Isopathic therapy for aminoglycoside sensorineural hearing loss and deafness

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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.

The treatment was carried out at 46 people with chronic ototoxic sensorineural hearing loss of severe degree (3-4 degrees) and deafness. Age from 19 to 58 years old, disease duration 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 anamnesis and the results of the electropuncture vegetative resonance test.

A positive effect has been shown in accordance with 4 criteria: the disappearance of subjective ear noise; expanding the range of perceived frequencies; lowering the perception thresholds at a frequency of 1 kHz or 2 kHz by at least 10 dB; reducing the degree of hearing loss, moving one step towards improvement. The treatment was well tolerated.

Conclusions. Results of a controlled clinical trialisopathic therapy in patients with severe chronic aminoglycoside sensorineural hearing loss indicate 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

This paper presents the results of a controlled clinical study of the efficacy of isopathic therapy for the ototoxic effects of aminoglycoside antibiotics, the idea of which was previously expressed and substantiated by us in [2], and preliminary results, which turned out to be very encouraging, were published in [3].

Materials and methods

The study was carried out in 46 patients with chronic sensorineural hearing loss of aminoglycoside etiology of varying severity and age of development (Table 1).

All patients underwent clinical examination, examination. Audiological examination (tonal threshold audiometry) (audiometer GSI-61, Germany) was performed before and during treatment every 3 months. All patients in the Laboratory of Molecular Genetics of the Research Institute of Physicochemical Medicine underwent 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 the mitochondrial 12sRNA gene (A1555G) [8] associated 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 one- or two-sided sensorineural hearing loss, etiologically associated with the pharmacotherapeutic use of aminoglycoside antibiotics. Availability with audiological signs of mixed hearing loss were 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.

Table 1

Characteristics of patients with chronic drug sensorineural hearing loss, who received therapy with potentiated aminoglycosides

	Пациент, Возраст, лет	Пол	Степень тугоухости	Тип тугоухости	Давность заболевания, лет	Анамнез, антибиотик	Результат ВРТ, антибиотик	Генотип 12sRNA (A1555G)	Генотип GJB2 (30-36 del G)
1	А., 19	М	5	НТ	18	?	NEO	–	–
2	Б., 19	М	4	НТ	18	?	AMI	AA	6G/6G
3	В., 20	М	5	См	19	STR	STR	AA	6G/6G
4	Г., 20	М	5	НТ	19	GEN	GEN	AA	6G/6G
5	Д., 20	Ж	4	См	19	?	SISO	AA	6G/6G
6	Е., 20	Ж	5	НТ	19	KAN	KAN	AA	**5G/5G**
7	Ж., 22	М	5	НТ	19	GEN	GEN	AA	6G/6G
8	З., 23	Ж	3	НТ	20	?	STR	AA	6G/6G
9	К., 46	Ж	5	НТ	41	STR	STR	AA	6G/6G
10	Л., 49	М	5	См	19	GEN	GEN	AA	6G/6G
11	М., 50	М	5	НТ	20	SISO	SISO	AA	**5G**/6G
12	Н., 54	Ж	5	См	15	KAN	KAN	AA	6G/6G
13	О., 56	Ж	5	НТ	15	KAN	KAN	AA	**5G**/6G
14	П., 56	М	5	НТ	36	STR	STR	AA	6G/6G
15	Р., 58	М	5	НТ	18	?	GEN	AA	6G/6G
16	С., 64	М	5	НТ	16	?	AMI	AA	6G/6G
17	Т., 58	Ж	3	НТ	30	?	NEO	AA	6G/6G
18	У., 17	Ж	2	НТ	11	SISO	SISO	–	–
19	Ф., 17	Ж	4	НТ	12	KAN	KAN	–	–
20	Х., 16	М	4	НТ	10	SISO	SISO	–	–
21	У., 16	Ж	4	НТ	12	KAN	KAN	–	–
22	Ч., 17	Ж	4	НТ	11	KAN	KAN	–	–
23	Ш., 19	Ж	4	НТ	15	SISO	SISO	–	–
24	Щ., 23	М	4	НТ	20	SISO	SISO	–	–
25	Э., 20	М	4	НТ	17	KAN	KAN	–	–
26	Ю., 19	Ж	4	НТ	15	SISO	SISO	–	–
27	Я., 16	М	2	НТ	10	STR	STR	–	–
28	АА, 17	М	4	НТ	10	STR	STR	–	–
29	ББ, 18	М	2	НТ	12	STR	STR	–	–
30	ВВ, 22	Ж	4	НТ	8	STR	STR	–	–
31	ГГ, 20	Ж	3	НТ	11	GEN	GEN	–	–
32	ДД, 16	М	4	НТ	6	STR	STR	–	–
33	ЕЕ, 16	М	4	НТ	14	STR	STR	–	–
34	ЖЖ, 17	М	4	НТ	11	GEN	GEN	–	–
35	ЗЗ, 23	М	4	НТ	20	SISO	SISO	–	–
36	КК, 20	М	4	НТ	17	KAN	KAN	–	–
37	ЛЛ, 19	Ж	4	НТ	15	SISO	SISO	–	–
38	ММ, 17	М	2	НТ	10	STR	STR	–	–
39	НН, 18	М	4	НТ	10	STR	STR	–	–
40	ОО, 22	М	2	НТ	12	STR	STR	–	–
41	ПП, 16	Ж	4	НТ	9	STR	STR	–	–
42	РР, 18	Ж	3	НТ	11	GEN	GEN	–	–
43	СС, 17	М	4	НТ	7	STR	STR	–	–
44	ТТ, 23	М	4	НТ	14	STR	STR	–	–
45	УУ, 20	М	4	НТ	11	GEN	GEN	–	–
46	ФФ,16	Ж	4	НТ	12	GEN	GEN	–	–

