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Immunosuppressive aspects of analgesics and sedatives used in mechanically ventilated patients: An underappreciated risk factor for the development of ventilator-associated pneumonia in critically ill patients

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Abstract

Objective—To evaluate the evidence describing the immunosuppressive and pharmacokinetic properties of commonly used analgesic and sedation agents in critically ill patients.

Data sources—MEDLINE (January 1980 – September 2013) was searched.

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Study selection and data extraction—All *in vitro* and *in vivo* studies that evaluated the immune modulating properties of analgesic and sedation agents commonly used in the critically ill. Full text articles and abstract only articles (noted) were included in this review. Inclusion criteria were met by 46 studies and were evaluated.

Data synthesis—Analgesia and sedation agents have been shown to be immunosuppressive in a variety of models. *In vitro* models use a variety of immune cells to demonstrate the immunosuppressive properties of opioids, benzodiazepines and, to a lesser extent, propofol. In each case, animal studies provide more robust data supporting the concept that opioids, benzodiazepines, and propofol exhibit immunosuppressive activities ranging from innate to adaptive immune alterations. Human studies, though more limited, provide further support that these agents inhibit the immune response. In contrast, data has shown that dexmedetomidine may attenuate the immune system. Clinical trial data evaluating the immunosuppressive properties of these agents is limited.

Conclusions—Analgesic and sedation agents have clearly been shown to alter cellular function and other mediators of the immune system – yet the clinical impact remains to be fully elucidated. The mechanism by which sedation interruption reduces ventilator-associated pneumonia may in fact be a reduction in immunosuppressive effects. Studies linking the immune modulating effects of analgesic and sedation agents in critically ill patients are needed.

Keywords

analgesia; sedation; ventilator-associated pneumonia; immune system

Introduction

Ventilator-associated pneumonia (VAP) is one of the most common nosocomial infections in the intensive care unit (ICU), complicating the course of up to 28% of patients receiving mechanical ventilation (MV).[1,2] MV increases the risk of developing pneumonia by 6 to 20-fold.[3] Furthermore, development of VAP leads to an increased ICU stay of more than six additional days, with an added $13,000 in hospitalization cost per patient, and a doubled risk of mortality. Thus, efforts to reduce VAP incidence in the critically ill population are a top priority.[1,3] Risk factors associated with the development of VAP may be modifiable (e.g. duration of MV) or non-modifiable (e.g. pre-existing pulmonary disease).[2,3] Clinical interventions, such as daily interruption of sedative infusions, are known to decrease MV duration; however, the immunologic benefit of such interventions remains unknown.[3–5] Furthermore, the mechanism of VAP reduction with sedation interruptions remains unclear.[6]

In vitro and animal studies have determined that analgesics (defined here as opioid analgesics), propofol, and benzodiazepines possess significant immunosuppressive effects. This is in contrast to the published literature on dexmedetomidine (a sedative with analgesic properties), which lacks the immunosuppressive properties seen with the other agents. Whether the immunosuppressive properties of analgesics or sedatives are clinically relevant to critically ill patients at risk for the development of VAP remains unclear. Therefore, determining the immunologic impact of analgesics and sedatives on the risk of developing VAP would provide clinicians with a new way to modify analgesics and sedatives as a risk

factor, and improve outcomes in this vulnerable patient population. This review will summarize pre-clinical and clinical studies that have evaluated the immunosuppressive effects of commonly utilized analgesics and sedatives in critically ill patients at risk for VAP. Moreover, it will link important pharmacokinetic (PK) properties of these drugs to relevant aspects of lung immune function, such that drugs with high potential for causing clinically relevant immunosuppression in the lungs can be identified for future studies evaluating their impact on the incidence of VAP.

Data sources and selection

A MEDLINE search was conducted to identify articles relevant to the immunosuppressive properties of analgesics and sedatives that are commonly used in critically ill mechanically ventilated patients. This search was limited to articles published between January 1980 and September 2013. The search used a combination of the following search terms: *analgesics, artificial respiration, critical illness, cytokines, deep sedation, dexmedetomidine, diazepam, fentanyl, hypnotics and sedatives, immune, immune system, immunity, immunologic, immunomodulatory, intensive care units, midazolam, morphine, opioid, pneumonia, propofol, remifentanil, and ventilator associated.* References from retrieved articles were reviewed for additional material. Articles describing *in vivo* or *in vitro* studies of analgesic and sedative medication effects at the cellular and animal level were included. The literature was summarized pertaining to the clinical setting in the context of this search. Results of the literature search were independently reviewed by the authors for relevance to the review.

