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The Application and Mechanism Exploration of N-Butylphthalide in the Treatment of Carbon Monoxide Poisoning

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Abstract

This study comprehensively explored the application and the mechanism of action of N-Butylphthalide (NBP) in the treatment of carbon monoxide (CO) poisoning. The article begins with an overview of the physiological impacts of CO poisoning, particularly highlighting its inhibition of blood oxygenation function and its extensive damage to the nervous system. Subsequently, the paper delves into the pharmacological characteristics of NBP, discussing its potential role in neuroprotection, and supports the application value of NBP in the treatment of CO poisoning with animal experiments and preliminary clinical data. Although current research results have preliminarily confirmed the neuroprotective effects of NBP, key parameters such as the specific dosage, therapeutic time window, and long-term safety in the treatment of CO poisoning still require further investigation and clarification. The paper concludes with a proposal for future studies to deepen the understanding of the mechanism of action of NBP, explore its synergistic effects with existing treatments, and validate its efficacy and safety in the treatment of CO poisoning through extensive clinical trials. In summary, as an emerging neuroprotective agent, NBP shows significant potential in the field of CO poisoning treatment, and it is hoped that future research will provide more effective and safe treatment options for patients with CO poisoning.

Keywords: carbon monoxide poisoning, N-Butylphthalide, neuroprotection, treatment mechanism

1. Introduction

Carbon monoxide (CO) poisoning, as a common and potentially fatal public health issue, has long challenged the boundaries of clinical treatment (Rose JJ, Wang L, Xu Q, et al, 2017). Due to its colorless and odorless nature, CO can silently bind with hemoglobin (Hb) to form carboxyhemoglobin (COHb), significantly reducing the blood's oxygen-carrying capacity, leading to tissue hypoxia and multi-organ dysfunction (Guzman JA, 2012; Grebenyuk A, Bykov V, 2021). Traditional treatments such as hyperbaric oxygen therapy, although providing a solution to some extent, still have considerable controversy over their actual effects due to limitations in availability, cost, and patient

tolerance (Chenoweth JA, Albertson TE & Greer MR, 2021).

Against this backdrop, seeking new treatment strategies has become a focal point of scientific research. N-Butylphthalide (NBP), a known H1 antihistamine, has attracted attention from the scientific community due to its potential protective effect on the central nervous system (Abdoulaye IA & Guo Y, 2016; Chen DP, Hou S-H, Chen Y-G, et al, 2018). As a drug widely used in other medical fields, NBP's effect on neuroprotection, particularly in the context of CO-induced neural damage, has encouraged researchers to explore its application in the treatment of such poisoning.

However, despite the relatively comprehensive understanding of the pharmacological basis of NBP, research on its specific application mechanisms, effect evaluation, and safety analysis in the treatment of CO poisoning is still in its infancy. The current challenge is how to combine the pharmacological characteristics of NBP with the treatment needs of CO poisoning to explore its effectiveness and feasibility in new clinical application scenarios. Therefore, in-depth study of the application of NBP in the treatment of CO poisoning and its mechanism of action, based on existing scientific knowledge and research progress, is not only of great significance for expanding the clinical application scope of NBP but also provides a new perspective and potential for the treatment of CO poisoning.

2. The Physiological Mechanism of Carbon Monoxide Poisoning

CO poisoning is a common and potentially lethal condition, primarily because the affinity of CO for Hb is far greater than that of oxygen (O_2), leading to the formation of COHb, which reduces the blood's capacity to carry oxygen to various parts of the body (Lippi G, Rastelli G, Meschi T, et al, 2012). This mechanism particularly affects the nervous system severely, due to the high oxygen demand of neural tissues, where hypoxic conditions can quickly lead to cellular dysfunction or even death (Jurič DM, Finderle Ž, Šuput D, et al, 2015). Next, we will discuss this process and its impact on the human body in more detail.

First, the formation of COHb by binding of CO with Hb reduces the amount of Hb available for oxygen transport in the blood, leading to tissue and organ hypoxia. Normally, Hb releases CO_2 in the lungs and binds to O_2, then transports O_2 throughout the body. However, when COHb is formed, the binding sites for O_2 are occupied by CO, reducing the capacity of the blood to deliver oxygen to the body's tissues, especially organs with high oxygen dependence, such as the brain and heart.

