Anti-Inflammatory Effects of Intravenous Anesthetics on Endotoxemia

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Abstract: Endotoxemia and endotoxin shock are common problems in the intensive care unit and carry a very high mortality rate. Endotoxemia increases production of endogenous cytokines, including tumor necrosis factor-alpha (TNF-alpha), interleukin-1 (IL-1), IL-6, and IL-8. Not only endotoxin but also cytokines have been implicated as important factors in the pathophysiology of endotoxic shock and the development of cardiovascular dysfunction in endotoxemia. Recently, it has been shown both *in vitro* and *in vivo* that several intravenous anesthetics have anti-inflammatory effects. Thiopental and ketamine inhibit the endotoxin-induced TNF-alpha, IL-1 and IL-8 responses and increase IL-10 release *in vitro*. Ketamine prevent the pro-inflammatory cytokine (TNF-alpha, IL-1, and IL-6) responses to endotoxemia *in vivo*. Moreover, thiopental and ketamine suppress the activation of nuclear factor-kappa B induced by endotoxin. Propofol have been proven its anti-inflammatory effects on endotoxemia both *in vitro* and *in vivo*, but several studies have shown that propofol does not have any anti-inflammatory effects and deteriorates the inflammatory response to endotoxemia. This article reviews the anti-inflammatory effects of intravenous anesthetics on endotoxemia and endotoxic shock.

Keywords: Anesthetics, Cytokine, Endotoxin, Inflammation, Lipopolysaccharide, Nuclear factor-kappa B, Shock.

INTRODUCTION

Endotoxemia and endotoxic shock are major diagnostic and therapeutic problems in the intensive care unit (ICU), and carry a very high mortality rate (40-50%). Endotoxemia increases production of endogenous cytokines, including tumor necrosis factor–alpha (TNF-alpha), interleukin–1 (IL-1), IL-6 and IL-8. Not only endotoxin but also cytokines have been implicated as important factors in the pathophysiology of endotoxic shock and the development of cardiovascular dysfunction in endotoxemia [1-4].

Critically ill patients with endotoxemia are under physical and mental stress. Endotoxemic patients who have supported by the mechanical ventilation and have received pre- or post operation suffer an especially high degree of stress because of pain and anxiety. An important objective in the management of these patients is thus to achieve an adequate level of sedation and analgesia [5,6]. Intravenous anesthetics such as thiopental, midazolam, ketamine, and propofol are widely used for these purposes. Moreover, surgical operations on severely endotoxemic patients have been increasing and it may be difficult to induce and maintain anesthesia in these cases. It has recently been shown that several intravenous anesthetics modify some immune responses *in vitro* and *in vivo*. This article reviews the anti-inflammatory effects, both *in vitro* and *in vivo*, of intravenous anesthetics on endotoxemia and endotoxic shock.

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THE BASIS OF ENDOTOXIN RESPONSE

Endotoxin or lipopolysaccharide (LPS) is the major virulent component of Gram-negative bacteria and one of the most potent microbial initiators of inflammation. Chemically, LPS consists of a polysaccharide O-chain separated from the highly conserved lipid A, a diglicosamine-based acylated phospholipid, by a relatively conserved core region, which is made up of a small number of oligosaccharide subunits and 3-Deoxy-D-manno-2-Octulosonic Acid. This polysaccharide chain shows a high variability between individual gram-negative bacteria and forms the chemical basis for the serotype-specific O-antigen.

