Optimization of the management of essential drugs in the COVID-19 pandemic through mathematical correlations

ABSTRACT

The Coronavirus disease-19 (COVID-19) led to an exponential increase in the number of people affected, with a higher need for ICU admission in those of greater severity. In this context, the risk of drug shortages of essential ICU drugs increases. An accurate knowledge on the consumption of these medications is therefore needed to foresee future COVID-19 outbreaks or other pandemics. The aim of the study was to describe the consumption of commonly used ICU drugs, which were essential during the COVID-19 pandemic, and to analyse their correlation with the number of admitted patients. This was a retrospective observational study conducted in the ICU of a 420-bed tertiary care hospital in Barcelona, Spain from 14th March to 30th April, 2020. Drugs analysed included morphine, sufentanil, cisatracurium, norepinephrine, dexmedetomidine, rocuronium, propofol and midazolam. A total of 159 patients were admitted to the COVID-19 ICU during the study period. The consumption of all the analysed drugs was significantly increased compared to the previous year: norepinephrine 118.7%, midazolam 285.2%, propofol 190%, dexmedetomidine 147.0%, sufentanil 665.6%, morphine 56.2% and cisatracurium 369.7%. On the day of higher consumption, at least two-fold higher consumption compared to the median of all period was detected. The average daily dose for each drug was: propofol 3,050.3 (736.1) mg, cisatracurium 292.4 (128.9) mg, midazolam 203.6 (64.0) mg, morphine 39.3 (6.6) mg, norepinephrine 16.7 (5.2) mg, sufentanil 1.2 (0.3) mg, dexmedetomidine 0.9 (0.4) mg. A positive and significant correlation was observed in all drugs with both the number of treated and admitted patients. A striking increase in the drug consumption of 56.2-665% was noticed throughout the study period. There was a significant correlation between the consumption of essential drugs in the ICU and the number of critically ill patients. These findings allow the optimization of the management of essential drugs for critically ill patients and prevent the development of drug shortages in future outbreaks of pandemics.

Key words: COVID-19, intensive care unit, propofol, cisatracurium, norepinephrine, drug shortage, correlation.

INTRODUCTION

Since the beginning of the Coronavirus disease 2019 (COVID-19) pandemic in Wuhan, the presentation of this disease has been estimated. In reports from China, around 5% of patients required assistance in an intensive care unit (ICU), being the average duration from symptom onset to ICU admission of 12 days (Li et al., 2020; Guan et al., 2019). However, in another study conducted in New York, 14.2% of patients was admitted to the ICU (Richardson et al., 2020). The average length of stay of ICU patients was 12-14 days (Bhatraju et al., 2020; Aziz et al.,...


MATERIAL AND METHODS

DESIGN AND PERIOD OF THE STUDY

RETROSPECTIVE, DESCRIPTIVE OBSERVATIONAL STUDY CONDUCTED AT THE HOSPITAL DEL MAR, BARCELONA, SPAIN, A 420-BED TERTIARY HOSPITAL FROM 14TH MARCH 2020 TO 30TH APRIL 2020. CURRENTLY THE HOSPITAL IS EQUIPPED WITH AN 18-BED ICU, WHICH ALSO INCLUDES THOSE PATIENTS ADMITTED TO THE CORONARY UNIT, A RECOVERY UNIT WITH 11 BEDS, 6 OPERATING ROOMS AND A SEMICRITICAL UNIT WITH 7 BEDS. ALL OF THEM WERE ENABLED AS COVID-19 UNITS FOR CRITICAL PATIENTS DURING THE PANDEMIC.

STUDY POPULATION

ALL PATIENTS DIAGNOSED WITH SARS-COV-2 PNEUMONIA REQUIRING ADMISSION TO ANY OF THE COVID-19 CRITICAL CARE UNITS DESCRIBED ABOVE WERE INCLUDED. PATIENTS ADMITTED TO OTHER NON-COV-19 CRITICAL CARE UNITS WERE EXCLUDED.

