PharmacologyOnLine

Archives • 2021 • vol.3 • 1493-1501

BIOCHEMICAL AND PATHOGENETIC MECHANISMS IN OFF LABEL CARBOXYTHERAPY IN RESPIRATORY FAILURE

Drogovoz S. M.[1], Shtroblya A. L.[2], Shchokina K. H.[1], Kalko K. O.[1], Taran, A. V.[1]
Vergolyas Maya[3], Orlenko I. V.[1]
[1]National University of Pharmacy, Kharkov, Ukraine
[2]Uzhgorod National University, Uzhgorod, Ukraine
[3]PHEI International European University. Kyiv, Ukraine
*ketrin27kalko@gmail.com

Abstract

Carboxytherapy is an alternative method of pharmacotherapy, a modern off label method. The term "off label use" was given by the US Food and Drug Administration in 1997. The use of off-label drugs expands the possibilities of pharmacotherapy, sometimes when nothing else meets the patient's needs or when the doctor is sure that the off-label drug in the on-label complex (according to the instructions) increases the effectiveness and safety of pharmacotherapy. Due to the antihypoxic, antioxidant and anti-inflammatory properties of CO2: carboxytherapy is an effective off label treatment for respiratory failure.

CO2 as a natural stimulator of respiration consists in the fact that at the slightest change in its concentration (by 0.1%), various natural mechanisms of a rapid return of the CO2 level to the physiological norm are activated. In this effect of CO2, an important biochemical and physiological role is played by central respiratory chemoreception, a mechanism by which an increase in pC promotes the stimulation of the act of respiration. A similar mechanism of respiratory stimulation is metabolic acidosis (blood acidification at normal CO2 levels).

Under hypoxia, the effect of CO2 on O2 consumption is paradoxical: with O2 deficiency with an increase in the CO2 concentration in the tissues, it should aggravate the hypoxic state, but in reality, under the action of carboxytherapy during hypoxia, an increase in CO2 concentration enhances the tissue oxygenation process, since CO2 is one of the most powerful natural stimulants of the respiratory center, and it also releases O2 from oxyhemoglobin (Verigo-Bohr effect).

Biochemical and pathogenetic mechanisms of CO2 action on the respiratory center are realized in two complementary ways: direct action - an increase in the concentration of CO2 in the blood affects the central chemoreceptors of the medulla oblongata, reflex - through vascular reflexogenic zones (peripheral chemoreceptors). Through these mechanisms of respiration regulation, under the influence of CO2, the structure of the respiratory reflex changes (respiration deepens and its frequency decreases), as a result of which the minute volume of pulmonary ventilation increases by 1-1.5 l / min. Compensatory enhancement of O2 diffusion in the lungs leads to an increase in the oxygen content in the blood and an increase in its delivery to tissues. In diseases of the respiratory system, carboxytherapy helps to reduce pathological symptom complexes of chronic and spastic bronchitis, bronchial asthma, pneumosclerosis, pulmonary emphysema, silicosis due to the biochemical and pathogenetic properties of CO2, providing antihypoxic, antioxidant, anti-inflammatory, antispasmodic, antiseptic and analgesic effects.

Keywords: *carboxytherapy, respiratory failure, biochemical and pathogenetic mechanisms, off label.*

Introduction

Carboxytherapy is a modern alternative method in off label therapy for many diseases, since CO_2 has a pronounced systemic and local effect: antihypoxic, antioxidant, anti-inflammatory, spasmolytic, analgesic, improves tissue trophism, stimulates reparative and metabolic processes [1, 2, 3] The term "off label use" was given by the US Food and Drug Administration (FDA) in 1997. Today, the use of off-label drugs has become a reality as one of the methods to increase knowledge about alternative pharmacotherapy options.

In all countries of the world, the use of off label drugs allows doctors to carry out medical practice when nothing else meets the patient's needs or when the doctor is sure that the off-label drug in the on-label complex (according to the instructions) increases the effectiveness and safety of pharmacotherapy [36, 37, 38]. In particular, in Ukraine, the 2019-2020 COVID 19 pandemic significantly influenced the situation regarding the use of off label drugs. In accordance with the order of the Ministry of Health of Ukraine and 762 dated 04/02/2020"On approval of the treatment protocol for corona virus disease (COVID 19)" it is allowed to use unregistered medicines recommended by the official countries of the USA, the EU, Japan, China, Canada. This law has taken the first steps to regulate the use of drugs off label.

