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Review Article

Review of Anaesthesia and Analgesia in Patients with COVID-19 in Brazil

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ARTICLE INFO

Article history:
Received: 11 August, 2020
Accepted: 25 August, 2020
Published: 8 September, 2020

Keywords:
COVID-19
SARS-CoV-2
anaesthetics
analgesics

ABSTRACT

Severe acute respiratory syndrome (COVID-19), produced by SARS-CoV-2, remains a challenge for modern medicine and a global health problem. For every 100 patients with COVID-19, about 20 need hospital care. In addition, some patients will be intubated and others under mechanical ventilation. Therefore, it is necessary to use drugs as a sedative and analgesic purpose, mainly. Thus, this study brings a survey on the drugs that can be used for the management of patients with COVID-19 in cases of intubation and mechanical ventilation in Brazil. In this paper, we will report the classes of anaesthetic and analgesic drugs. Highlighting the clinical indications for use, pharmacological characteristics of each drug in terms of doses, pharmacokinetics, pharmacodynamics and possible side effects and, in addition, peculiarities of drugs related to use in patients with COVID-19, when possible.

Introduction

The outbreak caused by the new coronavirus (SARS-CoV-2) started in the wholesale seafood market in Wuhan, China, in December 2019 [1]. The virus responsible for the new severe acute respiratory syndrome, called coronavirus disease 2019 (COVID-19), generated an epidemic and shortly thereafter, on March 11, 2020, the World Health Organization (WHO) updated the status to pandemic. The number of patients with COVID-19 has increased rapidly in many countries worldwide [2].

Scientific reports suggest that among those with COVID-19, up to 20% develop serious illness that requires hospitalization [3-6]. About 10% of critically ill patients will be considered for mechanical ventilation, and some may require emergency intubation [2, 3]. Guan *et al.* estimates that 2.3% of patients need tracheal intubation [7]. The purpose of intubation is to protect the airways, in the estimation of corroborating for potential recovery from the disease [8].

Anecdotal evidence suggests that the requirements for sedation and analgesia seem high in patients on mechanical ventilation with COVID-19 and that intensive use of sedatives, analgesics and even muscle relaxants is necessary [9]. Thus, this study brings a survey on the anaesthetic and analgesic drugs used in Brazil for the management of patients with COVID-19.

Review

Anaesthetic induction is important in severe cases related to the new coronavirus. Several drugs are used in general, anaesthetic practice, but the new health context requires adequacy and selection of drugs that best suit the clinical condition and the reality of the patient affected by COVID-19. The treatment of patients with COVID-19 in an intensive care unit has caused a significant increase in the prescriptions of sedatives at an international level, generating shortages of this class of drugs in all countries [10, 11].

Among drugs used in sedation, induction and maintenance of anaesthesia in COVID-19 patients, there is propofol [12]. This pharmacokinetics involves an onset of action less than 45 sec, with peak action of 1-2 min and a duration of 10-15 min [13]. It has a protein binding rate of 95%, hepatic metabolism and urinary excretion. Its acts

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http://dx.doi.org/10.31487/j.ACR.2020.01.08

depressing central nervous system, increasing the action of GABA, reducing heart rate, cardiac output, ventilation and myocardial [14]. The dose utilized in coronavirus patients is 1,5-2 mg/kg, with myotoxicity being observed due to the longtime of exposure to propofol [15]. Some patients develop critical illness myopathy. In children, the risk of propofol syndrome is increased, with a generalized myotoxicity effect after severe myalgia. Often, a lethal condition involving rhabdomyolysis can occur [12].

Etomidate is another drug indicated for anaesthesia induction and maintenance [14]. Its onset of action is lower than 2 minutes, with a peak action in 3-5 min and duration of 5-15 min. It has a protein binding rate of 76%, hepatic metabolism and urinary excretion [16]. So far, their action is potentialized by $GABA_A$, causing a reduction of cerebral blood flow and myoclonus, reducing eye pressure, peripheral vascular resistance, tidal volume, and respiration rate, which may cause apnea [14]. The dose used in COVID-19 patients is 20 mg associated with midazolam 5 mg [15].

