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Prospects for Rational Elaboration and Use of Medicinal Products in the Treatment of Sensorineural Hearing Loss

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Abstract

Over 6 million reports of adverse drug reactions have been recorded, approximately 50% of which are associated with the irrational use of medicinal products, medication errors, and inadequate consideration of individual patient characteristics.

Pharmacodynamics and pharmacotoxicology study the effects of drugs (biological effects) on the body, whereas pharmacokinetics investigates the effects of the body on drugs, including their absorption, distribution, metabolism, and elimination.

The interaction between endogenous or exogenous molecules and their corresponding structures within a living organism determines the pharmacodynamic properties of a drug. Although the pharmacodynamics of numerous pharmacotherapeutic groups has been extensively studied, the same cannot be said for the mechanisms of drug action, which constitute a fundamental component of pharmacodynamics. Our understanding of these mechanisms is continuously evolving in parallel with scientific advances. Therefore, studying the mechanism of action of each individual drug is of paramount importance, as without such knowledge, new medicinal products cannot be appropriately integrated into modern pharmacotherapy.

Research conducted at the intersection of thermodynamics, statistical physics, chemistry, pharmacy, and pharmacology is of particular importance, especially for predicting the pharmacological effects of novel substances. These principles are equally applicable to the groups of drugs used in the conservative treatment of sensorineural hearing loss (SNHL).

Keywords: Pharmacoterapy, hearing loss, drug elaboration, prognosis, adverse effects.

Case 1:

According to the World Health Organization (WHO), over 6 million reports of adverse drug reactions have been recorded, approximately 50% of which are associated with the irrational use of medicinal products, medication errors, and inadequate consideration of individual patient characteristics, comorbidities, and genetic factors (World Health Organization (WHO), 2024; Parii, 2018). Furthermore, by 2030, the number of people affected by various forms of hearing loss may reach 1 billion (Parii, 2018).

Pharmacovigilance plays an important role in preventing adverse drug reactions. According to the WHO definition, pharmacovigilance is the science related to the detection, assessment, understanding, and prevention of adverse reactions, adverse effects, or other problems associated with the use of medicinal products under real-world conditions. It is a shared responsibility among healthcare professionals (physicians, pharmacists, and nurses), national drug regulatory authorities, pharmaceutical manufacturers, and research institutions in the fields of pharmacy and pharmacology (WHO, 2024; Parii, 2018). Therefore, research aimed at improving the safety of medicinal products remains highly relevant and will continue to be of significant importance.

A drug is any product of plant, animal, mineral, or synthetic origin that interacts with the biochemical and morphofunctional structures of a living organism. It is based on endogenous or exogenous chemical molecules, whether already identified or yet to be discovered (Parii, 2018; Classifier of medicines authorized in the Republic of Moldova).

Pharmacodynamics and pharmacotoxicology study the effects of drugs (biological effects) on the body, whereas pharmacokinetics investigates the effects of the body on drugs, including their absorption, distribution, metabolism, and elimination. The interaction between endogenous or

exogenous molecules and the corresponding structures of a living organism determines the pharmacodynamic properties of a drug. Although the pharmacodynamics of numerous pharmacotherapeutic groups has been studied extensively, the same cannot be said for the mechanisms of drug action, which constitute a fundamental component of pharmacodynamics (Kuhn et al., 2016; Parii, 2007). Our understanding of these mechanisms is continuously evolving in parallel with scientific advances. Therefore, studying the mechanism of action of each individual drug is of paramount importance, as without such knowledge, new medicinal products cannot occupy their proper place among modern pharmaceutical products (Kuhn et al., 2016; Parii, 2007; Parii, 1999).

There are two forms of solidification of substances: crystalline and amorphous. A crystal is a homogeneous, anisotropic body whose constituent particles (atoms, molecules, or ions) are arranged in a well-defined three-dimensional internal structure according to various symmetry systems with periodic repetitions, known as crystal lattices (Parii, 2007; Parii, 1999; Shi et al., 2021).

The vast majority of drugs are crystalline substances, and it is in this form that they enter the body. According to its characteristic entropy, the body attempts to eliminate these substances as rapidly as possible. The amorphous form results from the fact that, during the cooling of a substance, its viscosity increases sharply, preventing atoms and molecules from forming crystals (Shi et al., 2021; Liu et al., 2023). In the case of solidification in the crystalline form, crystallites are formed in the cooled liquid at a specific temperature below 0°C. The prediction of pharmacological effects of drugs is applied in research through methods used for predicting the allergenic effects of medicinal products (Tukaram et al., 2010; González-González et al., 2022).

The spectrum of drug groups used concurrently in the pharmacological treatment of **Sensorineural Hearing Loss (SNHL)** requires the development of prognostic factors for assessing the efficacy of protective pharmacotherapy (Chandrasekhar et al., 2019; Ewert et al., 2012).

Aim of Study

To increase the effectiveness of drugs and predict their adverse effects in neurosensory pathologies of the auditory analyzer.

