

# Treatment of COVID-19 Patients with Anisodamine Hydrobromide: Three Cases Report and Literature Review

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**Abstract:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel virus which has caused an ongoing pandemic since 2020. It is estimated that 15% patients may develop severe pneumonia, 5% develop acute respiratory distress syndrome (ARDS), septic shock, and multiple organ failure. Anisodamine hydrobromide is a muscarinic receptor antagonist, and also shows anti-inflammatory effect. It has been approved in China to be used in patients with septic shock, organophosphorus poisoning and smooth muscle spasm. We describe three patients with positive results of NATs for SARS-CoV-2, persistent shortness of breath, reduced oxygen saturation and impaired physical endurance even after long-term routine treatments, who were diagnosed with Corona Virus Disease 2019 (COVID-19) infection. After the patients were additionally administrated anisodamine hydrobromide (20 mg twice daily) intravenously for 5 consecutive days based on the original routine treatments, the conditions of COVID-19 infection were rapidly improved, with ameliorated shortness of breath, coughing and sputum, increased oxygen saturation, and improved physical endurance. No obvious adverse effect was observed. Anisodamine hydrobromide might hold great prospect for potential clinical applications in treating COVID-19 patients and improving their conditions.

**Keywords:** COVID-19, anisodamine hydrobromide, muscarinic receptor antagonists, cholinergic anti-inflammatory pathway, pro-inflammatory factors

## 1. Introduction

The COVID-19 pandemic has evolved to a global outbreak for nearly 3 years<sup>[1]</sup>. Although most patients experience mild symptoms, some people will progress to severe conditions<sup>[2-3]</sup>. Cumulative evidence shows a cytokine storm syndrome and lymphopenia in severe COVID-19 patients<sup>[4]</sup>. Considerable efforts have focused on reducing the cytokine storm, such as tocilizumab and corticosteroids. However, there is still lacking evidence in the improvement of survival and outcomes. Effective drugs for treatment of COVID-19 are still a crucial demand at present<sup>[5]</sup>.

Anisodamine hydrobromide is a traditional medicine extracted from Chinese herbs. Being a muscarinic cholinergic antagonist, anisodamine hydrobromide can induce smooth muscle spasm, reduce the secretion of gland, as well as improve the microcirculation<sup>[6]</sup>. Besides, increasing evidence showed that anisodamine hydrobromide exerts anti-inflammatory effect though cholinergic anti-inflammatory pathways<sup>[7]</sup>. In clinic, anisodamine hydrobromide has been widely used in septic shock, disseminated intravascular coagulation (DIC) and acute respiratory distress syndrome (ARDS), which are all the pathological characteristics of COVID-19<sup>[8-10]</sup>. Based on pharmacological characteristics and clinical practice, Chinese scientists raised the notion that anisodamine hydrobromide

might has the potential to improve the conditions of patients with COVID-19<sup>[11-13]</sup>. They further analyzed the possible mechanism via the network pharmacological strategy, and also found anisodamine hydrobromide could suppress SARS-CoV-2 infection and entry<sup>[12-13]</sup>.

In the following cases report, we presented the use of anisodamine hydrobromide for the management in three of COVID-19 patients. They were admitted to the hospital from Jan. 2020 to Mar. 2020. They complained of persistent shortness of breath, reduced oxygen saturation and impaired physical endurance even after long-term routine treatment, which led to long-term hospitalization. Ethics approval was conducted by ethics committee of People's Hospital of Xinjin (Approval number: 2020-01), and written informed consent was obtained from the patient's family for the publication of the case details.