Cellular metabolic disturbances caused by hypoxia occur through several mechanisms. First, ATP production is reduced because the cell respiratory chain is impaired, leading to insufficient energy supply. Cells attempt to compensate through anaerobic glycolysis, but this metabolic pathway is inefficient, and the energy produced is far from meeting cellular demands. Moreover, the by-products of anaerobic glycolysis, such as lactate, accumulate within the cell, leading to acidosis and further damaging cellular function. Hypoxia also increases the production of reactive oxygen species (ROS), while the generation of antioxidants is limited (Stucki D & Stahl W, 2020). Excessive accumulation of ROS damages cell membrane lipids, proteins, and DNA, triggering cell death programs. In addition, oxidative stress can activate various cell death pathways, including apoptosis and necrosis, which is particularly dangerous in neural cells because once lost, their regenerative capacity is extremely limited. CO poisoning also triggers a strong inflammatory response, leading to the infiltration of inflammatory cells and the release of cytokines (Rose JJ, Wang L, Xu Q, et al, 2017; Weaver LK, Oliver LC, Deru K, et al, 2019). These inflammatory mediators can exacerbate cell damage and promote the breakdown of the blood-brain barrier, making neural tissue more susceptible to harm. The long-term inflammatory response not only exacerbates the initial damage but may also lead to chronic neurodegenerative changes.

These biochemical and physiological changes not only affect the immediate function of the nervous system, such as causing loss of consciousness and cognitive dysfunction, but may also lead to long-term neurologic consequences, including memory loss, motor function impairment, and mood disorders (Sykes OT & Walker E, 2016). These consequences may stem from the loss of neurons during the acute phase, as well as chronic neural tissue changes caused by inflammation and oxidative stress. In summary, CO poisoning reduces the oxygen transport capacity of the

blood by binding to hemoglobin, triggering a series of biochemical and physiological responses that lead to tissue hypoxia, especially in the nervous system. These responses include disturbances in cellular metabolism, increased oxidative stress, and inflammatory reactions, ultimately causing cell death and neurological dysfunction. Understanding these mechanisms is vital for developing therapeutic strategies to treat CO poisoning.

3. The Pharmacological Mechanism of Action of N-Butylphthalide

NBP, as a long-acting non-sedative H1 antihistamine drug, has shown its significant efficacy in the field of anti-allergic treatment. It mainly works by competitively blocking the histamine H1 receptors, effectively reducing or preventing the pathological effects mediated by histamine, such as inflammation and allergic reactions. Histamine, as an important bioactive mediator, plays a crucial role in allergic and inflammatory responses by binding to specific H1 receptors, triggering a series of pathological reactions (Wang Z, Yao N, Fu X, et al, 2019). The intervention of NBP, by competing with these receptors for the binding sites, effectively blocks this series of histamine's pathological actions.

Besides its fundamental anti-allergic effects, NBP's potential protective effects on the central nervous system have also attracted widespread attention (Zhao W, Luo C, Wang J, et al, 2014). Studies have shown that NBP can reduce cerebral edema and regulate the release of neurotransmitters, providing protection for neural cells (Zhang P, Guo Z, Xu Y-M, et al, 2016; Chen X, Qiu K, Liu H, et al, 2019). The brain damage caused by CO poisoning is mainly due to the reduction in oxygen transport and the enhancement of cytotoxic effects, leading to impaired neural cell function. NBP exhibits its protective role on the nervous system by regulating the brain environment and reducing cell damage during this process (Bi M, Zhang M, Guo D, et al, 2016; Tang S, Wang K & Qi X, 2023). Furthermore, NBP might also mitigate the damage caused by free radicals to the cells through antioxidant pathways, further protecting neural cells from harm (Xiong N, Huang J, Chen C, et al, 2012).

However, despite the pharmacological effects exhibited by NBP, its specific mechanism still requires further research and exploration. Current studies mainly focus on NBP's antihistamine effects and its potential for neuroprotection. Future research is expected to delve deeper into its mechanisms on specific neurotransmitter systems and the specific pathways of its action in different neuropathological states.