Airway Immunity

To fully describe the potential clinical connection between analgesics or sedatives and VAP, the pulmonary host immune response must be considered. Airway immunity consists of 2 distinct yet interfacing components that are subject to suppression or alteration by analgesics or sedatives. The innate immune response is the first line of defense against inhaled pathogens. It recognizes cellular structures and signals that are structurally conserved among invading pathogens or host cells under stressed conditions, referred to as pattern recognition receptors (PRRs).[7–9] These PRRs enable innate immune cells to respond rapidly to infection or tissue damage. PRRs bind their respective ligands and initiate a cascade of events that ultimately leads to the activation of innate immune cells such as monocytes, macrophages, neutrophils, dendritic cells (DCs), and natural killer (NK) cells.[7–9] Not only do activated innate immune cells destroy invading pathogens but they also damage tissue through the recruitment of inflammatory mediators and phagocytosis.

The lack of specificity that characterizes the innate immune response is in stark contrast to the highly specific nature of the adaptive immune system, comprised of B- and T-lymphocyte cells. Lymphocytes become activated in regional lymph nodes by antigen presenting cells (APCs), primarily DCs and some macrophages, which carry antigen from the site of infection to the lymphoid system.[7] Within this system, complex interactions between DCs, T cells, and B cells result in activated lymphocytes specific to a particular pathogen. Activated lymphocytes further differentiate to perform specific actions depending

on environmental and costimulatory signals.[7] Chemokines then guide immune cells to the site of infection to help in the elimination of the infection.

Activated T cells consist of CD8+ cytotoxic T cells and CD4+ T cells.[7] CD8+ cytotoxic T-cells are responsible for the destruction of virally infected cells as well as tumor cells. CD4+ T cells differentiate into T helper type 1 (T_H1), T_H2, regulatory T cells, and Th17 cells.[7,9] T_H1 cells play an important role in activating macrophages, eliciting antibody production from B-cells, and producing inflammatory cytokines, such as interferon (IFN)-γ (IFN-γ).[7] T_H2 cells are effective activators of B-cells and produce anti-inflammatory cytokines.[7] Cytokines produced by T_H1 cells antagonize the effects T_H2 cells, and vice versa.[7] Regulatory T-cells mitigate the effects of both CD8+ and CD4+ T cells to ensure that inflammatory processes are tempered once the invading pathogen has been eliminated. Th17 cells produce anti-microbial proteins at mucosal barriers, including the upper and lower airways; lack of Th17 cells may leave the host susceptible to opportunistic infections.[10] The biological activities of the anti- and pro-inflammatory cytokines is summarized in Table 1.[11]

Immunosuppression Caused by Analgesics and Sedatives

Though well-designed to defend against inhaled pathogens and foreign particles, clinical and pre-clinical studies have shown that the immune response to noxious stimuli in the lungs can lead to enhanced inflammation and multiorgan dysfunction over time.[20–22] The immune response of critically ill patients may also be a result of physical stress due to medical procedures or trauma. Patients may undergo surgical or bedside procedures, such as endotracheal intubation for the purpose of providing MV. As such, these patients are exposed to analgesics and sedatives for pain control, comfort, and sedation. Opioids, benzodiazepines, propofol, and dexmedetomidine are commonly used agents for critically ill patients.