DRUGS EVALUATED

THE DRUGS ANALYSED WERE MORPHINE (10 MG/ML, 1 ML) SUFENTANIL (50 MG/ML, 5 ML), CISATRACURIUM (150 MG/30 ML, 20 MG/10 ML AND 10 MG/5 ML), NOREPINEPHRINE (1 MG/ML 50 ML), DEXMEDETomidine (100 µG/ML, 2 ML), Rocuronium (10 MG/ML, 5 ML), Propofol (2% 50 ML, 1% 100 ML, 1% 50 ML AND 1% 20 ML) AND MIDAZOLAM (100 MG/100 ML, 50 MG/10 ML, 15 MG/3 ML, 5 MG/5 ML). THIS SELECTION WAS MADE ON THE BASIS OF CONSUMPTION, SUPPLY PROBLEMS DURING THAT PERIOD AND THE EXISTING LITERATURE (KANJI ET AL., 2020). DUE TO THE RISK OF DRUG SHORTAGES AND THE WORK OVERLOAD OF NURSERY, THE PREPARATION OF THE PERFUSIONS OF THESE DRUGS WAS ASSUMED IN THE PHARMACY SERVICE AND WAS PERFORMED IN A HORIZONTAL LAMINAR FLOW CHAMBER.

PRESCRIPTION

THE HOSPITAL DISPOSES OF ELECTRONIC PRESCRIPTION, WHICH IS INTEGRATED IN THE COMPUTERIZED MEDICAL HISTORY. THE INTENSIVE CARE AREA WAS COORDINATED BY SPECIALISTS IN INTENSIVE CARE MEDICINE. OTHER SPECIALITIES ALSO PARTICIPATED IN THE PRESCRIPTION OF THESE DRUGS, AS SPECIALISTS IN ANAESTHESIOLOGY, CARDIOLOGY AND PNEUMOLOGY.

DISPENSATION


RECORD OF DRUG ADMINISTRATION

THE COMPUTERIZED MEDICAL HISTORY ALSO CONTAINS THE CHART FOR RECORDING THE ADMINISTRATION OF MEDICATION BY THE NURSERY STAFF. FOR THE STUDY, ALL THE MEDICATION REGISTERED IN THIS CHART WAS COLLECTED. IN ADDITION, THE MEDICATION RECORDED IN THE CLINICAL COURSE WAS ALSO INCLUDED IN THE CASE OF EMERGENCY SITUATIONS, FOR WHICH VERBAL ORDERS ARE PERMITTED. GIVEN THE MULTIPLE PRESENTATIONS AVAILABLE OF THE
different drugs studied, and considering the supply problems that arose, all the daily doses of each patient were collected in milligrams (mg).

Statistical analysis

To analyse the correlations, the variables were distributed as follows. Each pair of series is shown by means of a graph whose abscissa axis represents the timing from the beginning of the series to the end. The ordinate axis is split into two, the left one representing the units of quantity of drug consumed expressed in mg, and the right axis representing the number of patients admitted. The dissimilarity between the different pairs of series was evaluated using the test proposed by Maharaj (2000; 1996) and implemented in the TSdist package of R (Montero et al., 2014). As a result of this test, p-values greater than 0.05 and the closer to 1, indicate that both series form a homogeneous cluster. For the statistical analyses, STATA 15.1 (Stata Corp.; College Station, Texas, USA) and R (3.5.3) software were used (R: A language and environment for statistical computing; R Foundation for Statistical Computing, Vienna, Austria; https://www.R-project.org/).

RESULTS

Patients

A total of 159 patients were admitted to a COVID critical care unit during the study period. Temporal evolution of number of patients admitted was described in Figure 1. The period with a higher number of admitted patients per day was from the 21st of March to 10th of April. Within this period, 1st of April was the day with the higher number of admitted patients, with a total of 67 patients, a 279% increase from the usual capacity.

Description of drug consumption

Norepinephrine and midazolam were administered in 70 patients, propofol in 68, dexmedetomidine in 60, sufentanil in 49, morphine in 48 and cisatracurium in 36 patients. All drugs presented a significant increase by comparison with the consumption from the same period the year before: norepinephrine 118.7%, midazolam 285.2%, propofol 190%, dexmedetomidine 147.0%, sufentanil 665.6%, morphine 56.2% and cisatracurium 369.7%. At Table 1, consumption data of all drugs during both complete period and period with a higher number of admitted critically ill patients, including the day with a higher consumption for each drug, were described. Average daily dose from all drugs was the following: propofol 3,050.3 (736.1) mg, cisatracurium 292.4 (128.9) mg, midazolam 203.6 (64.0) mg, morphine 39.3 (6.6) mg, norepinephrine 16.7 (5.2) mg, sufentanil 1.2 (0.3) mg, dexmedetomidine 0.9 (0.4) mg. During COVID-19 pandemic two drug-shortages occurred, being classified as of minor impact following the Spanish Agency for Medication and Healthcare Products classification, and were managed by the Pharmacy Service (Plan de garantías de abastecimiento de medicamentos, 2019). On March 26th, propofol 2% 50 mL presentation was
replaced by 1% 100 and 50 mL. Moreover, on March 28th, cisatracurium 150 mg/30 mL presentation was replaced by 20 mg/10 mL and 10 mg/5mL presentations.

