Physician drug prescribing preferences and availability for ventilation of patients with COVID-19

Ian D Coombes, Michael J Dooley, Shane Townsend, Sinead Carmichael, Susan G Poole, Nermin Karamujic, Brent Richards, Marc Ziegenfuss, Melissa J Ankravs, Hailie Uren, Jason A Roberts and Anthony Holley

The coronavirus disease 2019 (COVID-19) pandemic has overwhelmed many international health care systems, with a high number of patients having severe respiratory failure.[1,2] The mainstay of treatment for these patients is invasive mechanical ventilation requiring pharmacological induction, followed by ongoing sedation and analgesia.[3-5] In the setting of severe acute respiratory failure, neuromuscular blockade is often required.[6]

In Australia, early recognition of the potential implications of the COVID-19 pandemic facilitated direct action in addressing availability of intensive care beds, personal protective equipment, ventilators and trained critical care staff.[7] An important issue that has not received significant attention is physician medication preferences to support mechanical ventilation as well as the availability of those agents.

Medication shortages in Australia are not uncommon, with globalisation of the manufacturing process leading to vulnerability in the supply chain, particularly during disasters and pandemics. Medication shortages often require the use of alternative agents and altered methods of administration, which may present a risk of medication error resulting from clinician unfamiliarity.[8] In the context of ventilated patients with COVID-19, shortages of analgesics, sedatives and neuromuscular blocking agents (NMBAs) may severely compromise patient outcomes.

We sought to define medication preferences and availability in Australia during the COVID-19 pandemic by surveying Australian intensive care units (ICUs). The prescribing preferences for perceived optimal support of ventilation for patients with COVID-19 were investigated together with individual hospital pharmacy medication stocks. Suppliers' capacity to deliver on recent hospital orders for preferred medications was also explored.

Using the online Research Electronic Data Capture (REDCap) system, we conducted a voluntary survey of directors of pharmacy and ICUs in 119 public and 72 private Australian hospitals and of physicians anticipating the provision of critical care in the COVID-19 pandemic (Online Appendix, figure 1). Medical and pharmacy staff were asked to collaborate on survey completion. A low and negligible risk ethics approval was provided by the Royal Brisbane and Women's Hospital Human Research Ethics Committee in Queensland, Australia (LNR/2020/QRBW/63618).

Utilising the case of a hypothetical patient, respondents were asked to rank their choice of sedatives, analgesics and NMBAs at induction, for acute phase ventilation, in the presence of renal impairment, and subsequently, during ventilatory weaning. Respondents were also asked to provide information on available stock of relevant medications in their hospital on the day of the survey. Information was recorded by product quantities and vial strengths. Supply chain capability was determined by assessing the percentage of orders received that had been placed in the preceding week.

Data were analysed using Stata 16.1. The ordinal response categories (first to fourth drug preference) were assigned an ascending binary numerical value (eg, preferred agent = 1). The data were analysed descriptively; group comparisons were conducted using the non-parametric Wilcoxon rank sum test.

Participation and completion of de-identified data were taken as consent for analysis and publication of aggregated de-identified results. The survey opened on 14 April; completion of the survey over the subsequent 10 working days was requested, at a time when minimal elective surgery was being undertaken in Australian hospitals. The survey was closed at midnight 28 April 2020.

Results

Seventy-six sites initiated a REDCap session, 73 responses (96%) to the survey were analysed: 54 from public hospitals (45% of 119 public ICUs), 12 from private hospitals (17% of 72 private ICUs) and seven from hospitals without ICUs but preparing for a COVID-19 response. Seventy-two participants provided responses for prescribing preferences, 66 for stock on hand, and 66 for stock availability. Sixty responses

(82%) were entered by pharmacists and 15 (21%) by ICU consultants; there were four consolidated responses from ICU consultants and pharmacists. Queensland, Victoria and New South Wales provided most responses, with 21 (29%), 19 (26%) and 17 (23%) respectively (Online Appendix, table 1). Using the Australian and New Zealand Intensive Care Society Centre for Outcome and Resource Evaluation (ANZICS CORE) categorisation for ICU levels (https://www.anzics.com.au/anzics-registries), eight respondents (11%) indicated their ICUs were level 1, and 58 (79%) indicated their ICUs were level 2 or 3; seven respondents (10%) had no ICU beds at the time of the survey.