Examination of the correlation between cytokine concentrations in bronchoalveolar lavage (BAL) or lung tissue, and plasma, often show a time-dependent relationship.[21] Therefore plasma cytokine measurements may not be an accurate representation of the immune response that is present in the lung at the time of MV and VAP. Inflammatory cytokines produced by cells resident in the respiratory tract, such as airway epithelium and alveolar macrophages, are not detected in the plasma for a number of hours after exposure, indicating sequestration of the noxious stimuli to the pulmonary system for a finite period.[20–22] In conjunction with microscopic images from pre-clinical studies, correlations between BAL/lung tissues versus plasma cytokine concentrations have suggested that the increasing inflammatory cytokine concentrations over time may be responsible for overwhelming cellular damage resulting in breakdown of the alveolar-capillary barrier. Moreover, a number of preclinical studies have demonstrated that when compared to control groups, any form of MV increased the concentration of inflammatory cytokines in BAL or lung tissue,[23–25] which have been shown to increase in relation to time on MV.[25] As previously mentioned, MV directly introduces pathogens into the respiratory tract and can result in VAP. However, the analgesic and sedative medications that make MV physically and psychologically tolerable suppress the normal immune response, further reducing the body's

ability to fight this infectious complication of MV, and may lead to worsened clinical outcomes.

Based purely on in vitro and animal studies, it is difficult to ascertain whether enhanced inflammation with local injury but reduced infection is better or worse than, reduced inflammation with reduced local injury but potentially uncontrolled infection. A balanced immune response would most likely improve outcomes in critically ill patients receiving MV.

Opioids, benzodiazepines, propofol, and dexmedetomidine have been shown to modulate the immune system in various ways; this review will summarize the available data on the immune modulation and PKs of these agents.

Opioids

The immunomodulatory effects of the opioids used in critically ill patients, including morphine, hydromorphone, fentanyl, and remifentanil, will be discussed collectively except where differences are noted. Pharmacological effects of these drugs differ in their potency and receptor activity, while some PK characteristics are consistent (wide volume of distribution). These agents also retain differences in metabolism and half-life that lend to either intermittent administration (morphine and hydromorphone), or more commonly in the acute phase of critical illness, continuous infusions (fentanyl and remifentanil).

In vitro data indicates that opioids have a wide range of immunomodulatory properties, with the exception of morphine and hydromorphone for which no data is currently available. At low concentrations (0.001 to 1.0μM of fentanyl) B-cell proliferation is reduced, while migration of polymorphonuclear neutrophils was inhibited with similarly low doses (remifentanil 50 ng/mL and fentanyl 30 ng/mL).[26,27] The reduction in B-cell proliferation was not detected in a dose-dependent manner.[26] Production of interleukin (IL)-4 is decreased, as well as the function of cytotoxic T-cells and NK cells in these models. In contrast, an increase in tumor necrosis factor (TNF) production, an inflammatory cytokine, has been described.[26]

Opioid immune modulation in animal models is strikingly similar. A dose-dependent decrease in lymphocyte function, as well as a decrease in macrophage phagocytosis, neutrophil and monocyte migration, and lymphocyte proliferation has been demonstrated in rat and monkey models following opioid administration.[28–36] A decrease in NK cell function and IL-2 and IFN-γ production has been shown in rat models.[28,35] However, in one study, immune parameters returned to baseline 7 days post-opioid administration.[35] The transition from B-cell to plasma cell was also suppressed in a murine model.[37] Interestingly, these immunosuppressive effects have not been seen with the use of hydromorphone.[38]

Most evaluations of immunomodulatory effects in humans have been conducted on serum samples from patients in the perioperative setting. Among them, a decrease in lymphoproliferation, and cytokine production--namely, IL-1β, IL-6, IL-10, and TNF-α--has been observed.[39–41] Larger doses of fentanyl (75–100μg/kg) showed prolonged decreases in NK cell activity in comparison to smaller doses (1μg/kg initial, followed by an additional

5μg/kg) in patients undergoing abdominal surgeries.[42] Reductions in CD3, CD4, and NK cell activity were also shown to be dose-dependent, persisting for up to 48 hours post-dose.[43] In some clinical settings, the immunosuppressive properties of opioids may be beneficial. When compared to fentanyl, remifentanil shifted the Th1/Th2 balance by lowering the IFN-γ/IL-10 ratio in patients undergoing elective coronary artery bypass graft surgery. These immunosuppressive properties of remifentanil were believed to attenuate the exaggerated inflammatory response after cardiopulmonary bypass surgery.[44] Despite these observed effects, when remifentanil was given as a continuous infusion to healthy patients, the effects on NK cell counts and function were not seen.[45] Moreover, the consequences of remifentanil in critically ill patients in whom further immune suppression should be avoided are unknown. The literature is silent on the immune modulating effects of hydromorphone in humans.

