Isopathic therapy for aminoglycoside sensorineural hearing loss and deafness (preliminary results)

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Summary

The aim of this controlled clinical trial is to evaluatethe effectiveness of isopathic therapy for ototoxic sensorineural hearing loss with potentiated aminoglycosides.

Control baseline before starting isopathic therapy.

A number of criteria have been selected to assess the effectiveness: criterion A - the disappearance of subjective ear noise; Criterion B - expanding the range of perceived frequencies (according to tone threshold audiometry (TPA) data by at least 1 range for bone conduction and criterion C - reducing the perception thresholds at a frequency of 1 kHz or 2 kHz by at least 20 dB.

The treatment was carried out at 16 people with chronic ototoxic sensorineural hearing loss of severe degree (grade 4) and deafness. Age - from 19 to 58 years, duration of the disease - from 18 to 40 years. Potentiated aminoglycosides were used in potencies C3, C6, C12, C30 and C50. The drugs, potencies and the regimen of administration were selected individually in accordance with the history and the results of the electropuncture vegetative resonance test.

In accordance with criterion A, a positive effect was achieved in 15 patients, with criterion B - in 13, and the effect according to criterion C was only in 3 patients, which the authors associate with a short duration of treatment. In one case with observation for more than 12 months, there was a complete restoration of auditory function, confirmed by the dynamics of HAT indicators. The treatment was well tolerated.

Conclusions. The results of isopathic therapy in patients with severe chronic aminoglycoside sensorineural hearing loss indicates a positive effect of potentiated aminoglycosides on the function of the auditory analyzer.

Key words: isopathic therapy, sensorineural hearing loss, ototoxicity,potentiated aminoglycoside antibiotics.

Introduction

Currently, there are no effective medical and physiotherapeutic methods for treating hearing disorders caused by the use of aminoglycoside antibiotics. This is especially true in cases when there is sensorineural hearing loss with stabilization of hearing thresholds and the completion of the process of degeneration of cochlear receptors and neurons of a specific auditory pathway. In such cases, according to the generally accepted opinion of Soldatov I.B. et al. [5], expressed almost 30 years ago, the leading methods are reeduction, and drug therapy should be carried out mainly with the aim of stabilizing the process of degeneration of cochlear receptors and reducing tinnitus.

Earlier, we expressed and substantiated the idea of the possibility of treating chronic ototoxic effects of aminoglycoside antibiotics with small doses of the same aminoglycoside antibiotics used in a potentiated (and dynamized, as is customary in homeopathy) form [2]. The aim of this controlled clinical trial is to evaluate the effectiveness of isopathic therapy for ototoxic sensorineural hearing loss with potentiated aminoglycosides.

Materials and methods

The study was carried out in 16 patients with chronic sensorineural hearing loss of aminoglycoside etiology of varying severity and age of development (Table 1). All patients underwent clinical examination and examination of the ENT organs. Audiological examination (tone threshold audiometry) (audiometer GSI-61, Germany) was performed before and during treatment every 3 months. All patients underwent (laboratory of molecular genetics, Research Institute of Physical and Chemical Medicine) molecular genetic analysis for mutations in the gene of the protein connexin 26 GJB2 (30-36 del G), associated with 50% of all cases of prelingual congenital deafness [13], and in mitochondrial gene 12sRNA (A1555G) [8], coupled with high sensitivity to aminoglycosides.

Study design: study in one group, control with a baseline of up totreatment with potentiated aminoglycosides.

Criteria for the inclusion of patients in the study group:

- informed consent of the patient for examination and treatment;
- chronic unilateral or bilateral sensorineural hearing loss, etiologically associated with the pharmacotherapeutic use of aminoglycoside antibiotics. The presence of audiological signs of mixed hearing loss was not an obstacle to the patient's inclusion in the group in the absence of clinical signs of acute or exacerbation of chronic otitis media;
- the absence of chronic neurological pathology of the central or peripheral nervous system;
- absence of chronic kidney disease (glomerulonephritis, interstitial nephritis or chronic renal failure);
- no history of indication of allergic intolerance to aminoglycosides.Exclusion criterion from the group:
- high sensitivity (idiosyncrasy) to aminoglycosides with intolerance potentiated dosage forms detected by a subjective drug test [1] or after taking a trial dose at the beginning of treatment;
- the patient's desire to stop treatment.Performance criteria:

Criterion A. The disappearance of subjective ear noise.

