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Case Series

Cyproheptadine in Hospitalized Patients in the ICU for COVID-19: A Case Series

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Abstract

The COVID-19 pandemic has had a terrible toll in terms of mortality and overwhelming health care systems worldwide. The race to handle the disease had precipitated research on both repurposed drugs as well as the development of new ones. There is biological plausibility for cyproheptadine to be useful as an anti-serotonergic agent. In this retrospective case series, we show that cyproheptadine has no significant side effects in a monitored setting that would preclude a larger trial to be done to assess potential therapeutic efficacy.

Introduction

Since the onset of the SARS-CoV-2 (COVID-19) pandemic in December 2019, this rapidly evolving disease has officially infected at least 585 million people and killed 6.42 million people [1]. However, a new estimate from the World Health Organization (WHO) shows that the total number of deaths directly or indirectly associated with the COVID-19 pandemic (described as "excess mortality") between 1 January 2020 and 31 December 2021 was around 14.9 million (range 13.3 million to 16.6 million) [1].

In addition, the long-term consequences characterized by the persistence of various symptoms (dyspnea, headache, chronic asthenia, cognitive disturbance and other symptoms) grouped under the term long covid syndrome seem to be developing into a current and likely future public health issue [2,3]. Currently, recognized pharmacological treatment options for severe and critical COVID-19 are limited. Although several trials are underway to improve the management of COVID-19, the only treatments that have proven benefit to date on mortality in patients requiring oxygen and/or mechanical ventilation, and recommended by the WHO [4] are the administration of corticosteroids [5], IL6 inhibitors (Tocilizumab and Sarilizumab) [6] and JAK inhibitor (Baricitinib) [7]. Other COVID 19 treatments, such as fluvoxamine, heparin or colchicine, are still being evaluated [4].

Hence, it seems necessary to broaden the therapeutic arsenal, especially with the idea of affordable and easily accessible treatment for health systems with limited resources. Sadly, much of this process has been perverted by political and social forces that seemed to entrench institutions, physicians and the public into groups that supported repurposing existing drugs with potentially beneficial biopathways versus developing new drugs specifically for this disease. This has resulted in a very tumultuous and fragmented medical practice and something that the medical field should be ashamed of. It is necessary for the scientists and physicians to take a step back and examine each drug, new or old, assess them without bias, and then discard or adopt depending on the results of well-done studies. Hydroxychloroquine is a good example, as it had some theoretical promise, but when found not to have clinical impact, was largely discarded. To casually dismiss a repurposed drug because it is not backed by large pharmaceutical support is not scientific. Cyproheptadine (CHT) is an old drug with antihistaminic and antiserotonergic activity used since the 1960s for the symptomatic treatment of allergies and known to be relatively safe [8,9]. It has been used for several decades in the treatment of serotonin syndrome following drug intoxication like serotonin reuptake inhibitor antidepressants [10,11].

Several, experimental and clinical studies have found an abnormal rise in serotonin levels in the blood and platelet hyperactivation in experimental models and in patients infected with SARS-CoV-2 [12,13,14]. The conclusions of several studies in non-COVID and COVID patient populations provide interesting and potentially explanatory arguments for several clinical and biological manifestations found in COVID-19 such as pulmonary vascular abnormalities [17,18] or a state of hypercoagulability [14,15,16]. It was clear to many physicians that pulmonary vascular abnormalities must be present since often, parenchymal disease alone could not account for the degree of hypoxia noted in many of these patients. In COVID-19 patients, clinical data highlights the presence of symptoms resembling some of the serotonergic syndrome visible during poisoning with serotonergic treatments, especially neurological symptoms [19] In fact, in series of cases, a prevalence of symptoms that can be integrated into a serotoninergic syndrome (clonus, hypereflexia, hyperthermia, tachycardia, agitation, sweating) was close to 65% [20]. In view of these findings, CHT seems to be an interesting potential adjuvant treatment in COVID-19 patients. In our center, we chose to use this drug - which we felt was safe based on historical data - using the precautionary principle in patients with severe disease and high mortality. We share the data in hopes to help pave the way for an eventual randomized clinical trial by a larger group. To explore the clinical tolerance of cyproheptadine in patients with a severe form of COVID-19, we report a retrospective case series of patients admitted to intensive care for severe acute COVID-19 infection and having received treatment with CHT in addition to the standard management recommended by the WHO [4].

