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REVIEW ARTICLE

The immune response to anesthesia: Part 2 sedatives, opioids, and injectable anesthetic agents

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Abstract

Objective To review the immune response to injectable anesthetics and sedatives and to compare the immunomodulatory properties between inhalation and injectable anesthetic protocols.

Study design Review.

Methods and databases Multiple literature searches were performed using PubMed and Google Scholar from March 2012 through November 2013. Relevant anesthetic and immune terms were used to search databases without year published or species constraints. The online database for Veterinary Anaesthesia and Analgesia and the Journal of Veterinary Emergency and Critical Care were searched by issue starting in 2000 for relevant articles.

Conclusion Sedatives, injectable anesthetics, opioids, and local anesthetics have immunomodulatory effects that may have positive or negative consequences on disease processes such as endotoxemia, generalized sepsis, tumor growth and metastasis, and ischemia-reperfusion injury. Therefore, anesthetists should consider the immunomodulatory effects of anesthetic drugs when designing anesthetic protocols for their patients.

Keywords anesthesia, anti-inflammatory, immunomodulation, immunosuppression, injectable anesthetic, sedative.

Introduction

This article is the second installment of a two part series on the immune response to inhalation anesthesia and anesthetic drugs. The first part reviewed the pulmonary immune response, the pulmonary and systemic immune response to mechanical ventilation, and the immunomodulatory effects of inhaled anesthetics. This second part reviews the immunomodulatory effects of commonly used injectable anesthetics and sedatives and provides a brief comparison between the immunomodulatory properties of total intravenous anesthesia (TIVA) and inhalation anesthesia.

It is becoming clear that injectable sedatives and anesthetic agents exert pharmacologic effects beyond sedation, anesthesia, and analgesia (Table 1). Many injectable sedatives and anesthetics used in veterinary anesthesia have been evaluated for their effect on the immune system and the majority of these drugs demonstrated immunomodulatory properties. Though all of the drugs discussed below have been evaluated for their effects *in vitro* and in laboratory animal models, the majority of drugs have not been fully investigated for their immunomodulatory effects in clinical patients.

Drugs used by anesthetists may have anti-inflammatory properties, by which they modulate the innate immune response, or immunosuppressive properties, by which they modulate the adaptive immune response (Fig. 1). The innate immune

Table 1 Summary of injectable anesthetic drugs and their potential immunomodulatory effects

Drug	Primary immune cells affected	Immunomodulatory effects	Disease processes on which drug may exert positive effects	Disease processes on which drug may exert negative effects
Dexmedetomidine	Macrophages	Anti-inflammatory: Modulation of the TLR4-NFκB pathway, reduction in pro-inflammatory cytokine production, promotion of macrophage phagocytosis	Sepsis, endotoxemia, VILI, ALI	
Midazolam Diazepam	Macrophages, lymphocytes, neutrophils	Anti-inflammatory and immunosuppressive: Reduced oxidative burst in phagocytes, reduced lymphocyte proliferation, delayed neutrophil apoptosis, reduced COX2 and iNOS		Chronic inflammation, sepsis
Acepromazine Promethazine	Neutrophils	Anti-inflammatory: anti-oxidant, reduced ROS production, interferes with oxidation-reduction reactions in some bacteria	Acute inflammation, *Mycobacterium* spp infection	
Ketamine	NK cells, neutrophils, macrophages	Anti-inflammatory: Suppression of NK cells, suppression of neutrophil chemotaxis and superoxide formation, suppression of macrophage oxidative burst, modulation of the TLR4-NFκB pathway, reduction in pro-inflammatory cytokine production	Sepsis, ischemia-reperfusion injury, ALI	Tumor metastasis
Thiopental	T lymphocytes, macrophages	Immunosuppressive and anti-inflammatory: Suppression of T lymphocyte function, reduction in platelet tissue factor and TNF-α production, suppression of macrophage oxidative burst	Endotoxemia, renal ischemia-reperfusion injury	Nosocomial infection
Propofol	Dendritic cells, neutrophils, NK cells, macrophages	Anti-inflammatory: anti-oxidant, reduction in effects of PGE_2, suppression of neutrophil phagocytic function and ROS production, improve NK cell function, reduction of macrophage phagocytic function	Endotoxemia, ischemia-reperfusion injury, ALI, tumor metastasis	
Morphine	Macrophages, neutrophils, NK cells, lymphocytes	Immunosuppressive and anti-inflammatory: reduction of macrophage phagocytic function, reduction of NK cell activity, interference with antigen presentation, decreased activation and proliferation of T lymphocytes, reduction in cell-mediated (T_h1) T cell responses, increases lymphocyte apoptosis, disruption of B lymphocytes differentiation into plasma cells	Acute inflammation	Sepsis, microbial infection, chronic inflammation, tumor metastasis
Lidocaine	Neutrophils, endothelial cells	Anti-inflammatory: Reduced oxidative burst in phagocytes, stabilization of endothelial membranes, reduced PG production, reduced neutrophil adhesion and ROS production	Endotoxemia, ALI, ischemia and reperfusion injury	

TLR, Toll-like receptor; NF, nuclear factor; VILI, ventilator-induced lung injury; ALI, acute lung injury; COX, cyclooxygenase; iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; NK, natural killer; TNF, tumor necrosis factor; PG, prostaglandin.