The case considered by the respondents was of a COVID-19-positive 65-year old man (body mass index, 35 kg/m^2), smoker, with a history of controlled hypertension, presenting with severe respiratory failure requiring intubation, sedation and mechanical ventilation. For rapid sequence intubation, propofol (36/70, 50%) was the preferred sedative, fentanyl (62/69, 90%) was the preferred analgesic, and rocuronium (56/72, 78%) was the preferred NMBA (Online Appendix, figure 2, A–C). The second most preferred agents were ketamine, morphine and suxamethonium respectively (Online Appendix, table 2 and figure 2, A–C).

For the acute sedation phase, propofol (47/69, 68%) was the preferred sedative, fentanyl (53/70, 76%) the preferred analgesic and cisatracurium (50/67, 74%) the preferred NMBA. The second most preferred agents were midazolam, morphine and rocuronium respectively (Online Appendix, figure 2, D–F).

In the context of the patient developing anuric renal failure on day 4 of ICU admission, fentanyl was by far the preferred analgesic (n = 67, 99%) and propofol (n = 51, 76%) the favoured sedative.

For the respiratory weaning phase, propofol (n = 57, 84%) was the preferred sedative, followed by dexmedetomidine with fentanyl the preferred analgesic (n = 60, 88%), followed by morphine.

Current medication availability is reported for level 2 and 3 hospital ICUs (n = 52, 71%) for a man weighing 80 kg with rapid sequence induction, acute phase sedation followed by a ventilatory weaning phase of 2 days. Assuming all hospital stock was available only for patients with COVID-19 admitted to an ICU, the median number of 21-day courses of propofol available was estimated as 5 (interquartile range [IQR], 3–11), using a dose of 5000 mg/day for acute sedation and weaning phase days. For fentanyl, the median number of 21-day courses was 8 (IQR, 4–14), using doses of 2400 μg/day for acute sedation and 1200 μg/day for weaning phase days. For cisatracurium — used for acute neuromuscular blockade — a median of one course (IQR, 0–2) was available, assuming a dose of 3 μg/kg/min for 5 days in each scenario (Online Appendix, table 3).

The availability of medications from suppliers was based on the percentage of orders received that had been placed in the preceding week by the pharmacy department. Notable results were that propofol and midazolam were unavailable for 17% and 13% of respondents, with 20% and 27% of respondents having full availability (11% and 16% of respondents reported not ordering these drugs). Fentanyl and morphine were unavailable for 5% and 2% of respondents, with 38% and 50% of respondents having full availability (21% and 19% of respondents reported ordering these drugs). Cisatracurium, vecuronium and suxamethonium were unavailable for 38%, 24% and 33% of respondents, with 15%, 24% and 14% of respondents having full availability (30–32% of respondents reported not ordering these drugs) (Online Appendix, table 4).

Discussion

The number of patients with COVID-19 pneumonitis requiring mechanical ventilation is challenging to predict and, consequently, the availability of adequate volumes of necessary medications to support ventilation is also difficult to define. The major factors that influence demand for these drugs for COVID-19 cases include patient numbers, duration of ventilation, and medication choice and dosage. In this survey, we found that stocks of key medications supporting mechanical ventilation in Australian hospitals would not have met the demands caused by a significant surge in critically ill patients with COVID-19. For many medications, orders for hospitals were not being met by suppliers. Importantly, this finding was based on the assumption that none of these drugs would be directed to other patients (eg, other mechanically ventilated patients in the ICU or in operating theatres).

NMBAs, which are used at rapid sequence induction and often in the early maintenance phase for mechanically ventilated patients with COVID-19, have problematic availability. Our survey suggests that many Australian ICUs would exhaust available supplies of first and second line NMBAs with relatively limited patient presentations (median, 1 [IQR, 0–1] patient episodes for cisatracurium).

