NASA TECHNICAL MEMORANDUM

NASA TM 76425

ON THE MECHANISMS OF HARMFUL EFFECTS OF CERTAIN MEDICINAL PREPARATIONS ON THE AUDITORY ORGAN AND METHODS FOR THEIR PREVENTION (Survey of literature)

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Translation of "O mekhanizmakh povrezhdayushchego deystviya nekotorykh lekarstvennykh preparatov na organ slukha i yego profilaktika (Obzor literature)". Zhurnal Ushnykh, Nosovykh i Gorlovykh Bolezney, No. 5, Oct-Nov. 1979, pp. 78-84

NATIONAL AERONAUTICS AND SPACE ADMINISTRATION
WASHINGTON D.C. 20546 NOVEMBER 1980

STANDARD TITLE PAGE

1. Report No. NASA TM-76425	2. Government Accession No.	3. Recipient's Catalog No.
4. Title and Subtitle ON THE MECHANISMS OF HARMFUL EFFECTS OF CERTAIN MEDICINAL PREPARATIONS ON THE AUDITORY ORGAN AND METHODS FOR THEIR PREVENTION		5. Report Date NOVEMBER 1980 6. Performing Organization Code
7. Author(s) E. A. Bakay, L.B. Nesshetnaya		8. Performing Organization Report No. 10. Work Unit No.
9. Performing Organization Name and Address SCITRAN Box 5456 Santa Barbara, CA 93108		11. Contract or Grant No. NASW-3198 13. Type of Report and Period Covered Translation
12. Sponsoring Agency Name and Address National Aeronautics and Space Administration Washington, D.C. 20546		14. Sponsoring Agency Code

15. Supplementary Notes

Translation of "O mekhanizmakh povrezhdayushchego deystviya nekotorykh lekarstvennykh preparatov na organ slukha i yego profilaktika (Obzor literatury)." Zhurnal Ushnykh, Nosovykh i Gorlovykh Bolezney, No. 5, Oct-Nov 1979, pp. 78-84

16. Abstract

This is a study of the side effects of medical preparations and especially their effects on the inner ear.

Various drugs are discussed and many references are mentioned.

The authors conclude that the development of methods of pharmacological prevention of the harmful effect of drugs on the auditory analyzor is a necessity.

It includes 25 pages and 87 references.

17. Key Words (Selected by Author(s))	18. Distribution Statement
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19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22.
Unclassified	Unclassified	26	

ON THE MECHANISMS OF HARMFUL EFFECTS OF CERTAIN MEDICINAL PREPARATIONS ON THE AUDITORY ORGAN AND METHODS FOR THEIR PREVENTION

(Summary of Literature)

E. A. Bakay, L. B. Neschetnaya *

Every day the number of medicinal preparations used for treating various illnesses is constantly increasingly and, naturally, the solution to the problem of preventing side effects caused by these substances is becoming ever more important. Due to the anatomical and physiological specifics of its position, the inner ear is often subject to the effects of medicinal preparations, which necessitates a more detailed and in-depth study of the regularities and mechanisms of its affliction by medicinal substances. /78*

On the other hand, despite the general interest by researchers and physicians in the problem of treating medicinally caused, and especially antibiotically induced deafness and hypoacusis, there has been no significant success to date in restoring the auditory function. Even after discontinuing the use of ototoxic antibiotics in the initial stage of clinical manifestations of damage to the auditory organ, prevention of the further development of the illness may not always be fully possible. The process may progress independently, leading to a high degree of hypoacusis (M. S. Pluzhnikov, 1972). Medicinal substances used for the purpose of improving the auditory function, even in the early stages of

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** Numbers in margins indicate foreign pagination.

the illness, have no noticeable affect on it due to the destruction of the receptor elements of Corti's organ. In connection with this, the problem of studying methods for preventing the development of serious disruptions of the auditory function becomes critical.

The most common cause leading to damage or destruction of the cochlear receptor elements is the use of antibiotics. The ototoxicity of such antibiotics as streptomycin, neomycin, kanamycin, monomycyn are widely known (Ziemski, 1968; Kaneko et al., 1970; Brown, Diagneault, 1973; Aran, Darrouzet, 1975; Ryan, McGee, 1977).

