

Chronic Intoxication by Phosphorus Compounds: A Review of the Clinical Presentation, Pathogenesis, Diagnosis, and Treatment

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Abstract: Chronic intoxication by phosphorus compounds is a polysyndrome condition characterized by a polymorphic and dynamic clinical picture; pathological changes in the body become more intense with increase in the duration of phosphorus's effect. In some cases, the condition can have a trend towards progressing after contact with phosphorus is interrupted. The main occupational pathology in those working with yellow phosphorus is the affection of the person's organs and systems, mostly the liver. The treatment of this type of pathology is an issue that has not been completely resolved yet. Most of the preparations used today act just on the disorder's symptoms. In terms of the recently established role of the prooxidant-antioxidant system in the pathogenesis of phosphorus intoxication, which causes this system's imbalance, the effect of national herbal preparations inclusive of sensitivity to xenobiotics on pathobiochemical processes has not been explored altogether. [Pernebekova R.K., Ormanov N.Zh., Ormanova L.N., Zholymbekova L., Dzhakipbekova G.S., Ormanov T. N., Shingisbaeva Zh.A. **Chronic Intoxication by Phosphorus Compounds: A Review of the Clinical Presentation, Pathogenesis, Diagnosis, and Treatment.** *Life Sci J* 2014;11(2s):170-173]. (ISSN:1097-8135). <http://www.lifesciencesite.com>. 28

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Introduction.

Modern phosphorus production is a large branch of the chemical industry. Yellow phosphorus production deals with the electrochemical processing of phosphoric ore and release of yellow phosphorus, phosphine, and phosphoric anhydride fumes into the atmosphere. Due to the way furnaces are built and the nature of the technological process, there is a possibility of a substantial increase in gas and aerosol concentrations in the workplace, which exceeds the threshold limit value (TLV) several times [1].

This review is dedicated to chronic intoxication by phosphorus compounds, its pathogenesis, clinical presentation, diagnosis, and treatment.

There are over 200 different forms of apatite-group phosphoric minerals used in the industry [2]. There are three major allotropic modifications of phosphorus - white (or yellow), red, and black phosphorus - which are capable of interconversion [1,2].

Phosphorus was discovered by Hamburg alchemist Hennig Brand in 1669. Like other alchemists of the time, Brand was searching for the elixir of life, or the "philosopher's stone", and ended up arriving at a glowing substance. Some sources say that Arab alchemists knew how to produce phosphorus as early as the 12th century. It was Lavoisier who proved that phosphorus is a simple substance.

In 1669, Hennig Brand, in heating a mixture of white sand and evaporated urine, arrived at a

substance that glows in the dark, which was initially called "cold fire". The second title, "phosphorus", derives from the Greek words "phos" ("light") and "phero" ("bear"). Yellow phosphorus is the most volatile and active form of phosphorus: it is soft and can be easily dissolved in various organic solutions. In the dark it fluoresces with a pale yellow color. Under regular temperatures, it vaporizes forming a yellow mist, which settles on the bottom, being 4.3 times heavier than air [2]. Crude white phosphorus is normally called "yellow phosphorus". It is a highly-toxic (TLV - 0.03 mg/m³), flammable crystalline substance that can be light-yellow to dark-brown. Its specific gravity is 1.83 g/cm³, melting point is +34°C, and boiling point is +280°C. It does not dissolve in water, is easily oxidized in air, and self-ignites. It burns exuding a thick white smoke – little particles of tetraphosphorus decaoxide P₄O₁₀ [1]. Phosphorus is present in living cells in the form of ortho- and pyrophosphoric acid, is part of nucleotides, nucleic acids, phosphoproteins, phospholipids, coenzymes, and enzymes. Human bones consist of hydroxylapatite 3Ca₃(PO₄)₃·CaF₂. Tooth enamel contains fluorapatite. The liver plays the major role in transformations of phosphorus compounds in the body of humans and animals. The exchange of phosphorus compounds is regulated by hormones and vitamin D. Humans need 1-2 grams of phosphorus every 24 hours. A shortage of phosphorus can cause various bone disorders.

The minimum lethal dose of yellow phosphorus for humans is 1 mg/kg; the minimum dose causing poisoning is 0.3 mg/kg.