Materials

Several methods have been proposed to reduce the risk of drug allergy, including the formation of coupling compounds (clathrates), the transition of microcrystalline powders to an amorphous state, the use of the principle of eutectic mixtures, various methods for transforming organic and inorganic chemical substances into forms closer to the natural state, the application of modern methods for purifying medicinal substances and other chemical products widely used in everyday life, and the segmentation of cellular particles and macromolecules into molecules of intermediate molecular mass or, whenever possible, into micromolecules, etc. (Parii, 2018; Parii, 2007).

The above-mentioned concepts can be schematically presented as follows:

1. crystal → amorphous state in the body;
2. amorphous powder → amorphous state in the body.

Obviously, in the first case, a significantly greater amount of energy is required to achieve the necessary transformations compared with the second variant (Parii, 2007).

The methods proposed by Prof. Boris Parii aim to reduce, as much as possible, the amount of associated molecules (microcrystals) when the drug enters the body and to promote their individual isolation (separation). This process makes it possible to obtain specific pharmacodynamic effects while simultaneously significantly reducing nonspecific, i.e., undesirable, effects (Kuhn et al., 2016; Parii, 2007).

A study has shown that the higher the dose, the greater the probability of allergic reactions. It was determined that medicinal products administered at doses of up to 0.05 g/kg induce allergic reactions in 9% of cases, doses ranging from 0.05 to 0.5 g/kg induce reactions in 38% of cases, and doses exceeding 0.5 g/kg induce reactions in 89% of cases (Parii, 2018; Kuhn et al., 2016; Parii, 2007).

Results

Importance are the melting point and solubility in water or lipids. This proves the role of intermolecular forces in allergic reactions: the stronger they are, the greater the likelihood of allergic complications. Two groups of substances have been formed, which have been used in medicine for a long time. In the first we included preparations with a melting point up to 100 0C, and in the second – the same number of drugs with a melting point above 200 0C. The molecular mass, dose, solubility in water and fats were determined. Based on these data, Prof. B. Parii proposed the formula for determining the probability of the organism's allergy:

$$\mathbf{I=(0.001M+0.5d+0.01T)/0.1S,}$$

where:

I : the organism's allergy index;
M : the molecular mass of the drug in carbon units;
d : dose (grams);
T : melting point (degrees Celsius);
S : solubility in water or lipids (g/100 ml).

Considering that the above indices are expressed in different units, in order to bring them to a value close to each other, the following constants were introduced: T=0.01; M=0.001; d=0.5 and S=0.1. Drugs with a melting point above 200^0C also have a higher molecular weight and are less soluble in water or fats. The allergization index, calculated according to the respective formula, is equal to 0.44 in the first group and 3.24 in the second group. In patients, drugs from the first group cause allergic reactions only in 3% of cases, and those from the second – in 70% of cases. Therefore, the lower the allergization index (<1.5), the more harmless the drug is. A study has shown that the higher the dose, the greater the likelihood of allergic reactions. It was determined that medicinal products administered in doses of up to 0.05 g/kg provoke allergic

reactions in 9% of cases, from 0.05 to 0.5 g - in 38% of cases, and more than 0.5 g - in 89% of cases (Parii, 2018; Kuhn et al., 2016; Ewert et al., 2012).

Thus, according to the research of Prof. Boris Parii, the following medicinal products have increased safety: with a melting point < 100^0C; with a low molecular weight (≤ 1000 UC); in an amorphous form; used in doses < 0.5 g; with high solubility (≥ 20 g/l).

Since metabolic processes in the body occur in aqueous or lipid environments, the solubility of drugs in these environments is important for their pharmacological effects.

Therefore, the prediction of pharmacodynamics and pharmacokinetics of synthetic chemicals can be performed based on their physicochemical properties, including thermodynamic indices (solubility in water or lipids, state of aggregation, melting point).

Drugs used in the treatment of SNHL enter the inner ear from the systemic circulation either by transport mechanisms or by dissolution in the capillary endothelium. The crossing of the hemato-labyrinthine barrier by drugs depends on their chemical characteristics. Drugs with high molecular weight or electrical charge cross with difficulty, passively. High lipid solubility facilitates passage. Drugs that bind to proteins cross more difficult. The unusual positive potential in the labyrinth further complicates passage, as positively charged drugs have to face an electrical gradient (Parii, 2018; Fazel et al., 2017; Kemp et al., 1990).

In this study we have described the drugs frequently used in the treatment of SNHL according to the method of Boris Parii and have established the following aspects: most of the products have a melting point between 100 and 200^0C, low molecular weight, but in the crystalline form a medium degree of adverse reactions is noted. Therefore, the practicing physician must be very cautious, especially when using medicinal products in the treatment of SNHL (table 1).