According to WHO, from 30-50% of all medicines are prescribed for indications that are not in the instructions [4]. Thus, due to the antihypoxic, antioxidant and anti-inflammatory properties of CO_2: carboxytherapy is an effective method of off label therapy for respiratory failure. Diseases of the respiratory system occupy the third place in mortality in Ukraine after cardiovascular diseases and neoplasms [4]. Carbon dioxide, stimulating the respiratory (respiratory) center of the medulla oblongata, which is chemically sensitive to it, induces the act of inspiration and thereby initiates the delivery of oxygen to the body during respiration and eliminates hypoxia [5].

Therefore, the stimulation of CO_2, the respiratory center in respiratory failure such as hypocapnia, is of great therapeutic importance and is one of the main effects in the pharmacodynamics of CO_2: direct and reflex influence on the respiratory center. Inhalation of CO_2 in low concentrations (3-7%) causes rapid and deeper breathing, which increases pulmonary ventilation.

The role of CO_2 as a natural stimulator of respiration is that at the slightest change in its concentration (by 0.1%), various natural mechanisms of the rapid return of CO_2 level to the physiological norm are activated, since the human body is a self-healing and self-regulating system [6]. In this effect of CO_2, an important biochemical and physiological role is played by central respiratory chemoreception – a mechanism by which an increase in pCO_2 promotes the stimulation of the act of respiration. A similar mechanism of respiratory stimulation is metabolic acidosis (blood acidification at normal CO_2 levels) [7]. With a decrease in the natural metabolic rate of acidosis, central respiratory chemoreception acts as a biochemical pacemaker that helps to maintain a stable arterial pCO_2 within 40 (mmHg) regardless the metabolic production of CO_2. In human body, arterial pCO_2 strictly reacts to changes in the respiratory system.

Consequently, the central respiratory chemoreception is controlled by biochemical sensors located in the central nervous system, which usually act synergistically with peripheral chemoreceptors through an intermediary, pH [8, 33, 34, 35]. An increase in carbon dioxide in the tissues leads to an increase in the concentration of H + ions (that is, to a decrease in pH), since during the hydration of CO_2, H_2CO_3 is formed, a weak carbonic acid dissociating into hydrogen ions (H +) and bicarbonate (HCO_3^-) (Fig. 1). The reaction of H_2CO_3 formation in blood plasma is slow. In erythrocytes, its rate is increased approximately 10 thousand times by the enzyme carbonic anhydrase after CO_2 diffuses into erythrocytes from blood plasma [9]. Since various ion channels of neurons are pH sensitive, central respiratory chemoreception interacts with several specialized neurons. Two types of neurons are especially important for the regulation of respiration by CO_2: glutamatergic (strongly activated by hypercapnia in vivo) and serotonergic. Both of these types of neurons have a powerful stimulating effect on respiratory function and function as CO_2 sensors [10].

Consequently, there are two types of biochemical sensors for CO_2 and O_2 chemoreception in the human body: central chemoreceptors located in the respiratory center (detecting high blood CO_2 levels)

and chemoreceptors of the carotid bodies (detecting low O_2 levels). Under conditions of hypocapnia, the central chemoreceptors are much more sensitive than the chemoreceptors of the carotid bodies; therefore, even a small increase (by 0.1%) in the CO_2 content leads to a significant increase in the volume of pulmonary ventilation [5]. Hypercapnia and acidosis stimulate, and hypocapnia and alkalosis inhibit the central respiratory chemoreceptors.

It has been proven that the higher the CO_2 content in arterial blood, the easier it is for the dissociation of oxyhemoglobin and the transfer of oxygen to the tissues, and vice versa: the lack of CO_2 in the blood enhances the connection of O_2 with hemoglobin. A deficiency of carbon dioxide leads to oxygen starvation (hypoxia), while an increase in the level of CO_2 in the blood contributes not only to better tissue oxygenation, but to the expansion of small arteries and an improvement in cerebral blood flow. In addition, systematic physiological hypercapnia stimulates the formation of vascular growth factors, which leads to the formation of a more branched capillary network and optimization of tissue circulation, including in the lung tissues [6] (table 1).

