

# Successful weaning of a patient with severe COVID-19 pneumonia under prolonged midazolam sedation using morphine

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## Abstract

The coronavirus disease 2019 (COVID-19) pandemic continues to spread around the world. In April 2021, Japan experienced a fourth wave of COVID-19 infections, which led to the breakdown of the medical system. Osaka, Japan, was particularly affected, with many severe cases and the highest number of COVID-19-associated deaths in Japan. Herein, we present a patient with severe COVID-19 infection who received prolonged midazolam (MDZ) treatment since propofol was not available due to shortage of medical resources. Moreover, the duration of mechanical ventilation was extended due to the development of a pneumothorax. When MDZ tapering was initiated, tachypnea was observed, which resulted failure in ventilator weaning. However, the use of continuous morphine infusion led a successful weaning off the ventilator. We suggest that the administration of morphine may allow for a smoother weaning process for some patients with severe COVID-19 infection.

## INTRODUCTION

With the outbreak of a respiratory disease caused by severe acute respiratory syndrome coronavirus 2 in December 2019 in China [1], the emergence of coronavirus disease 2019 (COVID-19) has led to a global public health emergency [2]. The World Health Organization classified this outbreak as a pandemic [2], and several subsequent waves of the infection have occurred throughout the world [3]. During the fourth wave, new COVID-19 variants led to relatively high rates of severe and fatal cases in younger people, which was distinct from previous waves of the infection [4, 5]. Severe cases developed rapidly, leading to an unprecedented rate of critically ill patients requiring mechanical ventilation, which resulted in an unexpected shortage of sedatives. In Japan, the production of propofol (PF) could not meet the clinical demand, which led to the administration of long-term midazolam (MDZ) in some cases.

Here, we present a case of severe COVID-19 pneumonia in Japan during the fourth wave. Due to long-term

MDZ use, multiple attempts to wean the patient off the ventilator failed before he was successfully weaned using continuous intravenous morphine.

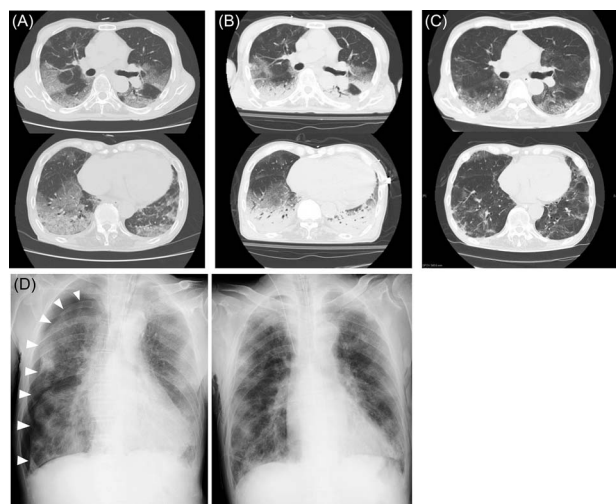
## CASE PRESENTATION

A 72-year-old male ex-smoker with a 20 pack-year smoking history, hypertension and chronic atrial fibrillation was transferred to our intensive care unit (ICU) for severe COVID-19 pneumonia treatment. The patient's weight and height were 62 kg and 179 cm, respectively. The patient had developed a fever and cough 10 days prior to admission and was positive for COVID-19 on polymerase chain reaction 4 days later. The patient was not vaccinated for COVID-19. Five days later, his SpO<sub>2</sub> (percutaneous oxygen saturation) on ambient air decreased to 88% with dyspnea, and he received oxygen and was admitted to the nearest hospital. Plain chest computed tomography (CT) on admission showed diffuse ground-glass opacities (Fig. 1A). Pneumothorax was excluded by the chest CT, and interstitial pneumonia,

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**Figure 1.** Serial plain chest CT and chest X-ray imaging of the pneumothorax; serial plain chest CT images (A) on admission to the previous hospital, (B) on admission to our hospital and (C) on Day 9 of ICU admission; (D) chest X-ray image of pneumothorax with the chest tube visible on Day 14 of ICU admission; white arrows show the outline of the collapsed lung caused by the pneumothorax.