Criterion B. Expansion of the range of perceived frequencies (according to tonal threshold audiometry) by at least 1 range in bone conduction. This indicator reflects the earliest reaction of the wax epithelium to the therapy.

Criterion C. Reduction of perception thresholds at a frequency of 1 kHz or 2 kHz by at least 20 dB after 3 months. from the start of treatment.

The indicators of the ear with the worst indicators were used for the analysis.

Table 1

Characteristics of patients with chronic sensorineural hearing loss who therapy with potentiated aminoglycosides was performed

№	Пациент, Возраст, лет	Пол	Степень тугоухости	Субъективный ушной шум	Тип тугоухости		Давность заболевания, лет	Анамнез, антибиотик	Результат ВРТ, антибиотик	Генотип 12sRNA (A1555G)	Генотип GJB2 (30-36 del G)
					Правое ухо	Левое ухо					
1	А.,9	М	5	-	НТ	НТ	8	?	NEO	-	-
2	Б.,19	М	4	+	НТ	НТ	18	?	AMI	AA	6G/6G
3	В.,20	М	5	+	См	См	19	STR	STR	AA	6G/6G
4	Г.,20	М	5	+	НТ	НТ	19	GEN	GEN	AA	6G/6G
5	Д.,20	Ж	4	+	См	См	19	?	SISO	AA	6G/6G
6	Е.,20	Ж	5	+	НТ	НТ	19	KAN	KAN	AA	5G/5G
7	Ж.,22	М	5	+	НТ	НТ	19	GEN	GEN	AA	6G/6G
8	З.,23	Ж	3	+	НТ	НТ	20	?	STR	AA	6G/6G
9	К.,46	Ж	5	+	НТ	НТ	41	STR	STR	AA	6G/6G
10	Л.,49	М	5	+	См	См	19	GEN	GEN	AA	6G/6G
11	М.,50	М	5	+	НТ	НТ	20	SISO	SISO	AA	5G/6G
12	Н.,54	Ж	5	+	См	НТ	15	KAN	KAN	AA	6G/6G
13	О.,56	Ж	5	+	НТ	См	15	KAN	KAN	AA	5G/6G
14	П.,56	М	5	+	НТ	НТ	36	STR	STR	AA	6G/6G
15	Р.,58	М	5	+	НТ	НТ	18	?	GEN	AA	6G/6G
16	С.,64	М	5	+	НТ	НТ	16	?	AMI	AA	6G/6G

Abbreviations:

NT - sensorineural hearing loss, Cm - mixed hearing loss.

STR - streptomycin, GEN - gentamycin, KAN - kanamycin, AMI - amikacin, SISO - sisomycin, NEO - neomycin.

? - the disease is associated with the use of an aminoglycoside antibiotic, but the drug is not exactly known.

The selection of potentiated drugs was based on the anamnesis and the results of the electropunctural drug test using the autonomic resonance test (ART) (MINI-EXPERT-DT and drug selector LLC CIMS IMEDIS) [6].

During drug testing, in the process of choosing a drug, aminoglycoside antibiotics in the C3 potency were used, and for treatment - in the C3, C6, C12, C30 and C50 potencies produced by JSC Holding EDAS (Moscow).

The preparations for this study were made according to an individual request. Drug testing was carried out directly and by filtration method [6] according to the scheme below:

1. Potentiated antibiotic in potency C3 ↓.
2. Organopreparation "cochlear nerve and duct" ↓
3. "Acquired Toxic Information (Intox II)" ↓.
4. Organopreparation "cochlear nerve and duct" ↓ + Antibiotic C3 ↑.
5. "Acquired toxic information (Intox II)" ↓ + Antibiotic C3 ↑.

When choosing the potency and regimen of taking potentiated aminoglycosides, we also proceeded from the results of the electropuncture drug test, which was carried out according to the algorithm, where gentamicin C6 is given as an example:

1. Ferrum met. D800 ↓ ("low potency efficacy") + gentamicin C6 ↑.
2. Manganum met. D800 ↓ ("low potency tolerance") + gentamicin C6 ↑.
3. Epiphysis D4 1 c.u. ↓ ("psychovegetative load") + gentamicin C6 ↑.

The optimal potency was considered that satisfies the tests "efficiency", "tolerance" and "psycho-vegetative load", and also did not cause negative subjective sensations when performing an individual drug test.

