

## Aminoglycoside ototoxicity risk screening based on vegetative resonance test

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### SUMMARY

The article presents the results of assessing the informativeness (sensitivity and specificity) of the diagnostic approach for screening persons with a high risk of aminoglycoside ototoxicity, based on the autonomic resonance test. According to the authors, the proposed test meets the requirements for screening diagnostic methods, allows one to assess the sensitivity to aminoglycosides by such a phenotypic trait as sensitivity to resonance between oscillations of neuroepithelial fiber cells of the auditory analyzer and oscillations of aminoglycosides.

One of the serious complications of pharmacotherapy with aminoglycosides is the ototoxic effect, which is expressed in auditory or vestibular disorders, which are unpredictable and, as a rule, irreversible. Therefore, there is no doubt that the most effective approach to increase the safety of aminoglycoside therapy is to predict the risk of their side effects on the auditory analyzer. However, within the framework of traditional biochemistry, pharmacology and otorhinolaryngology, approaches to predicting the risk of ototoxicity have not yet been developed.

Clarification of the biochemical mechanism of ototoxicity and the discovery of a number of genetic mutations associated with increased sensitivity to aminoglycosides made it possible to attribute these effects to idiosyncrasy. In accordance with these concepts, it is generally accepted that the sensitivity of the neuroepithelium of the organ of Corti to aminoglycosides is individual in nature, and it is based on oxidative stress: an imbalance between the reactive synthesis of reactive oxygen species (ROS) and their inactivation by cellular defense systems by antioxidants (glutathione) and enzymes (superoxide dismutase, glutathione peroxidase, catalase), where genetic factors play a leading role in the formation of this imbalance [12].

In our opinion, one of the effective approaches for predicting the risk of ototoxicity of aminoglycosides is a drug test based on the electropuncture autonomic resonance test (ART) [1]. The advantage of this approach is the ability to simulate the interaction of drugs and humans without introducing the drug into the patient's body (as opposed to pharmacological tests in clinical medicine) and assessing the sensitivity to certain xenobiotics using a small number of simple, standardized and reproducible measurements. The body's response to the introduction of a drug into the measuring chain, determined using ART, can be of diagnostic value for assessing individual sensitivity to a drug, since, as we assume, the response of a healthy cell and cell,

We substantiate this assumption by the well-known fact that the effect on cells of various damaging factors, including sources of electromagnetic oscillations (the possibility of resonant interaction between potentiated aminoglycosides and the structures of the inner ear was previously shown by us [3]), causes a change in the levels of active forms of oxygen (oxidative stress), and then the adaptive responses of cells, the nature of which depends on the current state of the cell, the intensity and duration of exposure, the spectral composition of the acting electromagnetic field [2, 8].

The aim of this study is to assess the informativeness of a drug test for the basis of ART for screening persons with a high risk of developing ototoxicity with pharmacotherapeutic use of aminoglycosides.

### MATERIALS AND METHODS

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Vegetative resonance test belongs to a group of methods of electro-acupuncture diagnostics, which use testing of medicines and comparison between changes in electrical conductivity at measurement points (TI) located on acupuncture meridians and the state of various organs and systems of the body [1].

To assess the state of the receptor formation of the organ of Corti and its sensitivity to aminoglycosides, we propose an algorithm of 4 consecutive measurements. The first step, a test with an organopreparation (OP), for example, with the OP "cochlear nerve and duct" (NPU). In the presence of damage to the receptor formation as a result of the action of etiological factors (genetic mutations of an acquired nature) or congenital genetic mutations:

OP "cochlear nerve and duct" ↓ (1)

If the test is negative (OP "cochlear nerve and duct" ↑ (1)), no further measurements are taken, the organ is "healthy". The second step, determining the sensitivity of the structure to the aminoglycoside drug [1]:

OP "NPU" ↓ + Aminoglycoside antibiotic in potency C3 ↑ (or applies official drug) (2).