Clinical trials to evaluate outcomes associated with immunomodulatory effects of opioids have not been conducted. However, their wide distribution into body tissues and fluids, including lung parenchyma, support the hypothesis that these immunomodulatory effects would manifest similarly in the airways and further alter the respiratory environment in favor of infection. In comparison with morphine and hydromorphone, fentanyl and remifentanil have a shorter onset of action and duration.[35,46] This lends to frequent use of these agents as continuous infusions. Inherent in the use of these agents is continuous exposure to drug with the possibility of more frequent titrations, which may result in increased total exposure time and more frequent peak effects, respectively. Fentanyl displayed prolonged immunosuppression[42]; however, remifentanil has been shown to induce more immune suppression when compared to fentanyl.[44] The lack of data in hydromorphone is most likely due to its limited use in the critically ill population as a continuous infusion[47]; however, it does have the capacity to reach the lung parenchyma given its volume of distribution (1.22 L/kg).[48]

Benzodiazepines

Midazolam, lorazepam, and diazepam are the principal benzodiazepines used in critically ill patients due to their parenteral formulations. Agonist activity at the γ-aminobutyric acid (GABA) neuroreceptor is thought to be responsible for the sedative and anterograde amnestic effects of the class. Onset, duration of action, and metabolic fate of each drug are differentiating PK characteristics; whereas propylene glycol (PG) solvent is present in only lorazepam and diazepam formulations.

The in vitro data on benzodiazepine immune modulation is limited; however, a decrease in IL-6, IL-8 and IFN-γ has been shown.[49–52] Additionally, inhibition of lymphocyte function has also been demonstrated *in vitro*.[42,43] Animal data is more robust and demonstrates that benzodiazepines bind to peripheral-type benzodiazepine receptors.[53] It is this affinity that may be responsible for the immunomodulatory effect of benzodiazepines. In rat models, benzodiazepines decreased mast cell and TNF-α production, as well as suppressed the activation of IL-6.[54–56] In other experiments, impaired chemotaxis of polymorphonuclear neutrophil cells and an increase in IL-1β have been demonstrated.[57,58] Mice treated with

longer durations of benzodiazepines suffered from more intense bacteremia as determined by generation rate of the bacteria ($p<0.01$).[57]

Human data is primarily reported in patients treated with midazolam, with the exception of one study in patients receiving lorazepam for migraines.[59] In 1 study, a dose-dependent decrease in neutrophil chemotaxis and phagocytosis was observed following midazolam administration.[60] In a separate study, post-surgical patients receiving midazolam by continuous infusion (0.02–0.06mg/kg/hr) showed decreases in IL-1β, IL-6, TNF-α, and IL-8, while IL-2 and IFN-γ were not affected.[61]

Although the benzodiazepines have slight differences in their PK profiles—namely, onset and duration of action--they share many similarities. They have a volume of distribution of approximately 1–3 L/kg, which suggests that receptors may reach saturation. Moreover, peripheral-type benzodiazepine receptors are present in the lung, suggesting that the immunologic properties associated with these agents are likely to elicit an effect locally in the lung. The presence of propylene glycol in the lorazepam and diazepam parenteral formulations may provide an additional mechanism of immunosuppression via inhibition of neutrophil cytotoxicity and chemiluminescence, an assay used to determine neutrophil activation.[62] It is intriguing to consider how these effects impact pulmonary defenses against infection, particularly for critically ill patients already at high risk.