Another sedative drug and anaesthesia inductor is midazolam. This drug has an onset of action lower than 5 minutes, peak action lower than 1 hour and a duration of 2-4 hours, with faster hepatic oxidation and urinary excretion [14, 17]. Midazolam increases neural inhibition centrally mediated by GABA, which causes sedation, amnesia, delirium, reduced cerebral blood flow, cardiac output, respiratory rate, tidal volume and apnea. It has a muscle relax property [14]. The dose used in COVID-19 patients is 5 mg associated with Etomidate 20 mg [15]. Some severe cases of Neuroleptic Malignant Syndrome were related after midazolam use, showing clinical signs as high fever with creatine kinase level elevated and development tachycardia, tachypnea, altered consciousness, and diaphoresis. Some patients develop delirium [18].

Fentanyl is another drug to induce and maintain anaesthesia. Its onset of action is about 1-2 minutes, with peak action of 3-5 min and duration 0.5-1 h, with a protein binding rate of 80%, hepatic metabolism and urinary excretion [14]. It is an opioid agonist, causing analgesia, drowsiness, reduction of cerebral blood flow, heart rate and blood pressure, urinary retention, constipation, apnea, bronchospasm, muscle stiffness, increased ADH, pruritus, nausea and vomiting [13]. The dose used in COVID-19 patients is 100-150 mcg [15]. High doses (more than 60-120 mcg for a 70 kg patient) of fentanyl for intubation are associated with elevated risk of development of postoperative respiratory complications, as pulmonary edema, atelectasis, pneumonia, respiratory failure or reintubation [19].

Alfentanil is a drug that acts as an opioid receptor agonist, with a rapid onset of action, between 1 and 1.5 minutes, reaching its peak of action between 3 and 5 minutes and having an effective duration of 15 to 30 minutes, for intravenous administration and in doses of 20 to 40 μg/kg for anaesthetic induction and 0.5 to 1.5 μg/kg/min for maintenance in elective procedures [13]. It has a 92% protein binding rate and is metabolized in the liver and excreted in the urine [20]. Its effects are the same as fentanyl. The study by Lovell *et al.* observed the drugs used in patients with COVID-19 in palliative care and found that the dose of alfentanil used in some patients was, on average, 500 μg/24h, ranging between 150 and 1000 μg/24 h [21]. The use of alfentanil in combination with inhaled anaesthetics, can potentiate nausea and vomiting [13, 14].

Sufentanil also acts as an opioid receptor agonist, with the onset of action between 1 and 2 minutes and peak action between 3 and 5 minutes, with an effective duration of 15 to 30 minutes for intravenous administration in doses of 0.5 to 1 μg/kg for anaesthetic induction and 0.3 to 0.6 μg/kg/h for maintenance in elective procedures [13]. Its protein binding rate is 90% and is metabolized in the liver and small intestine and excreted in the urine [22]. Its effects and possible complications are the same as those of fentanyl and alfentanil [13, 14]. Unlike alfentanil, no solid scientific material showing its use in patients with COVID-19 was found.

Remifentanil is another drug that does anaesthetic induction and maintenance and also acts as an opioid receptor agonist [13]. Its onset of action is faster, staying between 30 and 60 seconds with peak action between 3 and 5 minutes for intravenous administration in doses of 0.5 to 2 μg/kg for anaesthetic induction and 0.1 to 0.5 μg/kg/min for maintenance in elective procedures [13]. The protein binding rate is 70%, it is metabolized by non-specific esterases and its pharmacodynamics is the same as that of fentanyl, alfentanil and sufentanil [14]. Because it is an ultra-fast opioid with a short duration of action, it is associated with the rapid development of tolerance. In the case report by Ahmad *et al.*, 4 ng/ml remifentanil and 0.5 μg/ml propofol were used for conscious sedation, and 6 ng/ml remifentanil with 3 μg/mL propofol with 60 mg of rocuronium for anaesthetic induction [23]. In order to reduce the chances of coughing as much as possible during the intubation process, a higher than the recommended dose of remifentanil was used, and the procedure started after the drug reached its maximum effect.

