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CLINICAL PHARMACOLOGY (L BRUNETTI, SECTION EDITOR)

Indomethacin: Can It Counteract Bradykinin Effects in COVID-19 Patients?

Myasar Alkotaji[1,2] · Radhwan N. Al-Zidan[2]

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Abstract

COVID-19 represents the biggest health challenge. Although the mortality rate of COVID-19 is low, the high numbers of infected people and those with post-COVID-19 symptoms represent a real problem for the health system. A high number of patients with COVID-19 or people recovered from COVID-19 suffer from a dry cough and/or myalgia. Interestingly, an imbalance in bradykinin was observed in COVID-19 patients, which might be due to the accumulation of bradykinin as a result of a reduction in the degradation of bradykinin. This finding inspired the idea of possible similitude between the dry cough that is induced by angiotensin-converting enzyme inhibitors and the COVID-19-induced dry cough. Both of these types of cough are mediated, at least partially, by bradykinin. They both manifested as a persistent dry cough that is not responded to traditional dry cough remedies. However, several drugs were previously investigated for the treatment of angiotensin-converting enzyme inhibitor–induced dry cough. Here, we hypothesized that such treatment might be useful in COVID-19-induced dry cough and other bradykinin-related symptoms such as generalized pain and myalgia. In this article, evidence was presented to support the use of indomethacin as a potential treatment of COVID-19-induced dry cough. The choice of indomethacin was based on its ability to suppress the cyclooxygenase enzyme while also lowering the level of the inflammatory mediator bradykinin. Furthermore, indomethacin has been shown to be effective in treating angiotensin-converting enzyme inhibitor–induced dry cough. Moreover, indomethacin is a long-established, low-cost, effective, and readily available medication.

Keywords COVID-19 · SARS-CoV-2 · ACEI-induced dry cough · Indomethacin · Bradykinin

Introduction

Coronavirus disease 2019 (COVID-19) is a viral pandemic with a devastating global consequence. This virus has shown an unprecedented rise in cases that have burdened hospitals worldwide [1]. More than 80% of patients with the COVID-19 infection are asymptomatic or only develop a mild form of the disease, while the remaining proportion, unfortunately, suffer from the severe or serious form of the COVID-19 infection [2]. COVID-19 has a wide range of clinical manifestations, ranging from mild fever, sore throat to cough, malaise, headache, muscle pain, or nasal congestion to respiratory distress, severe dyspnea, or even respiratory failure [3]. Currently, there is an accumulating body of evidence suggesting that a significant percentage of patients with COVID-19 continue to suffer from one or more of the symptoms of COVID-19 even after recovery [4, 5]. Cough, besides fatigue and joint pain, has been reported as one of the most commonly persistent symptoms after gaining full recovery from the COVID-19 disease [5]. Patients with persistent symptoms, such as cough, after recovery are expected to need more medical consultations, outpatient visits, and even extended hospitalization, resulting in the depletion of healthcare providers' scarce time and economic strain [6].

A significant proportion of patients with moderate to severe cases of COVID-19 suffer from productive cough with thick mucus. Fortunately, there are a number of studies suggesting the use of *N*-acetyl cysteine (NAC) [7], bromhexine [8], and ambroxol [9]. Unfortunately, this is not the case in the management of the dry cough of patients with COVID-19. There is a lack of data that declares the effectiveness of antitussive medications in the treatment of dry cough in COVID-19

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✉ Radhwan N. Al-Zidan
radhwan.alzidan@uomosul.edu.iq

[1] College of Pharmacy, University of Nineveh, Mosul, Iraq

[2] College of Pharmacy, University of Mosul, Mosul, Iraq

patients [10]. Therefore, there is an urgent need to provide the healthcare workers with a safe and efficient drug to relieve the COVID-19-associated dry cough.

The precise etiology of the dry cough in patients with COVID-19 is not revealed, yet [11]. However, there is an increasing body of evidence implicating the role of bradykinin in the development of the respiratory symptoms, including dry cough, in COVID-19 patients [12–14]. The angiotensin-converting enzyme 2 (ACE2) receptor is used by the SARS-CoV-2 to penetrate body cells [13]. SARS-CoV-2 uses and inhibits the ACE2 receptor and has a similar reaction in the body as with patients who use one of the angiotensin-converting enzyme inhibitors (ACEIs) to treat cardiac disease [15].