Methods

This retrospective observational case series study was performed at Santa Cabrini Hospital, which is a community hospital in Montreal, Canada. Fourteen patients with laboratory-confirmed SARS-CoV-2 infection who presented to the hospital and subsequently admitted the ICU for the treatment of COVID 19 pneumonia requiring oxygen or mechanical ventilation, receiving cyproheptadine and standard care following WHO recommendation, between November 1, 2020 and

May 31, 2021, were enrolled. The institutional ethics board of the integrated university center for health and social services in the east Montreal approved this study and due to the nature of retrospective case series chart review, waived the need for informed consent from individual patients. According to the WHO guidance, laboratory confirmation for SARS-Cov-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RT- PCR) assay of nasal and pharyngeal swabs.

Data Collection

The data reported in this study were retrospectively extracted from the electronic patient record of our medical institution after approval by the research ethics board of our integrated university health and social services center. We extracted and reported data at days 1, 3, 5, 7, 10, 14, and 28 of hospitalization after initiation of cyproheptadine treatment.

Data reported

- Recorded data includes age, sex, medical comorbidities, vital signs (temperature, heart rate, systolic and diastolic blood pressure, sespiratory rate, SpO_2), presence of agitation, delirium or lower extremity clonus.
- Organ support with the type of therapy used for oxygen delivery (nasal cannula, venturi or non-rebreather mask, HFNC), type of mechanical ventilation (NIV or IMV), FiO_2, and use of renal replacement therapy.
- Pharmacological intervention with the use of sedatives, pharmacological hemodynamic support with dose, antithrombotic or antiplatelet drugs introduced at the time of the study, antibiotics, antifungals, steroid therapy, antiviral drugs introduced at the time of the study as well as other treatments specifically administered in the context of COVID-19 (Remdesivir, Tocilizumab etc.)
- The time from diagnosis of SARS-CoV-2 infection by RT PCR to initiation of CHT treatment, daily dose of CHT and total duration of CHT treatment.
- Acute thromboembolic events: Deep Vein Thrombosis (DVT), Pulmonary Embolism (PE) or ischemic events related to arterial thrombosis or embolism (ischemic stroke, Acute Coronary Syndrome (ACS), gastrointestinal tract ischemia or other acute ischemic events).
- Laboratory tests including creatinine, alanine amino transferase, bilirubin, CRP, D-dimer and platelet count.
- Length of hospital stay, length of ICU stay, and length of mechanical ventilation support.
- SOFA score, ROX index and SpO_2/FiO_2 ratio for days 1, 3, 5, 7, 10, 14 and 28 were calculated as well.

Results

Demographic and treatment characteristics **Table 1** shows the demographic and the clinical characteristics of the patients. 78% of patients were male, with a median age of 61 years (IQR, 54-68). The median BMI was 34 (IQR, 29-39) which corresponds to obesity.

Comorbidities

Chronic lung diseases (asthma and COPD) and arterial hypertension were the main comorbidities (50% and 43% respectively), followed by diabetes (14%) and chronic neurological diseases (14%, mainly epilepsy). A history of chronic heart disease, cancer and immunosuppression without cancer was each found in 7% of patients.

Chronic treatments

14% of the patients regularly took aspirin and 7% calcium channel blockers. None of the patients were taking blood thinners, other antiplatelet therapy, or NSAIDs at home.

Mechanical ventilation

36% of patients were intubated and placed on invasive mechanical respiratory assistance. The median duration of mechanical ventilation (NIV and IMV) was 11 days (IQR, 7-17).

