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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.