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CHANGES OF BLOOD COMPOSITION DURING GENTAMICIN INTOXICATION AND CORRECTION WITH PHOSPHOLIPIDS

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Contributions:
A Study design/planning
B Data collection/entry
C Data analysis/statistics
D Data interpretation
E Preparation of manuscript
F Literature analysis/search
G Funds collection

Abstract

Introduction: The purpose of this study was to determine the diagnostically significant laboratory parameters which are predictors of sensorineural hearing loss in the blood of children receiving gentamicin, and to develop ways of its correction.

Material and methods: The study included 50 children who were hospitalized at the Republican Perinatal Center of the Tashkent Pediatric Medical Institute in need of antibiotic treatment. They had not recently received aminoglycoside antibiotics but anamnesis showed that these children had experienced their prolonged use. The patients were divided into 2 groups, as follows. Group 1 comprised children who were prescribed gentamicin as a course of treatment at an age-appropriate dose of 2–5 mg/kg, 2 times a day (n = 25). The second group consisted of 25 patients who were prescribed gentamicin with simultaneous administration of phosphogliv. A control group (n = 20) consisted of children who did not receive gentamicin.

Results: Gentamycin-induced intoxication was determined by diagnostically significant laboratory criteria for neuron-sensitive deafness. It was found that phosphogliv, which contains essential phospholipids in complex with aminoglycosides, could prevent neuron-sensitive deafness in children. Accompanying the use of gentamicin and phosphogliv in the second group, there was a significant decrease in the average level of molecular peptides in the blood, and the concentration of malondialdehyde decreased 2.4 times relative to the first group ($p < 0.05$).

Conclusions: Use of gentamicin with simultaneous essential phospholipids helps to reduce the amount of malondialdehyde in the blood, reduce medium-molecular peptides, and increase the activity of enzyme-protecting superoxide dismutase.

Key words: perilymph composition• gentamicin • reactive oxygen species • phospholipids • hearing loss

ZMIANY SKŁADU KRWI PODCZAS ZATRUCIA GENTAMYCYNĄ I KOREKCJA FOSFOLIPIDAMI

Streszczenie

Wprowadzenie: Celem niniejszego badania jest określenie istotnych diagnostycznie parametrów laboratoryjnych w krwi będących czynnikami prognostycznymi niedosłuchu odbiorczego dzieci leczonych gentamycyną oraz opracowanie sposobów ich skorygowania.

Materiał i metody: W badaniu wzięło udział 50 dzieci hospitalizowanych w Republican Perinatal Center of the Tashkent Pediatric Medical Institute, leczonych antybiotykami. Dzieci te nie przyjmowały antybiotyków aminoglikozydowych w ostatnim czasie, lecz w historii choroby odnotowano ich przedłużone przyjmowanie w przeszłości. Pacjentów podzielono na 2 grupy: do grupy 1. zakwalifikowano dzieci, które były leczone gentamycyną w odpowiedniej do wieku dawce 2–5 mg/kg 2 razy dziennie (n = 25); grupa 2. składała się z 25 pacjentów, którym przepisano gentamycynę z jednoczesnym podawaniem phosphoglivu. Grupa kontrolna (n = 20) składała się z dzieci, którym nie podawano gentamycyny.

Wyniki: Na podstawie diagnostycznie istotnych kryteriów laboratoryjnych zatrucie spowodowane gentamycyną zostało powiązane z głuchotą typu odbiorczego. Wyniki wykazały, że phosphogliv, który zawiera podstawowe fosfolipidy w kompleksie z aminoglikozydami, może zapobiegać głuchocie odbiorczej u dzieci. W efekcie zastosowania gentamycyny i phosphoglivu w grupie 2. średni poziom peptydów we krwi znacznie się obniżył, a stężenie dialdehydu malonowego zmniejszyło się 2,4-krotnie w porównaniu z pierwszą grupą ($p < 0,05$).

Wnioski: Stosowanie gentamycyny z jednoczesnym podawaniem podstawowych fosfolipidów sprzyja zmniejszeniu ilości dialdehydu malonowego we krwi, zmniejszeniu ilości średniocząsteczkowych peptydów i zwiększeniu aktywności ochronnej dysmutazy ponadtlenkowej.

Słowa kluczowe: skład perylimfy • gentamycyna • reaktywne odmiany tlenu • fosfolipidy • niedosłuch

Introduction

Gentamicin (GM) is an effective aminoglycoside antibiotic that is still widely used against serious and life-threatening infections with gram-positive and gram-negative aerobic bacteria, but its nephrotoxicity and oxidative damage limit long-term clinical use [1]. It is known that gentamicin generates reactive oxygen species associated with an increase in lipid peroxidation and a decrease in the activity of antioxidant enzymes in the kidneys [2]. Moreover, it acts like an iron chelator by forming an iron –gentamicin complex that plays a role as a potent catalyst of radical generation [3].