In order to preserve the biochemical homeostasis of CO2 in tissues, in the process of evolution, such mechanisms of protection and adaptation have arisen as spasm of the smooth muscles of blood vessels and bronchi, an increase in mucus secretion in the bronchi and the production of cholesterol in the liver to stabilize cell membranes in the lungs and vessels. These biochemical and physiological mechanisms inhibit the removal of CO2 from the body, but spasm of the bronchi and blood vessels reduces the flow of O2 to the tissues of the brain, heart, and other organs, which aggravates the hypoxia.

In contrast, tissue hypoxia contributes to the retention of O2 in erythrocytes, i.e. a paradoxical state arises: there is enough oxygen in the blood, and the organs signal about its lack. A person begins to suffocate, breathing becomes more frequent, with even greater release of carbon dioxide from the blood, and oxygen is retained in erythrocytes. Whereas, the higher the CO2 content in the arterial blood, the easier it is to release O2 from the blood with hemoglobin and transfer it to tissues and organs [5].

With hypoxia, oxygen starvation occurs, as a result of which reserve anaerobic respiration is activated and the accumulation of under-oxidized products (lactic and pyruvic acid) in the tissues, which cause a painful reaction. Elimination of hypoxia with carboxytherapy reduces the formation of these under-oxidizing products and thereby eliminates pain.

Therefore, it is natural that in order to prevent the listed undesirable manifestations of hypoxia, it is necessary to maintain a normal concentration of carbon dioxide in the blood, since O2 only paired with CO2 effectively function in our body, i.e. in tandem with O2. Cells of animals and humans need about 6-8% CO2, and O2 2% of their content in the inhaled air [11]. In this case, oxygen is an oxidizer of organic substances in the process of energy generation, but when the oxidation process is disturbed, toxic products are formed - reactive oxygen species (ROS) [12, 18]. It is they that lead to the development of oxidative stress and are the main trigger mechanism of aging and pathology, disrupting the complex biochemical intracellular processes of the body. CO2 reduces the rate of oxidative reactions and thus exhibits antioxidant properties, slows down the pathological process and aging of the body, while prolonged hypocapnia and hypoxia serve as a trigger for pathological processes in the organs of the respiratory system [6].

A chronic inflammatory disease of the respiratory tract is bronchial asthma (BA), the prevalence of which has significantly increased in recent years [14]. Modern literature sources indicate the participation of ROS in the pathogenesis of asthma. Thus, changes in the normal processes of oxidation of proteins and lipids with the appearance of ROS in the cells of the respiratory epithelium lead to oxidative pathological stress: increased vascular permeability and mucus production, increased contraction of smooth muscles and hyper responsiveness of the airways [12].

There is compelling evidence supporting a significant role of oxidative stress in the development of BA [14]. Therefore, an increase in ROS production, a dysregulation of the cellular redox process, mitochondral stress and respiratory

dysfunction are now considered key links in the pathology of bronchial asthma. In addition, mitochondria are the main regulators of calcium homeostasis in the cell, their damage caused by oxidative stress leads to an increase in the cytosolic level of calcium, which negatively affects the contractility of airway smooth muscles [15].

Therefore, over expression of ROS in BA promotes oxidative stress and airway hyper responsiveness. The cells of the structural elements of the airways are important pacemakers; thus, they react to the inflammatory environment, bronchospasm, remodeling of the extracellular matrix and fibrosis occur [14].

Oxidative stress also contributes not only to the hypersensitivity of the pacemakers of the respiratory tract, but also increases the proliferation of fibroblasts. It is assumed that excessive ROS levels cause fibrosis either directly or through inflammatory reactions, as well as provoke mucus secretion, damage to the cilia of epithelial cells of the respiratory tract, all of which can contribute to the development of inflammation in the lungs and hyper reactivity of the functions of various parts of the respiratory system [6].

Damaged epithelial cells of the airways can initiate inflammation of the sensory nerves, which leads to the release of neuropeptides and induction of bronchospasm. In addition, the morphological and functional properties of airway endothelial cells, such as permeability and expression of adhesion molecules, can be altered by ROS, which also promotes the expression of inflammatory mediators. In BA, the lungs have reduced ROS and catalase activity, and in combination with reduced lung function in such patients, a concomitant increase in the production of superoxide anions is observed [6].

