NEW DRUGS

PRODUCTION AND CLINICAL USE OF OLEMORPHOCYCLINE

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Olemorphocycline is a complex antibiotic preparation containing oleandomycin and morphocycline (N-morpholinomethyltetracycline).

The combined use of antibiotics of the macrolide and tetracycline groups has been mentioned by a number of workers. The desirability of such use is explained by the possibility of a synergistic action on some microorganisms, mainly staphylococci, a simultaneous action on microbial associations with bacteria having different sensitivities to antibiotics, and also the possibility of preventing the development of strains resistant to oleandomycin and tetracycline.

At the present time there are several complex antibiotic preparations containing oleandomycin and tetracycline, namely sigmamycin (USA), tetraolean (Bulgaria), and oletetrin (USSR). Oleandomycin phosphate and tetracycline hydrochloride are used for their injection forms. These preparations have acquired wide use and as a whole deserve the favorable opinion of clinicians.

Morphocycline, a preparation of the tetracycline group (N-morpholinomethyltetracycline) that has been introduced into the Soviet Union, possesses a number of fundamental advantages as compared with tetracycline. The neutral pH of its solutions permits morphocycline to be injected instantaneously, while tetracycline hydrochloride and its medicinal forms in combination with oleandomycin are administered only dropwise. It has been shown that morphocycline possesses a higher capacity for penetrating into cells and accumulating in them than tetracycline [1, 2]. Morphocycline injected intravenously is excreted from the organisms comparatively slowly and when administered in a dose of 150 mg twice a day it ensures a medicinal concentration in the blood and tissues of the organism [3, 4]. On the basis of these properties of morpholinomethyltetracycline, the preparation olemorphocycline has been created in our institute by combining morphocycline and oleandomycin phosphate in a ratio of the first to the second with respect to activities of 1.5:1.

Olemorphocycline is a neutral phosphate consisting of two equivalents of N-morpholinomethyltetracycline and one equivalent of oleandomycin.

The preparation consists of a porous mass or an amorphous dark yellow powder bitter to the taste with a faint characteristic odor. It is very soluble in water, in 5% and 40% glucose solutions, in isotonic (0.9%) sodium chloride solution, and in methanol and is sparingly soluble in acetone and almost insoluble in diethyl ether.

The UV spectrum of olemorphocycline repeats the absorption spectrum of N-morpholinomethyltetracycline with absorption maxima at 276 ± 2 and 360 ± 2 nm, $R^\text{1%}_{\text{fcm}} = 170$. A 2% aqueous solution has pH 6.8-7.5.

The method of preparing the medicinal form of olemorphocycline [5, 6] is as follows: N-morpholinomethyltetracycline is dissolved in phosphate buffer with pH 8.0 and is kept at a temperature of −40 to −60°C. After thawing out and the separation by filtration of insoluble impurities of low activity formed as by products in the synthesis of N-morpholinomethyltetracycline in an alcoholic medium, the calculated amount of oleandomycin phosphate is added and the clear solution formed of N-morpholinomethyltetracycline phos-
Phosphate and oleandomycin is subjected to sterile drying by sublimation. This gives a polyantibiotic with a yield of 92% of that theoretically possible and an activity of not less than 430 units/mg of N-morpholino- methyltetracycline and 290 units/mg of oleandomycin.

A study of the pharmacological properties of oleandomycin in acute and chronic experiments has shown its comparatively low toxicity [7, 8]. The LD₅₀ for white mice on intravenous administration is 160-230 mg/kg. On subcutaneous and intraperitoneal administrations, the toxicity of oleandomycin falls by a factor of 2.5-3. The preparation has no appreciable influence on the arterial pressure and respiration and causes no pyrogenic reaction. The repeated prolonged administration of oleandomycin to various species of laboratory animals did not affect the blood and urine indices, the antitoxic function of the liver, or the weight of the animals.

It has been found experimentally that on intravenous injection the highest concentrations of the antibiotic appear in the bile, urine, and the tissues of the liver and kidneys. A comparative study of oleandomycin and oleandomycin in a number of experimental infections, including those caused by Bacillus coli and various species of pathogenic clostridia and staphylococci. In staphylococcal sepsis, the combined use of oleandomycin and morphocycline gives an additive effect [11].

The chemotherapeutic activity of oleandomycin has proved to be greater than that of morphocycline and oleandomycin in a number of experimental infections, including those caused by Bacillus coli and various species of pathogenic clostridia and staphylococci. In staphylococcal sepsis, the combined use of oleandomycin and morphocycline gives an additive effect [11].

An experimental study of an aerosol of oleandomycin has shown that on inhalation high concentrations of the antibiotic are created in the lungs. The preparation penetrates from the lungs into the blood and is found in the tissue of the liver and kidneys and in high concentrations in the urine. Oleandomycin administered in the form of an aerosol is effective in experimental pneumonia caused by Gram-negative and Gram-positive microorganisms [12].

Oleandomycin was approved for clinical use in 1968. The facts that have been accumulated at the present time show the high medicinal efficacy of oleandomycin in severe bacterial infections, groups and focal pneumonias, aggravations of chronic pneumonia, abscessing pneumonia, abscess of a lung, and other diseases of the respiratory organs [13-16], caused by staphylococci, klebsiellas, escherichias, streptococci, and other microorganisms. The preparation was given intravenously at the rate of 250 mg twice a day for 7-10 days. Where necessary, the treatment was repeated with the same daily dose for 5-7 days. During the treatment, therapeutic concentrations of the preparation were found in the blood, sputum, and urine, and also in the lung tissue.

Oleandomycin has been used successfully for the preparation of patients for operations on the respiratory organs and for preventing complications after operations on the lungs. For residual phenomena after pneumonia, acute attacks during chronic pneumonia, bronchitides, and catarrhs of the upper respiratory tract, oleandomycin has been applied by inhalation in a dose of 250 mg one to three times per day. The transmissibility of the inhalations was good. Information exists on the effectiveness of inhalation of oleandomycin in diseases of the upper respiratory tract in children [17].

Oleandomycin has also been used in inflammatory diseases of the bile ducts [18, 19]. The concentration of the preparation in the bladder bile taken during the operation varied between 3 and 7 μg/ml. A good result was obtained in the majority of patients with acute cholecystitis.

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