A case report: Does aminophylline have opportunity in COVID-19 management?

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Abstract

The novel coronavirus disease 2019 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), which causes severe acute respiratory distress syndrome (ARDS). ARDS causes the patient to have difficulty breathing, the appearance of pneumonia from chest radiological images, and from the examination results by pulse oximetry, the picture of oxygenation is poor. Most clinical complaints require mechanical ventilation and treatment in the intensive care unit (ICU). We made several attempts to increase oxygenation and ventilation from a pharmacological and non-pharmacological perspective. From pharmacology, given drugs that help from an immunological aspect, reduce preload, help cardiac contractility, and anti-virus. In this case report, we report aminophylline administration as a therapeutic modality in critically ill patients' handling due to COVID-19.

Key words: Intravenous aminophylline, COVID-19, immunomodulator.

Introduction

COVID-19 pneumonia is a deadly contagious disease. First appeared last 2019 in Wuhan, China, and spread very rapidly to all parts of the world. There is still no evidence therapy for dealing with COVID-19 until now. The thing that causes rapid death is oxygenation and ventilation problem, which requires ventilator assistance to assist oxygenation and ventilation in the intensive care unit (ICU). (1)

Bioinformatics research written by Sarma, et al (2020) states that theophylline has an anti-viral towards Severe Acute Respiratory Syndrome Coronavirus 2 (SARS COV-2) and has a bronchodilator and immunomodulatory effects. (2) In this case report, we present aminophylline administration in patients of COVID-19 who had oxygen desaturation after intubation.

Case description

A 36-year-old male, 70 kg BW, height 172 cm, was hospitalized in ICU because of COVID-19. He presented in emergency with clinical complaints of dyspnea and febrile. The respiratory rate before oxygen therapy was 40/minute, pulse oximetry was 94%. We gave oxygen therapy with a non-rebreathing mask of 15 litres per minute, and we examined blood gas analysis. The result of blood gas analysis with a non-rebreathing mask of 15 litres per minute showed in **Table 1**. After 9 hours of closed observation in the ICU, we changed the oxygen therapy method to high flow nasal cannula (HFNC) 30 litres per minute, FiO2 70%. The result of blood gas analysis with HFNC showed in **Table 1**. Cycle threshold value of reverse transcription polymerase chain reaction (RT-PCR) of nasopharynx on Sept 12, 2020, of this patient was E 30.30, RdRp 35.97, and N 34.03.

After five days using HFNC, there was deterioration, so we intubated the patient and continued with mechanical control ventilation. We adminis-

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tered aminophylline when we did not achieve a good value in pulse oximetry examination. We started with 240 mg/30 minutes aminophylline and continued with 480 mg/24 hours for four days. After four days of observation, there was an increasing pulse oximetry examination (97-98%). We continued the aminophylline administration with a lower dose (240 mg/24 hours for three days)—good achievement after providing aminophylline in 7 days as one of the therapy modalities. We referred the patient to the ward in good clinical condition.

Serial chest radiography is showed in **Figure 1**. The serial chest radiography did not show improvement, but clinical signs showed the improvement. Blood gas analysis results showed improvement in the day when we provided aminophylline for this patient. We administered aminophylline starting on Sept 16, 2020 and stopped on Sept 25, 2020 (PaO2/FiO2 ratio 222.66). In this satisfactory state of oxygenation, we tried to stop the muscle relaxant, and just gave sedation. But the patient was restless and retracted the endotracheal tube. We did not reintubate and just monitored the spontaneous respiration of this patient. With time, the patient was in optimal condition, no complaint of tightness, and could communicate with the healthcare team. After three days of observation of adequate spontaneous breathing, we referred him to the ward for follow-up care.

Discussion

This case report demonstrates a significantly clinical appearance improvement and maintaining spontaneous respiratory function after administering aminophylline. We were able to wean the patient from mechanical ventilatory support because of aminophylline due to one or a combination of the mechanisms noted below. Our hypothesize of providing aminophylline may affect through 1) Theophylline has beneficial effects on phrenic nerve and diaphragm activation; (3) 2) Aminophylline is a derivative of the xanthine alkaloids to use as a mild stimulant and bronchodilator impact, notably in treating asthma; 3) Theophylline mimics the effects of adrenaline and noradrenaline by raising blood pressure (BP); (4) 4) Theophylline has an immunomodulatory effect by exerting an inhibitory effect of T-lymphocyte on the airway, especially for the asthmatic patient; inducing neutrophil apoptosis and suppressing the inflammatory gene expression at low dose concentration; 5) Theophylline also has anti-inflammatory at low dose by restore histone deacetylase-2 (HDAC2) activity, which leads to improve steroid responsiveness. (5)

Banner and Page (1995) and Kerttula (1997) stated that in addition to having a bronchodilator effect, aminophylline also has anti-inflammatory, immunomodulatory, and bronchoprotective impact. (6,7) We did not check the level of inflammatory mediators in this patient. So, it is challenging for us to say that this aminophylline has an immunomodulatory and anti-inflammatory effects even though there may be.