All of the above pathological factors in respiratory failure contribute to the disruption of the physiological exchange of O_2 and CO_2 and the development of tissue hypoxia. A decrease in the O_2 content in arterial blood, caused, as a rule, by pulmonary disorders, is called hypoxemia. Regardless of the causes, hypoxia and hypoxemia lead to a decrease (up to a complete stop) of aerobic metabolism, depletion of intracellular reserves of high-energy compounds, dysfunction of cells and their death. The cells of the central nervous system are the most sensitive to hypoxia. Hypoxia initially causes cognitive impairment and psychomotor retardation. What is more, these disorders are aggravated, stunnedness and anxiety appear, and when pO_2 is below 30 mmHg sopor develops, coma and death occurs. The lifespan of a cell under hypoxic conditions depends on its metabolic needs, oxygen and energy reserves, as well as on its ability to maintain metabolism under anaerobic conditions [6, 16].

Under hypoxia, the effect of CO_2 on O_2 consumption is paradoxical: with an O_2 deficiency with an increase in the CO_2 concentration in the tissues, it should aggravate the hypoxic state, but in reality, under the action of carboxytherapy during hypoxia, an increase in CO_2 concentration enhances the tissue oxygenation process, because CO_2 is one of the most powerful natural stimulants of the respiratory center, and also provides the release of O_2 from oxyhemoglobin (Verigo-Bohr effect) [6, 8, 16].

Consequently, in respiratory failure, oxygen starvation in tissues leads to hypoxia, and to eliminate it, many European and American clinics use a method based on the homeopathic principle of "reverse" - offering carboxytherapy as an alternative off label treatment method [1, 2]. The introduction of CO_2 subcutaneously, intradermally, inhalation or transdermally eliminates the effects of oxygen starvation by creating artificial hypercapnia in the tissues, which in turn causes the excitation of the respiratory center and vasodilation with an increase in the process of delivery of oxygen to tissues, including the lungs [1, 6].

The pressure of CO_2 at the injection site causes a flow of impulses from the baroreceptors, and the rapid change in pH to the alkaline side (alkalosis) at the injection site of CO_2 stimulates chemoreceptors, which contribute to the analgesic and antispasmodic effect [14, 15]. In addition, relaxation of vascular muscle fibers is due to a decrease in the amount of calcium ions Ca^{2+} (the formation of calcium bicarbonate during the dissociation of carbonic acid) (Fig. 1), which leads to local vasodilation, acceleration of microcirculation and increased tissue trophism (Table 1) [2, 6].

In addition, carboxytherapy also affects the level of microcirculation of arterioles and precapillary sphincters by increasing the velocity of blood flow in

tissues, as well as by improving lymphatic drainage [6, 14]. These mechanisms of CO_2 action are widely used in medicine for inflammatory diseases of the respiratory system, accompanied by hypoxia and edema [1].

As can be seen from the above mentioned, carbon dioxide is the most important product of cellular respiration; therefore, there are many biochemical sensors in the body that regulate the concentration of this gas. A shift in CO_2 levels to either side from physiological values triggers numerous adaptation reactions. Thus, an increase in CO_2 concentration automatically serves as a signal to increase the intensity of respiration and blood circulation; decreases muscle tension and spasm, which contributes to anti-inflammatory, antispasmodic, analgesic effects; the body's resistance to harmful factors increases (Table 1) [2].

Consequently, the mechanism of action of CO_2 during hypoxia is associated with its indirect effect on the respiratory center through receptors in the medulla oblongata (central chemoreceptors) and vascular reflexogenic zones (peripheral chemoreceptors) located in the aortic arch (carotid sinus). Arterial chemoreceptors play a special role in controlling the concentration of CO_2, since they trigger the initial response in response to hypercapnia. Hypercapnic stimulation of arterial chemoreceptors is permanent [16, 17].

Thus, the biochemical and pathogenetic mechanisms of CO_2 action on the respiratory center are implemented in two complementary ways: a direct action – an increase in the concentration of CO_2 in the blood affects the central chemoreceptors of the medulla oblongata, reflex - through vascular reflexogenic zones (peripheral chemoreceptors). In addition, afferent impulses from peripheral chemoreceptors, irritating the central chemoreceptors of the medulla oblongata, reduce blood pH and the affinity of vascular adrenergic receptors for catecholamines, which causes pronounced visceral reactions (spasmolytic, hypotensive effect) [18, 19]. Through these mechanisms of respiration regulation, under the influence of CO_2, the structure of the respiratory reflex changes (respiration deepens and its frequency decreases), as a result of which the minute volume of pulmonary ventilation increases by 1-1.5 l / min [20, 21, 22, 24]. Compensatory enhancement of O_2 diffusion in the lungs leads to an increase in the oxygen content in the blood and an increase in its delivery to tissues.