Abbreviations:

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

STR - streptomycin, gentamycin - GEN, kanamycin-KAN, amikacin - AMI, sisomycin - SISO, neomycin - NEO,? - the disease is associated with the use of an aminoglycoside antibiotic, but the drug is not exactly known.

Performance criteria:

Criterion A. The disappearance of subjective ear noise.

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

Criterion B. Decrease in perception thresholds at frequency 1 kHz or 2 kHz by at least 10 dB after 3 months from the start of treatment.

Criterion D. Decrease in the degree of hearing loss, transition one step towards improvement. Criteria A, B were considered "surrogate", and criterion C and D - final "hard" points.

The ear indicators with the best indicators were used for the analysis.

When selecting potentized drugs, we proceeded from the history and the results of an electropunctural drug test using a vegetative resonance test (ART) (apparatus "MINI-EXPERTDT", registration number FS 022a3065 / 0415-04, manufactured by LLC "CIMS" IMEDIS ", Moscow) [6]. Potentiated aminoglycoside antibiotics in the C3 potency were used for the drug test in the process of choosing the drug, and for the treatment of the C3, C6, C12, C30 and C50 potencies, produced by JSC Holding "EDAS" (Moscow). The preparations were made according to an individual request for this study.

The drug test was carried out according to the

algorithm: 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 a subjective 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 a newly selected potency. The process of optimization of the choice of potency and the regimen of taking potentiated homeopathic medicines described above, called "vegetative resonance monitoring" (VR-monitoring) and described in detail in [1], in its tasks (increasing the safety and effectiveness of pharmacotherapy) 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 mode of administration 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