Propofol

Propofol is an intravenous anesthetic agent also used at lower doses for ICU sedation. It is known to have various immunomodulatory effects on cells and cell signaling.[63,64] One in vitro study found that clinically relevant concentrations of propofol impaired human neutrophil functions such as chemotaxis, phagocytosis, and reactive-oxygen species production in a dose-dependent manner.[65] Additionally, propofol significantly inhibited neutrophil polarization when compared to midazolam ($p<0.01$) at all concentrations, causing approximately 40–50% inhibition.[66] Using a coculture model of macrophages and NK cells, Inada et al[67] showed that propofol alters murine macrophages by inhibiting cyclooxygenase (COX) enzyme activity and suppressing prostaglandin E_2 (PGE_2) production resulting in increased IFN-γ production by NK cells. Galley et al[50] found that human neutrophils stimulated with lipopolysaccharides inhibited the release of IL-8 when treated with propofol compared to untreated controls. Moreover, animal studies have shown that mice treated with endotoxin had lower rates of mortality when treated with propofol.[68,69] Similar to in vitro findings, human studies have shown that blood samples from patients sedated with propofol found reduced levels of IL-8 and increased levels of IFN-γ, compared with those from who did not receive propofol.[61] A study by Yang and colleagues[70] recently confirmed these findings, showing that propofol significantly reduces chemotaxis in human neutrophils activated by N-formylmethionyl-leucyl-phenylalanine (fMLF).

Propofol has a large volume of distribution (nearly 4000 L[71]). It is highly lipophilic with widespread tissue penetration and readily distributes into lung parenchymal tissue and air spaces. No information was found regarding the contribution of propofol to the development of VAP during critical illness secondary to its immune modulation at the time this review was written. In addition to propofol itself, the lipid emulsion and ethylenediaminetetraacetic

acid (EDTA) used to solubilize and inhibit microbial growth, respectively, are thought to be immunomodulatory. EDTA may attenuate the pro-inflammatory response, whereas the lipid emulsion may be immunosuppressive.[63] The available immunologic and PK properties of propofol can inform future studies to better determine potential risks. Based on the extensive distribution of this agent, lipophilicity, and prolonged half-life (up to 44 hr) of this agent,[71] it can be postulated that the immunosuppressive effects of propofol would cause similar affects within the lungs.

Dexmedetomidine

Dexmedetomidine is an α2 adrenoreceptor agonist and sedative shown to possess anti-inflammatory and immunomodulatory effects.[72] In vivo animal studies showed that dexmedetomidine treatment of endotoxin-exposed rats lowered plasma levels of TNF-α and IL-6 attenuating the inflammatory response.[73] Qiao et al[74] found that treatment of induced sepsis in Sprague Dawley rats with dexmedetomidine lowered systemic levels of TNF-α and expression of splenic-caspase-3, a marker of apoptosis. In a separate study, dexmedetomidine, given at 10 times the clinical dose, was shown to decrease pulmonary concentrations of TNF-α, IL-6, macrophage inflammatory protein-2, and prostaglandin E_2. These decreases significantly reduced lung injury associated with high volume ventilation.[70] In humans, postoperative patients requiring sedation and ventilation and treated with dexmedetomidine were found to have significantly lower serum levels of TNF-α and IL-6 compared with those treated using propofol.[75]

Similar to propofol, dexmedetomidine also has a large volume of distribution (approximately, 173 L)[76]; however, it does not cause respiratory depression at usual doses.[6] It does, however, have the propensity to reach the lung tissue, as it is rapidly redistributed into peripheral tissues. In comparison to the aforementioned agents, dexmedetomidine's half-life is even shorter at 1.8–3.1 hours.[6]

Clinical Implications

Exposure to analgesic and sedative agents is a risk factor for the development of VAP in critically ill patients. In a single center, prospective study, Rello et al[77] evaluated potential risk factors for VAP associated with the first 48 hours of intubation. They identified that intubated patients who received continuous sedation infusions, versus those that did not, had a higher incidence of VAP in both medical and surgical ICUs (23.6% vs. 9.7%; $p < 0.01$). Patients were sedated with midazolam, propofol, or morphine; the dosages of the medications were not reported. Moreover, in a tertiary pediatric center, Srinivasan et al[78] conducted a prospective, observational study designed to determine risk factors for the development of VAP and patient outcomes. Use of narcotics was associated with the development of VAP (adjusted OR = 77.5, 95% CI = 7.11, 844.63; $p < 0.001$), however, the agent used and dose, was not reported.