Experimental data and clinical observations testify to the possibility of toxic effect on the auditory organ of other antibiotics as well, for example: bleomycin, whose considerable ototoxicity was confirmed experimentally (Dal et al., 1973); gentamycin (Debain et al., 1969; Stohnens, 1968, Federspil, 1970, Stange, 1970); sisomycin, which has a lower ototoxicity as compared with gentamycin (Robbins, Fettenborn, 1976); amicacyn, which in its effectiveness and toxicity approaches gentamycin, acts on the Gram-negative microorganism strains resistant to gentamycin (Federspil et al., 1976); (illegible) sulfate , which has a high specific activity in relation to Gram-negative flora (Logan et al, 1974; Postma et al., 1976). Chloramphenicol (chloromycetin) is also related to the class of ototoxic antibiotics, and its considerable toxicity has been shown during local application in experiments with guinea pigs (Proud et al., 1968). /79

A toxic effect on the inner ear is exhibited not only by antibiotics, but also by an entire series of other medicinal substances, for example, certain diuretics: ethacryn acid (Kohonen et al., 1970);

Jung, Machold, 1970; Mathod, Matz, 1972; Silverstein, Begin, 1974), furosemide (Jung, Machold, 1970; Brown, 1973; Chodinicki, Kostrzewska, 1974). Functional changes in hearing are also manifested in patients treated with propylthiouracil (Smith, Spaulding, 1972). After the use of this preparation was discontinued, auditory thresholds return to their initial level.

Temporary hearing impairment was noted by Bodis, Ralfalvi (1969) with the use of tranquilizers: pipolphen and seducsen, and these changes were explained by blocking of the reticular formation.

Functional hearing disorders are observed also with the use of local anesthetics -- tetracaine (2%) and lidocaine (4%). As a result of their influence on the cochlear window, the value of the total potential of auditory nerve action is reduced, as is the capacity for auditory adaptation (Flach et al., 1968; Hughes, Yagi, 1975).

The negative effective of cardioactive drugs (strophanthin , ouabain) on the ion exchange in the inner ear has been noted (Chon, 1970). With the introduction of ouabain into the perilymphatic spaces, a considerable inhibition of cochlear potentials is noted, the sodium content increases and the calcium concentration is reduced in the endolymph (Konishi, Mendelsohn, 1970).

There are clinical observations of development of deafness in a child whose mother used chloroquine (a universally administered anti-malaria preparation) before and during pregnancy (Matz, Naunton, 1968).

Experimental studies of the effect of dimethylsulphoxide on the inner ear -- a substance which is used primarily as a base in preparing

various medicinal substances (for example, antibiotics, corticosteroids) and used in application form in the outer and middle ear, showed an expressed reduction in the potential of auditory nerve action, which was intensified with increased time of application (Stange, Winter, 1970).

The ototoxic effect of salicylates has long been known. As a rule, it ceases after discontinuation of the preparations (De Moura, Hayden, 1968). McPherson and Mitter (1974), who studied the effect of cholin-salicylate (arthropan) on the cochlea (in guinea pigs), found a reduction in the amplitude of auditory nerve action potential.

The combined use of various ototoxic substances intensifies their harmful effect. Thus, it was established (West et al., 1973) that one-time separate introduction of kanamycin and ethacryn acid to guinea pigs caused a certain reduction in cochlear potentials, and after several hours these indicators gradually returned to their initial values. There were no histological changes found immediately after introduction of the substance, as well as one month later. Simultaneous introduction of kanamycin and ethacryn acid showed a considerable reduction in cochlear potentials, which remained at the same level a month later. There was histological evidence of degeneration of the internal and external pillar cells.

The combined application of kanamycin and furosemide in experiments on guinea pigs led to an expressed ototoxic effect (Brummett et al., 1975): a considerable inhibition of the microphonic potential of the cochlea

one and a half to two hours after intravenous introduction of 100 mg/kg furosemide and 2 hours after subcutaneous introduction of 400 mg/kg kanamycin , which was confirmed by the destruction of pillar cells. under histological study. Simultaneous introduction of kanamycin and ethacryn acid causes an expressed toxic effect, even if the dosage of the latter comprises 40 mg per 1 kg of weight, i.e., with simultaneous introduction the dosage of ethacryn acid turned out to be toxic, although with separate introduction in the same dosage it did not lead to a reduction of the endolymphatic potential (Prazma et al., 1974).