Table 1: Demographic, comordidities and treatments characteristics

Demographic characteristics	Median[IQR]	%(Percentage)
Age (Years)	61[54;68]	
Gender		78% Male
Weight(Kg)	92[82;105]	
Height(cm)	169[163;177]	
BMI	34[29;39]	
Length of Stay(Days)		
Hospital	26[18;48]	
ICU	10[7;20]	
Day 28 Outcome		64% Home 26% Rehabilitation
Mechanical Ventilation		
Invasive Mechanical Ventilation		36%
Mechanical Ventilation Duration (Days)	11[7;17]	
Comordidity		
Chronic Cardiac disease		7%
Hypertension		43%
Diabetes		14%
Chronic pulmonary disease		50%
Active Cancer		7%
Immunosuppression		7%
Chronic Hepatic Disease		0
Chronic Kidney Disease		0
Chronic Neurological Disease		14%
Other_Comorbidity		0
Chronic Treatment		
NSAID		0
ASA		14%
Other antiplatelets		0
Anticoagulant		0
Calcium Channel Blockers		7%
Treatment in ICU		0
Sedation		50%
Steroids		93%
Antibiotic		93%
Antifungal		0
Covid 19 Specific Treatment		21% Remdesivir
CHT Treatment		
Initiation since RT-PCR positive (Days)	8[6;10]	
Treatement Duration (Days)	9[6;12]	
Treatement Dosis (mg)	24[12;24]	
Thromboembolic event		21%

Treatments

50% of patients were sedated, 93% were receiving steroids, 93% antibiotics and 21% remdesivir during their stay in the ICU. None of the patients received antifungal treatment or other specific treatment for COVID 19.

Cyproheptadine treatment

The median time from RT-PCR diagnosis of SARS-CoV-2 infection to initiation of CHT treatment was 8 days (IQR,6-10). The median daily dose administered was 24mg (IQR, 12-24) with a median treatment duration of 9 days (IQR, 6-12).

Thromboembolic event

21% of patients experienced thromboembolic events, mainly deep vein thrombosis and/or pulmonary embolism.

Length of stay

The median length of hospital stay was 26 days (IQR, 18-48) with a median length of ICU stay of 10 days (IQR, 7-20)

Outcome

All patients were alive on day 28. After hospitalization, 64% were transferred home and 26% for rehabilitation.

Clinical and laboratory features

SOFA score

The median SOFA score was relatively low on day 1 with a score of 3(IQR,3-4) without variation until day 10 with a mean score of 2(IQR,1-2) stable until day 28.

Temperature

The median temperature was 38 degrees Celsius (IQR, 37-39) on day 1 and the median temperature was 37 degrees Celsius on subsequent days.

Neurological status

On Day 1, respectively, 21% and 28% of patients showed delirium and/or agitation and clonus of the lower limbs, on Day 2 and Day 7, 7% of patients were delirious and/or agitated. None of the patients presented with clonus or delirium and/or agitation on the other days.

Cardiovascular parameters

Median Heart Rate (HR) and median Systolic Blood Pressure (SBP)/Diastolic Blood Pressure were relatively normal and stable throughout follow-up. On Day 1, median HR was 88 Beat per minute (IQR, 80-103), median SBP 127 (IQR,120-130)

Respiratory parameters

- The Respiratory Rate was highest on day 1 with a median of 31 breaths per minute (IQR, 26-34) and steadily decreased on other days.
- The SpO_2 remained relatively stable during follow-up, with a median of 93% (IQR, 86.96) on day 1.
- The median SpO_2/FiO_2 ratio increased during the first 10 days with 113 (IQR, 100-169) on day 1 to 330 (IQR, 203-392) on day 10. The ratio decreased on day 14 with a median of 279 (IQR, 237-380) and remained stable at day 28.
- The median ROX index was low on day 1 with an index of 4 (IQR, 4-5) and increased until day 14 with an index of 14 (IQR, 9-17). On day 14, the median ROX index was lower with an index of 9 (IQR, 7-16), and increased again on day 28 with a median index of 12 (IQR, 10-20).

Oxygen therapy and mechanical ventilation

On day 1, 58% of patients were on high flow nasal cannulae (HFNC), 28% on invasive mechanical ventilation (IMV) and 14% on non-invasive mechanical ventilation (NIV), on day 3 more patients were intubated and 36% were on IMV, 43% on HFNC and 21% on NIV. The trend for the other days was the decrease in patients on MV and the increase in patients on nasal cannula and totally weaned from oxygen until day 14, with 18% on room air (RA), 36% on nasal canula (NC), 18% on HFNC, 18% on IMV and 9% on NIV.