This test was considered key to assess the risk of ototoxicity of aminoglycosides. To assess the etiology of the revealed violations, in particular, to assess their etiological relationship with the action of toxic factors, we used the test preparation "Acquired toxic information" (PTI, Intox II). We justify the need for measurements using this test preparation by the fact that, as shown by early clinical observations, external factors that increase the sensitivity of hair cells of the auditory analyzer to aminoglycosides include the previous use of ototoxic drugs and pathology of the inner ear [7]. In this regard, it seemed interesting and important to compare the results of measurements with PTI, OP and aminoglycosides in patients with chronic sensorineural hearing loss (NT) of drug etiology and NT,

OP "cochlear nerve and duct" ↓ + "Acquired Toxic Information (PTI)" ↑ (3) "PTI" ↓ + Aminoglycoside antibiotic in potency C3 ↑ (4).

In accordance with the interpretation accepted in ART [1], when performing tests 3 and 4, it was considered that with a known drug etiology, the damage to the receptor was caused by an aminoglycoside antibiotic, and if aminoglycosides were not previously used, then the test was regarded as false positive.

To carry out the drug test, we used equipment manufactured by CIMS "IMEDIS" LLC (Moscow): a device for electropunctural diagnostics and electro-, magnetic and light therapy "MINI-EXPERTDT", computerized with the software "MINI-EXPERT" and the device "IMEDIS -BRT-PC" (complete set 2).

All potentiated aminoglycosides (streptomycin, gentamicin, kanamycin, neomycin, sisomycin and amikacin) were made from official preparations at JSC "EDAS Holding" (Moscow) upon an individual request and were used in the C3 potency.

To assess the informativeness of the proposed tests, the following were determined: the sensitivity indicator  $Se$  (it was calculated as the ratio of truly positive results to the sum of truly positive and false negative results, this parameter was assessed in persons with diagnosed sensorineural hearing loss of various etiologies), the specificity indicator  $Sp$  (the ratio of true negative results to the sum of false positive and true negative results, this parameter was assessed in clinically healthy individuals in whom, according to the audiological examination, no pathology of the hearing organ was detected) and the indicator of the overall measurement accuracy (Likken's formula,  $Sp + Se / 2$ ) [11]. The study examined 352 people aged 17 to 70 years (Table 1). At the first stage, in 76 patients with NT of various etiology, the  $Se$  index of tests 1, 2,

Table 1

General characteristics of patients with sensorineural hearing loss of various etiology and clinical healthy individuals examined during the study

Исследование	Число обследованных	Возраст (M±m), лет
Оценка чувствительности тестов ВРТ у лиц с НТ различной этиологии, из них:	76	24,8±11,5
• лекарственная	27	23,7±10,1
• нелекарственная	49	25,1±12,3
Оценка специфичности ВРТ у клинически здоровых лиц	81	26,1±11,95
Молекулярно-генетический анализ на мутации 30-35 del G и A1555G, из них:	53	26,3±13,1
• лекарственная	13	22,1±12,3
• нелекарственная	40	26,1±10,4
ВРТ скрининг риска развития ототоксичности аминогликозидов	142	30±14,6

On the second - the specificity of measurements using the same tests in 81 clinically healthy individuals who were recognized as healthy during an audiological examination. To assess the dependence of the results of ART measurements on genetic mutations that may be associated with the disease, in 53 patients with sensorineural hearing loss of various etiologies, molecular genetic analysis was performed for the carriage of a mutation in the GJB2 gene encoding the connexin 26 protein (30–35 delG) and A1555G mutations in the gene 12S mitochondrial genome, which is associated with high sensitivity to aminoglycosides [14]. The studies were carried out in the laboratory of molecular genetics, Research Institute of Physical and Chemical Medicine, Moscow.

After assessing the informativeness (reliability) of ART tests, the risk of ototoxicity was screened in 142 healthy individuals without hearing complaints.