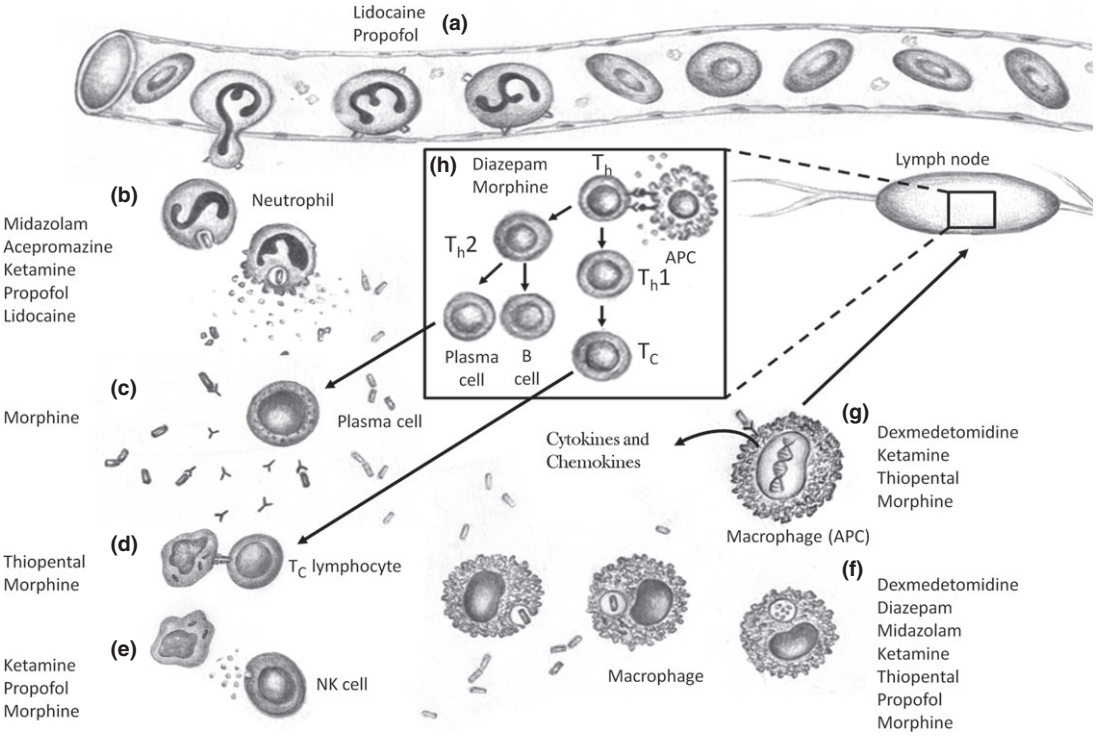

Figure 1 The immunomodulatory effects of injectable anesthetic drugs as described in Table 1 on the immune response to microbial invasion. (a) Extravasation of a neutrophil. Neutrophils roll (mediated by selectins), tether (mediated by E-selectin), and adhere to endothelial cells (mediated by intracellular adhesion molecules, ICAM), then diapedese between endothelial cells (mediated by platelet endothelial cell adhesion molecule, PECAM) out of the blood vessels. (b) Neutrophils phagocytose pathogens and produce reactive oxygen species (ROS). (c) Plasma cells release antibodies to neutralize antigens. (d) Cytotoxic T lymphocytes (T_C) recognize non-self or stress peptides presented by infected or dysfunctional cells, respectively, on their major histocompatibility complex 1 (MHC1) receptors. Once an abnormal cell is recognized, the T_C lymphocyte releases cytotoxins to induce apoptosis, resulting in the cell's death. (e) Natural killer (NK) cells function similarly to T_C lymphocytes, however, they can recognize abnormal cells with or without presentation on the MHC1 receptors. (f) Macrophages phagocytose pathogens and kill them in phagosomes via respiratory burst. (g) Macrophages recognize non-self molecular patterns with pattern recognition receptors leading to activation of intracellular signaling, upregulation of appropriate gene expression (e.g. nuclear factor kappa B (NFκB) pathway), and release of chemokines and cytokines. (h) Antigen presenting cells (APC), such as macrophages, travel through the lymph to a lymph node where they present their antigen to naïve T helper (T_h) cells. A T_h1 response results in the production of cytotoxic T cells (T_C) to generate a cell-mediated response. A T_h2 response results in the production of B cells and plasma cells to generate a humoral or antibody-mediated response.

response involves the recognition of foreign entities that have invaded the body via pattern recognition receptors and the initial local response that is mounted by innate immune cells such as neutrophils, macrophages, and natural killer (NK cells) and local adaptive immune cells such as cytotoxic T lymphocytes. These innate immune cells work to neutralize foreign entities in a non-specific manner using phagocytosis and oxidative burst (neutrophils and macrophages), production of reactive oxygen species (neutrophils), and production of cytotoxins that induce apoptosis (cytotoxic T lymphocytes and NK cells). Additional non-cellular responses such as activation of the complement system, coagulation cascade, and arachidonic acid pathway, along with production of acute phase proteins in the liver, are also activated during the initial immune response.