Our first hypothesis regarding the improvement in saturation that occured after the administration of aminophylline was the prompt treatment of the possibility of stacked breath due to post-intubation bronchospasm. But clinically, we did not hear wheezing as a sign of bronchospasm. We continued the administration of aminophylline for seven days, and the patient's clinical condition continued to improve.

The link between aminophylline and COVID-19

In COVID-19, there is a massive release of pro-inflammatory cytokines. The gigantic and long-term pro-inflammatory is very detrimental if it continues out of control because it will cause multiple organ failure. (6) Proximal cytokines such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6) are suspected to be very high in COVID-19 cases. This condition needs the administration of preparations to control the cytokines. Theophylline is an effective inhibitor against TNF-α and IL-6 released by human monocyte. (7) The improvements that occurred in the COVID-19 case that we handled in this case report was probably due to the immunomodulating effect of aminophylline that we provided. Our case report strengthens the writings written by previous authors on aminophylline.

Medications utilized to achieve vasodilation in high altitude pulmonary edema (HAPE) have been previously suggested and include acetazolamide, calcium channel blocker (CCBs), and phosphodiesterase inhibitors. Interestingly, aminophylline achieved similar results with increased oxygen levels with an even better effect than nifedipine in patients with HAPE. (8) Aminophylline may be an additional therapeutic agent with potential utility in COVID-19. (9)

ZINC00003118440 is a theophylline derivative under the drug class “bronchodilators.” Further screening with approved bronchodilators also studied to identify their ability to bind to the N protein's ribonucleic acid (RNA) binding region. The other identified top hit is ZINC0000146942, which is a 3,4-dihydropyrimidinone class molecule.

Hence this study suggests two important classes of compounds, theophylline and pyrimidone derivatives, as possible inhibitors of RNA binding to the N terminal domain of N protein of coronavirus, thus opening new avenues for in vitro validations. (2)

Conclusion

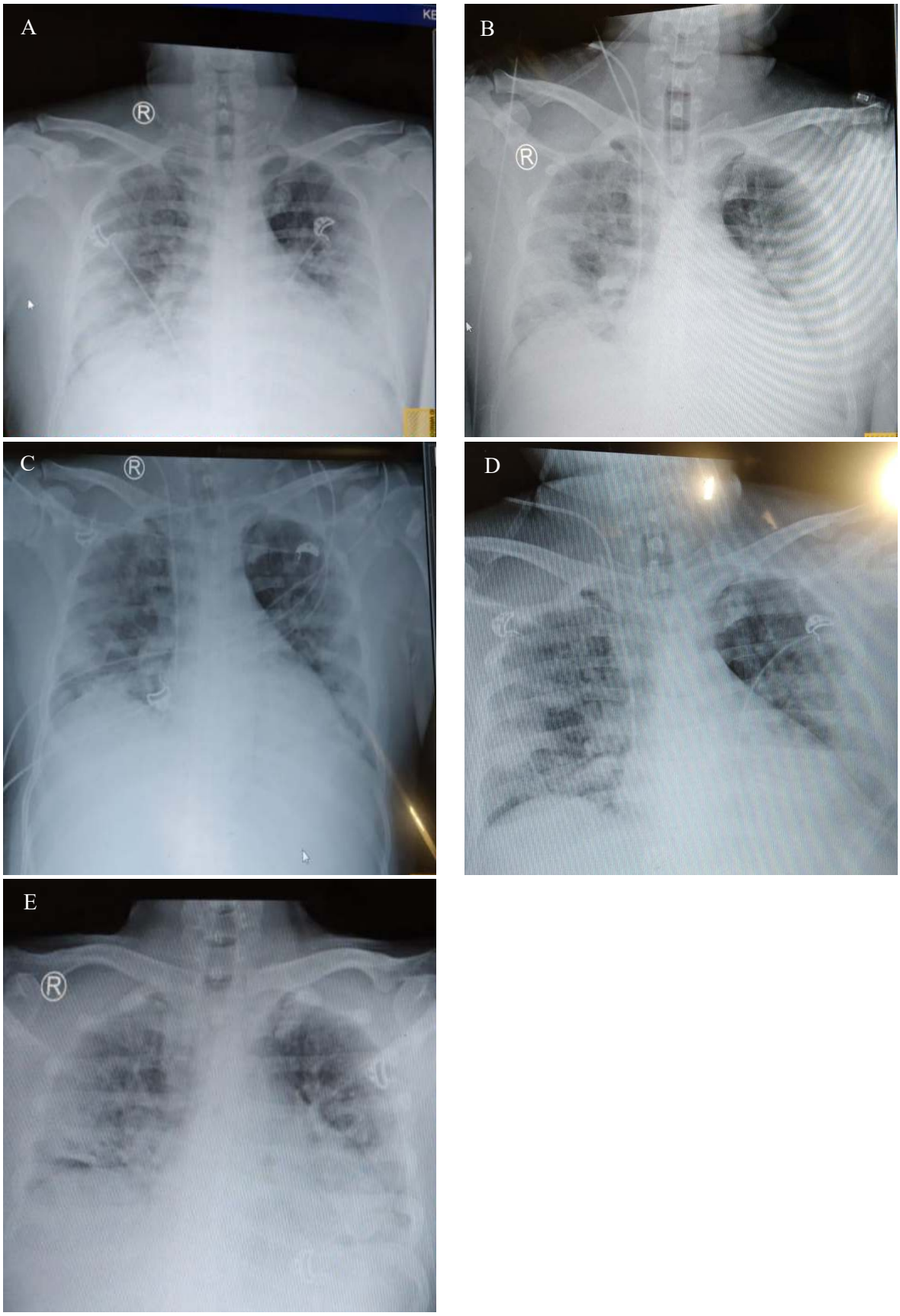
We conclude that aminophylline is an effective therapy for facilitating weaning from ventilatory support in this COVID-19 patient. Additional controlled studies are needed on more patients to confirm this conclusion.