Statistical analysis of the obtained data was carried out using nonparametric statistics (Chi-square) and calculations were performed using the statistical data processing tools of the Excel package (MS OFFICE).

table 2

The results of assessing the sensitivity (Se) tests in patients with sensorineural hearing loss different etiology

Этиология	N	Тест НПУ↓ p < 0,05	Тест Ул↓	Тест УлПр↓	Тест НПУ↓+Аг↑ P < 0,05	Тест НПУ↓+ПТИ↑ P < 0,05	Тест ПТИ↓+Аг↑
Лекарственная	27	24 (88,8%)	2 (7%)	1	24 (88,8%)	24 (88,8%)	24 (88,8%)
Нелекарствен	49	44 (89,7)	8 (11%)	8	44 (89,7)	44 (89,7)	44 (89,7)
Не известна	17	13 (76,4%)	1 (0,05%)	1	13 (76,4%)	13 (76,4%)	13 (76,4%)
Вирусная	5	5 (100%)	3 (60%)	3	5 (100%)	5 (100%)	5 (100%)
Род травма	5	5 (100%)	1	1	5 (100%)	5 (100%)	5 (100%)
Менингит	1	1	-	-	1	1	1
Прививки	1	1	-	-	1	1	1
Наследствен.	10	9 (90%)	1	1	9 (90%)	9 (90%)	9 (90%)
Комбинирован	10	10 (100%)	-	1	10 (100%)	10 (100%)	10 (100%)
<b>Итого:</b>	<b>76</b>	<b>68 (89%)</b>	<b>10 (13%)</b>	<b>9 (12%)</b>	<b>68 (89%)</b>	<b>68 (89%)</b>	<b>68 (89%)</b>

#### Results and its discussion

The results of measurements in patients with diagnosed sensorineural hearing loss showed that of the three organopreparations ("NPU", "UI" and "UIP") (Table 2), the test with OPNP had the highest sensitivity for detecting damage to the receptor formation of the auditory analyzer. The Se index of the test for the whole group (76 people) was 89% (for the other two OPs this index was low - 13% for OP UI and 12% for OP UIP). The Se index of the NPU test in the group of patients with drug sensorineural hearing loss was slightly lower than in the group of patients with non-drug sensorineural hearing loss (89.7), and the differences were statistically significant - p < 0.05 (0.015), which we explain by a relatively large number false negative results in patients with a drug etiology of the disease, which can, in turn,

The statistical analysis of the differences in the sensitivity of the tests with OP UI and UIP was not performed due to their low values (low sensitivity).

Se indices according to the tests LPU ↓ + PTI ↑, LPU ↓ + Ag ↑, PTI ↓ + Ag ↑ were practically the same and

coincided with those of the NPU test ↓. At the same time, during measurements in patients with drug-induced hearing loss, a positive test was usually observed with one aminoglycoside, while in individuals with non-drug hearing loss, more than one drug often met the sensitivity criteria (according to the NPU test ↓ + Ar ↑). This is especially true for the group of patients with hereditary forms of the disease. Three patients in this group showed high sensitivity to all tested drugs.

Comparable indices of Se tests of SPTI in patients with drug-induced hearing loss and a disease of non-drug etiology (the differences between which were, moreover, unreliable,  $p > 0.05$ ), in our opinion, is explained by the fact that the mechanisms of hair cell damage by various damaging factors, such as infectious, tactical, which are universally oppressive depends on the state of the antioxidant systems of the cell [4]. In this regard, the value of this test for the etiological diagnosis of the disease is questionable. The Se index of the NPU test ↓ in the group of patients with the 5G / 5G genotype (Table 3) was slightly lower than in the group with the 5G / 6G genotype, where the cause of the disease is at least one more undiagnosed mutation - 85.7% and 90 %, respectively, and the differences were insignificant ( $p > 0.05$ ). Differences in sensitivity of other tests were also insignificant (see Table 3), the indicators of which were comparable to the NPU test ↓. The A1555G mutation was not diagnosed in any of the 53 patients with chronic HT (13 had aminoglycosides as the etiology of the disease).

