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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

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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 others molecules involved in the pathogenesis of inflammation in several types of cells and tissues. Indeed C10 inhibits the production of cytokines such as inteleukin-1β (IL-1β), inteleukin-6 (IL-6), inteleukin-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, inteleukin-2 (IL-2), IL-6, inteleukin-7 (IL-7), inteleukin-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]. The

* 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).

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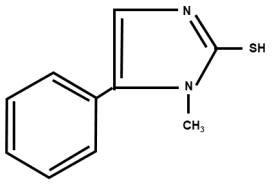

5-PHENYLMETHIMAZOLE
$C_{10}H_{10}N_2S$ MW: 190.27

Fig. 1. Chemical structure of phenylmethimazole (C10).

phenomenon is not peculiar of COVID-19 since it is involved in the pathogenesis of other serious viral infections such as Ebola virus disease (EVD). Indeed, a "cytokine storm" with an aberrant production of proinflammatory molecules, particularly IL-1β, IL-6, IL-10, TNF-α, IP10, MCP1, MIP1α, is involved in the pathogenesis of EVD [13,14]. Of note, 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, iNO, 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 "cytokines storm" is the main pathogenetic 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]. Pre-clinical and clinical studies are needed before the drug can be available for clinical practice. However, we believe it is of great importance to encourage these studies as it is essential to have alternative drugs for viral-induced cytokine storm, as we know indeed that it is not always possible to get an effective vaccine. Furthermore, as the current COVID-19 pandemic has shown the outbreak of novel viral diseases constitutes a constant threat for mankind.

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 coinventors of the United States patent U.S. 9326972 (2016) regarding the potential use of phenylmethimazole for the treatment of autoimmune/inflammatory diseases. Ines Bucci has nothing to disclose.

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