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New generation antihypoxants: alkaline hydrogen peroxide solutions as medical oxygen gas generators

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ABSTRACT

The cause of biological death in warm-blooded animals and humans is hypoxic brain cell damage. Consequently, *oxygen gas* is the leading antihypoxant in emergency medical care for all critical conditions. The most common method of oxygen administration is *mechanical ventilation*. However, in cases of asphyxia caused by airway obstruction with thick *sputum*, *mucus*, *pus*, and/or blood, inhaled oxygen does not reach the *alveoli* and is not absorbed into the bloodstream. In such situations, traditional mechanical ventilation becomes ineffective and fails to prevent biological death due to hypoxic brain cell damage. At the beginning of the 21st century, as an alternative to gaseous oxygen, mechanical ventilation, and extracorporeal membrane oxygenation, the development of *intrapulmonary oxygen-producing antihypoxants* through physicochemical repurposing of hydrogen peroxide was initiated in Russia. Professor P.D. Shabanov served as the mind behind and coordinator of the development of new-generation antihypoxants. A new group of antihypoxants—warm alkaline hydrogen peroxide solutions—was discovered. The most effective oxygen-producing antihypoxants, when applied locally via the intrapulmonary route, generate significant volumes of medical oxygen gas through catalase-mediated decomposition of hydrogen peroxide into water and molecular oxygen. The local intrapulmonary, endotracheal, and endobronchial pharmacodynamics and pharmacokinetics of warm alkaline hydrogen peroxide solutions are inseparable from interactions with catalase present in *sputum*, *mucus*, serous fluids, purulent masses, and blood that obstruct the airways during asphyxia and/or severe acute respiratory obstruction. The new generation of antihypoxants has demonstrated high therapeutic potential as powerful medical oxygen gas generators when administered intrapulmonarily, endobronchially, or endotracheally during acute severe suffocation caused by airway blockage with colloidal liquids containing catalase. It is hypothesized that intrapulmonary oxygen-producing antihypoxants could be considered therapeutic agents for emergency blood oxygen saturation through the lungs when mechanical ventilation is ineffective and extracorporeal membrane oxygenation is not feasible.

Keywords: hydrogen peroxide; oxygen gas; antihypoxants; catalase; oxygen generator; development; drugs.

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Антигипоксанты нового поколения: щелочные растворы перекиси водорода как генераторы медицинского газа кислорода

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АННОТАЦИЯ

Причиной биологической смерти теплокровных животных и людей является гипоксическое повреждение клеток головного мозга. В связи с этим газ кислород представляет собой антигипоксант номер один при оказании неотложной медицинской помощи во всех критических состояниях. Наиболее широко кислород используется для этой цели с помощью искусственной вентиляции легких. Однако при асфиксии, вызванной закупоркой дыхательных путей густой мокротой, слизью, гноем и/или кровью, ингаляционный кислород не достигает альвеол и не всасывается в кровь. В указанных ситуациях традиционная искусственная вентиляция легких теряет свою эффективность и не предотвращает биологическую смерть от гипоксического повреждения клеток мозга. В начале XXI в. в качестве альтернативы газообразному кислороду, искусственной вентиляции легких и экстракорпоральной мембранной оксигенации в России была начата разработка внутрилегочных кислород-продуцирующих антигипоксантов путем физико-химичсекого перепрофилирования перекиси водорода. Катализатором и координатором разработок антигипоксантов нового поколения стал профессор П.Д. Шабанов. В результате была открыта новая группа антигипоксантов, которые представляют собой теплые щелочные растворы перекиси водорода. Наиболее эффективные кислород-продуцирующие антигипоксанты при внутрилегочном местном применении обеспечивают мощную генерацию медицинского газа кислорода за счет каталазного расщепления перекиси водорода на воду и молекулярный кислород. Местная внутрилегочная, эндотратрахеальная и эндобронхиальная фармакодинамика и фармакокинетика теплых щелочных растворов перекиси водорода неотделимы от взаимодействия с каталазой, содержащейся в мокроте, слизи, серозных жидкостях, гнойных массах и крови, заполнивших собой дыхательные пути при асфиксии и/или тяжелой острой респираторной обструкции. Показан высокий терапевтический потенциал антигипоксантов нового поколения как мощных генераторов медицинского газа кислорода при их внутрилегочных, эндобронхиальных и эндотрахеальных инъекциях в состоянии острого тяжелого удушья, вызванного закупоркой дыхательных путей коллоидными жидкостями, содержащими каталазу. Предполагается, что внутрилегочные кислород-продуцирующие антигипоксанты могут рассматриваться как лекарственные препараты резервной сатурации крови через легкие в ситуации низкой эффективности искусственной вентиляции легких и невозможности применения экстракорпоральной мембранной оксигенации.