## 2. Case report

### Case 1

A 48-year-old previously healthy woman presented with intermittent fever, cough, weakness, muscular soreness and headache. Five days after her onset, she received nucleic acid tests (NATs) for SARS-CoV-2 on throat swab samples, and a positive result was found. Her chest computed tomography (CT) revealed multiple lesions in her lungs bilaterally. She received routine treatment including high flow oxygen therapy, expectorant, antivirals, corticosteroid, and thymosin. On the following days, she had partial recovery with improvement in her oxygen saturation (increased from 80 % to 99 % under oxygen therapy). Meanwhile, her lymphocyte ratio (normal range: 20-50 %) increased from 6.64 % to 29.5 %, and C-reactive protein (CRP, normal range: 0-4 mg/L) decreased from 212.9 mg/L to 6.07 mg/L. Although the interleukin-6 (IL-6) level (normal range: 0-7 pg/ml) before treatment was missing, its level after treatment was already normal (2.66 pg/ml) (Figure 1). However, she still complained of persistent cough, chest tightness and shortness of breath. She couldn't complete simple physical activity, even had difficulties in rolling over in the bed. Once oxygen therapy was stopped, her saturation reduced rapidly to 90 %. She was then additionally prescribed intravenous anisodamine hydrobromide 20 mg twice daily for 5 consecutive days. Her symptom quickly improved, and physical endurance also improved significantly. She could sit up by herself. Her oxygen saturation could remain 97 % without oxygen inhalation, although it will slightly reduce after physical activity. Before and after anisodamine hydrobromide treatment, lymphocyte number (normal range:  $1.1-3.2 \times 10^9/L$ ) remained at normal level, while lymphocyte ratio further increased from 29.5 % to 33 %, and CRP further decreased from 6.07 mg/L to normal level 3.48 mg/L. IL-6 was not detected after treatment. With improved clinical conditions, she was discharged to local hospital for further rehabilitation.

### Case 1

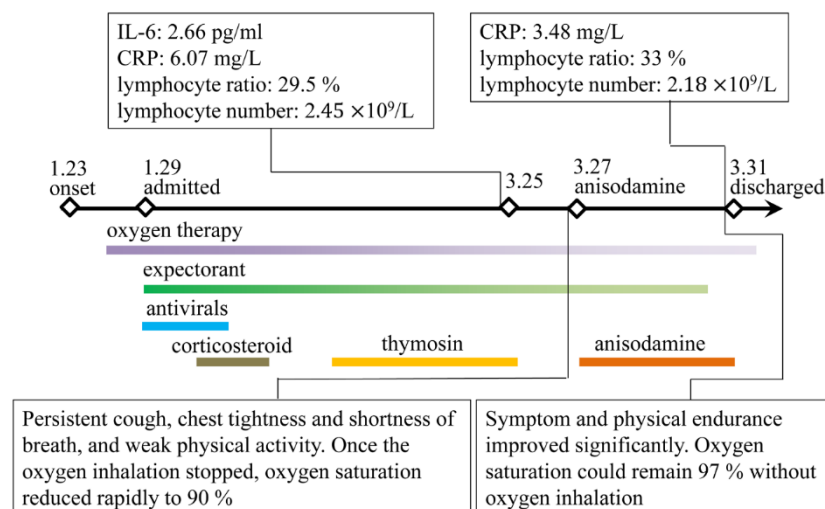


Figure 1: Timeline of treatment information for case 1

## Case 2

A 70-year-old woman with an unremarkable medical history was hospitalized with fever, cough and fatigue for 2 months. Her nucleic acid tests (NATs) for SARS-CoV-2 on throat swab samples was positive. On admission, she complained of chest tightness and shortness of breath, with breathing rate of 40 per minute and oxygen saturation of 80 %. Her laboratory tests revealed elevated CRP (103.09 mg/L) and IL-6 (210.1 pg/mL), and decreased lymphocyte number ( $0.51 \times 10^9/L$ ) and ratio (3.3 %). She experienced rapidly progressive respiratory distress after admission. Oxygen therapy was upgraded from high flow oxygen inhalation (40 litres/minute,  $FiO_2$  65%) to ventilator assistance (SIMV mode, with tidal volume 400ml, PEEP 5cmH<sub>2</sub>O and oxygen concentration 50%) within 2 days. She also received antivirals, methylprednisolone, immunoglobulin, thymosin and antibiotics intravenously (Figure 2). Over the following days, she experienced gradual improvement, until she completely detached from respirator, maintaining normal oxygen saturation with low flow oxygen inhalation (5 litres/minute). However, she still had difficulty in breathing after physical activity, with persistent anomaly in her laboratory tests (IL-6 118.10 pg/mL, CRP 14.27 mg/L, lymphocyte number  $0.43 \times 10^9/L$  and lymphocyte ratio 9%). Intravenous anisodamine hydrobromide (20mg, twice daily) was then administered for 5 days. Obvious improvement in her chief complaints was recorded, and also in her laboratory tests and laboratory testing was evident (IL-6 10.81 pg/mL, CRP 8.08 mg/L, lymphocyte number  $0.98 \times 10^9/L$ , lymphocyte ratio 17.7%). Her lung findings also regressed largely, until she could perform basic daily physical activity and was then discharged home.