As part of the initial immune response, antigen presenting cells such as macrophages, dendritic cells, mast cells, and B lymphocytes sample the environment for foreign antigens and other non-self molecular patterns. When a foreign antigen or molecular pattern is recognized by the antigen presenting cell's pattern recognition receptor, pathways are activated that cause it to propagate the innate immune response via cytokine and

chemokine release and to activate the adaptive immune response via antigen presentation within nearby lymphocytes.

Within the lymphocytes, naïve T lymphocytes transform into helper T (T_h) lymphocytes of two different varieties, T_h1 and T_h2, depending on the type of antigen presented. A T_h1 response is generated when intracellular aberrations are detected, resulting in the production of cytotoxic T cells that kill abnormal cells directly. Alternatively, a T_h2 response is generated when extracellular aberrations are detected, resulting in the production of B lymphocytes and plasma cells that use antibodies to neutralize antigens. These adaptive immune responses take days to mount, so they are critical for the neutralization of ongoing threats, such as a microbial infection.

Multiple literature searches were performed from March 2012 through November 2013 using online databases including PubMed and Google Scholar. Relevant anesthetic and immune terms were used to search databases without year published or species constraints. Initial searches used broad terms such as 'anesthesia and immune response.' Additional searches using more specific key terms such as a drug name, disease process, immune cell, species, or authors' last names were used to obtain information for specific topics. Review articles were used as a source for additional relevant articles and provided a basis for more specific literature searches using online databases. The online databases for Veterinary Anaesthesia and Analgesia and the Journal of Veterinary Emergency and Critical Care were searched by issue from 2000 to 2013 for relevant articles.

Immunomodulation by injectable sedative and anesthetic agents

Sedatives and tranquilizers

Alpha$_2$-adrenergic agonists

The effect of α_2-adrenergic agonists on the immune system is postulated to be mediated by stimulation of sympathetic adrenergic receptors on immune effector cells such as macrophages (Flierl et al. 2009). The majority of investigations into the modulation of inflammatory processes by α_2-adrenergic receptor agonist drugs have focused on dexmedetomidine due to its potential for clinical use in critically ill human patients.

Many studies report that α_2-adrenergic receptor agonist drugs demonstrate anti-inflammatory effects in models of acute inflammation, such as sepsis and acute lung injury (ALI; Yang et al. 2008; Qiao et al. 2009; Wu et al. 2013; Chen et al. 2014). Specifically, Yang et al. demonstrated that an intravenous (IV) infusion of dexmedetomidine (5.0 μg kg^{-1} $hour^{-1}$) significantly attenuated pulmonary inflammation associated with ventilator-induced lung injury (VILI) when using 20 mL kg^{-1} tidal volume (V_T) in rats. The anti-inflammatory effects of dexmedetomidine were ameliorated by the simultaneous administration of yohimbine, suggesting that the anti-inflammatory effects may be due to the agonist effects of dexmedetomidine at α_2- adrenergic receptors. Additionally, anti-inflammatory effects were not apparent at lower infusion rates of dexmedetomidine (0.5 or 2.5 μg kg^{-1} $hour^{-1}$), suggesting that the effects of dexmedetomidine on inflammation are dose-dependent (Yang et al. 2008). A dose-dependent effect of dexmedetomidine on inflammation has been demonstrated in a dog model of VILI. In that study, the highest dose (2.0 μg kg^{-1} $hour^{-1}$) ameliorated lung inflammation, while the lowest dose (0.5 μg kg^{-1} h^{-1}) had little effect (Chen et al. 2014). Qiao et al. evaluated the effects of higher infusion rates of dexmedetomidine (5.0 μg kg^{-1} $hour^{-1}$) in a rat cecal-ligation-puncture sepsis model and found that dexmedetomidine reduced systemic tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 cytokine concentrations, and reduced early mortality.

The anti-inflammatory effects of dexmedetomidine may also be independent of agonism of α_2-adrenergic receptors. In a cecal-ligation-puncture model of sepsis, rats treated with either 10 or 20 μg kg^{-1} of dexmedetomidine intraperitoneally had decreased IL-6 and TNF-α concentrations, decreased activity of nuclear factor kappa B (NFκB), and Toll-like receptor (TLR) 4/Myeloid differentiation primary response gene 88 (MyD88) expression was suppressed, suggesting that modulation of the TLR4-NFκB pathway plays a role in the anti-inflammatory effects of dexmedetomidine (Wu et al. 2013).