Among the various medicinal preparations which have a damaging effect on the auditory analyzor, the greatest damage is caused by antibiotics. With parenteral introduction of the latter, their concentration in serum considerably exceeds that in the ear lymph and reaches its maximum more quickly (Quante et al., 1974). Even a gentamycin content of more than 40 γ /ml in the blood serum does not cause a sharp increase in its perilymph concentration. In the opinion of the authors, this fact testifies to the absense of the effect of gentamycin on the transport system of the cochlea.

Damage to the cochlea under the influence of antibiotics occurs non-uniformly. Experimental studies conducted on guinea pigs using the example of neomycin showed (V. S. Muraveyskaya, 1972) that damage to Corti's organ begins with the lowest part of the basilar spiral of the cochlea, i.e., from its receptor area associated with the perception of maximally high frequencies,and with an increase in application time of the preparation it gradually spreads to the upper part of the cochlea. /80

As concerns the paths of penetration of the toxic substance into the inner ear cavity, in this case, in the opinion of A. A. Lantsov (1971), the hemato-liquorrhic route is the most probable. This is confirmed by the absence in the retrocochlear paths, including the cortical end of the analyzor, of one or the most ototoxic antibiotics -- neomycin sulfate -- even after a 30-day injection regime with simultaneous accumulation and retention of the preparation within the area of the receptor (N. S. Pluzhnikov, T. I. Teplitskaya, 1971, 1972).

Penetrating into the inner ear cavity, antibiotics are distributed non-uniformly in its various structures. Electron microscopic studies of the cochlea conducted by Portmann et al. (1974) 1 hour after the introduction of tritium-marked dihydrostreptomycin sulfate showed that most of the dihydrostreptomycin was contained in the Deiter's cells, less in the main membrane, and still less in the spiral plate, the vascular stripe, the spiral ligament, perilymph, and Reissner's membrane. Only traces of dihydrostreptomycin were found in the fibers of the auditory nerve, in the endolymph above the pillar cells and in the tunnel. Four hours after introduction of the preparation, large quantities of it were found in the Deiter's cells and in the main membrane. The antibiotic was manifested in even greater quantity in the external pillar cells, primarily in their ribosomes. Dehydrostreptomycin was also found in the nerve endings and fibers, and other elements of the cochlea.

The antibiotic accumulated in the external pillar cells. Therefore they exhibited earlier change, while the internal pillar cells were

much more resistant to the toxic action (Quante et al., 1970; Brummett et al., 1972; Toyoda, 1976; Kiang et al., 1976; Anniko, 1976). Damage to the external pillar cells, according to data of electron microscopic studies (Glikoski et al., 1974) begins with the appearance of dense granules and plastic bodies in the subcuticular zone, as well as with the disruption in the structure of their lateral cytomembranes. Later there is a vacuolization of the elements of the smooth endoplasmid reticulum and the cell membranes rupture, releasing their contents into Nuel's space.

Nerve endings and fibers turned out to be more resistant against the action of damaging factors (Lim, 1976), and the changes found in them were supposed to be secondary, since even 3 months after the onset of total degeneration of Corti's organ as a result of the influence of kanamycin (in guinea pigs), there was a large number of myelin-free fibers in Corti's organ and in the spiral plate, as well as a large number of neurons in the spiral ganglion. Thus, even after several years, viable neurons were found in persons with complete hearing loss (Kiang et al., 1976).

The efferent innervation of the cochlea conditioned by the olivi-cochlear fascicle has a definite importance in the manifestation of ototoxicity of medicinal substances. It has been established (Capps, Duvall, 1975, 1977) that the lack of innervation of the latter through the olivi-cochlear fascicle achieved by its severance, evidently facilitated the protection of the pillar cells against the damaging effect of

aminoglycoside antibiotics. With the irritation of decussated olivi-cochlear fascicle some time after the daily introduction of neomycin, the impulse transfer in the nerve endings was blocked, which was registered by the change in microphonic potential of the cochlea. The indicated changes were accompanied by degeneration of the pillar cells (Brown, Daigneault, 1973). In the opinion of the authors, blocking of the transmission along the olivi-cochlear fascicle is a result of the replacement of the synaptic mediator by neomycin. And since acetylcholinesterase is found in the stereocilia and efferent synapses of the pillar cells under histochemical study (Ya. A. Vinnikov, L. K. Titova, 1958), the question arises: is the influence of ototoxic antibiotics possible on stimulus transmission in the synapses?

