Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Phenylmethimazole is a candidate drug for the treatment of severe forms of coronavirus disease 2019 (COVID-19) as well as other virus-induced "cytokines storm"

Cesidio Giuliani*, Ines Bucci, Giorgio Napolitano

Unit of Endocrinology, Department of Medicine and Sciences of Aging, and Center for Advanced Science and Technology (CAST), University of Chieti-Pescara, Chieti, Italy

ARTICLE INFO

Keywords:
Phenylmethimazole
COVID-19
Cytokines storm
Chemokines
Inflammation
Acute respiratory distress syndrome

ABSTRACT

Severe forms of the Coronavirus disease 2019 (COVID-19) are characterized by an enhanced inflammatory syndrome called "cytokine storm" that produces an aberrant release of high amounts of cytokines, chemokines, and other proinflammatory mediators. The pathogenetic role of the "cytokine storm" has been confirmed by the efficacy of immunosuppressive drugs such as corticosteroids along with antiviral drugs in the treatment of the severe forms of this disease.

Phenylmethimazole (C10) is a derivative of methimazole with anti-inflammatory properties. Studies performed both in vitro and in vivo have shown that C10 is able to block the production of multiple cytokines, chemokines, and other proinflammatory molecules involved in the pathogenesis of inflammation. Particularly, C10 is effective in reducing the increased secretion of cytokines in animal models of endotoxic shock. We hypothesize that these effects are not limited to the endotoxic shock, but can also be applied to any disease characterized by the presence of a "cytokine storm". Therefore, C10 may be a potential drug to be used alternatively or in association with the corticosteroids or other immunosuppressive agents in the severe forms of COVID-19 as well as other viral diseases that induce a "cytokine storm". Preclinical and clinical studies have to be performed to confirm this hypothesis.

Introduction

Phenylmethimazole named also compound 10 (C10) is a derivative of methimazole (Fig. 1), a drug widely used to treat Graves' disease and other forms of hyperthyroidism [1].

Several experimental studies conducted both in vitro and in vivo have demonstrated that C10 is a powerful anti-inflammatory agent able to block the production of multiple cytokines and other molecules involved in the pathogenesis of inflammation in several types of cells and tissues. Indeed C10 inhibits the production of cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-12 (IL-12), interferon-γ-induced protein 10 (IP10), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein 1α (MIP1α), tumor necrosis factor-α (TNF-α), intercellular adhesion molecule-1 (ICAM-1), vascular adhesion molecule-1 (VCAM-1), inducible nitric oxide (iNO), cyclooxygenase-2 (Cox-2), nuclear factor-kB (NF-kB) [2-5].

An increased blood concentration of cytokines and chemokines has been observed in patients with Coronavirus disease 2019 (COVID-19) with values directly related to the severity of the disease [6-11]. In the most severe patients, admitted to the intensive care unit, the following molecules were particularly elevated: IL-1β, interleukin-2 (IL-2), IL-6, interleukin-7 (IL-7), interleukin-10 (IL-10), granulocyte-colony stimulating factor (GCSF), IP10, MCP1, MIP1α, and TNF-α. These data suggest that an enhanced inflammatory syndrome due to an aberrant release of high amounts of cytokines, chemokines, and other proinflammatory mediators, is involved in the pathogenesis of the acute distress respiratory syndrome (ARDS) and in other complications found in the severe cases of COVID-19. Indeed, it has been proposed that although the host immune response is essential for the resolution of virus infection, it can also be crucial for the pathogenesis of the severe complications of the disease [6-10]. For unknown reasons in some patients the disease causes a "cytokine storm" that produces a strong inflammatory reaction with severe damage of the infected tissues. Clinical data by showing a therapeutic effect of dexamethasone confirm this hypothesis [12].