**Consumption evolution**

Potential correlation of all drugs with both total number of patients receiving the mentioned drugs and total number of patients admitted at a COVID-19 critical care unit were described in Figure 2. All drugs showed a positive and significant correlation with both total number of patients receiving those medications and total number of admitted patients.

**DISCUSSION**

COVID-19 pandemic has generated a high number of publications in a short period of time. From a pharmacological point of view, those publications have been mainly aimed to the study of the effectiveness of different molecules in front of the pathology. However, from our knowledge, this is the first study analysing the consumption of the essential drugs in a COVID-19 critical care unit. Furthermore, the presence of a significant correlation with the number of admitted patients provides information of upmost importance in the management of these drugs. We believe that this information is essential for dealing with future outbreaks. Liu et al. (2020) published the experience of the Pharmacy Services in Chinese hospitals during COVID-19 pandemic (Liu et al., 2020). A fundamental strategy was to analyse the consumption of different drugs, especially in order to prevent shortages (Liu et al., 2020). However, this was difficult to perform. During the pandemic, information about the pathology was unknown so both the incidence of admitted patients and their drug consumption was difficult to ascertain. As expected, there was a significant increase of consumption from all the included drugs. It is important to highlight the wide variability of drug consumption during the analysed period, probably due to the volume of admitted patients at the unit and the characteristics and evolution of these patients. In terms of consumption, it should be underlined that, on the day of higher consumption, this was at least two times higher as the median of all period. In our experience, drug consumption increased 56.2-665.6% compared to the same period of the previous year. All these facts make easier the development of drug shortages.

In our study two shortages happened; propofol 2% and cisatracurium 150mg/30 mL presentations usually administered at critically ill patients’ units. Both shortages lasted 12 days. The impact of the change of presentation was minimal because the Pharmacy Service assumed the elaboration of the standard perfusions of these and other drugs. The problem of shortages should not go unnoticed. Drug shortages have been associated with a higher risk of developing adverse events, work overloading for health workers (clinicians, nursery, pharmacy) and administrations, and also an increase of direct costs (alternative presentations present higher prices) and indirect costs (inverted time) (Plan de garantías de abastecimiento de medicamentos, 2019; McLaughlin and Skoglund, 2015). In the context of COVID-19 pandemic, these shortages could lead to serious consequences for patients and the health system, even though it has not yet been formally quantified (Badreldin and Atallah, 2020). In a recent review performed in 2019 including 40 studies, shortages were associated with a higher mortality risk, adverse events and medication problems (Phuong et al., 2020). Specifically in critically ill patients, the shortage of anesthetic products led to a higher risk of medication errors, complications, surgery and recovery delays, as well as attributable deaths (Phuong et al., 2020). In the case of propofol, a retrospective observational study proved that its shortage led to a significant increase of 2 days on mechanical ventilation duration (Roberts et al., 2012). In a study that included 27,835 patients in the USA, norepinephrine shortage was associated with a significant increase of in-hospital mortality of 3.7% in patients presenting septic shock (Vail et al., 2017). Moreover, the use of therapeutic alternatives of cisatracurium due its shortage

### Table 1: Description of drug consumption over the study period.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Highest consumption period¹</th>
<th>Total consumption (mg)</th>
<th>Total period²</th>
<th>Day of maximum consumption</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>Mean/day</td>
<td>Total</td>
<td>Mean/day</td>
</tr>
<tr>
<td>Morphine</td>
<td>284.7 (106.5)</td>
<td>309.8 (88.9)</td>
<td>13,667.8</td>
<td>284.7 (106.5)</td>
</tr>
<tr>
<td>Sufentanil</td>
<td>15.4 (9.8)</td>
<td>21.3 (9.5)</td>
<td>737.5</td>
<td>15.4 (9.8)</td>
</tr>
<tr>
<td>Propofol</td>
<td>251,260.2 (106.5)</td>
<td>69,096.1 (17,617.9)</td>
<td>107,855.0</td>
<td>251,260.2 (106.5)</td>
</tr>
<tr>
<td>Dexmedetomidine</td>
<td>7.6 (6.3)</td>
<td>9.8 (7.1)</td>
<td>362.9</td>
<td>7.6 (6.3)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>121,089.4</td>
<td>2,771.8 (1,179.5)</td>
<td>5,125.0</td>
<td>2,771.8 (1,179.5)</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>11,019.7</td>
<td>238.1 (93.7)</td>
<td>485.6 (27.3)</td>
<td>238.1 (93.7)</td>
</tr>
<tr>
<td>Cisatracurium</td>
<td>45,851.0</td>
<td>1,105.2 (930.4)</td>
<td>3,377.0 (442.7)</td>
<td>1,105.2 (930.4)</td>
</tr>
</tbody>
</table>