In diseases of the respiratory system, carboxytherapy helps to reduce pathological symptom complexes of chronic and spastic bronchitis, bronchial asthma, pneumosclerosis, pulmonary emphysema, silicosis due to the biochemical and pathogenetic properties of CO_2, providing antihypoxic, antioxidant, anti-inflammatory, spasmolytic, antiseptic and analgesic effects (Table 1) [25, 26, 27, 28, 29, 30, 31, 32].

Conclusions

In medicine, carbon dioxide has been widely used for the treatment of diseases for more than 50 years, since carboxytherapy is an innovative, modern, polietiologic and polypathogenetic off label therapy option that complements the prevention and treatment of many diseases. The mechanisms of CO_2 influence on biochemical and physiological processes are diverse, providing a variety of local and resorptive pharmacological effects.

Today carboxytherapy is a vivid example of off label prescription of drugs, since without the results of its wide preclinical study, it has become a universal and safe method of additional and alternative therapy for most diseases, thanks to its rich pharmacodynamics, harmlessness and many years of effective experience of its off label application in medical practice.

References

1. Drogovos S. M., Shtrygol' S. Yu., Zupanets M. V., Kononenko A. V., Shtroblya. A.L. Carboxytherapy is an alternative to traditional pharma-cotherapy. Clinical pharmacology. 2016; 20(1):12–17. (In Russian).
2. Drogovos S. M., Shtrygol' S. Yu., Zupanets M. V., Levinskaya E. V., Grishenko N.V. The uniqueness of the pharmacotherapeutic capabilities of carbon dioxide (carboxytherapy). Rational Pharmacotherapy. 2016;1:37–39. (In Russian).
3. Leibaschoff G. Cellulite – Pathophysiology and treatment Carboxytherapy. New York : Taylor & Francis Group. 2010;21:151–157.