Drug testing was performed at each patient visit (2 times a month), and, depending on the measurement results and subjective dynamics, the drug was taken in the same or in a newly selected potency. The above optimization process

the choice of potency and regimen of taking potentiated homeopathic medicines, called "vegetative resonance monitoring" (VR-monitoring) and described in detail in [1], by its tasks (increasing safety and efficacy) is analogous to therapeutic drug monitoring used in clinical pharmacology ...

All drugs were used at a dose of 1 grain per dose, sublingually. Potencies and regimen of drug intake are presented in Table 2. The study was carried out in accordance with the plan of scientific research and the consent of the Ethics Committee of the State Educational Institution of Higher Professional Education "Russian State Medical University" of Roszdrav (Moscow).

table 2

Isopathic therapy results

№	Пациент, Возраст, лет	Препарат	Потенции и число приемов лекарства	Субъективный ушной шум	Диапазон по костному проведению , Гц		Порог восприятия по частоте 1 кГц, дБ		Порог восприятия по частоте 2 кГц, дБ	
1	А.,9	NEO	C6, C12,C30	-	-	500	1500	90	70	90	75
2	Б.,19	AMI	C12,C12, C30	+	-	1000	2000	80	60	85	65
3	В.,20	STR	C12,C30,C30	+	-	750	1000	100	100	100	100
4	Г.,20	GEN	C12,C30,C30,C30	+	-	500	1000	100	100	100	100
5	Д.,20	SISO	C12,C30,C50	+	-	6000	6000	75	75	70	70
6	Е.,20	KAN	C12,C30	+	-	500	750	100	100	100	100
7	Ж.,22	GEN	C12,C30,	+	-	125	1000	100	100	100	100
8	З.,23	STR	C12,C30,C30	+	-	1000	2000	70	50	75	70
9	К.,46	STR	C6,C12,C12	+	-	250	500	100	90	100	100
10	Л.,49	GEN	C12,C30	+	-	500	750	100	100	100	100
11	М.,50	SISO	C30,C50	+	-	500	750	100	100	100	100
12	Н.,54	KAN	C12,C12,C12	+	-	2000	2000	85	75	100	100
13	О.,56	KAN	C12,C12,C12	+	-	750	1500	100	100	100	100
14	П.,56	STR	C12,C12	+	-	250	750	100	100	100	100
15	Р.,58	GEN	C12,C30	+	-	500	500	100	100	100	100
16	С.,64	AMI	C12,C30	+	-	250	500	100	100	100	100

Abbreviations: STR, streptomycin, GEN, gentamycin, KAN, kanamycin, AMI, amikacin, SISO, sisomycin, NEO, neomycin.

results

Tolerability of therapy. In the process of isopathic therapy, any unwantedno effects were recorded in all 16 patients.

Effect according to criterion A.

The disappearance of the tinnitus was observed in almost all patients. This effect was the earliest, and some patients were noted as early as 2 weeks after taking the first dose of the drug. Along with the disappearance of ear noise, which significantly improved the quality of life of patients, almost all patients noted a significant improvement in mood, sleep, and work capacity. Somewhat unexpected was the result in patient N., 54 years old, who, after starting treatment with kanamycin in potency C12, stopped migraine headaches and dizziness when changing body position. In patient A., 9 years old, the effect according to criterion A was not assessed due to deafness.

Effect according to criterion B. Extending the frequency range(criterion B) (Fig. 1) for bone conduction after 3 months from the start of therapy was observed in 13 of 16 patients. At the same time, the degree of expansion of the range varied from one range to 3. The best results were obtained in patients A., 9 years old (from 500 to 1500 Hz), J., 22 years old (from 125 to 1000 Hz) and O., 56 years old (750 to 1500 Hz). Patient R., 58 years old, with complete deafness, the perceived frequency range of 500 Hz remained the same, although there was a disappearance of the ear noise and an improvement in the general state of health.

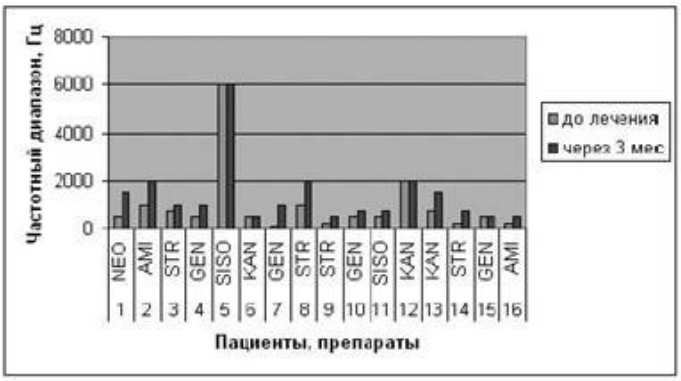

Fig. 1. Perceived frequency range (by bone conduction) before and 3 months after the start of isopathic therapy with potentiated aminoglycosides.