Various blood chemistry parameters have been evaluated in experimental animals, including of enzymes used to assess organ function. According to some researchers [2,5], there is a significant ($p < 0.05$) increase in blood levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP). The levels of ALT,

AST, and ALP in the blood indicate the functional efficiency of the liver and kidneys. The level of these enzymes is very sensitive to any diseases of these organs [3]. Also, the level of creatinine and urea in the blood has been assessed, since these two parameters are of particular importance in assessing renal function [4]. The level of free radicals in the blood of experimental animals has also been assessed to check for the presence of oxidative stress [5].

Acute diseases of the respiratory system occupy a leading place in child morbidity, one result of which is a high mortality rate. Dominating the treatment of such patients is the use of broad-spectrum antibiotics, in particular aminoglycoside antibiotics. These antimicrobials have certain disadvantages which often lead to negative consequences, including damage to the receptors of the inner ear.

Hearing loss is a problem that affects people across all cultures; it is also the fourth-largest cause of long-term disability. It is estimated to affect 6–8% of the world's population, representing 500 million people. In Uzbekistan, of 800,000 children born a year, 800 are deaf [6].

In addition, aminoglycosides are used to treat pulmonary exacerbations in patients with cystic fibrosis and are on the list of drugs recommended by the WHO for the treatment of sepsis in newborns. The frequent prescription of this group of drugs has led to the documentation of a wide range of antibacterial effects, but an important factor is the low cost of treatment [9]. Among the most commonly used drugs in this group are triamycin, kanamycin, amikacin, and gentamicin. The mechanism of action of aminoglycosides is based on disrupting the integrity of the bacterial cell membrane by interfering with the process of bacterial protein synthesis, thereby preventing further multiplication of bacterial cells and weakening the protective function of the cell membrane.

Ototoxicity is the most serious side-effect of hypertension treatment due to mitochondrial mutations, with the inner ear being one of the target organs [10]. One possible scenario for explaining the molecular ototoxicity of aminoglycosides (AGs) is that AGs cause a misreading of mitochondrial protein synthesis and a decrease in mitochondrial ATP synthesis. This leads to a decrease in the activity of the ion pump; as a result, the number of intermediate striae cells decreases, which leads to a decrease in endocochlear potential and the progression of hearing loss [11]. High frequency hair cells are more susceptible to AG ototoxicity than those responsible for lower frequencies.

Due to their pharmacokinetics, aminoglycosides are found in the cochlea a few minutes after systemic administration. Fluorescently labeled antigens, such as gentamicin, have been detected in the vasculature of mice within 10 min of injection (systemic administration), mainly in marginal cells adjacent to intermediate and basal cells such as fibrocytes. As a result, gentamicin enters the fluid of the inner ear from the capillaries of the stria vascularis through the edge cells. Consequently, in the organ of Corti, fluorescently labeled gentamicin is detectable 1 h after injection and can be detected within the hair cells after 3 h. An increase in hypertension of the anatomical and physiological structures of the cochlea demonstrates that the inner ear is sensitive to hypertension [12]. Possible entry sites are through mechanotransducer channels located on the stereocilia of hair cells, ATP receptors, transient receptor potential (TRP) channels, or endocytosis on the apical part of the basement membrane [13,14].

Studies have shown that in the inner ear, aminoglycosides lead to apoptotic or necrotic cell death caused by reactive oxygen species (ROS) [17,18]. In patients treated with aminoglycosides, hearing loss initially occurs at high frequencies due to early damage to hair cells at the base of the cochlea and then spreads to apical cells which are responsible for detecting low-frequency sounds. The level of damage to hair cells and the hearing loss associated with it is directly proportional to the dose of medication that the hair cells are exposed to. This process can be permanent or reversible. Losses can be assessed using such basic audiological tests as audiometry or otoacoustic emissions (OAEs) [19,20]. Loss of speech perception develops later when damage to the upper ganglia and lower frequencies increases. In addition, aminoglycosides persist in the tissues of the inner ear for 6 months or more, suggesting that hearing loss may begin immediately after treatment.

It is generally accepted that the sensitivity of hair cells of the organ of Corti to antibiotics of the aminoglycoside series is individual, and is based on oxidative stress: an imbalance between the synthesis of ROS and a decrease in the power of the enzyme protection system (superoxide dismutase, glutathione peroxidase, catalase) [2,4,12].

Material and methods

Written informed consent was obtained for the study. Also, the approval of the local ethics committee under the Ministry of Health of the Republic of Uzbekistan was obtained.