Ключевые слова: перекись водорода; газ кислород; антигипоксанты; каталаза; генератор кислорода; разработка; лекарства.

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INTRODUCTION

The cause of biological death in all warm-blooded animals and humans is hypoxic damage to brain cells, which occurs inevitably and very quickly in the absence of oxygen under normal body temperature conditions, regardless of the age or health status of these biological entities [1–3]. In particular, hanging in an adult leads to brain death within just a few minutes [4–6]. Combating hypoxia and hypoxic brain injury therefore represents the primary goal of emergency medical care. For this purpose, emergency medical personnel and specialists in intensive care and resuscitation units use inhaled *oxygen gas* as the first-line resuscitative measure. Oxygen gas is recognized globally as the number one revitalizing antihypoxic agent for all critical conditions without exception [2, 7–9].

Despite this, the use of oxygen according to general guidelines is not sufficient to eliminate cerebral hypoxia in all situations. For example, it has been reported that up to 88% of patients in the terminal stage of atypical pneumonia caused by the novel coronavirus infection (COVID-19), interpreted as severe acute respiratory syndrome, died from critical hypoxia despite the administration of inhaled oxygen gas via modern mechanical ventilators [10–13]. Due to the low effectiveness of ventilatory support, it has been hypothesized that the cause of suffocation, hypoxemia, and death in COVID-19 may be asphyxia resembling high-altitude pulmonary edema [10], or airway obstruction caused by excessive accumulation of thick *sputum*, *mucus*, and/or *pus* [10–19]. In such cases, lung ventilation with respiratory gases that contain oxygen does not ensure oxygen delivery to the *alveoli*, from where it can subsequently diffuse into the bloodstream. This conclusion is supported by cases of *blood-related asphyxia*, which also reduces the effectiveness of hypoxemia correction through mechanical ventilation. Therefore, it is not surprising that in such critical conditions, hypoxemia can only be eliminated through extracorporeal membrane oxygenation (ECMO) [9, 20–24].

The management of hypoxemia using ECMO is a very expensive and risky medical procedure that requires specialized equipment and respective licensed facilities [25, 26]. In recent years, active research has focused on the possibility of replacing lung ventilation and ECMO with novel pharmacological agents with antihypoxic activity that can increase the survival rate of patients with hypoxia [27]. In Russia, research attention has been centered on *antihypoxic agents* that include hydrogen peroxide, which, under the action of the enzyme catalase, can decompose into water and molecular oxygen at a very high rate [2, 9, 13, 14, 19, 27, 28].

CONVENTIONAL ANTIHYPOXIC AGENTS (NON-OXYGEN-PRODUCING)

Currently, the international classification of drugs does not include antihypoxic agents as a separate pharmacological class. Antihypoxic agents have been identified as a distinct pharmacological class of drugs only in Russia. This is largely explained by the fact that the development of antihypoxic agents was first initiated by the staff of the Department of Pharmacology at the S.M. Kirov Military Medical Academy (MMA) in Leningrad in the 1960s. The author of the *antihypoxant* concept was Professor Vasily M. Vinogradov (1924–2003) [1, 29]. The first antihypoxic agents (gutimin, amtizole, bemitil, almid, and etomerzole) were synthesized by F.Yu. Rachinsky. In terms of chemical structure, they belonged to aliphatic and cyclic aminothiols.