Based on the findings of a number of authors, just a 50 mg dose of phosphorus can lead to lethal results. When administered orally, the lethal dose for rabbits is 0.21 g (in oil), cats - 0.0-0.03 g, and dogs - 0.05-0.1 g. After having inhaled 0.15-0.16 mg/l of yellow phosphorus fumes, 50% of the animals (mice, rats, rabbits) died. According to experimental data, yellow phosphorus is a highly-toxic cumulative poison, which is capable of causing general toxic, gonadotoxic, mutagenic, and embryogenic effects.

Yellow phosphorus in its elementary state has a marked general toxic effect; its one-time lethal dose for humans, on average, is 0.08 g when administered internally [3].

Phosphorus is one of the general protoplasmatic poisons, which affects the heart, liver, and kidneys [4].

Some patients have demonstrated acute liver failure, coagulopathy, and a drop in liver function [5]. And some patients have had acute tubular necrosis with acute renal failure. There have been changes on the part of the central nervous system, such as clouding of consciousness, psychosis, hallucinations, and coma. On the part of heart activity, there have been hypotension, tachycardia, and cardiogenic shock [6].

There have been recorded the potential symptoms of chronic poisoning with yellow phosphorus after inhaling or swallowing it, such as cachexia, anemia, bronchitis, general weakness, and jaw necrosis [7]. The most important manifestation of chronic poisoning with phosphorus is osteomyelitis of the jaw bones, more frequently of the bones of the lower jaw and less frequently those of the upper jaw, which normally begins as dental disturbances [8].

In the process of phosphorus production, elementary phosphorus most often gets in the body through inhalation and less frequently orally, but can enter through the skin and mucous membranes [3].

Experimental studies by leading specialists have proved that the prevalent processes in the pathoanatomical picture of acute, subacute, and chronic poisoning with phosphorus in rats and rabbits is fatty degeneration of internal organs, toxic hepatitis, toxic gastritis, and focal necronephrosis [3].

At present, cases of acute poisoning with yellow phosphorus and its compounds are rare – it mostly happens during accidents at the plant [1].

The main occupational pathology in those engaged in yellow phosphorus production is chronic intoxication by phosphorus and its inorganic compounds [2].

The pathogenesis of chronic intoxication by

phosphorus compounds (CIPC) have not been investigated all the way yet. According to V.A. Kozlovsky, [1], phosphorus and its compounds turn in the body into metabolites, which are similar to organic ortho-phosphates. Note that there takes place competitive substitution of phosphates in their reactions, which leads to pathological changes in metabolism. Enzymes interact with metabolites instead of phosphates to facilitate the accumulation of citrate and pyruvate, under-oxidated tricarbon acids and fat in the body, which leads to the development of hypoxia and dystrophic changes in the organs, neuroendocrine disorders, impairment of all types of exchange, and suppression of the synthesis of compounds crucial to the body.

According to N.A. Strelyukhina [3], pathomorphological changes in organs (through the example of the liver as a target organ) in phosphorus intoxication can be caused, above all, by damaged mitochondria, which leads to disturbances in processes of oxidative phosphorylation, cellular respiration, and fatty acid oxidation. Damage to the membranes of the endoplasmic network of hepatocytes also leads to the impairment of the synthetic function of this compartment and facilitates the impairment of nuclear-cytoplasmic interrelations, entry of metabolites into the cell, and drawing out of catabolic products, as a result whereof the liver's antitoxic and glycogen-forming functions get affected. All this, in the author's view, leads to fatty degeneration of the liver.

Furthermore, as early as 1969 A.K. Ghoshal et al. [9] and later M.U. Dianzani [10,11] discovered that the fatty infiltration of the liver is associated in phosphorus intoxication with the peroxidation of the lipids of the biological membranes of hepatocytes.

N.Z. Ormanov [12] and D.A. Adilbekova [13], having explored the initial, intermediate, and end products of lipid peroxidation, established a boost in lipid peroxidation processes in workers who had worked in furnace areas for a long time and in patients with CIPC. Thus, in substantiation of the findings of experimental studies, facts on the important role of lipid peroxidation were obtained.