In summary, NBP shows important application potential in the fields of anti-histamine and neuroprotection through its multifaceted pharmacological actions. With a deeper understanding of its mechanisms, the role of NBP in the treatment of CO poisoning and other nervous system diseases will be further clarified, providing more effective treatment strategies for clinical therapy.

4. The Application of N-Butylphthalide in the Treatment of Carbon Monoxide Poisoning

NBP is a compound extracted from the seeds of the Chinese medicinal herb celery, which has already shown significant neuroprotective effects in the treatment of ischemic stroke. As research progresses, scientists have begun to explore the potential of NBP in the treatment of other nervous system injuries, especially neurologic damage following CO poisoning. Although hyperbaric oxygen therapy is one of the standard treatment methods for CO poisoning, research suggests that NBP may exert neuroprotective effects through various mechanisms, becoming an adjunct strategy in the treatment of CO poisoning.

4.1 Applications in Animal Models

In a study, the effect of NBP on the expression of Nogo/NgR was investigated using a rat model exposed to CO. Nogo and its receptor NgR are known inhibitory molecules for neural regeneration and play a crucial role in the restrictive environment following nervous system injury. The results showed that CO poisoning induced the expression of Nogo, MAG, and NgR1 proteins in rat brain tissue, while NBP treatment significantly reduced the expression of Nogo and NgR1, suggesting that NBP may promote neural regeneration and repair by regulating the expression of these molecules (Li Q, Cheng Y, Bi MJ, et al, 2015). Another study explored the neuroprotective effects of NBP on rats poisoned with CO, especially by regulating the expression of IL-2, AKT, and BCL-2. IL-2, AKT, and BCL-2 are key proteins related to cell survival, proliferation, and apoptosis regulation. The study found that NBP significantly increased the expression of

IL-2, AKT, and BCL-2 in the brain tissues of rats exposed to CO, implying that it might alleviate CO-induced neuronal damage by activating cell survival pathways (Tang S, Wang K & Qi X, 2023). A systematic review investigated the effect of pretreatment agents (including NBP) on the cardiac and neurotoxicity caused by CO poisoning. The review noted that pretreatment agents like NBP showed potential in reducing cardiac and neural damage following CO poisoning in animal models. Although the mechanisms have not been fully elucidated, these findings support further research on the application of NBP in the treatment of human CO poisoning (Baharara H, Ghasemi H, Samadi S, et al, 2023). In exploring the impact of NBP on the blood-brain barrier (BBB) function following CO poisoning, studies found that CO exposure impaired the BBB function in rats, while NBP effectively maintained the structural and functional integrity of the BBB, reducing cerebral edema. This effect might be achieved by increasing the expression of ZO-1 and claudin-5 proteins, which are key factors for the structural integrity of the BBB (Bi M, Zhang M, Guo D, et al, 2016). Furthermore, NBP was found to activate the Keap1/Nrf-2 signaling pathway in rats, thereby countering the oxidative stress response caused by CO poisoning. The Keap1/Nrf-2 pathway is one of the main intracellular antioxidant pathways, and its activation can improve the cell's resistance to oxidative damage (Li Q, Cheng Y, Bi M, et al, 2015).

4.2 Clinical Applications

Studies by Fang Pingping et al. (2017) have found that NBP capsules combined with hyperbaric oxygen therapy can significantly improve the levels of serum superoxide dismutase (SOD) and malondialdehyde (MDA) in patients with delayed encephalopathy following CO poisoning. Research by Liu Zengzhu et al. (2018) also confirmed that NBP combined with hyperbaric oxygen therapy can significantly increase the treatment effective rate, improve clinical indicators, and ensure patient life safety. Li Junji et al. (2017) found through research that NBP combined with ganglioside treatment can significantly increase the lactate clearance rate and immune function of patients with acute severe CO poisoning, reducing the incidence of delayed encephalopathy. Furthermore, NBP treatment can also significantly improve patients' Barthel scores and MMSE scores, enhancing neurological function. NBP has shown significant neuroprotective effects in the treatment of CO poisoning. Through combination with hyperbaric oxygen therapy, NBP not only improves the levels of SOD and MDA in serum but also increases lactate clearance rate, reduces the incidence of delayed encephalopathy, and significantly enhances neurological function in patients. The neuroprotective action of NBP may involve the regulation of key protein expression and protection of blood-brain barrier integrity, thereby reducing brain injury caused by CO poisoning. Future research needs to further explore the optimal treatment protocols and mechanisms of NBP to optimize treatment strategies for CO poisoning.