The mechanism of cell responses that LPS stimulates is gradually becoming clear. LPS binds to a variety of serum proteins, which affect the macrophage-mediated pro-inflammatory response [7]. Among those proteins, LPS-binding protein (LBP) is the most important and binds LPS to the macrophage cluster determinant 14 (CD14). The LPS-LBP interaction with CD 14 initiates recognition of LPS, which then leads to the rapid activation of an intracellular signalling pathway [8-10]. However, multiple lines of evidence have indicated that participation of CD 14 is necessary in the early phase of the process, but not in cell signaling, because the glycosylphosphatidylinositol anchor of CD 14 does not allow signal transduction [11-13]. From the beginning, at least one of the transmembrane proteins acting in concert with CD 14 has been postulated, and recently the toll-like receptor 4 (TLR 4) has been identified as one of the candidates for transmitting the LPS signal from the membrane-bound CD 14 to the cytoplasm [14-17]. TLR 4 has MD-2 which is an adapter molecule linking LPS and TLR 4, and MD-2 plays an important function in LPS signaling [18]. Signaling by TLR 4 occurs through sequential recruitment of the adapter molecule MyD88 and

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the IL-1 receptor-associated kinase (IRAK) [19]. LPS signaling operates in a manner that is very similar to IL-1 signaling, which is initiated by the formation of a complex consisting of IL-1 and IL-1 receptor. IRAK then dissociates from the receptor and interacts with the TNF receptor associated factor 6 (TRAF6), which results in cell activation through either nuclear factor-kappa B (NF-kB) or c-Jun N-terminal kinase/stress-activated protein kinase (JNK/SAP), two systems involved in the activation of numerous inflammatory genes [20]. (Fig. (**1**)).

LBP, LPS binding protein; TLR, toll like receptor; TRAF, TNF receptor associated factor 6; IRAK, IL-1 receptor-associated kinase; NF-kB, nuclear factor-kappa B; JNK/SAP, c-Jun N-terminal kinase/stress-activated protein kinase.

Upon release from the bacterial outer membrane, LPS activates monocytes and macrophages to produce inflammatory cytokines such as TNF-alpha and IL-1, which serve as endogenous mediators of inflammation. Although cytokine production is important for the efficient control of growth and dissemination of invading pathogens, overproduction of cytokines is harmful for the host, since it may lead to multiple organ failure and death. For example, TNF-alpha causes a reduction in myocardial contractile force, biventricular dilatation, and systemic vascular resistance [21]. In animal models, TNF-alpha administration has resulted in hypotension, metabolic acidosis, hemoconcentration, diffuse pulmonary infiltrates, gastrointestinal hemorrhages, and acute tubular necrosis.

ANTI-INFLAMMATORY EFFECT OF INTRAVENOUS ANESTHETICS

Intravenous anesthetics have different anti-inflammatory effects on endotoxemia, and reports on these effects are of conflicting. The most important intravenous anesthetics in terms of their anti-inflammatory effects on endotoxemia present here.

1) Thiopental

Thiopental [5-ethyl-5- (1-methyl-butyl)-2-thiobarbituric acid] (Fig. (**2-A**)) is a derivative of barbituric acid, and is commonly used for induction of anesthesia (Fig. (**2-A**)). Thiopental binds to the gamma-aminobutyric acid (GABA) receptor, and enhances the action of GABA that correlates with anesthetic potency [22].

Several investigators have demonstrated the anti-inflammatory effects of thiopental *in vitro*. Larsen and colleagues [23] showed that thiopental inhibits LPS-stimulated TNF-alpha release in cultured human whole blood, and Nishina and colleagues [24] reported that thiopental inhibits human neutrophil functions such as chemotaxis, phagocytosis, and reactive oxygen species production *in vitro*. Moreover, it is also reported that thiopental induces anti-inflammatory cytokines such as IL-10 from LPS-stimulated mononuclear cells *in vitro* [25]. Although there were few reports about the anti-inflammatory effects of thiopental on endotoxemia *in vivo*, several studies recently have shown that thiopental inhibits the activation of transcription factor NF-kB *in vitro* [26,27].