Compared to lorazepam sedation, dexmedetomidine sedation of critically ill patients was associated with a decrease in the number of days of mechanical ventilation, a reduction in brain dysfunction, and improved survival (Pandharipande et al. 2010). The authors of that study proposed that the difference in outcomes between patient groups could be produced

from drug effects on macrophages because it has been shown in other studies that benzodiazepines inhibit, and α_2-adrenergic agonists promote, macrophage phagocytic function *in vitro* (Weatherby et al. 2003; Kim et al. 2006; Pandharipande et al. 2010). The conclusion that the immunomodulatory effects of α_2-adrenergic receptor agonists are mediated primarily by macrophages during acute inflammation is reasonable given that α_2-adrenergic agonists (xylazine, dexmedetomidine, and clonidine) apparently have no effect on neutrophil chemotaxis, phagocytosis, or superoxide production *in vitro* (Nishina et al. 1999).

Benzodiazepines

Benzodiazepines have a suppressive effect on the innate and adaptive immune response, especially when used chronically (Sanders et al. 2009). Following midazolam administration to horses, neutrophil and peritoneal macrophage pathogen phagocytosis and phagocyte oxidative burst were reduced *ex vivo* (Massoco & Palermo-Neto 2003). Treatment with midazolam was also associated with a decrease in the upregulation of proinflammatory genes, including cyclooxygenase 2 (COX2) and inducible nitric oxide synthase (iNOS), after exposure to lipopolysaccharide (LPS) in a human macrophage cell culture line (Kim et al. 2006). Diazepam affects the adaptive immune response by inhibiting lymphocyte proliferation (Huemer et al. 2010). Benzodiazepines, at clinically relevant doses, inhibit neutrophil apoptosis *in vitro* (Goto et al. 2003) which could have implications for the pathophysiology of sepsis where delayed neutrophil apoptosis may contribute to the dysregulation of the systemic immune response (O'Brien & Kirby 2008).

Phenothiazines

Phenothiazines have anti-oxidant effects that may result in immunomodulation. When the effect of acepromazine on the production of reactive oxygen species (ROS) was evaluated *in vitro* using equine neutrophils, ROS production was reduced in a dose-dependent manner (Sandersen et al. 2011). In another study, administration of acepromazine or promethazine to horses resulted in a significant decrease in ROS production in activated neutrophils *ex vivo* compared to untreated horses (Péters et al. 2009). Based on the lack of *in vivo* data, the clinical significance of the studies reported here is unknown. Interestingly, phenothiazines are under intense investigation as human anti-tubercular drugs, including multi-drug resistant *Mycobacterium tuberculosis,* because they inhibit NADH:quinone oxidoreductase, thereby interfering with oxidation-reduction reactions within the bacterium (Warman et al. 2013).

Injectable anesthetic agents

Ketamine

Ketamine is considered to have anti-inflammatory and immunosuppressive effects, although the magnitude of its effect on modulating the immune system in clinical cases is speculative (Liu et al. 2012). Ketamine administration reduced total natural killer (NK) cell number and activity leading to increased lung tumor metastasis in rat models (Melamed et al. 2003; Estes et al. 2009). However, to the authors' knowledge, there are no clinical reports documenting increased tumor metastasis in patients treated with ketamine.

Ketamine exerts its anti-inflammatory effects by suppression of neutrophil chemotaxis and superoxide formation (Zahler et al. 1999; Lu et al. 2010) and by reducing pro-inflammatory cytokine production, including TNF-α, IL-1β, and IL-6, and reducing oxidative burst in macrophages (Chang et al. 2005, 2010; Chen et al. 2009). The anti-inflammatory effects of ketamine exerted during septic processes may be, at least partially, mediated by decreasing TLR4 expression leading to decreased NFκB expression and decreased pro-inflammatory cytokine production (Yu et al. 2007). Similarly, to the authors' knowledge, no clinical studies have evaluated the use of ketamine in septic patients, human or veterinary, though improved survival has been demonstrated following ketamine administration in multiple rodent models of sepsis (Liu et al. 2012).

The effects of ketamine on the immune system in LPS models of inflammation are variable. The effect of racemic ketamine, used at a sub-anesthetic infusion rate (1.5 mg kg^{-1} $hour^{-1}$), failed to reduce LPS-induced proinflammatory cytokine production, including TNF-α and thromboxane B2, concentration in the blood in conscious healthy horses administered LPS (Alcott et al. 2011). Alternatively, ketamine inhibited LPS-induced production of pro-inflammatory cytokines (IL-6, IL-8 and TNF-α) in an equine macrophage cell line (Lankveld et al. 2005)

and human whole blood *in vitro* (Kawasaki et al. 1999). Similarly, in mice challenged with LPS, the administration of intra-peritoneal ketamine, in addition to 0.2–0.5% sevoflurane, reduced TNF-α production by and phagocytic capacity of Kupffer cells (Takahashi et al. 2010). It is possible that ketamine and sevoflurane had additive anti-inflammatory effects in this study (Rodríguez-González et al. 2013).