Table 1: Physico-chemical properties of some medicinal products used in the treatment of SNHL

The Substance / Pharcaceutical form	Melting Point	Molecular Mass	Solubility	Form crystalline or amorphous
Vinpocetine (tab.)	147-153 ºC	350.45 g/mol	Insoluble in water, Soluble in ethanol	Crystals
Nicergoline (tab.)	136-138 ºC	484.39 g/mol	Insoluble in water, Soluble in ethanol	Crystals
Betahistine (tab.)	148-149 ºC	136.19 g/mol	Soluble in water, Soluble in ethanol	Crystals
Cinnarizine (tab.)	192 ºC	368.51 g/mol	Soluble in water, Soluble in ethanol	Crystals
Piracetam (tab.)	152 ºC	142.23 g/mol	Slightly soluble in water	Crystals
Glycine (tab.)	233 ºC	75.14 g/mol	Soluble in water, Insoluble in ethanol	Crystals
Pentoxifylline (tab.)	105 ºC	278.32 g/mol	Slightly soluble in water and ethanol	Crystals
Dexamethasone (tab.)	262-264 ºC	392.46 g/mol	Insoluble in water, Soluble in ethanol	Crystals
Metilprednisolone (tab.)	228-237 ºC	374.47 g/mol	Insoluble in water, Soluble in ethanol	Crystals
Neostigmine (tab.)	170 ºC	303.26 g/mol	Very soluble in water, soluble in ethanol	Crystals
Spironolactone (tab.)	431-451 ºC	416.57 g/mol	Insoluble in water, Soluble in ethanol	Crystals
Arginine	260 ºC	174.20 g/mol	Soluble in wather, slightly soluble in etanol	Crystals
Resveratrol	261-263 ºC	228.25 g/mol	Insoluble in water, Soluble in ethanol	Crystals

Discussion

Thus, the effectiveness of pharmacological treatment in subacute forms of SNHL remains limited, while chronic SNHL is, in most cases, non-responsive to pharmacotherapy (Fazel et al., 2017; Kemp et al., 1990). Therefore, it can be concluded that numerous pharmacological treatment approaches for chronic SNHL do not produce the expected beneficial effects, the main reasons being the limited penetration of medicinal products through the hematolabyrinthine barrier and their incomplete action on all etiological factors and pathogenetic mechanisms involved in SNHL. Improving the concept of medicinal otoprotection in SNHL requires both the development of new pharmacological products and the revision of currently used therapeutic agents, based on a comprehensive understanding of all aspects of pathogenesis and the mechanisms underlying otoprotective effects (Parii, 2018; Fazel et al., 2017; Kostal et al., 2017).

Considering the multitude of groups of drugs used in the treatment of SNHL, the combined administration of drugs, the correlation between the physicochemical characteristics of drugs and the clinical-biological characteristics of the

body, the polypharmacy encountered in the pharmacotherapy of the respective pathology, the use of drugs with ototoxic effects, especially in the treatment of acute SNHL (Kostal et al., 2017; Rus et al., 2025; Parii et al., 2025). The studies on the prognosis of the effect of combined pharmacotherapy in patients with sensorineural and mixed disorders of the auditory analyzer based on the following indices become opportune and promising: the nature and duration of the disease, the results of the audiometric assessment, the pharmacological preparation, the posology, the chemical-pharmaceutical properties, the melting point of the active principle (Kemp et al., 1990; Rus et al., 2025; Parii et al., 2025).

Prognosis of the effectiveness of drug treatment Factors of favorable prognosis: mild-moderate hearing loss, low- and medium-frequency hearing loss; lack of vestibular symptoms; early treatment (first hours-days after the onset of hearing loss); administration of cerebral vasodilators, antioxidants, and nootropics. Factors of unfavorable prognosis: advanced age; severe-profound forms of deafness; high-frequency hearing loss; objective vestibular symptoms; risk factors of vascular origin; late treatment, start of pharmacotherapy more than 2-3 weeks after onset (Parii, 2018; Raveh et al., 2007; Szczepek, 2024).

Based on these aspects, prospective studies will aim to: develop principles for predicting the otoprotective efficacy of drugs; establish rational combinations of otoprotective agents for the treatment of SNHL; enhance pharmacotherapeutic effects; assess the possibility of developing adverse reactions during the use of otoprotective preparations; and develop medicinal products in amorphous chemical forms, as well as coupling compounds and eutectic mixtures of medicinal products, with the potential to improve the tolerability of pharmaceutical products.

Conclusions

From the perspective of improving pharmacovigilance in pharmacotherapy, the use of biochemically characterized principles is encouraged, since endogenous products, which are naturally present in the human body, are considered to be the least harmful. In this case, an immune conflict does not develop, and pharmacological responses to the drug can be predicted based on known physiological and biochemical mechanisms.

Research conducted at the intersection of thermodynamics, statistical physics, chemistry, pharmacy, and pharmacology is of particular importance, especially for predicting the pharmacological effects of new substances. These principles are also applicable to the groups of drugs used in the drug treatment of SNHL.

Of particular scientific interest are studies focused on predicting the effects of combined pharmacotherapy in patients with sensorineural and mixed disorders of the auditory analyzer, based on the pharmacological preparation, dosage regimen, chemical-pharmaceutical properties, and melting point of the active substance.

In memoriam of Boris Parii (1944-2009), PhD, Professor, Nicolae Testemitanu" State University of Medicine and Pharmacy, Chisinau, Republic of Moldova.

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