On day 28, none of the patients still hospitalized were on mechanical ventilation, 33% were on RA, 16% on NC and 50% on HFNC. Median FiO_2 decreased during follow-up with a median of 80% (IQR, 55-75) on day 1, 33% (IQR, 25-39) on day 14, and 34% (IQR, 23-19) on day 28.

Biological parameters

Table 2 shows the clinical and biological characteristics at days 1, 3, 5, 7, 10, 14 and 28 after the initiation of CHT treatment.

PCR

Median CRP was elevated on day 1 with 202 mg/l (IQR, 139-238) and decreased throughout follow-up.

D-dimers

D-dimers were elevated on day 1 with a median of 1040 mg/L (IQR, 761-8718). The d-dimer level was increased twice, on day 10 with a median of 5075mg/L (IQR,4002-54160 and on day 28 with a median of 10311mg/L (IQR,5956-14677)

Table 2: Clinical and laboratories characteristics

	D1	D3	D5	D7	D10	D14	D28
SOFA Score	3 [3;4]	3 [2;4]	3 [2;3]	3 [2;3]	2 [1;2]	2 [1;2]	2 [0;2]
Temperature (Celsius)	38 [37;39]	37 [37;39]	37 [37;38]	37 [36;37]	37 [36;37]	37 [36;37]	37 [37;37]
Delirium Agitation	21% (3/14)	7% (1/14)		7% (1/14)			
Clonus	28% (4/14)						
HR (BPM)	88 [80;103]	83 [80;103]	79 [71;89]	80 [75;89]	88 [76;92]	85 [82;89]	93 [88;96]
SBP (mmHg)	127 [120;130]	133 [120;130]	121 [110;132]	119 [106;138]	121 [113;132]	110 [104;121]	128 [120;139]
DBP (mmHg)	70 [70;80]	75 [70;80]	72 [66;80]	70 [66;78]	75 [70;78]	70 [63;74]	78 [72;84]
RR (PerMin)	31 [26;34]	26 [26;34]	23 [20;25]	22 [17;24]	23 [20;24]	20 [20;21]	21 [20;24]
SpO2	93 [89;96]	93 [89;96]	95 [93;93]	94 [92;95]	94 [93;95]	92 [92;94]	93 [92;94]
SpO2/Fi02	113 [100;169]	153 [100;169]	142 [133;154]	228 [180;269]	330 [203;392]	279 [237;380]	282 [240;399]
ROX index	4 [4;5]	6 [4;5]	7 [6;14]	12 [9;16]	14 [9;17]	9 [7;16]	12 [10;20]

Oxygen Therapy					21% AA	18% AA	33% AA
				14% NC	14% NC	36% NC	16% NC
	58% HFNC	43% HFNC	50% HFNC	43% HFNC	21% HFNC	18% HFNC	50% HFNC
NIV	14%	21%	14%	14%	14%	9%	0
IMV	28%	36%	36%	28%	28%	18%	0
FiO2 (%)	80 [55;75]	60 [55;90]	48 [36;64]	41 [35;50]	29 [24;48]	33 [25;39]	34 [23;19]
CRP (mg/L)	202 [139;238]	79 [75;135]	44 [34;61]	39 [37;69]	36 [30;49]	36 [23;46]	2 [2;2]
D-dimer (mg/L)	1040 [761;8718]	1153 [753;7903]	1347 [1151,11354]	3007 [983;5408]	5075 [4002;5416]	1693 [1418;14714]	10311 [5956;14677]
Platelets (Giga/L)	211 [197;308]	331 [224;360]	330 [223;397]	275 [213;399]	323 [297;375]	274 [240;323]	236 [196;283]
Creatinine (µmol/L)	85 [63;112]	66 [60;99]	74 [56;95]	78 [55;92]	80 [60;89]	72 [68;91]	71 [58;83]
ALT (IU/L)	52 [31;70]	48 [24;70]	61 [30;82]	98 [37;165]	84 [48;106]	62 [44;99]	74 [47;125]
Bilirubin (mg/L)	15 [13;18]	12 [10;14]	11 [10;13]	9 [8;15]	12 [10;17]	13 [13;16]	16 [15;16]

Results were on median[IQR] Or %(n)

Abbreviations: GCS, Glasgow Coma Scale; HR, Heart Rate; RR, Respiratory Rate; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure;NIV, Non Invasive Ventilation; IMV, Invasive Mechanical Ventilation ;AA,Ambiant Air; NC, Nasal Cannula; HFNC, High Flow Nasal Cannulae; ALT, Alanine Amino Transferase.