### Case 2

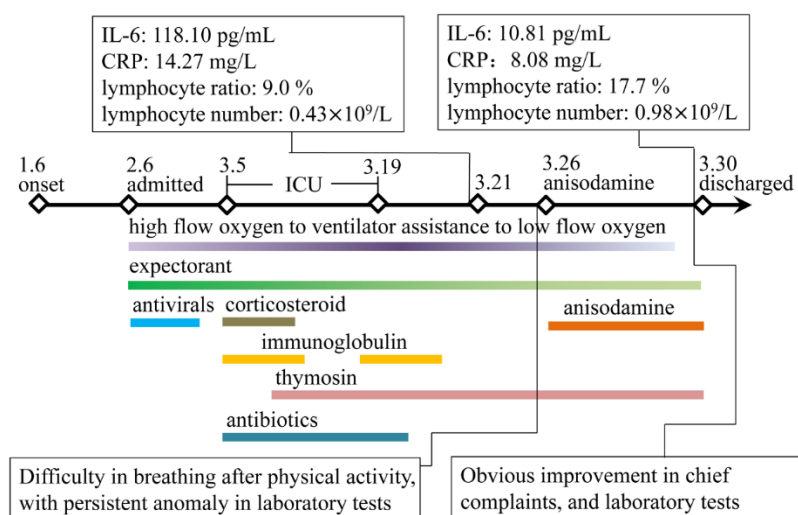


Figure 2: Timeline of treatment information for case 2

## Case 3

An 86-year-old man with a history of coronary heart disease for 10 years was admitted with coughing, wheezing and chest-tightness for 12 days. His nasal swab RT-PCR was positive for SARS-CoV-2, and a diagnosis was made of moderate COVID-19. On admission, he reported persistent and severe chest-tightness and shortness of breath, which led him to become bedridden. His chest CT revealed diffused interstitial lesions and infections in the lungs bilaterally. His oxygen saturation was as low as 70%. Over the following days, he received oxygen therapy, expectorant, antibiotics and thymosin. His laboratory tests revealed mildly increased CRP (36.17 mg/L) and IL-6 (18.25 pg/mL), and decreased lymphocyte number ( $0.94 \times 10^9/L$ ) and ratio (9.5%) (Figure 3). However, even under high flow oxygen therapy (oxygen flow 60 litres/minute,  $FiO_2$  40%), his oxygen saturation ranged from 90%-93% at rest state, and declined to 85% after rolling over in the bed, accompanied by significant shortness of breath. He therefore had to stay in bed most of the time. He was then started on intravenous anisodamine hydrobromide (20mg, twice daily) treatment. Six days later, his physical endurance improved. He could sit up by himself, remaining oxygen saturation of 95% after mild physical activity under high flow oxygen. Increased lymphocyte number ( $1.28 \times 10^9/L$ ) and ratio (16.1%) were observed, although his CRP (77.08 mg/L) and IL-6 (43.08 pg/mL) were still high. He was discharged to local hospital for further rehabilitation.