Ketamine may also exert protective effects, both locally and remotely, after organs are subjected to ischemia-reperfusion injury. In a rat intestinal ischemia-reperfusion injury model, ketamine administration attenuated intestinal damage when administered intra-peritoneally at a dose >12.5 mg kg^{-1} (Guzmán-De La Garza et al. 2010). In a rat model of renal ischemia-reperfusion injury, ketamine administration significantly reduced renal oxidative injury (Dogan et al. 2010). In a rabbit hepatic ischemia-reperfusion injury model, a single small dose of ketamine (0.5 mg kg^{-1}) administered 10 minutes prior to ischemia significantly decreased remote ALI (Shen et al. 2011). Based on the ability of ketamine to alter neutrophil function, as discussed above, it is not surprising that it exerts protective effects against ischemia-reperfusion injury in animal models, as neutrophil accumulation is associated with the adverse effects within tissues subjected to ischemia and reperfusion.

Barbiturates

Thiopental has immunosuppressive effects on T lymphocytes, inhibits TNF-α activation of the NF-κB pathway, and potentially increases the risk for nosocomial infection when used long term (Corrêa-Sales et al. 1997; Loop et al. 2003). Recently, barbiturates have been evaluated for their immunomodulatory properties in the face of endotoxemia and ischemia-reperfusion injury. In separate rodent LPS models, thiopental and pentobarbital reduced platelet tissue factor, a primary activator of coagulation due to inflammation, and TNF-α, respectively (Yang et al. 2007; Hartmann et al. 2009). Additionally, injection of sodium thiopental intra-peritoneally into rats resulted in decreased phagocytic activity of peritoneal macrophages (Salman et al. 1998). In a rat model of renal ischemia-reperfusion injury, thiopental significantly reduced renal oxidative injury (Dogan et al. 2010). The use of barbiturates in veterinary anesthesia is now limited by their availability in some countries.

Propofol

Propofol has been investigated for its potential immunomodulatory effects when used as a general anesthetic and when used at sub-anesthetic dosages. Overall, it is considered to have anti-oxidant and anti-inflammatory effects (Sanders et al. 2009). In mice, propofol suppressed *in vitro* dendritic cell prostaglandin E_2 (PGE_2) production, an end-product of arachidonic acid metabolism, and decreased PGE_2-mediated vasodilation, hyperalgesia, and fever (Inada et al. 2011). The immunomodulatory ability of propofol may be enhanced by preservatives and carriers such as ethylenediaminetetraacetic acid (EDTA) and fat emulsion due to their anti-inflammatory effects and neutrophil suppression, respectively (Heine et al. 1996; Haitsma et al. 2009).

Propofol may inhibit the pulmonary immune response to parenterally administered LPS (Gao et al. 2004; Gu et al. 2012). Cultured pulmonary epithelial cells were protected from LPS-induced apoptosis and autophagy by propofol (Gu et al. 2012). In a rat endotoxic shock model, propofol attenuated markers of inflammation and oxidation in bronchoalveolar lavage (BAL) fluid and was associated with improved survival (Gao et al. 2004). The exact mechanism by which propofol protects the lungs is unknown, but is likely related to its systemic anti-inflammatory properties.

Propofol may protect against ALI following intestinal ischemia and reperfusion injury through reduction in intracellular adhesion molecule-1 (ICAM-1) expression, which would, theoretically, reduce neutrophil influx into the lung (Hu et al. 2005). In a rabbit cardiopulmonary by-pass model, propofol reduced the effects of cardiac ischemia-reperfusion injury, but was not as effective as isoflurane (Asgeri et al. 2011). In rats, propofol significantly reduced subsequent oxidative injury in a renal ischemia-reperfusion injury model (Dogan et al. 2010) and reduced neuronal autophagy in a cerebral ischemia-reperfusion injury model that resulted in improved cell survival (Cui et al. 2012). In addition, propofol attenuated ALI following intestinal ischemia-reperfusion in rats (Vasileiou et al. 2012).

The effects of propofol on the adaptive immune response have been investigated, and in particular for its potential role as an anti-tumor therapy. In a cell culture model using murine peritoneal macrophages and NK cells, propofol suppressed peritoneal macrophage PGE_2 production resulting in increased

interferon gamma (IFN-γ) production by NK cells (Inada et al. 2010). Suppression of PGE_2 has implications in the development of anti-tumor therapies because of its positive effect on NK cell function, which is important for recognition and destruction of tumor cells. In an *in vivo* model, rats were anesthetized for 1 hour with ketamine, thiopental, halothane, or propofol, and then administered NK-susceptible tumor cells intravenously following anesthesia (Melamed et al. 2003). Rats anesthetized with propofol maintained normal NK cell activity, had decreased numbers of tumor cells, and reduced lung metastases compared to rats in all other anesthetic groups. Rats anesthetized with ketamine had the most lung metastases and the second greatest reduction in NK cell activity after thiopental (Melamed et al. 2003).