We examined 50 children who were treated in the intensive care unit for newborns at the Republican Perinatal Center of the Ministry of Health of the Republic of Uzbekistan. The study was carried out on residual blood taken for general analysis. The results showed that the total amount of protein was practically nil. A control group (n = 20) consisted of children who did not receive aminoglycoside antibiotics and were hospitalized at the Republican Perinatal Center, Tashkent Pediatric Medical Institute. Anamnesis of these children showed prolonged use of the antibiotic.

The experimental patients were divided into two groups. Group 1 included children who were prescribed gentamicin in the course of treatment at an age-appropriate dose of 2–5 mg/kg, 2 times a day (n = 25). The second group of patients consisted of 25 patients who were prescribed gentamicin with simultaneous intravenous administration of phosphogliv (50 mg of lyophilisate for solution preparation) at an appropriate age-specific dose for 10 days.

Phosphogliv is a combined preparation that contains glycyrrhizin acid, which has an anti-inflammatory effect, and essential phospholipids, which implement protective and restorative mechanisms. Phosphatidylcholine (an active substance of phospholipids), being the main structural element of cellular and intracellular membranes, is able to restore their structure and functions in case of damage,

providing a cytoprotective effect. It restores the detoxifying function of the liver, inhibits the formation of connective tissue, and reduces the risk of liver fibrosis and cirrhosis. Glyceride has an anti-inflammatory effect, has a hepatoprotective effect due to antioxidant, and membrane-stabilizing activity. It enhances the action of endogenous glucocorticosteroids, providing anti-inflammatory and anti-allergic effects in non-infectious liver damage. The active substances of phospholipids (lipoid C 80) are, in percentage terms, phosphatidylcholine, 73–79%, and sodium glycyrrhizinate (the trisodium salt of glycyrrhizin acid), 35%.

The following biochemical studies were carried out in the blood of all children: determination of malondialdehyde (MDA) by the method of Nagoev et al. [10], medium molecular weight peptides (MMWP) according to Gabrielyan et al. [4], the activity of catalase (Cat) according to the method of Korolyuk [6], and superoxide dismutase (SOD) by the method of Mirza and Fridovich [13].

The content of free malondialdehyde in perilymph was determined by the method of Nagoev et al. [16]. The method is based on the interaction of 2-thiobarituric acid (TBA) with the product of ROS-MDA generation at high temperatures in an acidic medium with the formation of a colored trimethine complex with an absorption maximum at 532 nm. The molar extinction coefficient of this complex is $E_{532} = 1.56 \times 10^5$ cm M^{-1}. To determine the intensity of spontaneous generation of ROS, the incubation mixture consisted of 0.2 ml of perilymph and 0.8 ml of Tris HCl buffer, which was incubated at 37°C for 30 min. The stop of spontaneous LPO in the incubation mixture was achieved by sharp cooling of the mixture and addition of 2 ml of 17% TCA (trichloroacetic acid). After centrifugation, 2 ml of the supernatant liquid was separated, to which 1 ml of 0.5% thiobarbituric acid solution was added. Then the samples were placed in a boiling water bath for 10 minutes for color development. After cooling, the absorption spectrum of the trimethine complex formed during the reaction of TBA with MDA was recorded on an SF-26 spectrophotometer. As a comparison, a sample containing all components of the incubation medium at 37°C was used. The accumulation of ROS generation products was expressed in nmol MDA/mg proteins for 30 min.

Average molecular peptides (AMP) were determined according to the method of Gabrielyan [4].

The total anti-peroxide activity (APA) was assessed by the ability to degrade 1% hydrogen peroxide solution of 0.1 ml of perilymph when incubated at 37°C for 30 min. The amount of residual hydrogen peroxide was determined by the perganometric method of Korolyuk [6].

Superoxide dismutase (SOD) activity was assessed by the method of Mirsa and Fridovich [13]. Enzyme activity was adjusted for the amount of total protein according to the Lowry method [15].

Results and discussion

It was found that in the control group, the content of AMP and MDA in the blood was in trace amounts, which corresponds to the literature data [3]. Such a low level of AMP and MDA is associated with the power of antioxidant activity – the high activity of SOD and blood catalase.

The content of AMP in the blood of children who received gentamicin was 2.4 times higher than the control level ($p < 0.05$). In the 4 surveyed children (19%) who received gentamicin, the level of AMP in the blood was above the average level. Anamnesis of these patients showed that they had been prescribed antibiotics for more than 10 days or a double course. In 5 patients (23.8%), the blood AMP content was below average; their anamnesis showed that these children received gentamicin for a short time (up to 5 injections).