The above research results indicate that NBP exerts neuroprotective effects after CO poisoning through multiple mechanisms, including promoting neural regeneration, inhibiting neuronal apoptosis, maintaining BBB integrity, and countering oxidative stress. These findings provide a scientific basis for the application of NBP in the treatment of CO poisoning, showcasing its value as a potential adjunctive treatment. Future research needs to further validate the efficacy and safety of NBP in clinical trials to allow for its broader application in the treatment of CO poisoning.

5. Challenges and Future Directions

In the application research of NBP for the treatment of CO poisoning, despite significant progress made, a series of challenges and issues still exist. The resolution and exploration of these challenges will determine the future wide application and effectiveness of NBP in clinical practice.

Determining the dosage and treatment window for NBP is a key challenge in current research. Differing dosages and treatment time points used in various studies may affect the evaluation of efficacy. Therefore, determining the optimal dosage and treatment time window for NBP through clinical trials and laboratory studies becomes an important direction for future research. Assessing the long-term therapeutic effects and safety of NBP is also a problem that needs to be addressed in clinical applications. Current studies are largely focused on short-term efficacy, with insufficient research on long-term therapeutic effects and potential

long-term side effects. Future studies need to systematically evaluate the long-term efficacy and safety of NBP to provide more comprehensive data support for clinical practice.

Although existing research has revealed the mechanisms of action of NBP in anti-oxidation and improving blood-brain barrier function, a comprehensive analysis of its mechanism of action remains a challenge. A deeper understanding of the mechanisms of action of NBP, especially at the molecular level, is crucial for optimizing treatment plans and discovering new therapeutic targets. Exploration of combined drug use becomes one of the important research directions for the future. Given the multifaceted nature of biological changes following CO poisoning, the combined use of NBP with other treatment methods (such as hyperbaric oxygen therapy, anti-inflammatory drugs, etc.) may yield more comprehensive therapeutic effects. Therefore, evaluating the combined application effects of NBP with other treatment methods will be one of the key focuses for future research.

By addressing the determination of dosage and treatment window, assessing long-term efficacy and safety, exploring the mechanisms of action in depth, and investigating the potential of combined drug use, future research is expected to provide more effective and safer treatment options for CO poisoning, further expanding the clinical application range of NBP.

6. Conclusion

In recent years, research on the treatment of CO poisoning has shown that NBP, as a novel neuroprotective drug, has certain potential. Although current research is mainly focused on animal models, the results revealed provide a scientific basis for the application of NBP in humans. With its multiple bioactivities, especially the protective effect on the nervous system, NBP provides a new strategy for the treatment of CO poisoning.

However, despite the neuroprotective effects displayed by NBP, including reducing brain injury and improving cognitive dysfunction, the effectiveness, safety, and optimal treatment protocol in clinical application still need to be further validated through more high-quality clinical trials. At present, there are some limitations to the research on NBP, such as small sample sizes, lack of long-term follow-up data, and an incomplete understanding of the treatment mechanisms.

Future research directions should include: in-depth exploration of the mechanism of action of NBP, especially its specific biological pathways in alleviating neural system damage caused by CO; conducting more large-scale, multi-center, randomized controlled clinical trials to verify the efficacy and safety of NBP in the treatment of CO poisoning at different stages; investigating the combined effects of NBP with other treatment methods (such as hyperbaric oxygen therapy) to find a more optimal treatment combination. In summary, although current research indicates that NBP has potential applications in the treatment of CO poisoning, particularly in the aspect of neuroprotection, further research and evaluation are needed regarding its comprehensive therapeutic effects and safety.

Through future research, it is anticipated that more effective and safer treatment strategies can be provided for patients with CO poisoning, thereby improving their current treatment situation and long-term prognosis.

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