Bevilacqua *et al.* suggest a high dose of remifentanil alone, which is then combined with small doses of midazolam or propofol during the rapid intubation sequence, based on an anaesthetic technique for carotid surgery, in which a venous infusion of remifentanil of 0.2 to 0.3 μg/kg/min until the patient had a profound state of analgesia and sedation, but still reacting to some verbal stimuli and responding to respiratory commands [24]. Tang and Wang responded to the letter from Bevilacqua *et al.* agreeing with the possibility of using remifentanil for intubation in positive COVID-19 patients, but noting that the method is not classified as a rapid sequence of intubation but as a deep induction, in addition to highlighting possible complications such as higher risks of aspiration because it requires more time and hemodynamic risk [24, 25].

Neuromuscular blockers (NMBs) are widely used for surgical anaesthesia, as well as for postoperative and non-surgical analgesia. NMBs offer distinct benefits over general or neuraxial anaesthesia in certain clinical situations [26]. American Society of Regional Anaesthesia, the European Society of Regional Anaesthesia and Pain Medicine and the European Society of Anaesthesiology have published practical recommendations for neuraxial anaesthesia and peripheral nerve block in patients with COVID-19 [27-29]. As with sedatives, neuromuscular blockers had their use drastically increased in the pandemic of COVID-19 in ICUs at the international level, generating shortages in several countries [10, 11].

NMBs are drugs indicated for orotracheal intubation, intraoperative muscle relaxation and better conditions for mechanical ventilation [30]. Cisatracurium presents itself as a NBMs that competitively binds to

cholinergic receptors and antagonizes the action of acetylcholine. It has an onset of action between 1 and 2 minutes, peaking between 3 and 4 minutes and has an average duration of 25 to 44 minutes for intravenous administration at doses of 0.15 to 0.20 μg/kg for induction and 1 to 3 μg/kg/min for maintenance [31]. It has a protein binding rate of 82%, is metabolized by non-specific esterases and via Hofmann, being excreted in the urine and feces [31]. It can cause muscle weakness and apnea, bradycardia and hypotension. Skin flushing, skin rash and bronchospasm are uncommon reactions and are not the NMBs of choice for the rapid sequence of intubation [30, 31]. No solid scientific material evidencing its use in patients with COVID-19 has been found.

Pancuronium acts antagonizing the action of acetylcholine on cholinergic receptors; it starts to act between 3-4 minutes IV and is metabolized primarily by the liver and has renal elimination [32]. As it is the first neuromuscular blocker of the ammonium steroid group discovered, there is no receptor selectivity and it can cause vagal block. Thus, high doses can cause tachycardia and hypertension [33]. There are few information regarding the dose due to its lower use and replacement by the new generations of the drug. Vecuronium is a pancuronium-like drug, with hepatic metabolism and elimination occurring in bile and urine [34]. Its onset of action is 2-3 minutes IV [32]. Because it is a more selective drug, there are fewer occurrences of cardiovascular effects [33]. Administration doses are normally 0.08-0.1 mg/kg IV for induction, 0.25 mg/kg for rapid sequence intubation and 0.05-0.1 mg/kg/h IV in maintenance [31].

Rocuronium is a neuromuscular blocker very similar to vecuronium with the same duration of action, but it starts to act much faster, 1 min IV [18, 34]. It is one of the most used drugs in orotracheal intubations in patients with COVID-19. The usual dose for induction is 0.6-1.2 mg/kg IV and for maintenance is 0.3-0.6 mg/kg/h IV [31]. In the current scenario, the use of a maximum dose of this drug is observed, as in hospital protocols in which the dose of rocuronium used is 1.2 mg/kg in the induction phase [35]. Thus, there may be greater complications with these patients, and anaphylaxis is what most occurs [36]. Another drug belonging to the same class is atracurium, which starts to act in 2-3 minutes IV and is metabolized by non-specific esterases and via Hofmann and has urinary excretion [18]. It can cause vasodilatation due to histamine release and it doesn't have a cumulative effect [33]. It is mainly used in the phase post orotracheal intubation in patients with COVID-19 [35].

Succinylcholine is a neuromuscular muscle blocker that also acts on nicotinic cholinergic receptors antagonizing acetylcholine; it has a rapid onset of action and a rapid duration [37]. The onset of action occurs within 1-2 minutes and is usually used at a dose of 0.5 to 1.5 mg/kg [32]. Despite being an important drug for the installation of an invasive airway, with a good safety margin in these procedures, its prolonged use can induce hypercalcemia, causing arrhythmia or even leading to cardiorespiratory arrest [38]. Despite its risks, succinylcholine is usually available and reliable [39].