To reduce the risk of adverse effects in critically ill patients, sedation protocols have been implemented. Quenot et al[79] examined the effects of a nurse-implemented sedation protocol on the incidence of VAP and duration of MV in a medical ICU. The protocol was based on the Cambridge sedation scale, whereby sedation was adjusted every 3 hours by bedside

nurses. The average daily doses of midazolam (92 mg ± 59 vs. 44 mg ± 31; p = 0.001) and propofol (2900 mg ± 1400 vs. 1840 mg ± 750; p = 0.01), were significantly decreased in the nurse-driven protocol group. It should be noted that the use of analgesics as sedation agents (e.g. fentanyl continuous infusion) was not permitted. The investigators found there was a significant decrease in incidence of VAP and duration of MV in the protocol group compared to the control group (15% vs. 6%; p = 0.005). In a retrospective study conducted by Schweickert et al,[80] the effect of daily interruption of sedative infusions on complications of critical illness was evaluated, including VAP in MV patients. Patients in the daily sedation interruption group had less complications overall compared to the control group (2.8% vs. 6.2%; p = 0.04), and fewer patients in the daily sedation interruption group developed VAP (n=2 vs. 5). The amount and the type of agents used in the study were not reported.

The level of sedation achieved by analgesics or sedatives used in MV critically ill patients has also been associated with the incidence of VAP. Metheny et al[81] conducted a prospective descriptive study to identify the risk factors associated with aspiration and pneumonia in critically ill tube-fed patients. Investigators used the Glasgow Coma Scale, adjusted for use with intubated patients to assess the level of consciousness and the Vancouver Interaction and Calmness Scale to assess the level of sedation. Glasgow Coma Scale scores < 9 (p = 0.018), sedation scores ≤ 35 (p = 0.01), and use of opioids (p=0.0347) were identified as some of the risk factors for pneumonia in these patients in a univariate analysis. In a logistic regression, sedation score ≤35 remained a risk factor for pneumonia (p=0.009). Again, specific information about the analgesics or sedatives used was not reported.

The dose-dependent effects of opioids and their relationship to infectious complications was evaluated in a clinical study. Schwacha et al[82] conducted a retrospective, nested, case-control study to determine whether opioids contribute to the development of infectious complications, including pneumonia, in burn patients. However, the incidence for each type of complication was not reported. The investigators converted all the opioids that patients received into opioid equivalents (OE) of 10 mg parenteral morphine sulfate. They did not report the original agents used. Cumulative analgesic use, expressed in OEs, was categorized into 2 groups, ≥ 34 OEs was considered high and < 34 OEs was considered low. Cases with infectious complications were more likely to be classified into the high OE group relative to controls (OR = 1.24; 95% CI, 1.00 –1.54; p = 0.0495) and the duration of opioid use was significantly longer in cases compared to patients in the control group (p <0 .001), with a 40% increase in duration of treatment. Several confounders should be noted, which may contribute to the increased risk of infections in burn patients. The size of the burn, presence of inhalation injury, and the patient age increase the risk of infections; however, these were matched in the study. Finally, the case group had a significantly longer length of stay, which could also increase their risk of complications.

Evaluating these studies for the role of the immunosuppressive effects of analgesia and sedation agents would not be possible without considering confounders. Risk factors for the development of VAP (or ways to reduce the incidence of VAP) are non-modifiable and modifiable. Studies have shown that protocols aimed at daily sedation interruptions reduce

the time of MV, which could be the driving force behind the reduction in VAP rates. Other confounding variables include risk of aspiration, comorbid conditions, and use of paralytic agents. One study showed that sedation scores ≤35 remained a risk factor for pneumonia, independent of the risk of aspiration.[81] What remains unclear is the independent risk associated with the use of analgesic and sedative agents. The risk of VAP is multi-factorial; however, these studies indicate that exposure to analgesics and sedatives lead to an increase in the incidence of VAP in critically ill MV patients and suggest a dose-response effect.

Conclusion

There have been significant advances in the studies that examine the immunosuppressive effects of analgesics and sedatives. These studies, however, are often in vitro or animal studies that investigate quantitative properties of cellular components of the immune response. Other studies have identified the incidence of infection, such as VAP, but only as secondary outcomes. To date, no studies have looked at the clinical implications of the immune modulating properties of these agents in critically ill patients. Critically ill MV patients are often on a combination of analgesics and sedatives and/or high doses of these agents. Multiple drugs or high dose treatment may further suppress the immune system and increase the risk for VAP and other infections in critically ill MV patients. Arguably, suppression of the host immune response may in some situations reduce damage caused by an exaggerated host immune response.