Table 1. Blood gas analysis with HFNC

Month of examination	September 2020															
Date	11	12	13	14	15	16	17	17	18	19	21	25	26	27	28	29
Mode	NRM 15 l/min	HFNC	HFNC	HFNC	HFNC	HFNC	PC-BIPAP	PC-BIPAP	PC-BIPAP	PC-BIPAP	PC-BIPAP	PSV	HFNC	HFNC	HFNC	O2 mask
Pressure high/pressure control							18	18	26	18	26	18				
Pressure support							22	26	18	26	18	10				
RR							28	30	30	30	28					
FiO2	100	70	70	70	70	70	100	50	50	40	40	30	50	40	40	60
PEEP							10	8	8	8	8	8				
TV output								353								
RR output								30								
MV output								10.4								
Flow (l/min)		30	30	40	40	40							40	30	30	
Blood gas analysis																
- pH	7.470	7.440	7.391	7.439	7.421	7.406	7.022	7.317	7.313	7.326	7.47	7.361	7.393	7.405	7.42	7.43
- pO2	68.8	71.40	82	74.2	91.6	63	73.7	63.2	68.7	79.5	79.2	66.8	83.2	81.2	78.5	80
- pCO2	25.5	31.1	33.2	26.2	28	30.5	118.1	47.6	31.7	54	43.9	39.6	38.4	40.5	38.5	36.5
- HCO3	18.4	20.7	19.7	17.3	17.8	18.8	29.9	23.8	25.6	27.6	28	21.9	22.9	24.8	24.4	23.8
- BE	-3.2	-2.2	-4.2	-5	-5.1	-4.6	-4.6	-2.7	-1.3	0.5	3	-3.2	-1.7	0.1	0.2	-0.1
- SaO2	94.7	94.7	95.7	95.1	97.1	91.5		89.4	91.5	94.5	96	91.9	96	95.9	95.7	96.1
- AaDO2	478.8	392.5	380.3	395.3	375.9	402.3	511.1	239.6	229.7	144.1	155.8	101.4	229.2	158.1	162.7	163.2
PaO2/FiO2 ratio	68.8	102	117.14	106	131	90	73.7	126.4	120.71	198.75	198	222.66	166.4	203	196	133.33

Legend: HFNC=high flow nasal cannula; NRM=non-rebreathing mask; PC-BIPAP=pressure control-biphasic positive airway pressure; PSV=pressure support ventilation; O2=oxygen; RR=respiratory rate; FiO2=fraction inspiration of oxygen; PEEP=positive end expiratory pressure; TV=tidal volume; MV=minute volume; pH=power of hydrogen; pO2=partial pressure of oxygen; pCO2=partial pressure of carbon dioxide; HHO3=bicarbonate; BE=base excess; SaO2=oxygen saturation in arterial blood; AaDO2=alveolar-arterial oxygen difference.

Figure 1. The chest X-ray: A) 14 Sep 2020; B) 17 Sep 2020; C) 20 Sep 2020; D) 23 Sep 2020; E) 26 Sep 2020



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