Adjuvant drugs are essential to avoid the potentially damaging consequences of physiological responses to airway manipulation during endotracheal intubation. These responses include vagal stimulation bradycardia, severe asthma, high intracranial pressure, exacerbated cardiovascular conditions, as well as the patient in shock [40]. Some peculiarities are to use lidocaine to reduce the likelihood of bronchospasm when beta-2 agonist therapy has not been administered. In the case of alpha-adrenergic agents, here exemplified by dexmedetomidine, used to increase systemic vascular resistance. Magnesium sulfate has minimal adverse effects at the indicated doses and is widely available and inexpensive [41].

Lidocaine is an amine ethylamide, a local anaesthetic and antiarrhythmic agent widely used for its rapid anaesthetic effect, especially when used parenterally [42]. In addition, studies suggest that this drug has a direct influence on improving the inflammatory response [43]. Special attention should be paid to its prolonged use in patients with liver disease due to their renal excretion and to patients with heart block without the use of a pacemaker, Stoke-Adams syndrome and Wolff-Parkinson-White [44]. Its safety dose for orotracheal intubation is 1 to 1.5 mg/kg in bolus with direct benefits in preventing bronchospasm [39]. Another adjuvant drug is dexmedetomidine, which has an alpha 2 agonist action contributing to sedation, decreasing heart rate, blood pressure and involuntary movements [45]. The onset of action is around 5 minutes, with a peak of action between 20 and 30 minutes [46]. The dose of 0.5 to 1 μg/kg is commonly used, and its transport occurs through binding with plasma proteins and its metabolism is hepatic [46]. Although there are data in the literature that suggest an improvement in hypoxemia in patients with COVID-19, the need for scientific evidence to prove this action cannot be ruled out [47].

Magnesium sulfate is a drug used for analgesia in surgical patients. It begins to act in 1 hour and has its peak of action in less than 30 minutes and the duration of action of 0.5 to 4 hours [48]. Magnesium can block N-methyl-D-aspartate receptor and calcium channel, leading to the central nervous system and breathing depression, somnolence and vasodilatation. When used intraoperatively, it decreases the consumption of anaesthetics and muscle relaxants [49]. Also, it reduces the requirement of opioid 24 hours postoperatively [37]. The dose ranges 30-50 mg/kg followed by 10-15 mg/kg for each hour of surgery [46]. Magnesium has side effects, including reduction of the blood pressure, electrocardiogram alteration, nausea and vomit [49]. Ketamine is a racemic mixture that has analgesic, anaesthetic, anti-inflammatory and antidepressant effort [50]. It starts acting in 30 seconds and reaches the peak of action in 3-5 minutes [42]. Ketamine activates the limbic system, induces dissociative anaesthesia and sedation, intense analgesia with minimal respiratory depression at sedative doses (0.25 to 0.5 mg/kg IV) [51]. Ketamine is recognized as a strong psychedelic drug that provokes dissociative states and psychotic symptoms [50]. Also, it causes hypnosis, delirium, tremors, hallucination and convulsion [42]. Besides that, ketamine exhibits neurotoxicity at high concentrations in animals [50].

An aggravating factor in the pandemic of the new coronavirus is the scarcity in several countries of the main drugs used in anaesthetic induction. Inhaled drugs are being proposed as alternatives in studies, associated with their low cost [52]. Nitrous oxide is an adjuvant, amnesic and analgesic gas used in medicine. It has a fast action in the organism and a partition coefficient of 0.47 [53]. Besides that, it has a minimum alveolar concentration of 104%. Nitrous oxide induces opioidergic neurons in the periaqueductal gray matter and noradrenergic neurons in the locus coeruleus [54]. This gas is used at a 40-70% in oxygen. It

causes disorientation, nauseous, vomit and excitement [42]. Also, it can increase myocardial risk in the perioperative period and is related to neurologic effects in long-term nitrous oxide abuse. Besides that, there are *in vitro* studies that suggest nitrous oxide can have genotoxicity by inhibition of methionine synthase [54].