To determine the clinical significance associated with any given drug, studies evaluating the known immune modulating properties of analgesics and sedatives in this patient population would be required. Such studies could take the following form. The immune function of critically ill MV patients could be assessed by collecting and analyzing BAL samples, tracheal aspirates, and blood samples over a pre-determined period of time and intervals. Careful consideration would be given to agent, dose, duration, time to VAP, and the time profiles of chemokines, among other factors. With proper assessment, rates of VAP among these patients could be compared through analysis of the dose and the duration of analgesics and sedatives administered. These studies would bridge the information about immune modulating properties of analgesics and sedatives discussed herein to the clinical implications of drug selection and use strategies on preventing VAP in critically ill MV patients.

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Table 1

Cytokines of the immune system and their biological activity

Cytokine	Inflammatory or Anti-inflammatory	Primary cell source	Cell Target	Biological Activity
IL-1α,β[9,11–14]	Inflammatory	Monocytes/Macrophages, fibroblasts, most epithelial cells, endothelial cells	All cells	Increases adhesion molecule expression, neutrophil and macrophage emigration, mimics shock, produces fever, upregulates hepatic acute-phase protein production, stimulates hematopoiesis
IL-2[9,12,15]	Inflammatory	T-cells, NK cells	T-cells, B-cells, NK cells, monocytes/macrophages	Promotes T-cell and NK cell proliferation and activation, enhanced monocyte/macrophage activity, Ig production
IL-4[9,12,13,16]	Anti-inflammatory	T_H2 cells, mast cells, basophils	T-cells, B-cells, NK cells, monocytes/macrophages, neutrophils, eosinophils, endothelial cells, fibroblasts	Stimulates T_H2 cell differentiation and proliferation. Stimulates B-cell Ig class switch to IgE, anti-inflammatory action on macrophages, produces allergic inflammatory responses
IL-6[9,11,16,17]	Inflammatory	Monocytes/Macrophages, fibroblasts, stromal cells	T-cells, B-cells, epithelial cells, hepatocytes, monocytes/macrophages	Induces acute-phase protein production, T- and B-cell differentiation and growth, proliferation of vascular smooth muscle cells and osteoclast growth and activation
IL-8[9,12,18,19]	Inflammatory	Monocytes/Macrophages, fibroblasts endothelial cells, keratinocytes	Neutrophils, T-cells, monocytes/macrophages, endothelial cells, basophils	Induces PML migration, histamine release from basophils, and stimulates angiogenesis. Suppresses proliferation of hepatic precursors. Stimulates the release of IFNγ
IL-10[9,12,13,16]	Anti-inflammatory	Monocytes/Macrophages, T-cells, B cells, keratinocytes, mast cells	Monocytes/Macrophages, T-cells, B cells, NK cells, neutrophils, dendritic cells	Inhibits proinflammatory cytokine production, downregulates class II MHC and co-stimulatory molecule expression, inhibits T_H1 cell development, promotes T_H2 cell development, inhibits production of ROS and adhesion molecule expression
IFN-γ[9,11,16]	Inflammatory	T-cells, NK cells	All cells	Regulates macrophage and NK cell activations. Induction of MHC class I and II proteins. T_H1 cell differentiation. Induces chemokine and cell adhesion molecule production. Induces thrombopoiesis
TNF-α[9,11]	Inflammatory	Monocytes/Macrophages, mast cells, basophils, eosinophils, NK cells, B-cells, T-cells, keratinocytes, fibroblasts, epithelial cells	All cells except erythrocytes	Fever, anorexia, shock, capillary leak syndrome, neutrophil production, increased production of coagulation factors, acute phase protein synthesis, proinflammatory cytokine induction, and fibroblast activation

Abbreviations: IL, interleukin; NK, natural killer; T_H1 – T helper type 1, Ig – immunoglobulin, PML – polymorphonuclear leukocyte, IFN, interferon, MHC – major histocompatibility complex, ROS, reactive oxygen species; TNF, tumor necrosis factor.

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