The results of the second stage of the study, assessing the specificity of Sp measurements with the same test preparations in persons who had not previously taken aminoglycosides and were found healthy according to the data of an audiological examination, are presented in Table 4.

The specificity indicator of the test, according to the results of measurements by the sOPNPU, was 83%. When measured with the NPU ↓, + PTI ↑, the specificity of the test was also 83%. This means that 7% (14 people) of healthy individuals without complaints of hearing disorders who have not taken aminoglycosides in the past have a high risk of developing ototoxicity if they are used pharmacologically.

Table 3

The results of assessing the sensitivity of tests in patients with nonsyndromic neurosensory hearing loss due to polymorphism of the GJB2 gene (mutation 35 del G)

Генотип	Число пациентов	Тест НПУ↓	Тест НПУ↓+Ar↑	Тест НПУ↓+ПТИ↑	Тест ПТИ↓+Ar↑
5G/5G	7	6 (85,7%)	5 (71%)	6 (85,7%)	6 (85,7%)
5G/6G	10	9 (90%)	8 (80%)	7 (70%)	7 (70%)
		$p > 0,05$	$p > 0,05$	$p > 0,05$	$p > 0,05$

Table 4

Results of evaluating the informativeness of ART tests in patients with sensorineural hearing loss different etiology

Тест	Чувствительность (Se) %		Специ- фичность (Sp) %	Общая точность, %
	Общая для группы	У носите- лей 30-35 del G		
НПУ	89	85,7	83	86
НПУ + ПТИ↑	88,1	85,7	83	85,5

The indicator of the overall accuracy of the tests (it is called ideal accuracy), the recognition of damage to the auditory analyzer receptor (Table 4) for the NPI was 86%, and for the PTI test ↓ + NPU ↑ 85.5%. These are quite high and quite acceptable indicators, comparable to those of other screening and diagnostic approaches used in medicine [11]. Using this hypothesis, the results of measurements with 7 potentiated aminoglycosides, which showed a high sensitivity (Se equal to 100%) of the drug IPT test ↓ hair epithelium (Table 5).

Table 5

Measurement results with potentiated aminoglycosides

Тестируемый аминогликозид	Лекарственная тугоухость n = 27		Мутация 30-35del G(5G/5G) n = 7	Мутация 30-35del G(5G/6G) n = 10
	Анамнез	Тест		
Неомицин				2
Канамицин	3	3	1	1
Стрептомицин	6	6	3	1
Амикацин				1
Генатмицин	15	15	1	2
Сизомицин				1
Тобрамицин				1
<b>Итого:</b>	<b>24</b>	<b>24 (100%)</b>	<b>5 (71%)</b>	
<b>Отрицательный тест</b>	<b>0</b>	<b>0</b>	<b>2</b>	<b>1</b>

In accordance with the obtained result, we evaluate the test with OP NPU as a key, pathognomonic test for detecting degeneration of the receptor formation of the organ of Corti without its etiological interpretation, which can be the manifestation of various genetic mutations (congenital and acquired) underlying the pathology of the inner ear. These observations are of great practical importance, since during the screening they allow one to restrict the measurements only with the help of the NPU test [1]. The results of the third stage of the study, screening in 142 individuals are presented in table. 6. All surveyed were divided into 2 age groups - up to 40 years old (85 people, average age  $22.1 \pm 6.36$  years) and over 40 years old (57 people, average age  $52.5 \pm 5.94$  years). [1 + Ar 1] was 25% (21 people), while in the older age group it was 4 times higher and amounted to 100% (57 people), which made it possible to conclude that this indicator depends on the age of the subjects ( $\chi^2 = 78, 1$  (df = 1)  $p < 0.001$ ). This is an argument in favor of the opinion prevailing in the literature that age is one of the most important risk factors that increase the sensitivity of the hair epithelium to aminoglycosides [7]. In the group of persons under 40 years of age, the risk indicator (the number of positive NPU tests [1 + Ar 1]) was 25% (21 people), while in the older age group it was 4 times higher and amounted to 100% (57 people), which made it possible to conclude that this indicator depends on the age of the subjects ( $\chi^2 = 78.1$  (df = 1)  $p < 0.001$ ). This is an argument in favor of the opinion prevailing in the literature that age is one of the most important risk factors that increase the sensitivity of the hair epithelium to aminoglycosides [7]. In the group of persons under 40 years of age, the risk indicator (the number of positive tests of NPU [1 + Ar 1]) was 25% (21 people), while in the older age group it was 4 times higher and amounted to 100% (57 people), which made it possible to conclude that this indicator depends on the age of the subjects ( $\chi^2 = 78.1$  (df = 1)  $p < 0.001$ ). This is an argument in favor of the opinion prevailing in the literature that age is one of the most important risk factors that increase the sensitivity of the hair epithelium to aminoglycosides [7].