Effect according to criterion C. Effectiveness according to datathe criterion was the least indicative (Fig. 2 and Fig. 3). Only in three patients (A, B, and C) there was a decrease in the thresholds of perceived frequencies according to the tonal threshold audiometry by more than 20 dB. A distinctive feature of patients B., 19 years old and Z., 23 years old, was a lower (compared to other patients) degree of hearing loss (grade 3 and 4) and a wider, up to 1000 Hz, initial range of perceived frequencies for bone conduction. They also noted a more noticeable subjective improvement in hearing.

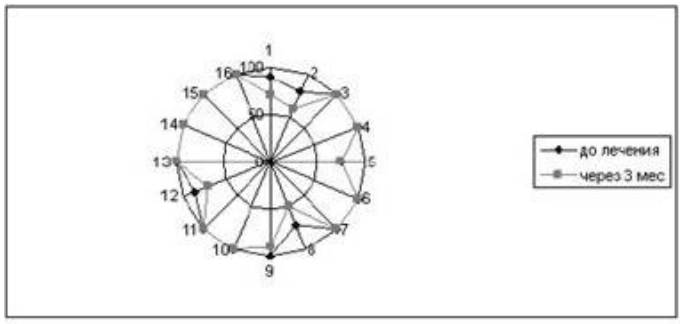

Fig. 2. Perceptual threshold changes in frequency1 kHz 3 months after the start of isopathic therapy with potentiated aminoglycosides. Numbers are indicated along the perimeter patients.

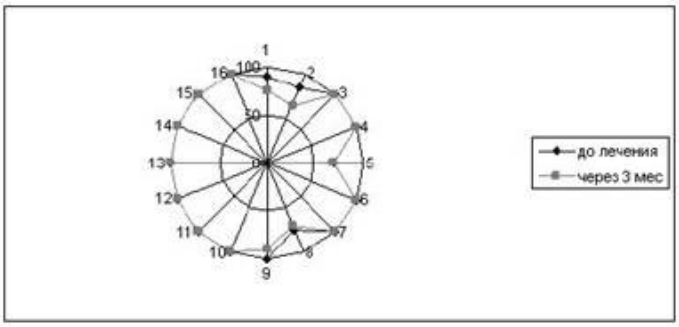

Fig. 3. Perceptual threshold changes in frequency2 kHz 3 months after the start of isopathic therapy with potentiated aminoglycosides. Numbers are indicated along the perimeter patients.

Follow-up of patient A., 9 years old, was the longest. After 12 months from the start of treatment, significant dynamics was achieved in terms of tonal threshold

audiograms, which practically normalized, although the dynamics in the first 3 months did not differ significantly from that of other patients. From this observation, it follows that isopathic therapy should be carried out for a long time, and the effect of this therapy should be assessed after a period of at least 12 months from the start of treatment.

According to a genetic study, no patient had an A1555G mutation in the 12S mitochondrial gene. Patient E., 20 years old, with prelingual deafness, which developed at the age of 1 year, which the parents associated with the use of kanamycin, in the GJB2 gene was found to have a 5G / 5G genotype mutation, i.e. in this case, we are talking about congenital prelingual deafness, in the development of which kanamycin played the role of a factor that caused the phenotypic manifestation of the mutation. Tolerance to drugs and the result of therapy in accordance with criteria A, B and C in this patient was similar to that of other patients who did not have this mutation. After the results of the genetic study became known (they became known after 3 months from the start of treatment), the parents decided to interrupt the patient's treatment. In most patients, according to the results of measurements, the initial potency was C12, repeated C30. In one case (patient K., 46 years old), treatment was started with C6, one grain once every other day, and then twice, with an interval of 2 weeks, potency C12 was used. In three patients, the C12 potency was effective and safe, while in three patients the C12 potency was required only at the beginning of treatment, subsequently repeated doses in the C30 potency were required (see table 1).

In the course of VR monitoring, it was noted that the decision on the choice of the drug, the potency of the initial dose, repetition of the dose or changing the potency of the next dose is possible only on the basis of the results of ART. This is due to the impossibility of identifying individual symptoms of the disease, which would be characteristic of individual aminoglycosides, the slow dynamics of the symptoms of the disease, difficulty, and often the lack of verbal contact with patients.

