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COMPARISON OF THE MANIFESTATION OF OTOTOXICITY OF PLATINUM-BASED CHEMOTHERAPEUTIC AGENTS IN EXPERIMENTAL RESEARCH CONDITIONS

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INTRODUCTION: Chemotherapy is one of the main components of treatment of common types of malignant tumors with early metastasis. Platinum-based chemotherapy drugs are widely used in the treatment of malignancies. Representatives of this group of drugs, such as cisplatin and carboplatin, have side effects such as nephrotoxicity, myelosuppression, neurotoxicity and ototoxicity. Ototoxicity is manifested by unilateral or bilateral hearing loss, which may be accompanied by tinnitus. Damage to the hearing organ depends on the dose and cumulative ability of the drug.

OBJECTIVE OF THE STUDY: Evaluation of the occurrence of ototoxicity against the background of the use of platinum-based chemotherapeutic drugs in laboratory rats.

MATERIALS AND METHODS. Albino rats with a body weight of 190-228 g were used as laboratory animals. Animals were handled according to standard animal care protocols. Laboratory animals were divided into three study groups (n=10 each):

1. Daily i.p. administration of 0.9% sodium chloride solution 2 ml/kg.
2. Daily i.p. administration of cisplatin (1 mg/ml) 6 mg/kg for four consecutive days
3. Daily i.p. administration of carboplatin (10 mg/ml) 8 mg/kg for four consecutive days. Experimental rats underwent 3 courses of drug administration, separated by 14 day breaks. During one course of chemotherapy, the drug was administered once a day, four consecutive days of injections of platinum-containing drugs. In total, the entire experiment lasted 54 days. The Preyer reflex was assessed according to the method of K.L. Khilova et al. Hearing testing of rats included recording of short-

latency auditory evoked potentials (ABR) before and after drug administration. ABR was performed using the Neuro-Audio apparatus (Neurosoft, Russia).

RESULTS: After completion of the 1st course of treatment in the control group, upon otoscopy, the eardrums of all rats were pearly gray in color and pale. The Preyer reflex is alive and responds to sounds. Assessment of hearing thresholds based on the results of the ABR showed that the average indicators of the appearance of the first peak were 16.3 ± 2.1. Analysis of the data showed that wave I was recorded in all cases and had a consistently high amplitude. Wave V also differentiated in all laboratory animals.

The main group received a course of chemotherapy with the drug cisplatin (1 mg/ml) at a dosage of 5 mg/kg for 5 days. After completion of chemotherapy, no otoscopic changes were observed. Extinction of the Preyer reflex was observed in 2 rats. The results of the ABR showed the presence of all waves in the examined laboratory animals. In 2 rats, according to the ABR data, there was a decrease in the amplitude of the first peak, without a significant change in the peripheral conduction time.

A comparison group of laboratory animals that were administered carboplatin at a dosage of 8 mg/kg had similar indicators to the control group; no pathological indicators were observed.

After a 14-day break, laboratory rats had their body weight measured and began a second (2nd course) course of chemotherapy with platinum drugs. Results of assessing auditory function in experimental animals after the second course of drug administration: In the control group, otoscopy did not reveal any pathologies, the Preyer reflex was alive. The results of the ABR also corresponded to the norm, i.e. registration of all waves of consistently high amplitude.

In the main study group, in laboratory rats treated with cisplatin, extinction of the Preyer reflex was observed in 4 rats, and no peaks of ABR were recorded in them. In the remaining animals, analysis of the ABR results showed an increase in peak registration thresholds, a decrease in the amplitude of the first peak, without a significant change in the peripheral conduction time.

In the comparison group, otoscopy was normal; extinction of the Preyer reflex was observed in 1 animal. When assessing hearing thresholds using ABR, the presence of the first peaks was noted at an intensity of 28±6. Wave I was recorded in all cases and had a stable amplitude.

14 days after the second course of chemotherapy, we started the third course of chemotherapy with platinum drugs. In the main group, after three courses of cyclic

administration of drugs at therapeutic concentrations, in 5 laboratory rats receiving cisplatin, complete extinction of the Preyer reflex was observed. ABR showed that at five of the six frequencies tested, threshold shifts in animals treated with cisplatin were significantly higher than in the control and comparison groups of rats. Larger threshold shifts were observed at higher frequencies. According to the results of a hearing study using the ABR method after the 3rd course of chemotherapy with cisplatin, 5 laboratory rats showed an increase in hearing thresholds and an upward change in wave latency values. The average threshold values in rats treated with cisplatin were 59.82 ± 0.08 dB. The first peak was recorded in all cases, but its latency increased and amounted to 1.88±0.02 ms. There was a tendency towards a decrease in waves II, III, IV and V.

CONCLUSION: After comparing auditory dysfunction in laboratory rats treated with cisplatin and carboplatin, our results showed a marked increase in SEP thresholds in rats treated with cisplatin. These results indicate the death of outer hair cells. No changes in auditory function were observed in rats treated with carboplatin. The occurrence of different degrees of ototoxicity between these two platinum-containing drugs indicates different degrees of platinum uptake by the cochlea.