Thus, there is a linear dependence of the increase in the blood volume of the AMP depending on the timing and dose of gentamicin administration. AMP is a product of the interaction of a protein molecule with ROS, and ROS leads to degradation of the protein molecule, which is an indicator of endotoxemia.

A study of the MDA content in the blood of children who received gentamicin showed values 3.3 times higher than the control. However, the number of children whose blood levels of MDA are higher than the average was 19 patients. Of these patients, a high level of MDA in 2 patients was combined with a high rate of AMP. In 2 patients, a high level of EMS was accompanied by an increase in MDA above the average. In 2 patients (9.5%), low values of EMS were accompanied by low values of MDA.

In the group of children treated with gentamicin, the activity of blood catalase increased 1.66 times relative to the control. However, in 8 children (38.1%), catalase activity was found to be 1.06 times higher than the average level, which was statistically insignificant ($p > 0.05$).

The activity of the antiradical defense enzyme, SOD, was 2.83 times lower than in the controls. In 11 patients (52.4%), blood SOD activity was within the average statistical range, and in 3 patients (14.3%) it was even higher than the average level. In this group of patients, a combination of high levels of SOD and catalase was found. In 6 patients (28.6%), the SOD activity was 1.12–1.21 times lower than the average.

A number of scientific works are devoted to the treatment of intoxication processes against the background of the use of aminoglycoside antibiotics (AGABs). The arsenal of pharmacological drugs used in the treatment of SNT developed against the background of the use of AGAB is wide, in particular: mydocalm [7], antihypoxants [11], plant antioxidants [1], L-carnosine with zinc [9], D-methionine [14], and cavinton [8]. However, studies on the clinical efficacy of essential phospholipids in the treatment of hearing loss have not been noted in the available literature.

There were clinical and laboratory changes in the blood of children who received gentamicin in conjunction with essential phospholipid preparations. Most notably, as shown in Table 1, the content of AMP in the blood decreased relative to the 1st subgroup by 1.85 times ($p < 0.05$). Normalization of the indicator was not observed, and the content of AMP in the second subgroup was 1.31 times higher

Table 1. Comparison of some biochemical parameters of blood in children who received gentamicin and in the group of children who received gentamicin with phosphogliv

Group of patients	AMP E/mg protein	MDA mmol MDA/mg protein*min	Khat mmol H_2O_2 /mg protein*min	SDM mmol adrenalin/mg protein*min
1. Group of children given gentamicin	0.0102 ± 0.0003	1.65 ± 0.06	0.88 ± 0.01	1.52 ± 0.07
2. Group of children given gentamicin + phosphogliv	0.0055 ±0.0002	0.68 ± 0.03	0.64 ± 0.02	2.57 ± 0.13
3. Control group	0.0042 ± 0.0001	0.50 ± 0.03	0.53 ± 0.01	4.30 ± 0.04
$p_{1:2}$	<0.01	<0.01	<0.05	<0.01
$p_{1:3}$	<0.01	<0.01	<0.05	<0.01
$p_{2:3}$	<0.05	<0.05	<0.05	<0.01

than the control value, which was within statistically significant limits (p <0.05).

Among the examined children, in 2 patients (9.5%), the value of the AMP in the blood was 1.15–1.20 times higher than the average value. The number of patients with EMC content below the average was 5 children (23.8%). In 5 sick children of this group (23.8%), the number of EMPs was 1.14 times higher than the control values, which was not statistically significant (p > 0.05).

As Table 1 shows, the simultaneous administration of gentamicin with phosphogliv (group 2) led to a significant decrease in AMP in the blood, and the amount of MDA also decreased 2.4 times relative to the 1st group of patients (p <0.01). However, the decrease in the amount of MDA in the blood of children of this group did not reach the values of the control group, and was 1.36 times more (p > 0.05). Thus, the simultaneous administration of phosphogliv with gentamicin led to a significant decrease in the amount of MDA in the blood of sick children.

The tendency to normalize the blood levels of AMP and MDA in group 2 patients indicates a positive effect of phospholipid preparations.

The antioxidant system of the body of children treated with both gentamicin and phosphogliv recovered, although their values did not reach the control level. Catalase activity decreased by 1.38 times compared to the first group, while SOD activity was increased by 1.59 times.

Conclusions

1. While the activity of superoxide dismutase was significantly reduced, an increase in the blood of malondialdehyde by 2–3 times and medium-molecular peptides by 2–4 times relative to the control level was found in the blood of children treated with gentamicin.

2. The simultaneous use of gentamicin with essential phospholipids helps to reduce the amount of malondialdehyde in the blood, medium molecular peptides, as well as to increase the activity of the enzyme-protecting superoxide dismutase.

3. Trials of phospholipids should be extended, especially because gentamicin use should be limited and yet is still in common use.

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