Opioids

It is well recognized that opioids, specifically morphine, are immunosuppressive, although the exact mechanisms by which they modulate the immune system are incompletely understood (Sanders et al. 2009; Odunayo et al. 2010; Roy et al. 2011). In addition, some opioids (e.g. morphine) exert greater immunosuppressive effects than others (e.g. tramadol; Sacerdote et al. 2000). The innate and adaptive immune suppression caused by opioids is independent of their anti-nociceptive effects and is probably mediated by μ opioid receptors expressed on immune cells, including macrophages, neutrophils, NK cells, and lymphocytes (Shavit et al. 1984; Roy et al. 1998; Sanders et al. 2009; Odunayo et al. 2010). In addition, opioids act on opioid receptors in the central nervous system and may alter neuroendocrine and autonomic functions to cause immunomodulation. These effects are summarized in a review article and are beyond the scope of this article (Odunayo et al. 2010). Some immunosuppressive functions of opioids are amplified following sympathetic activation, resulting in catecholamine and corticosteroid release by κ and δ receptor activation (Sanders et al. 2009; Roy et al. 2011).

Morphine, especially when used chronically, suppresses the innate immune system by inhibiting cytokine secretion, interfering with leukocyte recruitment, and decreasing bacterial clearance by inhibiting macrophage-mediated phagocytosis (Choi et al. 1999; Martin et al. 2010a; Roy et al. 2011; Ninkovic & Roy 2012). In particular, morphine administration, both acute and chronic, may have a negative effect on wound healing (Rook et al. 2009; Martin et al. 2010a,b). Morphine, especially when used chronically, suppresses the adaptive immune system by interfering with antigen presentation, preventing activation and proliferation of T lymphocytes and decreasing cell-mediated T cell responses, increasing lymphocyte apoptosis, and interfering with the differentiation of B lymphocytes into antibody-secreting plasma cells (Börner et al. 2009; Sanders et al. 2009; Roy et al. 2011; Brown et al. 2012; Mizota et al. 2013). Therefore, the use of opioids (morphine) may be advantageous early in a disease process to decrease inflammation, such as in equine septic arthritis (van Loon et al. 2010) but, because morphine also suppresses immune responses after the initial inflammatory stage, its administration may lead to increased infection rates (Roy et al. 2011).

Opioids exert a variable effect on the immune response to sepsis and infection. In general, morphine administration, especially when used chronically, potentiates infection and interferes with the innate immune response generated to control sepsis (Ocasio et al. 2004; Odunayo et al. 2010; Roy et al. 2011; Banerjee et al. 2013). In addition, it may potentiate LPS-induced clinical signs by decreasing an animal's tolerance to LPS, a protective mechanism to prevent an excessive, and possibly counterproductive, response to LPS by the innate immune system (Banerjee et al. 2013). Alternatively, cardiovascular protective effects of buprenorphine have been demonstrated in swine and rat models of sepsis (Donaldson et al. 1988; Tseng & Tso 1993). In two separate rat cecal-ligation-puncture models, tramadol, buprenorphine, and fentanyl had little to no effect on measured inflammatory parameters or survival (Hugunin et al. 2010; Nardi et al. 2013). Slow-release morphine potentiated the virulence of *Pseudomonas aeruginosa* in mice (Babrowski et al. 2012). Increased mortality has been associated with the chronic use of morphine in animals infected with *Streptococcus pneumonia*, *Salmonella typhimurium*, *Salmonella enterica*, *Toxoplasma gondii*, and *Listeria monocytogenes* (Sanders et al. 2009; Roy et al. 2011). Perhaps caution should be exercised when choosing to administer opioids, especially morphine, to immunocompromised patients or to patients experiencing infectious processes, although the negative effect of pain on the activity of the immune system cannot be ignored.

The effect of opioids, especially morphine, on tumor growth and metastasis has been investigated

and reviewed extensively (Sacerdote et al. 2000; Bimonte et al. 2013; Mao et al. 2013). The reduction in T lymphocyte population, particularly cytotoxic T lymphocytes, with chronic opioid use may inhibit the adaptive immune response to tumor formation (Sanders et al. 2009; Bimonte et al. 2013). Morphine has been shown to have differing effects on tumor growth, and these effects are thought to be exerted by μ receptor activation of cell growth or apoptosis pathways (Gupta et al. 2002; Sasamura et al. 2002; Iglesias et al. 2003; Bimonte et al. 2013; Mao et al. 2013). In addition, morphine may contribute to tumor metastasis via increased angiogenesis that may be mediated, at least in part, by increased COX2 and PGE_2 concentrations in tumor cells (Gupta et al. 2002; Farooqui et al. 2007; Bimonte et al. 2013; Mao et al. 2013). Moreover, treatment with the COX2 inhibitor, celecoxib, ameliorated the increase in COX2, PGE_2, and angiogenesis, reduced tumor growth weight, and reduced metastasis associated with chronic morphine administration in a mouse model of breast cancer (Farooqui et al. 2007). Therefore, co-administration of non-steroidal anti-inflammatory drugs with opioids may reduce the deleterious effects of opioid administration to cancer patients.