Results of isopathic therapy of drug sensorineural hearing loss

№	Пациент, Возраст, лет	Препарат	Потенции и число приемов лекарства за время лечения	Динамика диапазона воспринимаемых частот по костному проведению через 3, 6 и 12 месяцев, Гц			Степень понижения слуха на лучше слышащем ухе до лечения, дБ	Степень понижения слуха на лучше слышащем ухе через 12 мес. на фоне лечения, дБ	Изменение степени понижения слуха в результате терапии 0 – без изменений 1 – переход с уменьшен
1	Ж., 22	GEN	C12, C30	125	1000	1000	96,6	88,6 (8,0)	1 (гл → 4 ст)
2	Ш, 19	SISO	C12, C30	250	250	500	86,6	80,8 (7,8)	0
3	ЖЖ, 17	GEN	C12, C12, C12	250	500	750	93,3	92,6(0,7)	0
4	К., 46	STR	C6, C12, C12	250	500	750	100,0	95,0 (5,0)	0
5	С., 64	AMI	C12, C30	250	500	750	95,0	92,6 (2,4)	0
6	П., 56	STR	C12, C12	250	750	1000	95,0	90,0 (5,0)	1 (гл → 4 ст)
7	33, 23	STR	C12, C30	500	1000	2000	83,3	78,6 (4,7)	0
8	Г., 20	GEN	C12, C30, C30, C30	500	1000	1500	71,6	66,6 (5,0)	1 (4 → 3)
9	А., 19	NEO	C6, C12, C30	500	1500	4000	88,3	65,0 (6,7)	1 (4 → 3)
10	Ч, 17	KAN	C12, C30, C30	500	500	1000	67,6	65,0 (2,6)	0
11	Р., 58	GEN	C12, C30	250	500	500	93,3	86,6 (6,7)	1 (гл → 4 ст)
12	Е., 20	KAN	C12, C30	500	750	750	96,6	90,0 (6,6)	1 (гл → 4 ст)
13	Л., 49	GEN	C12, C30	500	750	1000	96,3	90,0 (6,3)	1 (гл → 4 ст)
14	М., 50	SISO	C30, C50	500	750	1000	97,8	93,3 (4,4)	0
15	В., 20	STR	C12, C30, C30	750	1000	1500	95,0	90,6 (4,4)	1 (гл → 4 ст)
16	О., 56	KAN	C12, C12, C12	750	1500	1500	95,0	80,0 (15)	1 (гл → 4 ст)
17	Т., 58	NEO	C12, C12, C12	1000	1500	2000	64,6	60,0 (4,6)	0
18	Б., 19	AMI	C12, C12, C30	1000	2000	4000	78,3	58,3 (20)	1 (4 → 3)
19	З., 23	STR	C12, C30, C30	1000	2000	4000	57,3	41,6 (16,3)	1 (3 → 2)
20	Я., 16	STR	C12, C30	8000	8000	8000	35,0	18,3 (17,3)	1 (1 → 0)
21	ББ,18	STR	C12, C12, C12	8000	8000	8000	32,0	21,6 (10,4)	1 (1 → 0)

results

Tolerability of therapy. In the process of isopathic therapy, any unwantedno effects were recorded in all 46 patients.

Effect according to criterion A

Subjective ear murmur appeared in the complaints of almost all patients (45 out of 46). During isopathic therapy, a decrease in subjective ear noise was noted by 35 patients (76%), 5 patients noted its disappearance (11%), and 6 people (13%) did not notice changes in noise intensity. Reduction of noise intensity was the earliest effect and was noted by some patients as early as 2 weeks after taking the first dose of the drug. Along with the positive dynamics in the subjective assessment of ear noise, almost all patients noted a significant improvement in mood, sleep, and performance. The result was somewhat unexpected in patient T., 54 years old, who, after starting treatment with kanamycin in potency C12, stopped migraine headaches and dizziness when changing body position. Patient No. 1 (I., 19 years old),

Effect according to criterion B

Expansion of the reproducible frequency range in terms of bone conduction parameters during the observation period was noted in 21 out of 46 patients (45.6%). The observation results are presented in table. 2 and fig. 1 As can be seen from Fig. 1, there is a high individual variability in the response of the neuroepithelium of the organ of Corti to the therapy, which was expressed in varying degrees of expansion of the reproducible frequency range during the observation period, which was 12 months.

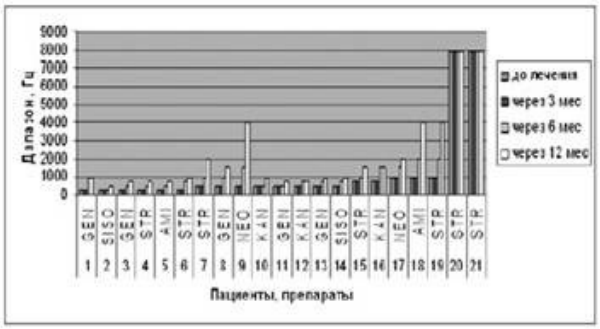

Fig. 1. The dynamics of the expansion of the range of perceived frequencies (by bone conduction) through3,

6 and 12 months after initiation of therapy.