Discussion

Given the severity and age of the development of auditory disorders, the most important result of the analysis is the presence of any effect at all. There are a number of experimental studies in the literature [for example, 11, 12], which indicate the possibility of restoration of the neuroepithelium of the organ of Corti when hair cells are damaged by local administration of aminoglycosides. According to these data, the supporting cells of the environment (Deiters cells) show the ability to transform into specialized hair cells of the vestibular and auditory analyzers. The absence of such changes in the control ear indicates that damage to hair cells by aminoglycosides serves as a stimulus for such transformation [11, 12]. It should be emphasized that that supporting cells are resistant to the toxic effect of aminoglycosides, despite the fact that the same order of magnitude of drug concentrations is found in them and in hair cells [9, 10]. These data allowed us to formulate and substantiate a working hypothesis that explains the mechanism of restoration of auditory function with isopathic therapy. This hypothesis is based on a number of phenomena that are described in sufficient detail in the scientific literature. These are the phenomena of hormesis (inversion of the effect of toxicants when the dose is reduced by more than 10-15 times compared to the toxic one) [7], the features of the action of small and ultra-low doses of xenobiotics and biologically active substances of endogenous origin [3], mitogenetic radiation [4], cell transformation. that in them and hair cells are found the same order of magnitude of drug concentrations [9,10]. These data allowed us to formulate and substantiate a working hypothesis that explains the mechanism of restoration of auditory function with isopathic therapy. This hypothesis is based on a number of phenomena that are described in sufficient detail in the scientific literature. These are the phenomena of hormesis (inversion of the effect of toxicants when the dose is reduced by more than 10-15 times compared to the toxic one) [7], the features of the action of small and ultra-low doses of xenobiotics and biologically active substances of endogenous origin [3], mitogenetic radiation [4], cell transformation. that in them and hair cells are found the same order of magnitude of drug concentrations [9,10]. These data allowed us to formulate and substantiate a working hypothesis that explains the mechanism of restoration of auditory function with isopathic therapy. This hypothesis is based on a number of phenomena that are described in sufficient detail in the scientific literature. These are the phenomena of hormesis (inversion of the effect of toxicants when the dose is reduced by more than 10-15 times compared to the toxic one) [7], the features of the action of small and ultra-low doses of xenobiotics and biologically active substances of endogenous origin [3], mitogenetic radiation [4], cell transformation. This hypothesis is based on a number of phenomena that are described in sufficient detail in the scientific literature. These are the phenomena of hormesis (inversion of the effect of toxicants when the dose is reduced by more than 10-15 times compared to the toxic one) [7], the features of the action of small and ultra-low doses of xenobiotics and biologically active substances of endogenous origin [3], mitogenetic radiation [4], cell transformation. This hypothesis is based on a number of phenomena that are described in sufficient detail in the scientific literature. These are the phenomena of hormesis (inversion of the effect of toxicants when the dose is reduced by more than 10-15 times compared to the toxic one) [7], the features of the action of small and ultra-low doses of xenobiotics and biologically active substances of endogenous origin [3], mitogenetic radiation [4], cell transformation.

In accordance with the phenomenon of hormesis, aminoglycoside antibiotics, used in a potentiated form, have a reverse, stimulating effect on the residual hair epithelium, which leads to the emergence of a secondary biogenic

radiation (mitogenetic radiation, in accordance with the biological field theory of A.G. Gurvich [4]), which, in turn, initiates mitosis and transformation of undifferentiated supporting cells (Deiters cells) into hair cells of the organ of Corti. In other words, in isopathic therapy, potentiated aminoglycosides are the missing signal that stimulates the replenishment of the hair cell population when damaged by the same aminoglycosides.

conclusions

Despite the fact that the treatment has not yet been completed and the results presented are preliminary in nature, a number of conclusions can be drawn:

1. Isopathic therapy with potentiated aminoglycoside antibiotics has a positive effect on the function of the auditory analyzer, expressed in the disappearance of tinnitus, expanding the range and lowering the thresholds of perceived frequencies according to tonal threshold audiometry.

2. Isopathic therapy with potentiated aminoglycosides should be carried out for a long time, and its effect should be assessed at least 12 months after the start of treatment.

3. The use of the ART method is a prerequisite for optimizing the choice potency and mode of administration of potentiated aminoglycosides in the process of isopathic therapy.

The final results of this study will be reflected in subsequent publications.

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