---

* Corresponding author at: Unit of Endocrinology, CAST, Università 'G. D’Annunzio’ Campus Universitario, via Luigi Polacchi 11/17, 66013 Chieti, Italy.
E-mail address: cesidio.giuliani@unich.it (C. Giuliani).

https://doi.org/10.1016/j.mehy.2020.110473
Received 3 December 2020; Accepted 18 December 2020
Available online 24 December 2020
0306-9877/© 2020 Elsevier Ltd. All rights reserved.
Also be applied to any disease characterized by the presence of a cytokine storm (EVD). Indeed, a proinflammatory molecules, particularly IL-1β, endotoxic shock, C10 has prevented mortality observed in 100% of the animal model of endotoxic shock [4].

reducing the increased secretion of proinflammatory molecules in an animal model of endotoxic shock. [15]. Given these data, it is of particular interest the observation that C10 is effective in this process resembles the one observed in toxic shock [15]. Given these data, it is of particular interest the observation that C10 is effective in reducing the increased secretion of proinflammatory molecules in an animal model of endotoxic shock [4].

Hypothesis

In a murine experimental model of lipopolysaccharide (LPS)-induced endotoxic shock, C10 has prevented mortality observed in 100% of the control group [4]. The therapeutic effect of C10 has been associated with a decrease in the serum concentrations of IL-6, TNF-α, IL-1β, IL-12, and IFN-γ, all significantly elevated in the control group. Furthermore, C10 inhibited LPS-induced expression of IP-10, MCP1, ICAM-1, VCAM-1, iNOS, Cox-2, IP-10, MCP1 and interferon regulatory factor-1 (IRF-1) in several tissues such as kidneys, heart and lungs. Regarding the latter, histologic analysis has showed a marked decrease of inflammatory features in the lungs of mice treated with C10. In more detail, the treatment with C10 decreased LPS-induced ICAM-1 and VCAM-1 expression on endothelial cells and decreased leukocyte infiltration and septal thickening. The anti-inflammatory effect of C10 on lungs is particularly important since these organs are the main target of COVID-19. An important point to be stressed is that although LPS-treated mice are no longer considered an appropriate model of human sepsis, most of the data regarding the inflammatory process have not been refuted [16,17]. Furthermore, the mouse model is considered valid if the data are replicated in another animal model (mammal) [18] and indeed the efficacy of C10 has been observed also in a preliminary study performed in horses [5]. In this study the pretreatment with C10 has prevented clinical manifestations and mortality in LPS- and peritonitis-induced endotoxic shock.

An important point that need to be highlighted is that C10 acts on multiple pathways of the inflammatory process. Indeed, the anti-inflammatory effects of C10 are due both to the downregulation of the Toll-like receptors (TLRs) expression (particularly TLR-3) and to mechanisms independent from the TLRs pathways. Experiments performed in vitro [3] have showed that C10 inhibits the increase of IFN-β gene expression independently of the specific receptor activated (TLRs or IL-1) or the intracellular signaling involved (TRIF or non-TRIF). In more detail C10 inhibits the interferon response factor (IRF)-3 transactivation induced by various stimuli such as Poly (I:C), LPS, or IL-1β. Additionally, C10 inhibits the phosphorylation of STAT-1 induced by the influenza A virus or by the IFN-β. These data are of particular interest since an abrupt release of IFN-β and IRF-3 activation has been described in the severe forms of COVID-19 [19]. Furthermore, C10 inhibits TNF-α induced IRF-1 expression in human aortic endothelial cells (HAEC) [2].

In view of these data it seems logical to hypothesize that the therapeutic effects of C10 are not limited to the endotoxic shock, but it can also be applied to any disease characterized by the presence of a cytokine storm. Therefore, we hypothesize that C10 can represent a potential agent for COVID-19, EVD and all the life-threatening infectious diseases where a cytokine storm is the main pathogenic process. An important remark that comes from all the studies cited above is the lack of toxic effects in the animal treated with C10. No significant side-effects were noted, in particular anti-thyroid effects were not detected [4,5].

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Giuliani Cesidio and Napolitano Giorgio are co-inventors of the United States patent U.S. 9,326,972 regarding the potential use of phenylmethimazole for the treatment of autoimmune/inflammatory diseases. Ines Bucci has nothing to disclose.

Acknowledgements

The therapeutic uses of phenylmethimazole were conceived by the late Dr. Leonard D. Kohn. The authors are grateful to Prof. Rosa Angela Giuliani for linguistic revision of the manuscript.

