there was appeared an unknown disease at delayed periods.

DISCUSSION

To clarify the problem with ultra low concentrations and, first of all, concerning to VX type substances, it is necessary to present our experimental data on clinic picture and pathogenesis of delayed neuroendocrinal toxicity (DNET) of organophosphorous compounds (OPC). It will help to explain the dramatic consequences of the Gulf War, acts of chemical terrorism in Japan where sarin (chemical warfare agent) was used, and the high occupational morbidity of the personal participated in production of VX (14.2 per 100 working people) [1].

In our experiments during 6 months there were observed 156 animals (rabbits and dogs) that may be divided into three groups by an acute toxic exposure – slight, moderate and severe degree of intoxication after percutaneous exposure to agent being destructed according to Chemical Stockpile Destruction Program. Today these substances are the most aggressive chemicals at such application. There were used VX (substance 1) and its Russian analogue (substance 2).

The experimental animals after application were regularly (each 10th day) weighted and examined. Often in neurologic aspect there were revealed organic disturbances in movement function mainly in central genesis: stiffness in motion, spastic gait with ataxia of different extent, reduce in muscular tonus of extremities, imitation synkinesis, and intensive tendon reflexes with widened reflexogenic zone. Special attention was focused on the development of a number of metabolic-and-trophic disturbances:

fluctuation of mass, eczema of skin surface, sometimes nonhealing bleeding sores, putrefaction of ears, shedding of hair resulted in slovenly and pitiful appearance.

In some cases during 1 month cachexy was developed among the animals with loss in weight up to 42% from the initial mass. Rarely there were observed the signs of obesity among the animals, and then sexually mature animals during a month gained weight by 35%.

According to the publications such changes in weight during these periods are possible only due intoxication of hypothalamus nuclei of any etiology [2, 3, 4].

The described symptoms of toxic encephalopathy and violent metabolic-and-trophic abnormalities were appeared after apparent clinical recovery usually in a few days or weeks after acute exposure, and clinical picture was similar to general adaptation syndrome (Selye) [5] resulted in death of considerable part of animals (Table 1).

Table 1. Remote lethal outcomes among animals after percutaneous affection by agent

Substance	Animals	Severity of an acute intoxication	Total number of animals	Among them died in					Percent of animals died in late periods
				3 days	10 days	20 days	30 days.	60 days	
Substance 1	Rabbits	slight	18	0	0	0	1	1	11
		medium	14	1	2	0	1	1	36
		grave	17	5	3	0	5	0	77
	Dogs	slight	9	0	0	0	2	0	22
		medium	8	0	2	0	1	0	37
		grave	9	1	2	1	0	0	44
Substance 2	Rabbits	slight	18	0	0	0	0	0	0
		medium	16	0	2	0	0	0	10
		grave	21	2	2	0	1	0	24
	Dogs	slight	9	0	0	0	0	0	0
		medium	8	0	0	0	0	0	0
		grave	9	0	0	0	0	0	0

Pathologic and morphologic studies and histochemical studies of animals died or slaughtered in grave condition have revealed the development of pathologic changes in pituitary-adrenal system.

The described secondary disturbances and death of animals in a long-term period of intoxication were more frequent after exposure to substance 1.

Percent of remote lethal outcomes not always depended on evidence of observed clinical picture and blood cholinesterase activity. It is related in a greater extent to the substance 1 when it caused no visual signs of intoxication and the remaining cholinesterase activity was about 60 % there were occurred single lethal outcomes. At the same time when inhibition of blood cholinesterase was more evident and clinical symptoms reflecting medium or sever intoxication, the animals exposed to substance 2 have survived. It turned out, that the cause of this phenomenon is unconformity between the accepted indexes of an acute intoxication (clinical symptomatology in combination with activity of blood cholinesterase) and action of agent on basal ganglia responsible for integration of vegetative and neuroendocrinal

functions of organism.

To confirm the above stated there were conducted special studies on estimation the effect of chemicals on the activity of cholinesterase in different brain structures.

In this case, to exclude specific anticholinesterase action of chemicals on clinical picture of intoxication in a long-term period there were studied the duration of the recovery of inhibited enzyme in different organs and tissues.

The results of biochemical studies have shown that by the anticholinesterase effect on cerebral cortex the substances discussed are very close to each other. However, the activity of cholinesterase of subcortical structures and cerebellum was inhibited after exposure to substance 1 more significantly against substance 2. It allows concluding that in contrast to substance 2 its American analogue has more evident capability to penetrate through blood-brain barrier of the brain parts studied and to render significant anticholinesterase action and possibly direct action on subcortical structures including centers of hypothalamic integration.

It may be considered ascertained that the grave consequences of intoxication were connected in lower degree with strength of enzyme-inhibition complex because the duration of the recovery of cholinesterase activity in different organs and tissues do not differ significantly and occurs earlier than delayed pathology. Therefore, the leading pathogenic mechanism of development of secondary and irreversible signs was realized as disturbances caused by exposure of brain subcortical centers. In this case, there was observed strong dependence of the severity of the long-term consequences of exposure against the inhibition degree of cholinesterase in the pointed structures of central nervous system.

It was demonstrated experimentally by an example of the dependence of long-term consequences of intoxication against enzyme inhibition in some parts of brain among dogs in a comparison with rabbits at exposure to equitoxic doses of substance 2 (Table 2).