2) Midazolam

Midazolam (Fig. (**2-B**)) is a benzodiazepine receptor agonist, commonly used in the practice of anesthesia. Because midazolam is associated with minimal cardiovascular changes and is eliminated with a half-life of 45 min in healthy volunteers [28], it is widely used for

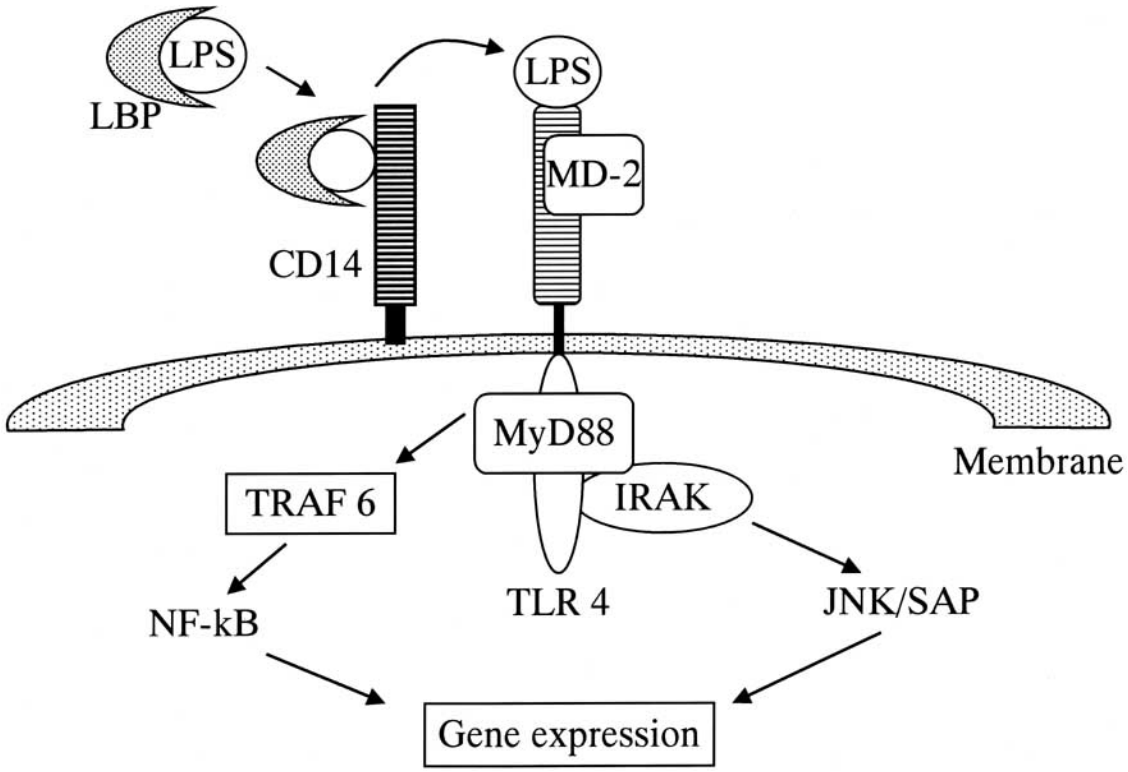

Fig. (1). Current view about LPS-stimulated macrophage activation.

sedation of critically ill patients in ICU. Midazolam has a molecular weight of 362 and is lipid-soluble at physiologic pH. It is water-soluble only in a specific buffered acid medium (pH3.5) [29]. Midazolam as well as other benzodiazepines have hypnotic, sedative, anxiolytic, amnestic, anticonvulsant, and centrally produced muscle relaxation properties.

