AMINOPHOSPHONE—A NEW PREPARATION
FOR THE TREATMENT OF DERMATOMYCOSES


The All-Union Scientific Research Institute of Chemical Means of Plant Protection, jointly with S. Ordzhonikidze All-Union Chemicopharmaceutical Scientific Research Institute, has been conducting work for a number of years on the search for and investigation of new and effective fungicidal and bactericidal preparations [1-3].

One of the trends in the synthesis of such substances is the reaction of alkylation of nitrogen containing organic bases by esters of phosphoric acids. The organophosphorus anion increases the solubility of the compounds in lipids, increases the rate of their penetration into living cells, and also promotes an increase in the bactericidal and fungicidal activity of the preparations [1-3].

Of the large group of compounds investigated, an original antifungal preparation—aminophosphone—bis-(N-ethyl-N-octadecylammonium) bis-(ethoxy-thiophosphine)disulfide [4, 5]—has been selected for a detailed clinical study.

Its synthesis consists of the following steps.

Production of O,O-diethyldithiophosphoric acid from P₂S₅ and ethanol:

\[ P₂S₅ + 4C₂H₅OH \rightarrow 2(C₂H₅O)₂P(S)SH + H₂S. \]

Production of the sodium salt of O,O-diethyldithiophosphoric acid:

\[ (C₂H₅O)₂P(S)SH + NaOH \rightarrow (C₂H₅O)₂P(S)SNa + H₂O. \]

Oxidation of the sodium salt of 0,0-diethyldithiophosphoric acid to bis-(diethoxythiophosphine)disulfide:

\[ 2(C₂H₅O)₂P(S)SNa + 2NaNO₂ + 2H₂SO₄ \rightarrow (C₂H₅O)₂P(S)SS(S)P(OC₂H₅)₂ + Na₂SO₄ + 2NO + 2H₂O. \]

Production of aminophosphone:

\[ \text{The preparation is recrystallized from petroleum ether. The aminophosphone obtained is a white crystalline powder, soluble in hot water, alcohol, acetone, and most organic solvents.} \]

In the Laboratory of Chemotherapy of Infectious Diseases at the S. Ordzhonikidze All-Union Chemicopharmaceutical Scientific Research Institute, it has been studied experimentally in vitro for fungistatic and fungicidal activity with respect to pathogenic fungi, expressed in concentrations from 1:4000 to 1:8000.

The preparation retards the growth of the yeast-like fungus *Candida albicans* in a concentration of 1:2000 and is fungicidal for this fungus in the same concentration.

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### TABLE 1. Chemotherapeutic Action of Aminophosphone in Experimental Microsporia of Guinea Pigs

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<tr>
<th>Concentration of preparation (in %)</th>
<th>No. of animals</th>
<th>Intensity of injury at various periods of investigations (according to weeks)</th>
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Notations: ++++, ++, + degrees of intensity of injury; - absence of injury.

Aminophosphone exerts an antibacterial action with respect to a broad spectrum of microorganisms. The preparation is ineffective on Bacillus pyocyaneous and Proteus vulgaris. The bactericidal action with respect to cocci and spore-bearing bacteria is expressed in concentrations from 1:400 to 1:800.

The therapeutic action of aminophosphone has been tested in experiments on guinea pigs infected with the pathogenic fungus Microsporon lanosum.

Aminophosphone was used in the form of a salve according to the following prescription: aminophosphone 3%, emulsifier T-2 18%, glycerin 6%, anhydrous lanolin 4%, nipagin (methyl ester of para-hydroxybenzoic acid) 0.15%, nipazol (propyl ester of para-hydroxybenzoic acid) 0.05%, distilled water 68.8%.

The aminophosphone salve is prepared by the following method. Emulsifier T-2 and anhydrous lanolin are melted at 65-70°. Distilled water containing dissolved nipagin and nipazol, preliminarily heated to 70°, is added in small portions to the melted mass with mixing. The aminophosphone is thoroughly triturated with glycerin until lumps of the preparation disappear. The triturated aminophosphone is gradually added to the cooled emulsion base, and the mass is mixed thoroughly until the formation of a homogeneous consistency. The finished salve is light cream-colored, odorless, pH 4.5. It is packaged in aluminum tubes, coated with BF-2 lacquer, with a capacity of 50-60 g.

In a study of the therapeutic and irritating effects, aminophosphone was used in concentrations of 0.5 and 1% in the salve base indicated above.

Guinea pigs weighing 250 g were infected with the fungus Microsporon lanosum. For this purpose, the fur was shaved from the side surfaces of the body or back on portions of about 5 x 7 cm, the surface of the skin wiped with alcohol, the skin cautiously scarified until the appearance of drops of serous fluid (bleeding should be avoided). The inoculum was rubbed into the portion of skin thus prepared for 1-2 min.

The first signs of disease appeared on the fifth to seventh day after infection; on the eighth to tenth day all the guinea pigs were examined with a fluorescent lamp; the degree of infection of the animals was determined according to the characteristic green luminescence of the hair. Treatment with aminophosphone salve was begun after the appearance of distinct clinical signs of disease (approximately on the ninth or tenth day after infection). The salve was rubbed into the foci of infection once daily for three weeks.

After four weeks of treatment, the guinea pigs were kept under observation for another two weeks, during which the control animals still showed foci of fungus infection.

On the basis of the positive experimental data, aminophosphone was studied in the Biological Control Laboratory (Head Yu. I. Syrneva) for toxicity and local irritating action, and its influence upon the morphological picture of the blood was also determined.

Aminophosphone possesses low toxicity. In the case of repeated applications of 0.5, 1, and 2% aminophosphone salve on the skin of rabbits, the salve produced no local skin reaction, and also did not influence the morphological composition of the rabbit blood. In a histological investigation of the blood and internal organs of the animals, no local or general pathological changes were detected.

Aminophosphone has been studied in skin clinics as an external antifungal remedy in the treatment of fungus diseases of the skin (epidermophytia, rubrophytia, and blastomycosis).