M. S. Pluzhnikov (1972) established a reduction in acetylcholin concentration and an increase in time of intoxication with local effect of a solution of neomycin sulfate, and its complete absence 48 hours later in the ear lymph with simultaneous total disintegration of the pillar cells on the one hand and no change in the fine structure of the nerve endings with well preserved vesicules on the other. This data confirms the possible intervention of neomycin in the acetylcholin metabolism, although the mechanism of this process remains unclear.

The results of experimental studies indicate the reduction in oxygen content in the ear lymph under the influence of streptomycin (B. S. Ivanov, 1972) and neomycin (B. S. Ivanov, 1972). Since the

reduction in partial pressure of oxygen in the ear lymph leads to considerable reduction in pillar cell succindehydrogenase activity (Ayani et al., 1975), we may speak of the influence of certain antibiotics on the system of respiratory enzymes. This supposition is confirmed by the data of Kaku et al (1973) on the almost total absence of succindehydrogenase and diphospholipidine nucleotide-diaphorase activity in the external pillar cells under the influence of kanamycin. With an increase in the dosage of the antibiotic, similar changes are found in the internal pillar cells and the vascular stripe. The introduction of the preparation in a dose of 400 mg/kg for a period of 10 days led to a reduction in adenosine triphosphatase activity as well.

However, the effect of medicinal preparations having a damaging effect on the auditory apparatus was not limited to the system of /81
respiratory enzymes. A reduction in the amount of acid mucopolysaccharides (MPS) in the lateral wall of the cochlea (in the guinea pig) increases the ototoxic effect of kanamycin (Saito, Daly, 1971). Considering the active participation of acid MPS in ion exchange, in the transfer of nutrient substances from the blood to the cell, as well as metabolytes in the opposite direction, the reduction in their quantity may be a reason for the lengthy retention of antibiotics in the labyrinth liquid (Stupp et al., 1967). The important role of acid MPS for the functioning of the inner ear structure is confirmed by their high content in the lateral wall (vascular stripe, spiral ligament) and in the cochlear membranes as compared with other organs (Saito, Daly, 1970; Saito et al., 1976).

A parallelism has been noted in damage to the external pillar cells by antibiotics and the reduction in glycogen content (Postma et al., 1976), which plays an important role in the metabolic-energetic processes in the cochlea (Ya. A. Vinnikov, L. K. Titova, 1957).

In ototoxicoses, a certain role is played by the affliction of the microcirculatory channel of the labyrynth artery system and the arteries of the brain (A. K. Pokotilenko, A. A. Gyul'khasyan, 1975). Pathomorphological studies in the arterioles and capillaries of the auditory system revealed the phenomena of stasis, plethora, as well as in the central sections -- perivascular circular cell infiltrates and swelling of the capillary endothelium with a sharp constriction of the vascular opening. However, with the introduction of neomycin in doses leading to destructive changes in the external and internal pillar cells of Corti's organ (150 mg per 1 kg of body weight, subcutaneously), no histological changes were exhibited in the vascular stripe (V. S. Muraveyskaya, 1971). They are noted only with the application of the preparation in very large dosages (Logan et al., 1974).

There is an opinion about the intervention of preparations having harmful effects in the processes of protein synthesis. This is confirmed by data (I. M. Tereshin, V. S. Cherkasov, 1973) on the significant statistically reliable reduction of RNA in the cochlea of temporal bones, combined with the significant or total disconnection of the function of the auditory analyzor in the absence of significant changes in DNA content in these same organs under the influence of neomycin. The inhibition

of nuclear RNA synthesis and the increase in cytoplasmic RNA content in the inner ear was discovered by Kraus, Gerlach (1970) after the application of streptomycin.

A factor facilitating the manifestation of the described effects of certain medicinal substances on cochlear structures is the disruption in the process of extracting these substances.