1. The period with highest consumption was from 21st March 2020 to 10th April 2020.
2. Total period was from 14th March 2020 to 30th April 2020.
was associated with a higher duration of mechanical ventilation and ICU stay (Sottile, et al., 2018). Several factors are responsible for all these suboptimal results. The use of alternative therapies has been related with a higher
toxicity and lower effectiveness (Mazer-Amirshahi et al., 2020). The use of other drugs different as the usual ones has demonstrated a higher risk of medication errors, even when the same drug but a different concentration is available, or when the Pharmacy service elaborates the medication (Kanji et al., 2020; McLaughlin and Skoglund, 2015; Badreldin and Atallah, 2020; Mazer-Amirshahi et al., 2020).

In the case of COVID-19, the case of propofol should be further analysed. Even though it was considered a shortage with minimal impact (Plan de garantías de abastecimiento de medicamentos, 2019), the change on presentation meant a double amount of refined soy oil (FTPL, 2020). This required a more intense monitoring on triglycerides plasma levels in patients that, for its own pathology and its severe inflammatory state, presented a high risk to present hypertriglyceridemia (Ballesteros et al., 2020). Thus, it is importrant to consider other adverse events derived from excipients and not just those derived from the change of the drug (Fox and McLaughlin, 2018). The increase of a more accurate patients’ monitoring due alternative-drugs administration has been related with an increase of costs (Badreldin and Atallah, 2020). Furthermore, the use of other therapies increases the risk of drug related problems because of lack of awareness (Kanji et al., 2020; Badreldin and Atallah, 2020). This has an especial importance in the context of emergency such as in the COVID-19 pandemic. In this setting, a high number of healthcare professionals can be destined to non-familiar work places or new incorporations can occur, which together with the work overload and stress can lead to a higher risk of medication errors (Badreldin and Atallah, 2020). In Spain, the shortage problems are mainly due fabrication problems (32%), plant capacity (20%), and the increase of the demand (16%) (https://www.aemps.gob.es, 2020). In the COVID-19 pandemic, worldwide shortages have been derived from a higher number of prescriptions (especially in ICU) and also because of supplying chain problems (Kanji et al., 2020; Liu et al., 2020; Fox and McLaughlin, 2018). It is estimated that during March, the demand on sedative agents increased by 51% in USA, while demand on analgesic agents increased a 67% (Mazer-Amirshahi et al., 2020). These numbers are lower than the ones found in our study, which are probably due to a shorter time of analysis and a
different period during the pandemic, since COVID-19 hit the USA later.

Beyond the description of the global consumption, the analysis of the correlation of drugs is important to try to plan the management of these drugs. All the studied drugs presented a significant correlation either with the number of patients in treatment with the drugs or with all the admitted patients. This data is crucial for planning, since it proves the hypothesis that all follow a standard pattern related to the number of admitted patients. In order to face future outbreaks or other pandemics and due to the aforementioned problems, it is essential that all Pharmacy Services adjust its emergency drugs available stock (Fox and McLaughlin, 2018). However, caution is advised when purchasing excessive amounts of drugs as this could lead to drug shortages in other centres and to an increase in the immobilized stock (Fox and McLaughlin, 2018). Thus, we believe that our study could help to mitigate the consequences of drug shortages as it would allow a better planning of the consumption at all levels, including hospitals, regulatory agencies, and pharmaceutical industry. To this purpose, an analysis performed in China, USA, Australia and Canada determined that countries should optimize its emergency products supply system, including drugs (Wang et al., 2020). Our study has some limitations. It was a single-centre study and considering the variability on prescription and ICU management, the data exposed could not be applied in other settings. Only a few drugs were included, even though it would have been interesting to broaden the study to other drugs administered at ICU such as low molecular weight heparins, corticosteroids, antibiotics, etc.

CONCLUSION

In conclusion, the present study shows an overwhelming increase in the consumption of ICU essential drugs. Furthermore, a significant correlation between the consumption of essential drugs in ICU and the number of critically ill patients was found. Therefore, the mathematical strategy has proven to be useful for the correct management of essential drugs in the ICU.

REFERENCES