References

[1] Giuliani C, Bucci I, Montani V, et al. Regulation of major histocompatibility complex gene expression in thyroid epithelial cells by methimazole and phenylmethimazole. J Endocrinol 2010;204:57-66.
[2] DagiNM, Harii N, Meli AE, et al. Phenyl methimazole inhibits TNF-α-induced VCAM-1 expression in an IFN regulatory factor-1-dependent manner and reduces monocyte cell adhesion to endothelial cells. J Immunol 2004;173:2041-9.
[3] Harii N, Lewis CJ, Vasko V, et al. Thyroxines express a functional toll-like receptor 3: overexpression can be induced by viral infection and reversed by phenylmethimazole and is associated with Hashimoto’s autoimmune thyroiditis. Mol Endocrinol 2005;19:1231-50.
[4] Benavides-Peralta U, Gonzalez-Murguindo M, Harii N, et al. Phenylmethimazole inhibits production of proinflammatory mediators and is protective in an experimental model of endotoxic shock. Crit Care Med 2012;40:886-94.
[5] Kohn LD, Harii N, Benavides-Peralta U, et al. Use of phenylmethimazoles, methimazole derivatives, and tautomeric cyclic thiones for the treatment of autoimmune/inflammatory diseases associated with toll-like receptor overexpression. United States patent 2016 U.S. 9,326,972.
[6] Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020:395:497-506.
[7] Pedersen SF, Ho YC. SARS-CoV-2: a storm is raging. J Clin Invest 2020;130:2202-5.
[8] Han H, Ma Q, Li C, et al. Profiling serum cytokines in COVID-19 patients reveals IL-6 and IL-10 are disease severity predictors. Emerg Microbes Infect 2020;9:1123–30.
[9] Tay MF, Poh CM, Renia L, MacArty PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol 2020;20:363-74.
[10] Cron RQ. Coronavirus is the trigger, but the immune response is deadly. Lancet Rheumatol 2020;2(7):e370-1. https://doi.org/10.1016/S2665-9913(20)30116-5.
[11] Zhong J, Tang J, Ye C, Dong L. The immunology of COVID-19: is immune modulation an option for treatment? Lancet Rheumatol 2020;2(7):e428–36. https://doi.org/10.1016/S2665-9913(20)30120-3.
[12] Cantini F, Goletti D, Petroni L, Naijai Fard S, Nicolli L, Fotti R. Immune therapy, or antiviral therapy, or both for COVID-19: a systematic review. Drugs 2020;80:1-18. https://doi.org/10.1007/s40265-020-01421-w. Epub ahead of print. PMID: 33068263; PMCID: PMC7568461.
[13] Paesler S, Walker DH. Pathogenesis of the viral hemorrhagic fevers. Annu Rev Pathol Mech Dis 2013;8:411–40.
[14] Hendricks K, Parrado MG, Bradley J. Opinion: an existing drug to assess in vivo for potential adjunctive therapy of Ebola virus disease and post-Ebola syndrome. Front Pharmacol 2020;11:1691. https://doi.org/10.3389/fphar.2019.01691.
[15] Cavalloni JM. Exotoxins and endotoxins: Inducers of inflammatory cytokines. Toxicon 2018;149:45–53.
[16] Guillou A, Preau S, Abeab J, et al. Preclinical septic shock research: why we need an animal ICU. Ann. Intensive Care 2019;9:66. https://doi.org/10.1186/s13613-019-0543-6.
[17] Libert C, Ayala A, Bauer M, et al. Part II: minimum quality threshold in preclinical sepsis studies (MQTIPSS) for types of infections and organ dysfunction endpoints. SHOCK 2019;51:23–32.

[18] Zingarelli B, Coopersmith CM, Drechsler S, et al. Part I: minimum quality threshold in preclinical sepsis studies (MQTIPSS) for study design and humane modeling endpoints. SHOCK 2019;51:10–22.

[19] Berthelot JM, Lioté F. COVID-19 as a STING disorder with delayed over-secretion of interferon-beta. EBioMedicine 2020;56:102801. https://doi.org/10.1016/j.ebiom.2020.102801.