Hypothesis

We hypothesize that indomethacin could alleviate some of the COVID-19 symptoms, particularly the dry cough, through its ability to inhibit the cyclooxygenase (COX) enzyme and reducing the level of inflammatory mediator bradykinin which might be responsible, at least partially, for the COVID-19 persistent dry cough.

Evaluation of Hypothesis

Bradykinin in COVID-19

Physiologically, ACE2, which is a part of the counteracting hypotensive axis of renin-angiotensin system (RAS), increases the production of the angiotensin$_{(1\text{-}9)}$, which, in turn, enhances the actions of the bradykinin. In contrast, the ACE, which is a part of the hypertensive axis of RAS, degrades bradykinin and limits its actions [16]. There are an increasing number of studies connecting some of the reported signs and symptoms in patients with COVID-19 with elevated level of bradykinin or as sometimes termed "bradykinin storm" [16–19]. However, the most accurate and well-documented role of bradykinin in COVID-19 patients came from the data generated by the second fastest supercomputer in the world. Garvin et al. [20] reported that the genetic analysis of the cells in bronchoalveolar lavage fluid (BALF) from COVID-19 patients shown harmful imbalance in RAS characterized by decreased expression of ACE in conjunction with increases in ACE2, angiotensin, renin, main RAS receptors, kininogen besides various kallikrein enzymes, and R1 and R2 receptors of bradykinin. To sum up, Garvin et al. [20] found that SARS-CoV-2 downregulates the expression levels of ACE in the lung cells by 8-fold, while it upregulates the expression level of ACE2 by 199-fold. This aberrant pattern of RAS is expected to increase bradykinin levels in many tissues with the subsequent effects such as the increased vascular permeability and dilation, hypotension [21], hypokalemia [22], arrhythmia, and sudden cardiac death [23]. Most of these effects have been recently reported in patients with COVID-19 [24–27].

Indeed, the idea of using indomethacin might contradict the general assumption that COVID-19 patients should not take NSAIDs, specifically ibuprofen [28]. This trend started in France in March 2020 and spread in Europe [29]. Even the WHO recommended against using ibuprofen in COVID-19 patients before relenting [30]. However, at that time, there was no scientific evidence that ibuprofen could increase the severity of COVID-19 or increase the risk of SARS-CoV-2 infection [28]. A more recent prospective cohort study concluded that using ibuprofen and other NSAIDs, whether for acute use or chronic use, is not related to the worse outcome with COVID-19 [31].

Bradykinin-Induced Dry Cough

Persistent dry cough is one of the common side effects of ACEIs. The estimated incidence of dry cough is up to 35% in ACEI-treated patients [15]. The compiled literature well documented the central role of bradykinin elevation with the ACEI-induced dry cough [15, 21, 32]. Basically, bradykinin stimulates the airway's sensory neurons through increasing the production of the prostaglandins PGI2 and PGE2 [32]. Moreover, bradykinin was shown to sensitize the cough reflex through the activation of the bradykinin receptor 2 (B2R) [33]. Interestingly, the recent genetic analysis of the cells in BALF of COVID-19 patients shows a tremendous increase in the expression of the genes responsible for the production of the bradykinin. Moreover, the same study found a remarkable decrease in the degradation of the produced bradykinin [20]. A number of medications such as theophylline [34], inhaled sodium cromoglycate [35], indomethacin [36], sulindac [37], aspirin (500 mg/day) [38], the calcium channel blockers nifedipine and amlodipine [36], and ferrous sulfate [39] have been clinically evaluated in alleviating the ACEI-induced dry cough. Interestingly, indomethacin was found to be the most effective medication in reducing the ACEI-induced dry cough. Indomethacin, at a dose of 50 mg, twice daily, was able to eliminate or significantly reduce the intensity of the ACEI-induced dry cough in 96% of patients [36].