Many authors dispute the existence of cumulation of ototoxic antibiotics in the inner ear. However, a detailed study of the circulation of some of them has shown definite regularities in their extraction (T. I. Teplitskaya, 1971). It was also established that the speed of extracting various antibiotics from the ear lymph varies, but in all cases it is less than from other liquid mediums of the organism (Federspil et al., 1976). With repeated introduction of neomycin for 5 days, despite the intensified entry of the antibiotic into the inner ear, it is also energetically extracted (N. S. Pluzhnikov, T. I. Teplitskaya, 1972). Therefore the concentration of the antibiotic remains at approximately the same level 24 hours after injection. In connection with this, the difference between 12- and 24-hr concentrations increases. However, starting with the 10-th day, there is a disruption in the processes of extracting the toxic substance and possibly other metabolytes also, and its accumulation occurs. The significance of increased concentration of toxic substance in the inner ear fluid is demonstrated by data on the dependence between damage to Corti's organ and the dosage, duration, and method of application: locally or parenterally (E. A. Bakay, L. B. Neschetnaya, 1976; Stange, Winter, 1970; Brun et al., 1970; Brummett et al., 1972; Chodynicki, Kostrzewska, 1974; Johnstone, 1975),

as well as data on the intensification of the ototoxic effect of medicinal substances in people with one degree or another of kidney deficiency (McCurdy et al., 1974; Logan et al, 1974).

On the basis of a large amount of data on the toxic effect of numerous medicinal substances on the auditory organ, and primarily of antibiotics, which have a wide spectrum of anti-bacterial action, the question arises as to the expediency of developing methods of pharmacological influence on the degree of ototoxicity of these preparations. The necessity of research in this direction is also confirmed by the fact that existing preventive measures such as proper dosing of ototoxic preparations, prescribing them for short periods, adhering to intervals between the latter, consideration of the significant intensification of ototoxicity with simultaneous application of substances having such properties in prescribing them to people with kidney output disorders, do not always protect the auditory organ. Data available in the literature on the use of pharmacological preparations for the purpose of preventing the harmful action of the indicated substances on the auditory analyzor is not of a systemic character and is very scarce. Efforts have been made at using glutathione, neamide, otoneurine, as well as group B vitamins and amino acids. However, this did not yield positive results (Darrouzet, 1967). However, the authors used massive doses of kanamycin (400 mg/kg for a period of 14 days). Introduction of this antibiotic in smaller

doses would possibly have shown a "protective" action of the studied preparations.

Jankowski and Ziemski (1968), originating from data on biochemical changes taking place in the inner ear under the influence of ototoxic antibiotics, first introduced cytochrome C. As we know, the respiratory function of cytochrome consists of transferring electrons by iron atoms, which may take on or give off electrons from the outer orbit. The state of the auditory analyzor was judged according to the value of the microphonic potential of the cochlea registered from the cochlear window, and its change was studied under the influence of local introduction of cytochrome C or without it. The authors established that a more obvious "protective" action of cytochrome C was exhibited for high frequency tones. The difference in effectiveness of various doses of cytochrome C as a preparation reducing the toxic action of antibiotics on Corti's organ is insignificant. /82

On the other hand, on the basis of known data on the various mechanisms of pathogenesis of medicinal damage to the auditory organ, an effort may be made to prevent its occurrance and development with the aid of the directed action of appropriate medicinal preparations. Such studies were conducted by A. A. Gyul'khasyan (1971), who used nicotinic acid, cystein, a regenerator, glutathione, cystein, suprastine, heparin, and ATP with a background of introducing neomycin, monomycin, streptomycin, as well as soluble saluside (with proven ototoxic properties). The obtained results confirm the significant preventative role of the tested preparations, and especially ATP, cystein and nicotinic acid in the prevention of toxic effect on hearing caused by neomycin sulfate

and streptomycin. It should also be noted that the effect obtained from the application of preventative measures in complex exceeded that for the same preparations used separately (A. A. Gyul'khasyan, 1971,b).

