EXPERIENCE WITH KANAMYCIN ELECTRO-AEROSOLS IN PEDIATRIC PRACTICE

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I. I. Prokhorova, V. S. Lutsik, A. I. Khoperia, G. P. Marisenko, S. I. Eidelshtein

The data presented are indicative of satisfactory tolerance by children of kanamycin electroaerosol inhalation, it is shown that an inhalation absorption of the antibiotic was poor, while the levels in the respiration organs were high. Inhalations of kanamycin electroaerosols was effective in the treatment of evacuated chronic pneumonia and asthma of children. Besides favourable clinical changes, it was confirmed by the results of analysis of the blood gas and certain indices of acid-alkali equilibrium.

EXPERIENCE IN THE PEDIATRIC USE OF KANAMYCIN ELECTROAEROSOL

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[Paper by I. I. Prokhorova, V. S. Lutsik, A. I. Khoperiya, G. P. Marisenko and S. I. Eydel'shteyn; All-Union Scientific-Research Institute of Antibiotics, and the Clinic of Children's Diseases, First Moscow Medical Institute]

Aerosols in pediatric practice have proved themselves to be merciful, highly effective remedies in the treatment of respiratory diseases [1-6]. However, the resistance which microorganisms build up to many preparations now in use [7, 8] necessitates the introduction of new antibiotics into medical practice, particularly in the area of aerosol therapy. One such antibiotic, among those effective against staphylococci and other microbes resistant to penicillin, streptomycin, tetracyclin and other drugs, is kanamycin sulfate [9, 10].

The high solubility of this drug and its stability in solutions of various pH values, make possible its use in combination with a great number of other medications. Experimental studies reveal a high degree of tolerance of kanamycin aerosol by the body [12, 13]. The aerosol of kanamycin is more effective than the equivalent of the drug administered subcutaneously, as far as treatment and prophylaxis of induced pneumonia are concerned [14]. Studies of absorption of kanamycin by animal tissues show that upon inhalation it is absorbed by the blood only in small quantities, but remains in the lungs for extended periods, and in high concentration. This makes possible a high concentration of the antibiotic at the focus of infection while at the same time avoiding the full power of its toxicity [15]. According to published data [12, 16-20], kanamycin in the treatment of respiratory diseases (staphylococcic pneumonia, chronic bronchitis, bronchiectasis, pulmonary abcesses, tuberculosis, and so on) has proved itself to be both relatively harmless and highly effective.

On the basis of experimental work done on this aerosol by the All-Union Scientific-Research Institute of Antibiotics, and also foreign studies made of the use of kanamycin with the inhalation method, the Pharmacological Committee, Ministry of Health USSR, undertook tests of the inhalation administration of kanamycin.

The Children's Clinic of the First Moscow Medical Institute imeni I. M. Sechenov (chair of children's diseases held by Academician Prof. Yu. F. Dombrovskaya) has studied a number of questions connected with the use of this

aerosol in pediatrics.

Material and Methods

Kanamycin electroaerosol was used to treat cases of chronic pneumonia and diseases of the otorhinolaryngological organs. Daily doses of the aerosol (250-600 mg, depending on age) were administered, dissolved in 5-7 ml of a mixture of medicinal substances (ephedrine, 0.2, euphyllin, 0.3, novocaine, 0.25, distilled water, 50.0). Children took one inhalation a day, with use of the E-62 apparatus or the "Elektrozol'-1" manual appliance.

Kanamycin concentration in blood, urine, sputum and so forth, was determined with the agar diffusion method, at pH 7.8-8.0, using Bax. subtilis 6633 (S-shaped spores) as the test microbe.

The effect of kanamycin electroaerosol treatment was studied in chronic pneumonia cases among children; changes in indices of the acid-base balance and gas exchange [21] were studied. Determined were the hydrogen ion concentration (pH), partial carbon dioxide pressure (pCO_2 in mm Hg, with use of the "Mikro-Astrup apparatus), degree of oxygen saturation of hemoglobin (HbO_2 in percents, with use of the 0-30 oxyhemometer). These indices were measured before and after inhalation, and throughout the course of the therapy.

In the laryngoscopic and bronchoscopic studies, the condition of the mucous membranes was scrutinized in order to determine what irritating effect the kanamycin might have on them. All of the children, in addition, were studied clinically.

Results and Discussion

Mucus and saliva from throat and mouth taken during bronchoscopy were used to prepare cultures, in which the microflora and the sensitivity of the latter to antibiotics could be determined; this was done for all the children. Staphylo-, strepto- and pneumococci cultures (less often, rod flora was used). As a rule, the staphylococci were sensitive to kanamycin, and the pneumo- and streptococci were resistant to it.

Particular attention was paid to the children's tolerance to inhaled kanamycin aerosol. In no single case was there a complaint of unpleasant taste or odor, nor was there any irritation of the respiratory tract, sign of stimulation of the mucous membrane of trachea and bronchi, or hypersecretion of the tear ducts. Further, there was absolutely no evidence of temporary impairment of hearing or disturbance of kidney function.

We studied the absorption of kanamycin by the blood during the administration of the drug by inhalalation. The results are shown in Table 1 below, for single and multiple inhalations, in terms of $\mu g/ml$ of kanamycin. As is evident from the table, a single inhalation produces only low blood concentrations of kanamycin. Repeated inhalation produces a certain increase in con-

centration, which, however, is only a small fraction of its magnitude in the case of subcutaneous administration of kanamycin in the same dosage [22, 23]. A kanamycin blood concentration of around 40 units/ml is potentially dangerous to the sense of hearing [24]; but this level is 10 times higher than that measured in our tests (mean concentration of kanamycin 1 hr. following inhalation by patients already treated with the inhaled drug over an extended period).