4. Sekh M., Zimenkovsky A. Community-acepired pneumonia: quality of phar-macotherapy and expense of irrationality. Pharmacia. 2018;65(4):25-37.
5. Julu P.O.O., Shah M., Monro J.A., Puri B.K. Carbon dioxide therapy in hy-pocapnic respiratory failure. Honey Hypotheses. 2018;110(1):101-104.
6. Carboxytherapy: mechanisms, effects, applications. Handbook / Ed. S.M. Drogovos. Kh. «Titul», 2019. 192 p. (In Russian).
7. Laffey J. G., Honan D., Hopkins N., Hyvelin J.-M., Boylan J. F., Mcloughlin P. Hypercapnic acidosis attenuates endotoxin–induced acute lung injury. Am. J. Respir. Crit. Care Med. 2004;169:46–56.
8. O'Toole D., Hassett P., Contreras M., Higgins B. D., McKeown S. T. W., McAuley D. F., O'Brien T., Laffey J. G. Hypercapnic acidosis attenuates pul-monary epithelial wound repair by an NF–κappaB dependent mechanism. Thorax. 2009;64: 976–982.
9. Esbaugh A. J., Tufts B. L. The structure and function of carbonic anhydrase isozymes in the respiratory system of vertebrates. Respir. Physiol. Neurobiol. 2006;154:185–198.
10. Colasanti A., Esquivel G., Schruers K. J., Griez E. J. On the psychotropic effects of carbon dioxide. Curr. Pharm. Des. 2012;18(35):5627–5637.
11. Drogovos S. M., Shtrygol' S. Yu., Kononenko A. V., Zupanets M. V. Pharmacological rationale for carboxytherapy (CO2–therapy). Pharmacology and Drug Toxicology. 2017;1(52):73–78. (In Russian).
12. Lutsky M. A., Kuksova T.V., Smelyanets M.A., Lushnikova Yu.P. Free radical oxidation of lipids and proteins is a unique process of the body's vital activity. Advances in modern natural science. 2014;12:24-28. (In Russian).
13. Kogan A. Ch. The modulating role of CO2 in the action of reactive oxygen species. M.: GEOTAR – Media, 2006. 224 p. (In Russian).
14. Dairova R. A., Bolevich S., Kogan A. Ch. Hypercapnotherapy and free radical processes in bronchial asthma / 5th Nat. Respiratory Diseases Congress. M., 1995. 1658 p. (In Russian).
15. Dean J. B. Hypercapnia causes cellular oxidation and nitrosation in addi-tion to acidosis: implications for CO2 chemoreceptor function and dysfunc-tion. J. Appl. Physiol. 2010;108:1786–1795.
16. Drogovos S. M., Shtrygol' S. Yu., Zupanets M. V., Kononenko A. V., Shtroblya. A.L. The mechanism of action of carboxytherapy. Pharmacology and drug toxicology. 2016;6(51):12–20. (In Russian).
17. De Goursac C. La carboxytherapie. J. Med. Est. Chir. derm. 2010;XXXVII (145):11–19.
18. Zelenkova G. Carboxytherapy. Methodical manual / Samara LLC "Media-Kniga", 2015. 95 p. (In Russian).
19. Yermolaev O. Yu. Correct breathing. Practical guide / O. Yu. Ermolaev. 2nd ed. - M .: Flinta, 2014. 192 p. (In Russian).
20. Chernich V. P., Drogovoz S. M., Zupanets I. A., Siroshtan G. N., Zupanets M. V., Kornienko V. I., Drogovoz E. V. Carboxytherapy – style off label use (drugs outside the label). Medicinal business. 2017;5-6:112–116. (In Russian).
21. Bunyatyan N. D., Drogovoz S. M. , Shtroblya A. L., Kononenko A. V. , Zelenkova H. , Prokofyev A. B. , Sapovsky M. M. , Nikolaeva L. L. The mech-anism of the pulmoprotective action of carboxytherapy. Vopr Kurortol Fizioter Lech Fiz Kult. 2019;96(4):58-62.
22. Drogovos S. M., Shtrygol' S. Yu., Kononenko A. V., Zupanets M. V., Lev-inskaya E. V. Physiological properties of CO2 - substantiation of uniqueness of carboxytherapy. Medical and clinical chemistry. 2016;18(1): 112–116. (In Russian).
23. Bunyatyan N. D., Drogovoz S. M., Kononenko A. V., Prokofiev A. B. Carboxytherapy – an innovative trend in resord medicine. Vopr Kurortol Fizioter Lech Fiz Kult. 2018;95(5):72-76.
24. Dean J. B. Hypercapnia causes cellular oxidation and nitrosation in addi-tion to acidosis: implications for CO2 chemoreceptor function and dysfunc-tion. J. Appl. Physiol. 2010;108:1786–1795.
25. Esbaugh A. J., Tufts B. L. The structure and function of carbonic anhy-drase isozymes in the respiratory system of vertebrates. Respir. Physiol. Neu-robiol. 2006;154:185–198.
26. Akça O., Doufas A. G., Morioka N., Iscoe S., Fisher J., Sessler D. I. Hy-percapnia improves tissue oxygenation. Anesthesiology. 2002;97(4):801–806.
27. Zelenkova H., Drogovoz S.M., Shtrygol' S.Yu., Shtroblia A.L. , Tovchiga O.V. Mechanisms of