Isoflurane is widely used and helps maintain general anaesthesia, further reducing the level of consciousness. It is a volatile, non-flammable and poorly metabolized drug (0.2%, with urinary excretion). Its pharmacodynamics is related to inhibition of neurotransmission, an increase of intracranial pressure above 1 MAC (minimum alveolar concentration), headache, excitement in the emergence of anaesthesia, reduction of peripheral vascular resistance, cardiac output and blood pressure and increases heart rate. It also intensifies muscle relaxation, reduces tidal volume and increases respiratory rate [53, 55-58]. It strengthens the effect of NMBs, opioids, nitrous oxide and benzodiazepines. The usual dose is maintained between 0.5 and 1 MAC (0.6-1.2% - expired concentration). This drug is contraindicated in cases of malignant hyperthermia, inhalation induction (irritating to the airways in high concentrations) and procedures that require electrophysiological monitoring [53, 55-58]. Isoflurane offers the highest potency with the lowest dosage requirements for patients in the ICU, it increases heme oxygenase and assists in cytoprotection during cardiac and liver surgeries, and in the long term it helps in the recovery and reduction of bronchospasm from pneumonia by herpes simplex [59, 60].

Sevoflurane, as well as isoflurane, is also widely used, following basically the same indications and pharmacokinetic and pharmacodynamic properties. However, it differs in metabolism, which is hepatic (2-5%) and forms compound A (potentially nephrotoxic) in contact with soda lime. In the dynamic part, it can cause nausea and vomiting. Contraindications and interactions are also quite similar to isoflurane. The usual dose is maintained between 0.5 and 1 MAC (1-2% - expired concentration) [53, 55-58]. Like isoflurane, sevoflurane also increases heme oxygenase and assists in cytoprotection during cardiac and liver surgeries, also helping to improve lung mechanics and gas exchange in a series of cases of babies with severe bronchiolitis and acute respiratory distress syndrome [60]. Nieuwenhuijs-Moeke *et al.* discuss, in their article, a clinical study carried out in animals that shows the superiority of sevoflurane in relation to other anaesthetic drugs in terms of length of stay and mortality and that treatment with sevoflurane improved the partial pressure of oxygen (PaO_2)/ inspired oxygen fraction (FiO_2) and reduced the concentrations of interleukin-6 and TNF-α in patients treated with sevoflurane [52].

Desflurane is a less used drug compared to other inhalation agents, because it is related to rapid awakening, agitation if there is no adequate analgesia and it requires electronic vaporizer. In general, it has the same pharmacokinetics and pharmacodynamics as isoflurane. Its dose is usually maintained between 0.5 and 1 MAC (3-6% - expired concentration) [53, 55-58]. There is a shortage in the literature of studies that suggest its use for patients affected by COVID-19.

Nieuwenhuijs-Moeke *et al.* conclude that the current situation makes it possible to investigate the potential beneficial effects of volatile anaesthetics on systemic inflammation, sepsis and acute respiratory distress syndrome in mechanically ventilated patients with COVID-19, while increasing the range of sedative drugs in this population still growing in the ICU [52]. Preclinical data showed that inhaled anaesthetics attenuate lung inflammation and dilate the airways, effects mediated by type A γ-aminobutyric acid ($GABA_A$) receptors, which are expressed in different types of cells in the lung, promoting a reduction in the production of pro-inflammatory cytokines, while the activation of $GABA_A$ receptors in airway smooth muscle cells stimulates bronchodilation and improves oxygenation [61]. Inhaled sedative regimens have shown modest benefits in faster extubation times after discontinuation of the drug, which is attributable to its exclusive clearance by pulmonary expiration with negligible systemic metabolism [59].

Conclusion

The pandemic scenario causes both rapid technological and scientific advances in order to find solutions to the problems which arise as a result of SARS-CoV-2 and, in accordance with this situation, there should exist an efficient administration of drugs. One of the problems found was the shortage of drugs and the lack of a protocol that gathers all the drugs used in the treatment of COVID-19, introducing details such as the indication of use, pharmacokinetics, pharmacodynamics, doses and side effects. Therefore, we conclude that more in-depth studies on the specific action of each drug and its particularities in a COVID-19 patient should be carried out, aiming to determine possible implementations in its administration.

Author Contributions

All authors have read and agreed to the published version of the manuscript.

Acknowledgments

The authors dedicate this article to all health professionals who are facing COVID-19.

Funding

None.

Conflicts of Interest

None.

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