TABLE 1

Dynamics of Kanamycin Blood Concentration in Children following a Single and following 10 Inhalations of the Electroaerosol

No. of inhalations	Hours blood sample taken following inhalation				
	1	3	6	24	48
	kanamycin concentration (in μg/ml)				
1	2.17±0.28 (1.60-2.74)	1.4±0.46 (0.41-2.39)	0.91±0.07 (0.64-1.08)	0.41±0.12 (0.44-0.68)	— —
10	4.12±0.8) (2.43-5.81)	1.73±0.28 (0.96-2.01)	— —	0.86±0.31 (0.96-1.66)	0.22±0.04 (0.12-0.32)

NOTE: Numbers in parentheses represent confidence intervals with P = 0.05, obtained on the basis of study of more than 100 blood samples.

Study of samples taken showed that the amount of the antibiotic excreted in the urine in 24 hours did not exceed 3% of the administered dose. This also supports the thesis of the low degree of absorption of the drug during inhalation of the aerosol, since, as is well known [25, 26], intramuscular administration is followed by a 40-80% excretion in the urine.

The pattern followed by the urinary excretion of kanamycin is of interest. The greater part of the drug (about 70%) was excreted during the first 6-9 hours. Toward the end of the 24-hour period, the kanamycin concentration in the urine was insignificant. It can be considered that practically all of an inhaled dose of kanamycin is dissipated in the course of 24 hours.

The low absorbability of kanamycin aerosol does not allow the rise of conditions favoring toxic action. In addition, during treatment of respiratory conditions, it is important to achieve high concentrations of the antibiotic within the affected organ. As is well known, with intramuscular administration of kanamycin, the substance is either notfound in the sputum at all, or is present only in small quantities [18].

Our study of kanamycin concentration in the sputum showed that even

24 hours following a single inhalation, as much as 2.35 units/ml of kanamycin could be found in the sputum, and, at the end of the course of treatment as much as 33.2 units/ml. There is a definite accumulation of this antibiotic during treatment.

Kanamycin was observed sporadically in the lavage fluid used during punctures of the maxillary sinuses. Probably, this irregular appearance of the antibiotic is associated with the condition of the nasal passages or with passability of the semilunar canal. In any case, increase in the concentration in the sinuses followed loading the nasal cavity, and also the addition of vasoconstrictors (ephedrine solution, euphyllin and the like) to the aerosol. Whenever kanamycin appeared at all in the lavage fluid, in our tests, its concentration was quite high (Table 2).

TABLE 2

Content of Kanamycin in Maxillary Sinus Lavage Fluid following Sinus Puncture

Kanamycin content (mg)	Trace	0.03	0.1-0.5	1.5-7.5	Total
Number of tests in which the given amount of kanamycin was observed.	3	1	4	4	12

In our studies, 22 children suffering from first-, second- and third-degree chronic pneumonia were treated with kanamycin electroaerosol for a period of 15-20 days. In addition to this, the patients received all-round therapy. Twenty of the patients showed either improvement or cure (disappearance of pulmonary catarrh and endobronchitis, reduction or elimination of cough, improvement of peripheral circulation, and reduction of the erythrocyte sedimentation reaction). In two cases, the patient's condition improved only after prolonged massive therapy. Both of these patients had untertaken therapy after the appearance of extensive lung damage.

In 10 cases the kanamycin electroaerosol therapy was aimed at suppurative and catarrhal highmoritis which had been demonstrated clinically and by X-ray examination; these patients took 5-16 inhalations. All 22 patients experienced cure of nasal secretion and restoration of clear breathing. Control punctures revealed no pathological content in the sinuses, and the latter were not obstructed, as shown by X-ray examination.

The treatment was successful, both for resistant and for nonresistant microflora; and this is explainable, obviously, as due to the creation of an

directly on the gravity of the illness: in the initial forms, blood pH was 7.35 on the average; in the case of the second and third degrees, 7.32 and 7.27. Following the course of treatment, pH had risen perceptibly—to 7.32 in the third-degree pneumonia patients who also had bronchiectasis. Patients with first- and second-degree pneumonia, in whom the pH was already high, showed no change in this respect as a result of treatment.

Comparison of the HbO_2, pCO_2 and pH figures obtained before and immediately following inhalation (Figure 3, above) shows that improvement in these indices was due not only to the prolonged course of treatment and to reduction of inflammatory processes in the respiratory organs, but also to the procedure of inhalation itself. The favorable effect of a single inhalation on blood gases and the acid-base balance was evidently due to reflex deepening of breathing and increase in the per-minute volume; also to the action of negative electrization.

Conclusions

1. The children treated in our tests tolerated the inhalation of kanamycin electroaerosol quite well; in no case was any irritation of the mucous membranes of the respiratory tract, or impairment of hearing or of kidney function, observed.

2. Absorption of kanamycin during inhalation of the electroaerosol was insignificant, and did not give rise to any threat of general toxic action. Not more than 3% of the inhaled dose was excreted in the urine.

3. High concentrations of kanamycin were observed in the sputum after 24 hours of treatment. A significant quantity of the antibiotic was also found in the lavage fluid following puncture of the maxillary sinuses.

4. Inhalation of kanamycin electroaerosol is an effective method of treating flare-ups of chronic pneumonia and highmoritis in children. Apart from favorable clinical signs, this is confirmed also by studies of blood gases and certain indices of the acid-base balance.

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