Morphological and electrophysiological studies conducted by Holz et al. (1968) showed an almost total absence of toxicity of streptomycin introduced together with ozotine. Ozotine is a component part of the soluble oxidizing products of terebenthene oil. The bacteriostatic effect of streptomycin when combined with ozotine was not disrupted. The authors believe that possibly the streptomycin is re-absorbed from the cells of the acoustic system. However Cada et al. (1968) proved that no significant difference was found between concentrations of streptomycin sulfate with ozotine or without it determined in blood serum and in the perilymph. Moreover, the degree of effectiveness of ozotine did not depend on its concentration.

A partial reduction in the ototoxicity of antibiotics could also be achieved by breaking up their daily dosages, which was demonstrated by Federspil (1972) with the example of gentamycin.

A. I. Braude (1969, 1970) studied the side effects of antibiotics which are conditioned by the direct harmful effect of these preparations on tissue culture cells, and the reduction of this effect with the aid of substances which increase cell resistance to the harmful action. Based on their own data on increased cell resistance to harmful effect with intensification of the intracellular protein synthesis, the authors used two substances with anabolizing effect -- pyrimidine derivative

4-methyluracil (methacil) and purine derivative 1.8 mercapto-adenine (meradine), and studied their effect on the resistance of the small intestine epithelium to high dosages of tetracycline preparations (dichlortetracycline and tetracycline) and the effect of meradine on the nephrotoxic effect of neomycin, kanamycin, and gentamycin. It was shown that the irritating effect of both tetracycline antibiotics was not manifested when they were used simultaneously with methacil. Meradine in a dosage of 5 mg/kg had a significant positive effect in combination with various doses of aminoglycoside antibiotics. The use of substances which increase cell resistance for purposes of reducing the direct harmful effects of antibiotics on them may prove to be expedient for the study of their effectiveness in relation to the auditory organ.

There is data (V. A. Kochetkova, 1970) on the reduction of toxicity of certain antibiotics, particularly streptomycin sulfate and monomycin, when they are introduced in polyvinylpyrrolidone solution, particularly of low molecular weight (molecular weight of 12,600), and calcium chloride. The authors have noted that in rats who have received toxic doses of streptomycin, it was possible to remove all visible manifestations of toxicity by this preparation with the aid of 4% solution of calcium chloride and 6% solution of polyvinylpyrrolidone. The most expressed effect of detoxification was observed during the earlier stages of its introduction. With monomycin intoxication, the effect was less expressed, especially in using calcium chloride.

There is information on the application of natural biopolymer collagen for obtaining lasting preparations of certain medicinal substances (R. K. Aboyants, 1972; I. A. Sychenikov et al., 1974; Ye. V. Batashova et al., 1975; A. N. Khil'kin et al., 1976). It has been established that antibiotics, entering into interaction with the collagen, do not lose their specific activity, while the formed complex has an expressed prolonged action (N. A. Preobrazhenskiy et al., 1973; A. Sh. Vaisov et al., 1975). Using a collagen as a monomycin carrier reliably reduced the toxicity of the latter (T. G. Rudenko, 1977). However, the effect of the indicated substances on the auditory organ was not studied in these works, although it is known that a reduction of the auditory function is one of the main reasons for limiting their use in the clinic. At the same time, predicting ahead of time which preparation can prevent antibiotic induced damage to the auditory organ is unlikely. For example, the prophylactic introduction of unithiol prevented the death of animals intoxicated with saluside, and considerably increased their resistance to streptomycin (R. A. Yushkova, 1970). However, the use of unithiol for "protecting" Corti's organ during the introduction of streptomycin in clinical experiment did not yield significant effect (A. N. Ageyeva et al., 1971).

Positive results of using preparations for the purpose of preventing the development of drug induced deafness was noted not only with the action of antibiotics. According to the preliminary results obtained by Brown (1973), triamterene evidently exhibits a blocking effect on the

depression N_1 of the action potential of the auditory nerve caused by furosemide. Triamterene in a dose of less than 8 mg/kg had an insignificant preventative effect on reducing N_1 caused by furosemide. However, in larger doses, the prior introduction of triamterene reduced N_1 depression to a level approaching that attained with the use of physiological solution.

The development of methods of pharmacological prevention of the harmful effect of drugs on the auditory analyzor is a necessity. The solution of this problem would considerably enlarge the indicators for the application of these drugs and would contribute significantly to the problem of studying the fine mechanism of the effect of drugs on the auditory system.

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