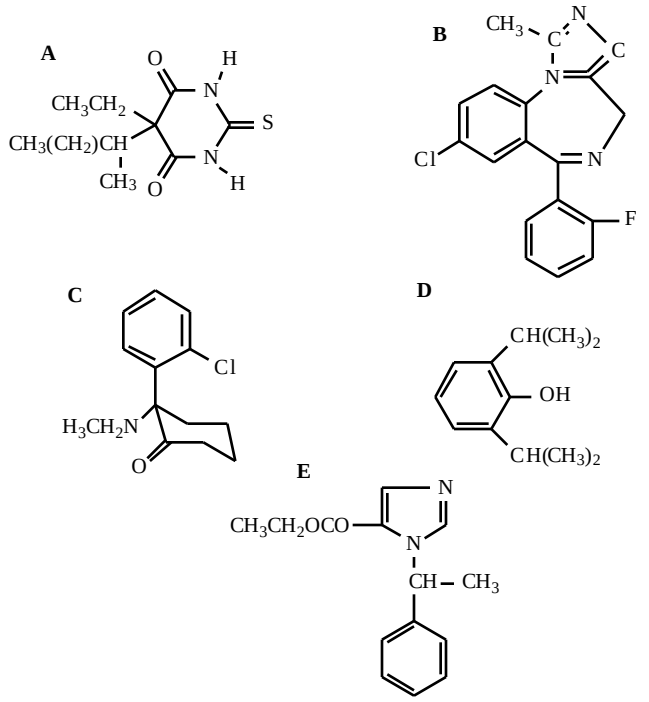

Fig. (2). The structures of five intravenous anesthetics.

A, thiopental; B, midazolam; C, ketamine; D, propofol; E, etomidate.

The *in vitro* anti-inflammatory effects of midazolam on endotoxemia have been the subjects of several reports. Taupin and colleagues [30] demonstrated that midazolam administration inhibits LPS-stimulated TNF-alpha, IL-1, and IL-6 production by monocytes isolated from peripheral blood, while Galley [31] showed that midazolam suppresses IL-8 release from human polynuclear leukocytes *in vitro*. Moreover, several studies have found that midazolam inhibits human neutrophil functions [24] and the activation of mast cells induced by TNF-alpha [32] *in vitro*, and also suppresses the expression of IL-6 mRNA in blood monoclear cells [33]. In a clinical study, Helmy and colleagues [34] found that midazolam administration suppressed the production of inflammatory cytokines TNF-alpha, IL-1, and IL-6 in critically ill surgical patients. In contrast, several investigators reported that midazolam did not alter LPS-stimulated cytokine response *in vitro* [23,25], but that it increased the intracellular concentration and mRNA of IL-8 in LPS-stimulated human leukocytes [31].

3) Ketamine

Ketamine (Fig. (**2-C**)), a phencyclidine derivative, has a molecular weight of 238. It is partially water-soluble and forms a white crystalline salt with a pKa of 7.5 [35]. Ketamine produces dose-related unconsciousness and analgesia, and has been recommended for anesthesia and sedation of septic or severely ill patients because of its stimulating cardiovascular effects. The mechanism that ketamine stimulates the circulatory system appears not to be a peripheral mechanism such as baroreflex inhibition [36,37], but rather to be central [37,38], and ketamine produces sympathetic nervous system response and release of norepinephrine [39].

There are many studies about the anti-inflammatory effects of ketamine on endotoxemia both *in vitro* and *in vivo. In vitro*, Larsen [23] and Kawasaki [40] showed that ketamine inhibited LPS-stimulated TNF-alpha, IL-1, IL-6 and IL-8 responses in human whole blood. Moreover, ketamine was found to inhibit the expression of LPS-stimulated adhesion molecules such as CD 18 and CD 62L on human neutrophils [41] and of nitric oxide synthase in LPS-stimulated rat alveolar macrophages [42]. *In vivo*, Takenaka [43] and Koga [44] demonstrated that ketamine administration suppressed TNF activity after endotoxin injection in mice and rats. In addition, a study of ours [45] also showed that ketamine suppressed IL-6 production and improved survival rate after endotoxin injection in rats. In clinical studies, ketamine administration has been shown to attenuate IL-6 response after cardiopulmonary bypass [46] and abdominal hysterectomy [47], and to suppress superoxide production by neutrophils after cardiopulmonary bypass [48]. Recently, several investigators demonstrated that ketamine suppresses LPS-stimulated NF-kB activation in human glioma cells [49] and attenuates LPS-stimulated TNF mRNA and protein responses in human whole blood [50].