In 2000, Professor Petr D. Shabanov was elected the Head of the Department of Pharmacology at the MMA [30]. He led the search for and development of new antihypoxic agents. To date, various agents with different mechanisms of antihypoxic action have been developed in Russia [31]. It has been established that antihypoxic agents improve the utilization of circulating oxygen in the body and increase the body's resistance to hypoxia (oxygen deficiency) [31–38]. Known agents are usually divided into two groups: antihypoxic agents of direct energizing action (correctors of energy metabolism disturbances, also known as correctors of mitochondrial respiratory chain dysfunction) and antihypoxic agents of indirect energizing action (correctors of metabolic pathway disturbances) [29, 39]. It has been shown [29] that all antihypoxic agents belonging to aliphatic and cyclic aminothiols (gutimin, amtizole, bemitil, almid, etomerzole, and many of their analogs) exhibit three main types of activity:

1) antihypoxic action;
2) antioxidant effect;
3) ability to accelerate the reparative and adaptive synthesis of RNA, enzymes, functional, and structural proteins in response to various types of damage, including hypoxic, infectious, toxic, stress-related, as well as in the process of adaptation to challenging conditions.

The classification of antihypoxic agents adopted in Russia [1, 29, 31, 39] includes:

1) fatty acid oxidation inhibitors;
2) succinate-containing and succinate- producing agents;
3) natural components of the respiratory chain;
4) artificial redox systems;
5) macroergic compounds.

Currently, research on antihypoxic agents is being conducted not only in Russia but also in other countries. However, the most important results have been obtained by Russian researchers [40]. Traditionally, research is based on chemical elements, chemical formulas, and the names and symbols of biologically active substances [1, 41]. Unfortunately, large-scale studies on the efficacy of real pharmaceutical products that belong to this pharmacological class of medicines in acute critical asphyxiation and drowning of experimental animals have not yet been conducted. In addition, there is no convincing evidence of high efficacy of known antihypoxic agents in acute asphyxia caused by subtotal and/or total obstruction of the airways by colloidal

biological fluids such as *sputum*, *mucus*, *pus*, blood, and/or starch-like fluid. In cases of critical hypoxia developing in the terminal stage of COVID-19 due to acute respiratory obstruction, conventional antihypoxic agents did not meet expectations and did not become an alternative to mechanical ventilation and ECMO in emergency conditions in clinical settings [9, 12, 42–44]. For this reason, at the beginning of the COVID-19 pandemic, Russian researchers decided to develop antihypoxic agents with high oxygen-producing activity that could become an alternative to ECMO [13, 14, 19, 42, 43]. It was assumed that hydrogen peroxide solutions could be the basis for oxygen-producing antihypoxic agents. The development of new-generation antihypoxic agents was based on the Russian initiative of physicochemical repurposing of "old" drugs, including their enrichment with special gases [45–48]. Professor P.D. Shabanov [2, 9, 29, 44, 49] assumed the role of coordinator of the development of new-generation antihypoxic agents.

WARM ALKALINE HYDROGEN PEROXIDE SOLUTIONS AS NEW-GENERATION ANTIHYPOXIC AGENTS CHARACTERIZED BY PRONOUNCED RELEASE OF MEDICAL OXYGEN GAS

The study of the oxygen-producing antihypoxic activity of hydrogen peroxide solutions began in Russia in December 2013. At that time, the first patent application for the invention *Method of transportation and storage of live fish in water* was registered. This method involves adding a 6% hydrogen peroxide solution to the water with live fish, where it serves as an antihypoxic agent that, through the action of catalase, decomposes into water and molecular oxygen [50].

By mid-2024, 14 inventions had been developed in Russia, in which original hydrogen peroxide solutions were used as oxygen-producing antihypoxic agents [44, 51].