Local anesthetics

Lidocaine has been evaluated extensively for its well-recognized immunomodulatory effects in many disease processes, including endotoxemia and ischemia-reperfusion injury (Mikawa et al. 1994; Sevimli et al. 2004; Jinnouchi et al. 2005; Xu et al. 2006; Cook et al. 2009a). In one study in anesthetized rabbits, lidocaine pre-treatment attenuated the pulmonary inflammatory response to *Escherichia coli* endotoxin (Mikawa et al. 1994). Similarly, lidocaine administration reduced remote lung injury due to intestinal ischemia-reperfusion injury in horses (Montgomery et al. 2014). Using an *ex vivo* model with rat lung, in which ALI was induced with *N*-formyl-L-leucin-methionyl-L-phenylalanine (fMLP, a component of the bacterial cell wall), lidocaine and mepivicaine reduced the release of endothelin-1 and decreased the model-created acute neutrophilic alveolitis (Konrad et al. 2006).

The anti-inflammatory effects of lidocaine, in the presence of LPS, may be due to its inhibition of pathways required for phagocyte respiratory burst, such as impairing up-regulation of cytochrome b558, an electron transport molecule for NADPH, and priming of NADPH oxidase. If phagocyte respiratory burst is impaired, the ensuing collateral damage from that process would be decreased resulting in a reduction of subsequent inflammatory cell influx (Jinnouchi et al. 2005). Additionally, expression of high mobility group box 1, a marker of inflammation due to sepsis, and activation of NFκB were reduced in various tissues in rats treated with lidocaine, compared to controls, after cecal ligation and puncture (Wang et al. 2013).

Although the exact mechanism of action of lidocaine on the immune system is unknown, it has been shown to affect neutrophil function *in vitro*, stabilize endothelial cell membranes, decrease prostaglandin production in injured tissues, and have anti-apoptotic effects (Mikawa et al. 1994; Lan et al. 2004; Sevimli et al. 2004; Xu et al. 2006; Cook et al. 2009a,b; Kaczmarek et al. 2009; Maeda et al. 2010). Cook et al. (2009b) demonstrated that lidocaine did not affect equine neutrophil migration *in vitro*. Lan et al. (2004) and Ploppa et al. (2010) demonstrated, in separate studies, that lidocaine decreased neutrophil cluster differentiation (CD) 18/CD11b receptor expression, a receptor necessary for neutrophil adhesion, after hypoxic-reoxygenation and oxidative burst induction in whole blood, respectively. Similarly, Maeda et al. (2010) found a reduction in CD11b expression, reduced adhesion to vascular endothelium, and decreased ROS production after canine granulocytes were incubated with lidocaine *in vitro*. It is possible that the benefits of lidocaine are due to an indirect effect on white blood cells, specifically neutrophils, by preventing the priming or activation of those cells (Mikawa et al. 1994; Lan et al. 2004; Cook et al. 2009b; Kaczmarek et al. 2009; Ploppa et al. 2010).

Comparison of immunomodulatory properties between inhaled and injectable anesthetic protocols

Recent research has demonstrated a distinct difference in the effects of volatile anesthetic agents and various injectable anesthetic agents on the immune response associated with anesthesia. Volatile anesthetics consistently protect against the effects of lung inflammation-inducing models, whereas injectable anesthetics do not consistently offer protection against local- or remote-induced lung inflammation. In a clinical trial evaluating human patients undergoing one-lung ventilation during thoracic surgery, mechanical ventilation induced alveolar

inflammation (increased TNF-α, IL-8, IL-1β within BAL fluid) that was suppressed by sevoflurane and desflurane, but not by propofol (Schilling et al. 2011). In a similar study, post-operative morbidity was reduced in sevoflurane anesthetized and ventilated patients compared to those anesthetized with propofol and mechanical ventilation (De Conno et al. 2009). In mice, sub-anesthetic concentrations of isoflurane (0.5 minimum alveolar concentration, 0.5 MAC) improved the activities of superoxide dismutase and catalase within the lung and serum, thereby decreasing lung injury and improving survival, compared to pentobarbital (Mu et al. 2010). Similarly, isoflurane globally improved the recovery from cardiac ischemia compared to propofol in a rabbit cardiopulmonary by-pass model (Asgeri et al. 2011).

Alternatively, in humans, the systemic immunological effect of TIVA using propofol with sufentanil was compared to partial intravenous anesthesia (PIVA) using sevoflurane and thiopental in patients undergoing elective lumbar discectomy (Schneemilch & Bank 2001). In the PIVA groups, IL-6 was significantly increased upon induction of anesthesia and interleukin-1 receptor antagonist (IL-1RA) and interleukin-2 receptor antagonist (IL-2RA) were decreased compared to TIVA. These findings suggest that this particular PIVA protocol induced greater pro-inflammatory effects compared to the TIVA protocol. In another human study, TIVA using propofol and fentanyl or PIVA using isoflurane and fentanyl were evaluated for their effects on pulmonary alveolar macrophages (PAMs) in mechanically ventilated (V_T 8–10 mL kg^{-1}) patients undergoing non-abdominal and non-thoracic surgical procedures lasting >6 hours and paralyzed with vecuronium (Kotani et al. 1999). All pro-inflammatory cytokine expression, except IL-6, increased with the duration of anesthesia, but compared to propofol, isoflurane resulted in a greater increase in IFN-γ and IL-8 gene expression from PAMs isolated from BAL fluid. All other cytokine gene expression including IL-1β, Il-6, and TNF-α were not different between groups. Additionally, there was a slight, though significant, increase in total neutrophils retrieved from BAL fluid in patients anesthetized with isoflurane compared to propofol; although, there was a significant increase in neutrophil count in BAL fluid over the course of anesthesia in both groups. As with other studies, the confounding effect of surgical procedures and mechanical ventilation on the pulmonary immune response cannot be ignored and may have contributed to the differences between groups in that study.