In the first three months of treatment, there was practically no dynamics, however, after 6 months, already in 16 patients, an expansion of the range of reproducible frequencies was recorded, and the number of expansion ranges was individual - from 1 (in 10 patients) to 4 ranges (in 6 patients) and, as this follows from the obtained data, did not depend on the initial state. Most patients with a positive effect in accordance with criterion B had a break in the curve at 250–500 Hz, i.e. these are patients with very severe hearing impairments bordering on deafness.

The best results were obtained in patients No. 1, 9, 17, 18, 19, especially for patient No. 1 - in this case, almost complete restoration of auditory function occurred. The observation over him was the longest. After 12 months. From the start of treatment, significant dynamics were achieved in terms of tone threshold audiograms, although the dynamics in the first 3 months did not differ significantly from those 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.

Effect according to criterion B

The effect in accordance with this criterion (a decrease in the thresholds of perception at speech frequencies according to the tonal threshold audiometry by 10 dB or more) was only in 5 patients out of 46 (11%). These are patients Nos. 1, 4, 10, 18 and 21, and at a frequency of 2 kHz, the effect was more pronounced in patients Nos. 1, 18 and 21 (Fig. 2a and Fig. 2b).

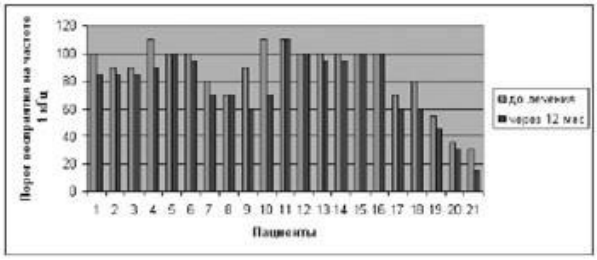

Fig.2a. Perceptual threshold changes in frequency1 kHz 12 months after the onset of isopathic therapy.

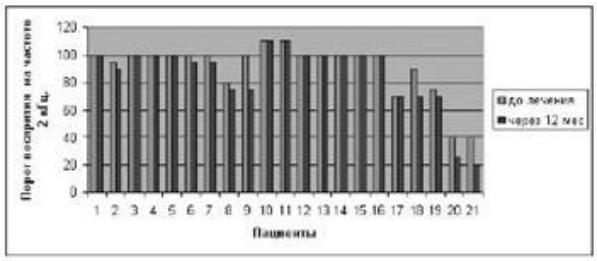

Fig.2b. Perceptual threshold changes in frequency2 kHz 12 months after the onset of isopathic therapy.

A distinctive feature of all the listed patients, except for patient No. 1 (in this case, there was deaf-dumbness), 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 according to bone conduction (Fig. 1).

According to the genetic study, no patient was found to have the A1555G mutation in the 12S mitochondrial gene. Patient No. 6 G, 20 years old, with prelingual deafness, developed in

At the age of 1 year, which the parents associated with the use of kanamycin, a mutation was revealed in the GJB2 gene - genotype 5G / 5G, 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 the indicated 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.

Effect according to criterion D

In accordance with criterion D, a change in the degree of hearing loss in the better hearing ear was noted in 13 patients out of 46 (28.2%) (Table 2). This was especially felt by 7 patients with deafness, who moved to the group with 4 degrees of hearing loss. In these patients, despite the fact that the magnitude of the gain was relatively small (from 4 dB to 15 dB), an improvement in general condition, sleep, and mood was observed at the same time. The transition was least noticeable in patients with an initially low degree of hearing loss (grade 3 and 2).

In most patients, according to the results of measurements, the initial potency was C12, repeated - C30. In one case (patient No. 9), treatment was started with C6, one grain once every other day, and then twice, with an interval of 2 weeks, a dose of C12. 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 (Table 1).

In the course of VR monitoring, it was noted that the decision to choose a drug, the potency of the initial dose, repeat the dose, or change the potency of the next dose is possible only on the basis of the results of VRT measurements. 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 the 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 [4], mitogenetic radiation [5], cellular 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 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 (cells

Deiters) into the 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

1. Isopathic therapy with potentiated aminoglycosides has a positive the effect on the function of the auditory analyzer, which is expressed in the disappearance of tinnitus, expansion of the range and lowering of the thresholds of perceived frequencies, as well as the degree of hearing loss 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 vegetative resonance test is a prerequisite optimization of the choice of potency and the regimen of taking potentiated aminoglycosides in the process of isopathic therapy.

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