Propofol was the preferred sedative for the acute and weaning phases of mechanical ventilation and supplies were precarious. Future shortages are likely if ICU demand increases significantly, and will be potentially compounded with the resumption of elective surgery. Local substitution of midazolam for propofol, with attendant risks of delirium and prolonged length of stay, may add to supply problems, resulting in continued shortages of both agents. However, midazolam's availability would be less affected by the resumption of elective surgery. Alternative agents including dexmedetomidine and diazepam are not

universally suitable substitutes; adverse events and active metabolites with extended half-lives may preclude their use in some populations.[9,10] Indeed, given the apparent limited availability and higher demand for propofol, it may be pragmatic to spare this agent during sustained ventilation, employing propofol, with its shorter half-life during the weaning phase, to facilitate extubation.

A key limitation of this work is that, at the time of the survey and our analysis, we had no information regarding the pharmaceutical companies' ability to increase supply to Australia to meet the expected demand of an increased patient load. There exists an opportunity for the Australian Therapeutics Goods Administration to work with key clinical bodies, such as intensive care and anaesthetic groups, statewide pharmacy representatives and pharmaceutical suppliers, to model supply and demand of essential medicines in order to manage surges of COVID-19 in Australia.

Conclusion

Our survey highlights the preferred medications to support ventilation of patients with COVID-19, the tenuous nature of availability, and a need for active collaboration between medical and pharmacy staff to sustain supplies and plan for suitable alternatives. Of concern are the NMBA supply, which would be rapidly depleted with a small number of patient presentations, and the likely exhaustion of preferred induction and sedatives agents, leading to the use of less familiar options and associated risks. The relatively low number of cases of COVID-19 pneumonitis that have required mechanical ventilation in Australian ICUs, combined with reduced usage in operating theatres and in emergency departments, is the reason that hospitals have not exhausted these medications. We should continue to collaborate at a local, state and Commonwealth level to ensure medication availability in order to provide optimal care to all critically ill patients in the event there are significant numbers of patients with COVID-19 admitted to our ICUs.

Competing interests

Anthony Holley is current president and Marc Ziegenfuss is the immediate past president of the Australian and New Zealand Intensive Care Society (ANZICS).

Author details

Ian D Coombes[1,2]
Michael J Dooley[3,4]
Shane Townsend[5,6]
Sinead Carmichael[1]
Susan G Poole[3,4]
Nermin Karamujic[5,7]
Brent Richards[8,9]
Marc Ziegenfuss[10,11]
Melissa J Ankravs[12,13]
Hailie Uren[8,14]
Jason A Roberts[1,5,7]
Anthony Holley[5,7,15]

1 Pharmacy Department, Royal Brisbane Women's Hospital, Brisbane, QLD, Australia.
2 School of Pharmacy, University of Queensland, Brisbane, QLD, Australia.
3 Alfred Health, Melbourne, VIC, Australia.
4 Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia.
5 Department of Intensive Care Unit, Royal Brisbane and Women's Hospital, Brisbane, QLD, Australia.
6 School of Medicine, University of Queensland, Brisbane, QLD, Australia.
7 Centre for Clinical Research, Faculty of Medicine and School of Pharmacy, University of Queensland, Brisbane, QLD, Australia.
8 Health Care Improvement Unit, Clinical Excellence Division, Queensland Health, Brisbane, QLD, Australia.
9 Department of Intensive Care, Gold Coast University Hospital, Gold Coast, QLD, Australia.
10 Department of Intensive Care, Prince Charles Hospital, Brisbane, QLD, Australia.
11 Intensive Care, State-wide Network, Queensland Health, QLD, Australia.
12 Department of Pharmacy and Intensive Care, Royal Melbourne Hospital, Melbourne, VIC, Australia.
13 School of Medicine, University of Melbourne, Department of Medicine and Radiology, Royal Melbourne Hospital, Melbourne, VIC, Australia.
14 Pharmacy Department, Logan Hospital, Queensland Health, Brisbane, QLD, Australia.
15 Australian and New Zealand Intensive Care Society, Melbourne, VIC, Australia.

Correspondence: ian.coombes@health.qld.gov.au

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