Interestingly, there appears to be a difference in the results from the studies discussed above based on when studies were performed. Studies performed more than 10 years ago tended to find increased inflammation occurring with inhalation anesthesia compared to TIVA, whereas more recent studies have demonstrated a greater protective effect of inhaled fluorinated hydrocarbon anesthetics compared to injectable anesthetics. The discrepancy in findings among studies could be based on the advancement of immunologic assays, such as quantitative polymerase chain reaction (qPCR), or it could be due to an evolution in anesthetic protocols.

In anesthetized, mechanically ventilated pigs, the pulmonary inflammatory and oxidative injury was greater in the pigs anesthetized with sevoflurane or desflurane than in the pigs anesthetized with propofol or thiopental (Takala et al. 2004; Kalimeris et al. 2011). The reason for the discrepancy in these authors' findings compared to many other studies is not readily apparent based on their reported protocols, but may be due to species differences. For example, some species including horses, pigs, cattle, sheep, rabbits and cats have pulmonary intravascular macrophages (PIMs; Parbhakar et al. 2004). PIMs are intimately involved in the pulmonary immune response although they have not been extensively studied in anesthetized patients. Taken together, this species difference highlights the need for species-specific research to elucidate differences in the pulmonary response to various anesthetic protocols.

In ponies anesthetized with halothane, isoflurane, or thiamylal IV and administered oxygen, structural changes in PIMs resulted in platelet trapping (Atwal & McDonell 2005). These changes also occurred with thiamylal suggesting that either thiamylal exerted effects on the lung despite IV administration, or more likely, that inhaling oxygen has an effect on the pulmonary immune response. The clinical significance of these structural changes is unknown, but the authors of that study proposed that the PIMs activated the platelets as part of the inflammatory cascade (Atwal & McDonell 2005). To the authors' knowledge, no other studies designed to assess the pulmonary or systemic immune response to anesthetics have been performed in horses.

The difference in systemic effects between TIVA and inhalation anesthesia are inconsistent. In a mouse liver transplant model, there was no

difference in the systemic inflammatory response between TIVA with xylazine-ketamine-acepromazine compared to isoflurane (He et al. 2010). Similarly, in a swine hemorrhagic shock model, there was no difference in the production of inflammatory cytokines measured in the serum between swine anesthetized with ketamine-midazolam-buprenorphine or swine anesthetized with isoflurane (Englehart et al. 2008). Alternatively, in human patients undergoing open cholecystectomy and anesthetized with either TIVA using propofol-remifentanil or isoflurane, patients in the TIVA group had significantly lower proinflammatory cytokine, IL-6 and TNF-α, concentrations in their serum at the end of the surgical procedure (Ke et al. 2008).

In regard to the stress response induced by anesthesia, TIVA may be superior to inhalation anesthesia in reducing hypothalamic-pituitary-adrenal axis (HPAA) activation. In the study by Schneemilch & Bank discussed above, cortisol, epinephrine, and norepinephrine concentrations were significantly increased in the inhaled anesthetic group compared to the TIVA group indicating that the HPAA stress response was enhanced in the group administered inhaled anesthetics (Schneemilch & Bank 2001). The stress response to anesthesia has also been evaluated in ponies anesthetized with a TIVA protocol using detomidine, ketamine, and guaifenesin or halothane. Similar to humans, it was found that TIVA elicited a decreased stress response compared to halothane in ponies (Luna et al. 1996). Immunomodulation by suppression of the HPAA is important to consider when critically evaluating any study investigating the immune response to anesthetics; however, a full evaluation of this phenomenon is beyond the scope of this review.

Conclusion

In the future, anesthetic protocols may be chosen not only for their anesthetic and analgesic effects but also for their immunomodulatory effects. There is a growing body of evidence suggesting that the choice of anesthetic is important when considering the underlying disease for which an animal is being anesthetized (Kurosawa & Kato 2008; Sanders et al. 2009; Odunayo et al. 2010; Mao et al. 2013). For example, immunosuppressive effects may be desirable in anesthetizing a septic horse for exploratory laparotomy, whereas an immunosuppressive protocol for anesthesia of a dog for tumor removal is contra-indicated. In summary, the immunomodulatory effects of the entire anesthetic protocol should be considered when anesthesia is required for a particular patient.

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