4) Propofol

Propofol (Fig. (**2-D**)) belongs to a group of alkylphenols that have a hypnotic effect on animals [51]. Propofol is oily at room temperature and is insoluble in aqueous solutions but is highly lipid-soluble. Propofol is therefore formulated as a 10 mg/mL oil in water emulsion and commonly used for induction and maintenance of anesthesia. In addition, because propofol is easily titratable and offers the prospect of rapid recovery for the patient [52,53], it is used for sedation of critically ill patients in ICU.

Several investigators have proven the anti-inflammatory effects of propofol on endotoxemia both *in vitro* and *in vivo*. *In vitro*, propofol was found to inhibit IL-6 and IL-8 production by LPS-stimulated human mononuclear cells [25,31], as well as human neutrophil functions [54]. In addition, Weiss and colleagues [55] showed that propofol inhibited N-formyl-methionyl-leucyl-phenylalanine (FMLP)-induced oxidative burst formation in neutrophils. Our reports have demonstrated that propofol administration *in vivo* attenuates TNF-alpha and IL-6 responses as well as activation of neutrophils after endotoxin injection in rats [56,57]. Moreover, in a clinical study propofol anesthesia attenuated release of IL-6 in response to abdominal hysterectomy [58].

In contrast, several studies have shown that propofol does not have any anti-inflammatory effects and deteriorates the inflammatory response to endotoxemia. Larsen and colleagues [23] showed that propofol even increased the TNF-alpha response by LPS-stimulated human whole blood *in vitro*, while Helmy [34] found that propofol administration stimulated the productions of TNF-alpha, IL-

1 and IL-6 in critically ill surgical patients. Moreover, several investigators have reported that propofol increases LPS-stimulated TNF-alpha mRNA and protein responses in human whole blood [50] and IL-8 mRNA response in human leukocytes [31]. Thus, it remains unclear whether propofol has in fact anti-inflammatory effects on endotoxemia or not.

5) Etomidate

Etomidate (Fig. (**2-E**)) is an imidazole derivative [59]. Etomidate has a molecular weight of 342, is water insoluble, has been formulated with several solvents [60], and has been used for both the induction and maintenance of anesthesia. With regards to the anti-inflammatory effects of etomidate on endotoxemia, Larsen et al. [23] showed that etomidate reduced the expression density of CD 14 and increased LPS-stimulated IL-10 release *in vitro*. However, it is difficult to evaluate the anti-inflammatory effects of etomidate because of the secondary effect induced by the drug's solvent.

6) Other Intravenous Anesthetics

Many other intravenous anesthetics such as steroid anesthetics and alpha2-adrenergic agonists [61] have been used to induce anesthesia and to provide sedation and analgesia. However, few reports about the anti-inflammatory effects of these drugs to endotoxemia are available at present.

CONCLUSIONS

Many investigations have shown that intravenous anesthetics have anti-inflammatory effects on endotoxemia both *in vitro* and *in vivo*. However, several questions remain about these effects. Although some intravenous anesthetics have been found to inhibit the *in vitro* responses of LPS-stimulated cytokines, these effects are dose-dependent and it is not clear whether the dose of the drug used in these experiments is clinically relevant. At the same time, it should be remarkable that several *in vivo* studies do not support the *in vitro* findings. While most clinical studies have been small and not randomized, few of them support the idea that administration of intravenous anesthetics is clinically beneficial because of their anti-inflammatory effects on endotoxemia. Other factors, such as the inhibition of neuroendocrine stress responses by anesthetics, rather than the direct effect of anesthetics may play a role here. Further studies are needed to focus on these questions.

Many intravenous anesthetics are available for the surgical anesthesia and sedation in the ICU. The selection of a particular drug must be based on the individual patient's need for hypnosis, amnesia, and analgesia. If the anesthetics discussed here have clinically proven anti-inflammatory effects on endotoxemia and endotoxic shock, it would be highly beneficial to use intravenous anesthetics not only as anesthetics or sedative drugs but also as the therapeutic agents for endotoxemia and endotoxic shock.