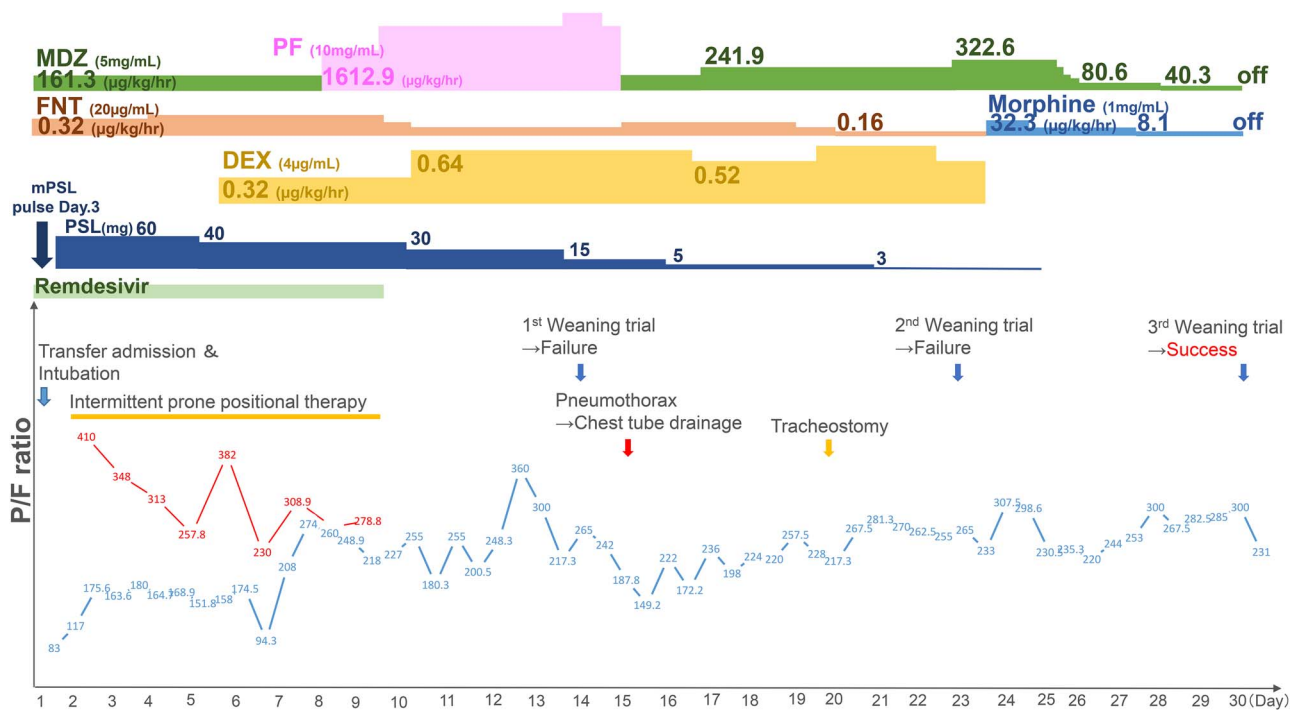
based on the shadows, interstitial pneumonia, atypical pneumonia and viral pneumonia were considered in the differential. Based on the clinical course, pneumonitis caused by COVID-19 was considered as the most likely cause. Steroid pulse therapy with 1000 mg of methylprednisolone sodium succinate for 3 days and intravenous remdesivir were started. Tazobactam piperacillin hydrate was also started at concurrently for fear of complications of bacterial pneumonia. Sputum culture on admission did not detect any bacteria that could be considered as a cause of pneumonia. However, since there was no sign of improvement in his respiratory condition, intubation management was indicated, and he was transferred to our hospital. Plain chest CT upon admission showed diffuse infiltrative shadows and air bronchogram in the dorsal areas of both lungs (Fig. 1B). Laboratory test

results and airway aspirates and blood cultures during intubation are shown in Table 1.