1. Urakov AL, Urakova NA, Agarval RK, et al. Method of maintenance of live fish during transportation and storage. RU 2563151C1, 20.09.2015. (In Russ.)
2. Urakov AL, Urakova NA, Reshetnikov AP, et al. E.M. Soikher's hyperoxygenated agent for venous blood oxygen saturation. RU 2538662C1, 10.01.2015. (In Russ.)
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6. Urakov AL. Means for physical endurance increase. RU 2634271C1, 24.10.2017. (In Russ.)
7. Urakov AL, Urakova NA, Gurevich KG, et al. Method for extracorporeal blood oxygenation. Application RU 2020120367A, 2020.06.15. *Inventions. Utility Models.* 2021: 35. (In Russ.)
8. Samylina IA, Ales MYu, Urakov AL, Urakova NA, Nesterova NV, et al. Aerosol for inhalations in obstructive bronchitis. RU 2735502C1, 03.11.2020. (In Russ.)
9. Urakov AL, Urakova NA. Aerosol for invasive mechanical ventilation in COVID-19. RU 2742505C1, 08.02.2021. (In Russ.)
10. Urakov AL, Urakova NA, Reshetnikov AP, et al. Method for lung oxygenation in COVID-19. Application RU 2021102618A, 04.02.2021. *Inventions. Utility Models.* 2022:22. (In Russ.)
11. Urakov AL, Urakova NA, Shabanov PD, et al. Warm alkaline solution of hydrogen peroxide for intrapulmonary injection. RU 2807851C1, 21.11.2023. (In Russ.)
12. Urakov AL, Urakova NA, Fisher EL. Oxygenated warm alkaline solution of hydrogen peroxide for intrapulmonary injection. Application RU 2023128553C1, 02.11.2023. (In Russ.)
13. Urakov AL, Shabanov PD. An alkaline solution of hydrogen peroxide and a method of its application to eliminate blood asphyxia. Application RU 2024100268C1, 09.01.2024. (In Russ.)
14. Urakov AL, Shabanov PD. Method of endobronchial injection of drug for emergency elimination of asphyxia. Application RU 2024102289C1, 29.01.2024. (In Russ.)

Analysis shows that 8 inventions (i.e. more than half of all inventions) were developed between 2020 and 2024, specifically during the COVID-19 pandemic. To prevent hypoxic damage to brain cells under hypoxemia, oxygen-producing antihypoxic agents, which represent alkaline solutions of hydrogen peroxide, were used. They consist of hydrogen peroxide, sodium bicarbonate, and distilled water. A distinctive feature of these agents is their mildly to moderately alkaline activity with pH 8.4, osmotic (isotonic) activity within 280–300 mOsm/L of water, and temperature range of 37–45 °C (these agents are used warm and can provide safe local hyperthermia) [52].

The most recent four inventions represent the world's first pharmaceutical products developed for intrapulmonary and endobronchial injections. Unlike the previously developed alkaline hydrogen peroxide solutions, these products are enriched with oxygen under excess pressure. It should be emphasized that, prior to this, neither such pharmaceutical products nor the procedures of intrapulmonary, endobronchial, or endotracheal injections had been known.

The composition and key physicochemical properties of the next-generation antihypoxic agents are clearly demonstrated by the formula of the invention titled *Warm alkaline solution of hydrogen peroxide for intrapulmonary injection* (RU 2807851C1):

"A warm alkaline hydrogen peroxide solution intended for intrapulmonary injection to rapidly increase the oxygen content in the airways and bloodstream, having a certain volume, temperature, and alkalinity, and containing hydrogen peroxide, sodium bicarbonate, oxygen gas added to create

an overpressure of 0.2 atm at 8 °C, and water for injection, wherein the 30 mL solution is heated to 42 °C and contains the components in the following proportions (wt. %):

Hydrogen peroxide —4.5

Sodium bicarbonate —1.8

Oxygen—up to an overpressure of 0.2 atm

Water for injection

The remainder—to balance, providing an osmotic activity of 280–300 mOsm/L of water and an alkalinity within a pH range of 8.4–8.5."

The choice of *hydrogen peroxide* as the main ingredient was due to its ability to decompose into water and oxygen gas under the action of catalase—an enzyme present in all parts of the human and animal body, which accelerates the decomposition of hydrogen peroxide and the release of oxygen gas by hundred thousand times. The choice of *sodium bicarbonate* as an auxiliary ingredient was explained by the fact that it is a natural alkaline buffer of the blood in warm-blooded animals and humans, ensuring a safe yet effective alkalinity within a pH range of 8.4. It has been shown that increasing local temperature and raising the pH level (alkalization) of hydrogen peroxide solutions accelerates their catalytic decomposition into water and molecular oxygen, up to the point of intensive oxygen gas generation manifested as a phenomenon called *cold boiling* [9, 28, 44, 53]. Moreover, it was found that as a result of catalytic decomposition of hydrogen peroxide, 100 mL of a 6% hydrogen peroxide solution generates 1.97 L of oxygen gas with a mass of 2.816 g [54]. This means that, under certain conditions, 1 L of a 6% hydrogen peroxide solution can release approximately 20 L of oxygen gas. No other known medicinal product has such oxygen-generating capacity.