In all 78 people (54%) with a high risk of ototoxicity, the largest number of positive tests was noted with gentamicin - 23 (33%) and streptomycin - 18 (26%) tests. The minimum - 1 and 2 were registered with tobramycin and sisomycin, respectively (Table 6). If we take into account the fact that we are talking about people who have not previously taken these drugs, the higher frequency of positive tests for natural antibiotics (gentamicin and streptomycin) compared to semisynthetic ones (sisomycin, amikacin, tobramycin) has not yet been explained. In young people (21 people), who, in accordance with the results of screening, revealed damage to the receptor formation of the organ of Corti, we performed an audiological study (tone threshold audiometry, TPA), as a result of which normal TPA indices were revealed in 19 people.

Table 6

## Results of ART screening for the risk of ototoxicity of aminoglycosides

Тест	Возраст до 40 лет n = 85	Возраст после 40 лет n = 57
НПУ+Антибиотик СЗ	21 (25%)	57 (100%).
НПУ+ПТИ	21 (25%)	50 (91%)
Неомицин	1	7
Канамицин	3	15
Стрептомицин	4	14
Амикацин	-	6
Гентамицин	11	12
Сизомицин	1	3
Тобрамицин	1	

In persons of the older age group, the TPA data (lowering the thresholds at high frequencies) were more pronounced and exceeded 15 dB in almost all persons with a positive NPU test ↓.

The detection of high sensitivity to one of the aminoglycosides in accordance with the NPU test ↓ + Ar ↑ should be regarded as high sensitivity to the pharmacological group as a whole, since, in our opinion, when used in high pharmacotherapeutic doses, the differences in sensitivity to potentiated aminoglycosides revealed during measurements, will be erased. The fact that practically all patients with damage to the receptor (according to the NPU test ↓) had positive tests with aminoglycosides is consistent with the opinion formed on the basis of clinical observations about the inadmissibility of the use of aminoglycosides in auditory or vestibular disorders, regardless of their etiology and severity [9].

The proposed screening methodology based on ART, based on the detection of damage to the receptor formation, along with audiological [3, 5], will significantly reduce the incidence of hearing loss and deafness due to early detection of persons with latent pathology of the auditory analyzer and the risk of ototoxicity, since aminoglycosides have not yet lost their clinical significance as a means of antibacterial chemotherapy, especially tuberculosis and nosocomial pneumonia [9].

An important advantage of ART-based screening, along with high sensitivity, is the simplicity of execution, speed (measurement takes 5-6 minutes per subject), and also, which is very important, it does not require specially equipped rooms (in contrast to audiological examinations) and can be performed by physicians with no training in audiology.

#### conclusions

1. Measurement with the cochlear nerve and duct OP test ↓ is a qualitative test that reveals damage to the receptor formation of the organ of Corti with a reliability comparable to the reliability of other diagnostic methods used in medicine.
2. A positive test with OP "cochlear nerve and duct" ↓ indicates the risk of developing ototoxicity when using aminoglycosides.
3. ART-based screening is the method of choice for identifying high-risk individuals the development of auditory disorders when using both aminoglycosides and other ototoxic drugs.

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