Platelet count

The median platelet count was globally stable during follow-up, with a median of 211 Giga/L (IQR, 197-308) of platelets on day 1, 275 G/L (IQR, 213-399) on day 7 and 274 G/L(IQR,240-323) at day 14.

Creatinine

Median serum creatinine was also generally stable during follow-up, with a median of 85 µg/L(IQR,63-112) on day 1, 78 µg/L(IQR,55-92) on day 7 and 72µg / L (IQR,68-91) at day 14.

Alanine-amino-transferase

Alanine-amino-transferase (ALT) was mildly elevated on day 1 with a median of 52 IU/L (IQR, 31-70), elevated on day 7 with a median of 98 IU/L (IQR37-165) and still mildly elevated on day 14 with a median of 62 IU/L (IQR,44-99).

Bilirubin

Bilirubin was normal and stable during follow-up with a median of 15mg/L(IQR,13-18) on day 1, 9 IU/L(IQR,8-15) on day 7 and 13IU/L (IQR,13 - 16) on day 14.

Discussion

In this case series of intensive care patients who received CHT therapy in addition to standard therapy for the treatment of severe SARS-COV 2 pneumonia we found several points for discussion.

First of all, there is no signal for a poor tolerance of CHT for this category of patients. The side effects of CHT are mainly linked to an atropine effect with mainly neurological effects with excessive drowsiness or agitation, cardiovascular with arrhythmias, hepatic with drug-induced hepatitis (21), urological with acute retention of urine and ophthalmological with acute angle-closure glaucoma. None of these were noted in a monitored setting. Apart from a modest elevation of ALT without elevation of bilirubin found on day 7, there was no strong signal of poor metabolic tolerance of CHT. The proportion of patients with initial delirium on day 1 of treatment (21%) does not seem to be linked to taking CHT given its early onset. Another notable result concerns the elevation in a second time of D-dimer on day 7 then on day 28, possibly related to nosocomial infections and, in particular, ventilatory associated pneumonia or hospital acquired pneumonia frequently found in patients ventilated for COVID 19 and under high dose of steroids [22]. This elevation of D-dimers could also be related to the occurrence of thromboembolic events, the incidence of which found in this series of cases is similar to that reported in the literature. Also, the drop in the SpO_2/FiO_2 ratio and the ROX score at D7 can be interpreted as consecutive to weaning from mechanical ventilation and the onset of VAP.

Limitation

There are many limitations in this study. Firstly, this study is limited by the lack of standardization of the data and its character as a serial case study.

Secondly, the population seems to differ from the population usually found in studies on Covid-19, in particular, the distribution of patient comorbidities, the main ones being not diabetes and cardiovascular disease but chronic respiratory and neurological diseases. In addition, the illness severity of the patients was low, with a median SOFA score of 3 initially. None of the patients in this case series had died by day 28, but data from the larger cohort from which this case series is drawn found a total mortality of 49% by day 28. We cannot infer a CHT treatment effect from our limited data pool.

Thirdly, the exploration and documentation of a serotonin syndrome according to the criteria of Hunter or Sternbach (23,24) was not feasible in the absence of numerous unreported clinical data. In addition, certain neurological characteristics that are very suggestive of a serotoninergic syndrome such as the search for clonus or hypereflexia were very certainly under-documented and under-reported.

Finally, there is major heterogeneity in CHT treatment modalities, with doses ranging from single to double with unequal treatment durations. In addition, treatment initiation was often late after diagnosis of SARS-Cov 2 infection by RT PCR, with a median of 8 days with an IQR of 6-10 days.

Conclusion

In this small case series study carried out on a population of patients hospitalized in intensive care for severe SARS-CoV-2 pneumonia and treated with Cyproheptadine in addition to standard recommended care, no signals of CHT intolerance or notable side effects were found. More robust studies seem necessary to explore the therapeutic potential of CHT in patients with severe forms of COVID 19.

Conflicts of Interest: None

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