Possible Role of Indomethacin

Besides its important role as non-selective COX inhibitor, indomethacin has been shown to be remarkably effective in

mitigating the pro-inflammatory actions of the abnormally elevated bradykinin level. Moreover, indomethacin has been shown to be one of the best medications for alleviating the dry cough associated with the ACEIs [40]. In the line of the increasing number of reports implicating bradykinin in COVID-19 patients, therefore, indomethacin could also have beneficial effects in alleviating or stopping the dry cough in COVID-19 patients. Furthermore, in response to Professor Little's editorial in the BMJ [41], Rothstein et al. reported a remarkable clinical efficacy for indomethacin in treating dry cough in COVID-19 patients in New York City. The mechanism of bradykinin-induced dry cough has yet to be revealed; however, the available data suggest a central role of the increased pro-inflammatory prostaglandins PGI2 and PGE2 [15]. PGI2 and PGE2 are key mediators of inflammation, pain, and fever. These prostaglandins are mainly produced by the COX enzyme, which is potently inhibited in the presence of indomethacin. Additionally, indomethacin has a potential role as an inhibitor of the phospholipase A2 enzyme, which is also important in the production of the PGI2 and PGE2. Interestingly, in vitro evaluation of indomethacin demonstrated more powerful phospholipase A2 inhibitory action than betamethasone and hydrocortisone [42].

Moreover, we should not forget to mention that indomethacin has antiviral efficacy; it inhibits viral replication, and researches have demonstrated its antiviral activity toward hepatitis B virus, rhabdovirus vesicular stomatitis virus, and coronavirus [43–45]. Indomethacin is not only more effective in reducing the bradykinin-induced cough, than the medications mentioned above in subsection "Bradykinin-Induced Dry Cough" [40], but it also has a long history of clinical use; therefore, its safety profile has been well established better than other potential medications that interfere with bradykinin such as Berinert, Cinryze, Haegarda, danazol, stanozolol, icatibant, lanadelumab, and ecallantide [20].

Finally, indomethacin is much cheaper than most of the abovementioned medications, which would promote its worldwide use for alleviating the common symptoms of COVID-19, such as the dry cough, myalgia, and fever.

Despite the various benefits of using indomethacin, there are side effects, as with other drugs, ranging from mild (such as nausea) to severe (such as ulceration and increasing the tendency of bleeding) adverse effects that might lead to stopping the use of the drug. The most common adverse effect of indomethacin is gastrointestinal adverse effects. The incidence of nausea, indigestion, and heartburn is about 3–9% of patients. Other gastrointestinal side effects are less common (1–3%) including, diarrhea or constipation and abdominal pain, whereas the dangerous side effects of ulcerations of the esophagus, stomach, duodenum, or intestine represented less than 1% of patients [46]. The risk of bleeding could be increased when indomethacin, or any other NSAIDs, is concomitantly administered with dexamethasone, which is usually used in COVID-19 patients with moderate to severe condition [47]. Additionally, NSAIDs could induce renal toxicities such as increased serum creatinine and blood urea nitrogen (BUN), tubular necrosis, glomerulitis, renal papillary necrosis, nephrotic syndrome, and renal dysfunction. However, these renal toxicities are linked to long-term use of the NSAIDs [48].

Conclusion

To conclude, the recent reports about the possible role of bradykinin in COVID-19 support our hypothesis of the usefulness of drugs tried for the treatment of ACEI-induced dry cough. This article highlights the recent finding of the role of pro-inflammatory mediator in the etiology of the disease and the actions of indomethacin on the cyclooxygenase that interferes with bradykinin accumulation. Although this article is an outcome of a comprehensive understanding of the mechanism of action of a drug (indomethacin), the mechanism of adverse effect of group of drugs (ACEIs), and the pathophysiology of a disease (COVID-19), a further well-designed clinical study is vital to prove such theoretical prediction of possible remedies for COVID-19-induced dry cough or other bradykinin-induced symptoms.

Code Availability Not applicable.

Author Contribution M.A. and R.N.A.-Z. wrote the first draft of the manuscript together. M.A. and R.N.A.-Z. planned, edited, and reviewed the manuscript. All authors have read and agreed to the published version of the manuscript.

Data Availability Not applicable.

Declarations

Ethics Approval and Consent to Participate Not applicable.

Consent for Publication Not applicable.

Conflict of Interest The authors declare that there is no conflict of interest.

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