CIPC develops in as many as 3-5 years under high concentrations of phosphorus, which exceed the TLV several times. Under a relatively low atmospheric gas pollution with phosphorus compounds, the first symptoms can appear in 8-12 years [14]. The pathological process involves almost all of the systems and organs [3].

The diagnosis of chronic intoxication by phosphorus compounds, especially in the early stages of the disorder, has been a hard task to tackle.

In 1991, M.I. Dauletbakova, N.Z. Ormanov, and M.I. Berdykhodzhin [14] proposed new clinical-

diagnostic indicators for chronic intoxication by phosphorus compounds for the early diagnosis of CIPC. The authors suggest determining disturbances in a number of specific laboratory indicators, such as the serum toxicity index, lipid peroxidation, the chemiluminescence coefficient, sensitivity to yellow phosphorus, and sulfhydryl group determination.

N.Z. Ormanov [15] proposes studying indicators for the body's non-specific resistance for assessing the severity of intoxication.

Thus, CIPC is a polysyndrome disorder of the body, which is characterized by a polymorphic and dynamic picture; pathological changes in the body become more intense with increases in the duration of phosphorus's effect. In some cases, the condition can have a trend towards progressing after contact with phosphorus is interrupted.

In treating patients with CIPC, one should keep in mind that the primary nature of means and treatment methods employed in the process should be defined by the dominating symptom-complex associated with the affection of a particular system in the body. The prevalence of toxic hepatitis in the treatment of chronic phosphorus intoxication necessitates that in treating patients with CIPC one primarily focus on the therapy of the affected liver.

The free-radical concept of liver affections has opened up new opportunities for applying medicinal preparations with antioxidant action (tocopherols, ascorbic acid, polyphenols, β -carotene), which are part of the body's antioxidant system, and indirect action antioxidants, which boost the tissues' antioxidant potential (essential phospholipid preparations, zixorin, seleno-organic compounds, preparations that induce the cells' enzymatic antioxidant components, etc.) [16].

Thus, ascorbic acid takes part in oxidation-reduction processes and metabolism, regulates cholesterol levels in blood, takes part in the formation of steroid hormones, influences immunobiological reactions, normalizes capillary permeability, facilitates the accumulation of glycogen in liver cells, boosts detoxication, and improves the liver's protein-building function, having a beneficial effect in terms of the regeneration of liver tissue. In addition, when the liver is affected, ascorbic acid helps maintain the normal levels of serum ceruloplasmin, facilitates the cytochrome-oxidase activity of the liver's mitochondria, boosts the activity of succinate dehydrogenase and cytochrome oxidase, restoring the processes of cellular respiration. This vitamin's antioxidant action is associated, above all, with antiradical activity and the ability to restore the reserves of glutathione, tocopherols, and SH-containing proteins, which are oxidized in the lipid peroxidation process. As an auxiliary, vitamin C is

used in the integrated treatment of liver affections using various hepatotoxic agents in acute and chronic hepatitis, liver cirrhosis, concomitant disorders of the bile ducts. Therefore, the application of ascorbic acid in the early stages of chronic acting with phosphorus forestalls the development of pathological changes in the body and boosts their defensive properties [16].

For the drug therapy of toxic hepatitis in phosphorus production workers, G.A. Kulkybayev [16] offers integrated treatment that mainly includes such membrane-stimulating and antioxidant preparations as tocopherol acetate, legalon, and ascorbic acid.

Based on glycyrrhizic acid, the preparation Ruvimin has been developed and adopted for clinical use [17]. According to preliminary reports, this preparation has a positive effect on the course of phosphorus intoxication [18].

Several studies have addressed the therapy of heart intoxication by phosphorus compounds and isadrine.

According to R.K. Pernebekova [20], *Rhodiola rosea* extract has a cardio-protective effect on the functions of the heart in phosphorus intoxication.

Inferences.

Thus, the primary occupational pathology in yellow phosphorus production is the affection of the above organs and systems, predominantly the liver. The treatment of this pathology is an issue that has not been resolved completely yet. Most preparations employed today act just on the disorder's symptoms. In terms of the recently established leading role of disorders of the prooxidant-antioxidant system in the pathogenesis of phosphorus intoxication, which causes this system's imbalance, the effect of national herbal preparations inclusive of sensitivity to xenobiotics on pathobiochemical processes has not been explored altogether.

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