carboxytherapy action with diseases of nervous system. J. Derma. 2018; XVIII(1-2):66–70.
28. S. Ito S., Mardimae A., Han J., Duffin J., Wells G., Fedorko L., Minkovich L., Katznelson R., Meineri M., Arenovich T., Kessler C., Fisher J. A. Non–invasive prospective targeting of arterial PCO2 in subjects at rest. J. Physiol. 2008;586:3675–3682.
29. Order of the Ministry of Health of Ukraine № 762 "On approval of the protocol" Provision of medical care for the treatment of coronavirus disease (COVID 19)» 02.04.2020. – https: // moz.gov.ua/article/ministry-mandates/nakaz-moz-ukraini-vid-2042020-762-pro-zatverdzhenja-protokolu-nadannja-medichnoi= dopomogi-dlja-likuvannja-koronavirusnoi-hvorobi-covid-19. (In Ukranian).
30. The antioxidant action of CO2 - one of the universal mechanisms of car-boxytherapy / Drogovoz S. M., Kalko K. O., Ivantsyk L. B., Shtroblya A. L., Stoletov Yu. V., Drogovoz K. V., Ostasko V. F. Pharmacologyonline. 2021. Vol. 2. P. 158-166. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A019_Drogovoz.pdf
31. Carboxytherapy as an alternative off lable method for diabetes mellitus treatment: a review / Drogovoz S. M., Kalko K. O., Hailat I. A., Ivantsyk L. B., Kireyev I. V. Pharmacologyonline. Vol. 3. 2021. P. 447-455. https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A051_Drogovoz.pdf
32. Experience and prospects of carboxytherapy in diabetes mellitus / Drogovoz S. M., Belik G. V., Kalko K. O., Shevchenko S. I., Derymedvid L. V., Kireyev I. V., htroblya A. L. Problems of Endocrine Pathology, 78(4), 110-116. https://doi.org/10.21856/j-PEP.2021.4.15
33. Feshchenko, H., Marchyshyn, S., Budniak, L., Slobodianiuk, L., Basaraba, R. Study of antibacterial and antifungal properties of the lyophilized extract of fireweed (Chamaenerion angustifolium L.) herb. Pharmacologyonline. 2021. Vol. 2. P. 1464-1472.
34. Budniak, L., Slobodianiuk, L., Marchyshyn, S., Basaraba, R., Banadyga, A. The antibacterial and antifungal activities of the extract of Gentiana cruciata L. herb. Pharmacologyonline. 2021. Vol. 2. P. 188-197.
35. Experimental studies on expectorant effect of extract from Pimpinella saxifraga L. / L. Slobodianiuk, L. Budniak, S. Marchyshyn, E. Parashchuk, L. Levytska. Pharmacologyonline. 2021. Vol. 1. P. 404-410.
36. Causes and legal aspects of the off-label drugs emergence: literature review / Kalko K. O., Drogovoz S. M., Komarova A. P., Hailat I. A., Drogovoz K. V., Ivantsyk L. B. Pharmacologyonline. Vol. 3. 2021. P. 179-186. https://pharmacologyonline.silae.it/files/archives/2021/vol1/PhOL_2021_1_A024_Kalko.pdf
37. Frequency of off-label drug use in medicine / Drogovoz S. M., Shchokina K. G., Komarova A. P., Kalko K. O., Orlenko I. V., Belik G. V., Fesenko W. Yu. Pharmacologyonline. 2021. Vol. 2. P. 138-144. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A017_Drogovoz.pdf
38. Positive and negative aspects of the off-label drugs use / Drogovoz S., Kalko K., Tsyvunin V., Horoshko V., Levkov A., Verholias O., Zhurenko D. Pharmacologyonline. 2021. Vol. 2. P. 1179-1185. https://pharmacologyonline.silae.it/files/archives/2021/vol2/PhOL_2021_2_A132_Drogovoz.pdf

Table 1. Interaction of physiological and pharmacological properties of CO2 - biochemical and pathogenetic mechanism of carboxytherapy

Systems and organs	Physiological properties	Pharmacological effects
Respiratory	Stimulating effect on chemoreceptors of the respiratory center of the medulla oblongata: stimulates respiration, eliminates hypoxia. Normal ratio of CO_2 and O_2 is 3:1	Antihypoxic Analeptic Strengthening of tissue respiration
Heart	Stimulating effect on the chemoreceptors of the vasomotor center of the medulla oblongata.	Cardiotonic Antiischemic Antianginal
Vessels	Direct vasodilator action: enhances blood and lymph circulation, reduces swelling, accelerates the body's cleansing of toxic metabolic products. Provides a rapid release of O_2 from the bond with hemoglobin (tissue oxygenation). Increases vascular endothelial growth factor: stimulates neo-angiogenesis. Participates in the regulation of the aggregation process.	Vasodilator Coronary Dilating Decongestant Anti-inflammatory Antihypoxic Optimization of tissue circulation Antiplatelet
Metabolism	It is part of the body's buffer system. The pH value of blood plasma depends on the ratio of the concentration of CO_2 dissolved in it and bicarbonate ions (CO_2 in the alveoli 65%, in the blood 77.5%).	Participates in biochemical, humoral, oxidative processes (in the reactions of biosynthesis of carbohydrates, fats, nucleic acids).
Immune	Increases the body's resistance by preventing damage to cells by reactive oxygen species (reduces the rate of oxidative reactions).	Antioxidant

Figure 1. Biochemical conversion of CO2 during carboxytherapy