The clinical course of the present case is shown in Fig. 2. Upon admission to the ICU, mechanical ventilation management was initiated after intubation with intravenous injection of MDZ, 5 mg, and rocuronium, 1 mg/kg; the 10-day course of remdesivir was continued, and maintenance therapy of prednisolone (PSL) at 1 mg/kg along with a continuous intravenous heparin infusion was started. The initial ventilator settings were as follows: fraction of inspired oxygen (FiO<sub>2</sub>): 50%, positive end-expiratory pressure: 9 cmH<sub>2</sub>O, PaO<sub>2</sub>/FiO<sub>2</sub> (P/F) ratio: 163.6 and tidal volume: 310 ml/body. Sedation was controlled using continuous MDZ and fentanyl (FNT), maintaining a Richmond Agitation-Sedation Scale (RASS) score between -3 and -4. From Day 6, additional dexmedetomidine (DEX) was administered to obtain stable sedation (Fig. 2). During sedation, the Glasgow Coma Scale was E1V1M1. Intermittent prone positioning was performed for 9 days over 6–10 hours based on the patient's condition (e.g. presence of arrhythmias) and using rocuronium, 1 mg/kg. As the P/F ratio improved and the chest CT showed significant improvement in dorsal infiltrative shadows (Fig. 1C), the positioning treatment was discontinued and MDZ was switched to PF for an extubation trial. On Day 14, we reduced the sedative dose and attempted to wean the patient off the ventilator; however, tachypnea and violent body movement occurred with the dose reduction, making extubation impossible. Laboratory test results and airway aspirates and blood cultures on Day 14 are shown in Table 1. The result showed no signs of new-onset sepsis and other infection. There were also no large fluctuations in blood pressure. On the same day, a chest X-ray was performed, which showed a pneumothorax and a chest drainage tube was inserted (Fig. 1D). Therefore, the chest X-ray showed no worsening of shadows, no decrease in P/F ratio, no need to increase the dose of PSL, no increase in CRP and

**Table 1.** Results of laboratory tests

Variable, blood	Reference range, adults	On admission	Day 14	Day 20	Day 30
Hemoglobin (g/dl)	12.0–16.0	16.1	13.3	11.0	10.2
Hematocrit (%)	41.0–53.0	49.4	41.4	34.2	31.5
White-cell count (per $\mu$ l)	4500–11 000	7200	6310	6760	5800
Differential count (per $\mu$ l)					
Neutrophils	1800–7700	6500	5680	5430	3550
Lymphocytes	1000–4800	475	357	516	900
Monocytes	200–1200	108	132	411	382
Eosinophils	0–900	22	25	290	600
Basophils	0–300	14	6	40	98
Platelet count (per $\mu$ l)	150 000–450 000	278 000	202 000	348 000	276 000
C-reactive protein (mg/dl)	<0.14	2.38	1.43	8.76	2.03
Culture test					
Tracheal aspirate		Negative	Negative	Negative	
Peripheral blood		Negative	Negative		



**Figure 2.** Clinical ICU course; the upper row shows the changes made to the sedative, steroid and remdesivir doses for the current case; the number of sedative represents the volume of drug solution administered per hour (ml) and (µg/kg/hour); the bottom row shows the P/F ratio over time; the blue line plots the P/F ratio at 8 AM and 8 PM in 1 day; the red line indicates the P/F ratio measured during prone position therapy; mPSL, methylprednisolone.