Table 2. Death among dogs and rabbits in a long-term period after grave exposure to substance 2 depending on inhibition degree of cholinesterase activity (by acetylcholine) of some parts of brain

Brain parts	Mean value of cholinesterase in %		Remote lethality in %	
	dogs	rats	dogs	rats
Cortex of cerebral hemisphere	94.9	87.7	0	24
Medulla oblongata	52.2	68.8		
Cerebellum	46.3	76.1		

From the data presented it is evident that among rabbits there was observed, even against a background of less inhibition in cortex, more significant inhibition of enzyme in subcortical structures in a comparison with dogs that may prove difference in hemato-encephalitic barrier among these animals. Affection of subcortical area among dogs even at severe exposure did not yet achieve the level that took place at medium degree of intoxication among rabbits, and their remote lethality was 10 %.

In turn, the same percent of death among rabbits was observed at late periods when they were

exposed to slight degree of intoxication by substance 1 due to its more expressed capability to penetrate, as it was mentioned above, into medulla oblongata and the other subcortical structures. In other words, medium degree of intoxication by substance 2 and slight intoxication by substance 1 have close enzyme disturbances in subcortical of brain formations (structures).

It gives one more argument to conclude that long-term effects are in direct relation to damage of subcortical formations of CNS. Undoubtedly, there is a certain threshold level of intoxication of subcortical structures when the higher level intoxication causes more complex occurrence. Under threshold level it is necessary to conceive both intensity and duration of exposure to agent. At intravenous introduction in a comparison with prolonged percutaneous action of poison a probability of delayed neuroendocrinal toxicity was significantly reduced.

In this connection the data obtained the last time was rather interesting. It turned out, that if some days in a row a highly toxic nerve agent will be applied on coverlet of rabbits in a dose which in sum does not exceed 0.001 of the value of a single median lethal dose, among the animal there was distinctly observed during 3 months the regular changes in weight of body and formation among some of them characteristic clinical signs of delayed neuroendocrinal toxicity (DNET).

Involvement into pathologic process of medulla oblongata and other subcortical formations included centers of hypothalamic integration, as a result of anticholinesterase action (possibly direct action) of agent, may be considered as stating mechanism in development of severe consequences of none-anticholinesterase nature ended as a rule by lethal outcome. It is the main point (essence) of delayed neuroendocrinal toxicity.

Based on the stated above we could expect that curing effect of known antidotes against nerve agents at intoxication with VX would have low efficiency. Currently, only during the stage of an acute toxic exposure these preparations eliminated or rendered those effects that were stipulated by specific anticholinesterase and direct action of this agent. In a later time the development of a secondary pathology there was formed independently from antidote therapy.

How the data obtained in the experiments on animals are agreed with real consequences of intoxication with nerve agents in Gulf War, acts of chemical terrorism in Japan and occupational intoxication of people worked in former production facilities of VX.

1. Delayed neuroendocrinal toxicity occurred among each fifth from the total number of exposed to nerve agent people during Gulf War, act of chemical terrorism in Japan and on former production facilities of VX. The same ration was observed in the experiments with animals as well.
2. Clinical picture of delayd neuroendocrinal toxicity and its characteristic signs with predominance of neuroendocrinal pathology in the experiments with animals and in actual conditions among people was similar.

Therefore, both in the experiment and in real conditions there was confirmed unshakable regularity of toxicology “dose – effect”.

In this connection, a cause of development of delayed neuroendocrinal toxicity of organophosphorous compounds are doses significantly exceeding maximum allowable concentrations but not ultra low concentrations.

As a result of long-term clinical, experimental, and expert studies of characteristics of damaging action of high toxic organophosphorous compounds there was established that the phenomenon of delayed neuroendocrinal toxicity, we described for the first time, has so regular beginning, course, and outcome of organism intoxication that may be used for toxicological expertise and for medical monitoring of personnel involved into dangerous works at chemical weapons destruction.

CONCLUSION

The following regularities of etiology and pathogenesis of DNET have been revealed:

1. Course of pathologic process in two stages: neurogenic and endocrine. The first stage is characterized by the fact that the animals do not have visual clinical abnormalities, as a rule, during 6 to 60 days and from the function-topographic point of view at the same time is a specific starting mechanism (possibly of cholinergic nature) hypothalamic nuclei-level of diencephalic region of brain.

The second stage is a nonspecific one and shows in the form of various degree of evidence of vegetative, endocrinic and trophic disturbances which have irreversdable character, resists to therapy and often has lethal outcome.

2. Probability of DNET development is increased in direct proportion to the duration of the involvement of front, middle and back groups of hypothalamus nuclei, i.e. capability of agent to surmount hemato-encephalitic barrier of the pointed brain parts and exerts biodamaging action on them.

3. The duration of biodamaging action of agent on hypothalamus nuclei in a comparison with its concentration influences more significantly on formation of starting mechanisms of DNET.

It means that a probability of development of delayed pathology first depends on the way and character of agent entering into organism but not on toxic dose.

4. Degree of blood cholinesterase suppression and duration of its reparation practically does not influence on the main regularities of formation and outcome of DNET, though it correlates with severity of organism lesion at acute intoxication being reliable quantitative estimation of OPA dose.

5. In this connection, the use of anticholinergic antidotic drugs and reactivators of cholinesterase does not block the beginning, course and outcome of delayed neuroendocrinal toxicity of OPA.

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