## Case 3

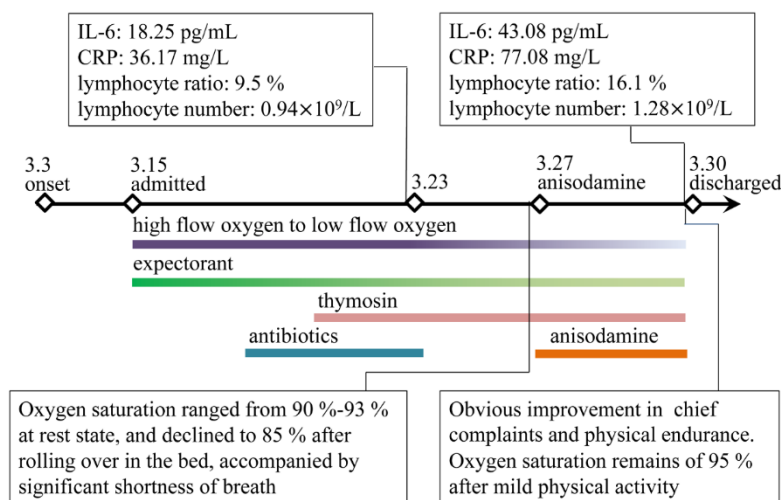


Figure 3: Timeline of treatment information for case 3

### 3. Discussion

Here, we first report the administration of anisodamine hydrobromide in three COVID-19 patients. Although they received routine treatments, they still had persistent respiratory symptoms, reduced physical activity and inability to detach from oxygen therapy, which resulted in long-term hospitalization. Also, they displayed persistent inflammatory state and/or decreased lymphocyte. Overall, after 5-6 days administration of anisodamine hydrobromide, their clinical conditions improved quickly verified by acceptable oxygen saturation even without oxygen therapy, accompanied by ameliorated shortness of breath, coughing and sputum. It was noteworthy that three patients have improved physical endurance, enabling to complete basic daily activities independently, and could be discharged after long-term hospitalization. Meanwhile, it was observed decreased inflammatory mediators (IL-6 and CRP) in 2 cases, and elevated lymphocyte in 3 cases. Based on these cases, we proposed that anisodamine hydrobromide might help to ameliorate respiratory symptoms and promote the rehabilitate in some COVID-19 patients, especially those with unsatisfied response to routine treatments.

Pharmacologically, anisodamine hydrobromide can relieve smooth muscle spasm and dilate the bronchia, inhibit gland secretion, and finally improve the function of pulmonary ventilation<sup>[6]</sup>. Marked ameliorations in coughing and sputum in 3 patients after anisodamine hydrobromide administration was observed, which might be resulted from reduced respiratory secretions and released bronchial spasm. These further led to improved lung function, oxygen saturation and the physical endurance eventually. Additionally, anisodamine hydrobromide could counteract LPS-induced endothelial cell injury by inhibiting the NF- $\kappa$ B pathway<sup>[14]</sup>, and play its anti-inflammatory effect by indirectly activating the cholinergic anti-inflammatory pathway<sup>[7]</sup>, which might be responsible for the improvement of inflammatory state in COVID-19 patients including the reduction in IL-6 and CRP and the elevation of lymphocytes.

The potential adverse effects of anisodamine hydrobromide include reduce salivation, lacrimation and sweat, diminished gastrointestinal motility, mydriasis, and increased heart rate, which is tolerable and will disappear within 1-3h<sup>[6]</sup>. Of three cases, Case 1 described temporary dryness in her mouth, which diminished rapidly within several hours. Case 3 showed an increase in his heart rate from average of 86 beats/min to 108 beats/min after anisodamine hydrobromide. No other hyoscyaminization manifestation were observed. Therefore, anisodamine hydrobromide showed to be tolerable in these patients.

Severe complications of COVID-19 include septic shock, ARDS, DIC and multiple organ failure. Anisodamine hydrobromide may also provide protection in these cases. Reportedly, anisodamine hydrobromide could improve microcirculation in patients with septic shock, and reduce the occurrence

of sepsis by 50 %<sup>[9,15]</sup>. It exerted manifest therapeutic effect on ARDS and traumatic acute lung injury<sup>[8,16]</sup>, and attenuated DIC through anti-platelet-aggregating and microcirculation-facilitating<sup>[10]</sup>. For severe patients that developed multiple organ failure, anisodamine hydrobromide could be a feasible treatment for its effect of improving microcirculation of myocardial infarction<sup>[17]</sup>, suppressing cardiomyocytes apoptosis<sup>[18]</sup>, protecting against ischemic stroke<sup>[19]</sup>, and ameliorating renal dysfunction<sup>[20]</sup>.

This report has several limitations: only 3 patients were treated with anisodamine hydrobromide, and some laboratory data are lost before or after treatment at the early stage of COVID-19 outbreak. However, the three patients showed quick improvement in chief complain, oxygen saturation and physical endurance after the administration of anisodamine hydrobromide and could be quickly discharged after long-term hospitalization. This preliminary data gave us some beneficial hints and could lead to the organization of multicenter studies to further confirm this effectiveness.

In conclusion, this report firstly describes the use of anisodamine hydrobromide in the management of three COVID-19 patients with unsatisfied response to routine treatment and demonstrated a rapid clinical improvement after the intravenously administration of anisodamine hydrobromide for 5 consecutive days. In the context of global COVID-19 pandemic and lack of effective medicine, it is worth trying to use some pre-approved drugs especially for those patients in developing and under-developed countries.

### Author contributions

F.W. and C.P. conceptualized the study. The data were provided by author F.W. K.C. were involved in the patient's clinical care and supervised the work. X.L. and F.C. expanded and refocused scientific rationale. F.W., F.C. and X.T. interpreted the patient data and prepared the first draft of the manuscript. X.L. and C.P. subsequently revised it. All authors reviewed and approved it.

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