Assessment of narcotic, sedative, and neuromuscular blocker needs of patients with COVID-19 requiring invasive mechanical ventilation

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As of November 15, 2020, over 11 million cases of Coronavirus disease 2019 (COVID-19) have been reported in the United States.[1] In hospitalized patients with COVID-19, 20% of them will develop critical illness and require admission in intensive care.[2,3] Among patients who developed critical illness, 39% to 79% required invasive mechanical ventilation.[2,3] Patients requiring mechanical ventilation for COVID-19 appear to need uncommonly high amounts of sedatives, opioids, and neuromuscular blockers. Pharmacy departments across the nation are struggling to maintain an adequate inventory of drugs typically used in intubated patients amid COVID-19 surges. This letter aims to report the average narcotic, sedative, and neuromuscular blocking agent (NMBA) requirements for intubated patients with COVID-19.

A retrospective review of patients at Saint Luke's Health System with confirmed COVID-19 requiring mechanical ventilation was performed to determine average daily doses of narcotics, sedatives, and NMBAs. This review was conducted from March 1, 2020 to August 22, 2020, with approval from Saint Luke's Health System Institutional Review Board. Secondary outcomes were assessed for association between several baseline variables such as age, sex, weight, and baseline PO_2/FiO_2 ratio and the patient's daily requirements of narcotics, sedatives, and NMBAs. Descriptive statistics were utilized to describe the baseline characteristics. Multiple regression was used to assess the effect of variables on daily requirements.

Fifty-three patients were included in the review. The mean (SD) age was 65.5 (15.6) years, and 36 (67.9%) patients were male. The mean (SD) actual body weight and body mass index were 94 (30) kg and 31.8 (9), respectively. The median (IQR) baseline PO_2/FiO_2 ratio after intubation was 88 (65.5, 139.5). The median (IQR) intubation duration and hospital length of stay were 14.8 (7, 22) days and 21 (14.5, 33) days, respectively. The mean (SD) total daily opioid dose, in morphine milligram equivalents (MME) per 24 hours, was 965 (753) MME. Mean (SD) daily propofol, midazolam (continuous infusion [CI]), lorazepam,

diazepam, and dexmedetomidine doses were 3,040 (2,240) mg, 79 (75.7) mg, 2 (1.8) mg, 15 (12.8) mg, and 492 (845) mcg, respectively. Twenty-six (49%) patients received NMBAs through CI. The mean (SD) daily cisatracurium and rocuronium CI amounts were 237 (138) mg and 618 (349) mg, respectively (Table 1). Younger age and male gender were associated with statistically significant higher opioid and sedative requirements ($P < 0.05$).

The daily narcotics doses, and propofol requirements, were significantly higher in patients who received NMBAs compared to no NMBAs (Table 2). Furthermore, more patients received midazolam infusion in the NMBAs group ($n = 19$) compared with the no NMBAs group ($n = 6$) (Table 2).

The average daily propofol dose in the ACURASYS trial was 1,939 mg and 1,422 mg in the NMBA and placebo groups, respectively, compared with 3,040 mg in this cohort (3,990 mg in NMBAs group and 1,804 mg in the non-NMBAs group), but the daily midazolam dose in the ACURASYS trial was 142 mg and 171 mg in the NMBA and placebo groups, respectively, compared with 79 mg in this cohort.[4] The propofol mean daily dose in the SPICE III trial was also lower compared with this cohort.[5] The median daily propofol dose in the usual care group was approximately 1,495 mg, compared with the median daily dose of 2,721 mg in this cohort. (The mean propofol dose was 1,804 mg in the non-NMBAs group.) In the SPICE III trial, the mean daily midazolam dose in the usual care group was significantly lower than the mean daily midazolam doses in this cohort and in the non-NMBAs group (26 mg vs 70.8 mg vs 105.7 mg).[5] This cohort required significantly higher opioid doses compared with the SPICE III cohort (965 MME vs 270 MME).[5] The non-NMBAs group also required higher opioid doses compared with the SPICE III cohort (692.8 MME vs 270 MME).[5] However, the sedation and opioid dosing requirements in this cohort were lower than in the MIDEX and PRODEX studies.[6]

To our knowledge, this review is the first analysis of the narcotics, sedatives, and NMBA requirements in mechanically ventilated patients with COVID-19. Severely ill patients with COVID-19 who are intubated may require substantially higher doses of narcotics, sedatives, and paralyzing agents to maintain adequate sedation and ventilation, based on our data. The results of this study suggest pharmacy departments may need to create new models to ensure they have adequate inventory during COVID-19 surges. The analysis also gives a brief glimpse into baseline characteristics that may affect dosing requirements in these unique patients.

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Table 1. Baseline Characteristics and Daily Doses of Sedatives, Narcotics, and NMBAs

Baseline Characteristics		**Number of Patients**
Age, years	63.5 (15.6)	53
Gender		53
Male	36 (67.9%)	
Female	17 (32.1%)	
Ethnicity		53
White	28 (52.8%)	
African American	17 (32.1%)	
Hispanic	5 (9.4%)	
Native Hawaiian	2 (3.8%)	
Asian	1 (1.9%)	
ABW, kg	94 (30)	53
BMI	31.8 (9)	53
CrCl	59 (43.5, 96.5)	53
Hospital LOS	21 (14.5, 33)	50
Days on mechanical ventilator	14.8 (7, 22)	53
P/F ratio	88 (65.5, 139.5)	53
Mortality	21 (39.6%)	53
Sedatives, Narcotics, and NMBAs	**Doses Mean (SD)**	**Number of Patients**
Daily narcotics dose, MME	965 (753)	53
Daily narcotics scheduled dose and/or continuous infusion, MME	941 (727)	49
Daily narcotics PRN dose, MME	70 (55.6)	53
Daily propofol infusion, mg	3,040 (2,240)	46
Daily midazolam infusion, mg	79.2 (75.7)	25
Daily total midazolam dose, mg	67 (75.4)	30
Daily dexmedetomidine dose, mcg	492 (845)	26

Cisatracurium, mg		
Daily continuous infusion	237.3 (137.6)	22
Daily PRN doses	107 (115)	23
Number of days on continuous infusion	4.8 (3)	22
Rocuronium		
Daily continuous infusion	618 (349)	12
Daily PRN doses	527 (677)	34
Number of days on continuous infusion	5.3 (4.8)	12
Total days on NMBAs	6.5 (4)	26

Abbreviations: ABW, actual body weight; BMI, body mass index; CrCl, creatinine clearance; LOS, length of stay; MME, morphine milligram equivalents; NMBAs, neuromuscular blocking agents; P/F, pressure of oxygen to fractional inspired oxygen; PRN, as needed.

Table 2. Narcotic and Sedation Requirements in Patients Who Received NMBAs vs No NMBAs

Sedatives and Narcotics	NMBAs		No NMBAs		*P* Value
	n	**Mean**	***n***	**Mean**	
Daily narcotics dose, MME	26	1247.4 (819)	27	692.8 (576.6)	0.005
Daily narcotics scheduled dose and/or continuous infusion, MME	26	1177 (795)	23	674.8 (544.6)	0.01
Daily narcotics PRN dose, MME	26	70 (54.6)	27	70.5 (57.5)	0.9
Daily propofol infusion, mg	26	3,990 (2,500)	20	1,804 (904)	0.001
Daily midazolam infusion, mg	19	70.8 (65)	6	105.7 (106)	0.3
Daily total midazolam dose, mg	21	65.1 (65.1)	9	71.2 (100)	0.6

Abbreviations: MME, morphine milligram equivalents; NMBAs, neuromuscular blocking agents; PRN, as needed.