These oxygen-generating properties of hydrogen peroxide decomposition, obtained through chemical calculations, were confirmed by the results of laboratory and experimental trials. It was reported that warm alkaline hydrogen peroxide solutions, when locally interacting with liquid colloidal tissues containing catalase, intensively generate oxygen, rapidly forming gas bubbles in the colloidal fluids. The process of oxygen bubble formation in liquids resembles cold boiling, which quickly transforms colloidal fluids into oxygen foam. Moreover, it has been demonstrated that intrapulmonary administration of warm alkaline hydrogen peroxide solutions exhibits the highest capacity for oxygen enrichment of the respiratory tract and blood compared to all known medicinal agents [13, 14, 44, 51]. Endobronchial, endotracheal, and intrapulmonary injections of warm alkaline hydrogen peroxide solutions cause immediate and intense foaming of *sputum*, *mucus*, *pus*, blood, and/or *meconium* in the respiratory tract. The developed oxygen gas generators used for intrapulmonary, endobronchial, and endotracheal injections can act as geyser-like perforators in the airways in cases of their obstruction with *sputum*, *mucus*, *pus*, and/or blood. The advantage of warm alkaline hydrogen peroxide solutions as oxygen-producing antihypoxic agents lies in their ability, upon intrapulmonary, endobronchial, and/or endotracheal injection into the airways completely obstructed by colloidal liquids containing catalase, to almost instantly transform the entire liquid mass into oxygen foam, ensuring simultaneous oxygen absorption into the blood independent of pulmonary ventilation.

It has been demonstrated that, in cases of total asphyxia caused by artificial *sputum* or blood in the lungs of mongrel rabbits and/or sheep, a single intrapulmonary, endotracheal, and/or endobronchial injection of a warm alkaline hydrogen peroxide solution can almost instantaneously and completely inflate the lungs with oxygen foam, which immediately begins to exit the upper airways, and the oxygen gas that forms its basis begins to penetrate the bloodstream via the lungs, eliminating hypoxemia within seconds.

Therefore, intrapulmonary, endotracheal, and endobronchial injections of alkaline hydrogen peroxide solutions in cases of airway obstruction with *sputum*, *mucus*, or *pus* in the terminal stage of COVID-19, as well as in blood-related asphyxia, open up new possibilities for oxygenating the blood via the lungs, without the need for traditional mechanical ventilation or ECMO.

CONCLUSION

Thus, there is every reason to believe that a promising direction in the search and development of new-generation antihypoxic agents has emerged in Russia—namely, powerful generators of medical oxygen gas created through the physicochemical repurposing of hydrogen peroxide solutions. It has been established that oxygen-producing antihypoxic agents are warm alkaline solutions of hydrogen peroxide. Their primary constituents are hydrogen peroxide, sodium bicarbonate, and water. A novel method has been developed to boost the oxygen-generating capacity of these medicinal solutions by saturating them with oxygen gas under excess pressure. The mechanism of action of these oxygen-producing antihypoxic agents differs fundamentally from that of all other known agents: when administered locally (intrapulmonarily), they generate oxygen gas, transform colloidal fluids within the airways into oxygen foam, and oxygenate the blood via the lungs. Their pharmacological target is catalase, found in *sputum*, serous fluid, *pus*, and/or blood in cases where they obstruct the airways.

Comprehensive, large-scale studies are needed to fully elucidate all aspects of the local use of warm alkaline hydrogen peroxide solutions as new-generation antihypoxic agents and to draw definitive conclusions. There is hope that active research into the local application of these solutions as effective oxygen gas prodrugs may optimize their use in combating hypoxic and ischemic cell damage under conditions of severe asphyxia and hypoxemia, especially when mechanical ventilation is ineffective and ECMO is not available.

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