no signs of new infection in the blood test; therefore, we tried to extubate the patient. However, when the sedative was reduced, tachypnea occurred and the P/F ratio decreased; therefore, extubation was deemed difficult. Therefore, a tracheostomy was performed on Day 20. Laboratory test results and airway aspirates, and blood cultures on Day 20 are shown in Table 1. Although weaning from the ventilator was attempted, tachypnea and decreased SpO<sub>2</sub> were observed, leading to the need for an increase in MDZ to maintain the RASS at an acceptable level and an inability to wean the patient off the ventilator. On Day 24, the patient was switched from FNT to a continuous intravenous morphine infusion, which enabled the rapid tapering of MDZ and successful weaning of the patient from the ventilator. Additionally, the noradrenaline dose was gradually reduced around 2 weeks after morphine was initiated, and the patient was successfully discharged from the ICU. During the 30 days between intubation and extubation, a combination of sedatives and analgesics required the administration of noradrenaline to maintain systolic blood pressure >90 mmHg. After discharge from the ICU, the patient did not show signs of tachypnea, severe body movements or anxiety related to opioid withdrawal syndrome and was transferred to another hospital for respiratory rehabilitation on the 14th day after ICU discharge. Four months later, tracheostoma was successfully closed and the patient was discharged home.

## DISCUSSION

Patients with COVID-19 are stratified as severe illness if they have SpO<sub>2</sub> < 94% in room air, P/F ratio < 300 mmHg, a respiratory rate > 30 breaths/min or lung infiltrates > 50% [6]. These patients are classified as COVID-19 severe, and if an ICU is warranted including mechanical ventilation, they are classified as COVID-19 critical infection cases. In cases of critical COVID-19 infection that requires invasive mechanical ventilation and admission to the ICU, the mortality rate is reported to be ~45% [7]. In Japan, considering the unprecedented effects of the fourth wave of COVID-19 infections, the production of PF was not sufficient to meet the demand, and long-term administration of MDZ was required to manage sedation in some patients, such as in the current case. However, introducing morphine allowed for the current patient to be weaned from MDZ and mechanical ventilation and, therefore, it may be effective for other patients with severe COVID-19 pneumonia.

There are several advantages with regard to MDZ use for sedation in the ICU, including its compatibility with intravenous solutions and stability in aqueous solutions and the absence of associated pain at the injection site [8]. On Day 8, while receiving FNT and DEX, our patient was switched to PF; however, he had already developed dependency on MDZ (Fig. 2). Although the patient's oxygenation had improved, he began to experience tachypnea and severe body movements with a gradual decrease in MDZ resulting in desaturation, and MDZ withdrawal

syndrome was suspected; thus, such a clinical course necessitated continued administration of MDZ (Fig. 2) to maintain the patient's oxygenation [9].

Although the use of FNT and morphine is recommended as sedatives for ICU use, morphine is avoided in part because of its negative effects on circulatory dynamics and the tendency for prolonged action in the presence of renal dysfunction [10, 11]. In this case, we believe that the difficulty in weaning might come from the difficulty in breathing and dyspnea that the patient was feeling; therefore, we decided to introduce morphine. Whether morphine relieves dyspnea more than FNT is currently being investigated in a Phase III trial in chronic obstructive pulmonary disease patients (MoreFoRCOPD trial; NCT03834363). There are no direct comparisons yet, but it has been demonstrated that morphine reduces central respiratory drive and alleviates air hunger [12]. After the introduction of morphine, the dose of MDZ was reduced smoothly, and weaning from the ventilator was successfully achieved without tachypnea by the alleviation of dyspnea by morphine.

In conclusion, in the present case, after two failed attempts of weaning off the ventilator considering the high rate of MDZ required to maintain sedation, the smooth tapering of MDZ was possible only after the introduction of morphine. It was suggested that the effects of morphine on the respiratory center might have alleviated dyspnea and air hunger caused by MDZ withdrawal syndrome and sequelae of COVID-19 infection. Low dose of morphine can be considered as an adjunct in patients who received prolonged high infusion of MDZ due to unexpected shortage of sedatives. Since the spread of COVID-19 infection is unlikely to subside soon and given the concern in Japan regarding a potential fifth wave of cases in the near future, the use of morphine should be reviewed for severe cases of COVID-19 infection requiring mechanical ventilation as a potential option for weaning in case of medical resource shortages.

## CONFLICT OF INTEREST STATEMENT

None declared.

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No funding was secured for this report.

## ETHICAL APPROVAL

Not applicable.

## CONSENT

Written informed consent for publishing this report was obtained from the patient.

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