REFERENCES

[1] Wintroub, B.U. *Int. J. Dermatol*., **1980**, *19*, 436.
[2] Till, G.O.; Johnson, K.J.; Kunkel, R.; Ward, P.A. *J. Clin. Invest*., **1982**, *69*, 1126.
[3] Tracey, K.J.; Beutler, B.; Lowry, S.F.; Merryweather, J.; Wolpe, S.; Milsark, I.W.; Hariri, R.J.; Fahey, T.J. 3rd.; Zentella, A.; Albert, J.D. *Science*, **1986**, *234*, 470.
[4] Minghini, A.; Britt, L.D.; Hill, M.A. *Shock*, **1998**, *9*, 210.
[5] Crippen, D.W. *Crit. Care. Clin*., **1990**, *6*, 369.
[6] Wheeler, A.P. *Chest*, **1993**, *104*, 566.
[7] Schumann, R.R. *Res. Immunol*., **1992**, *143*, 11.
[8] Lamping, N.; Dettmer, R.; Schroder, N.W.; Pfeil, D.; Hallatschek, W.; Burger, R.; Schumann, R.R. *J. Clin. Invest*., **1998**, *101*, 2065.
[9] Schumann, R.R.; Kirschning, C.J.; Unbehaun, A.; Aberle, H. P.; Knope, H.P.; Lamping, N.; Ulevitch, R.J.; Herrmann, F. *Mol. Cell Biol*., **1996**, *16*, 3490.
[10] Wright, S.D.; Ramos, R.A.; Tobias, P.S.; Ulvitch, R.J.; Mathison, J.C. *Science*, **1990**, *249*, 1431.
[11] Hedlund, M.; Svensson, M.; Nilsson, A.; Duan, R.D.; Svanborg, C. *J. Exp. Med*., **1996**, *183*, 1037.
[12] Pugin, J.; Ultevitch, R.J.; Tobias, P.S. *J. Exp. Med*., **1993**, *178*, 2193.
[13] Wright, S.D. *J. Exp. Med*., **1999**, *189*, 605.
[14] Gay, N.J.; Keith, F.J. *Nature*, **1991**, *351*, 355.
[15] Morisato, D.; Anderson, K.V. *Cell*, **1994**, *76*, 677.
[16] Smiley, S.T.; King, J.A.; Hancock, W.W. *J. Immunol*., **2001**, *167*, 2887.
[17] Medzhitov, R.; Preston-Hurlburt, P.; Janeway, Jr. C.A. *Nature*, **1997**, *388*, 394.
[18] Shimazu, R.; Akashi, S.; Ogata, H.; Nagai, Y.F.K.; Miyake, K. Imoto, M. *J. Exp. Med*., **1999**, *189*, 1777.
[19] Muzio, M.; Natoli, G.; Saccani, S.; Levrero, M.; Mantovani, A. *J. Exp. Med*., **1998**, *187*, 2097.
[20] Re, F.; Strominger, J.L. *J. Biol. Chem*., **2001**, *276*, 37692.
[21] Meldrum, D.R. *Am. J. Physiol*., **1998**, *274*, R577.
[22] Olson, R.W. *Int. Anesthesiol. Clin*., **1988**, *26*, 254.
[23] Larsen, B.; Hoff, G.; Wilhelm, W.; Buchinger, H.; Wanner, G.A.; Bauer, M. *Anesthesiology*, **1998**, *89*, 1218.
[24] Nishina, K.; Akamatsu, H.; Mikawa, K.; Shiga M.; Maekawa, N.; Obara, H.; Niwa, Y. *Anesth. Analg*., **1998**, *86*, 159.
[25] Takaono, M.; Yogosawa, T.; Okawa-Takatsuji, M.; Aotsuka, S. *Acta Anaesthesiol. Scand*., **2002**, *46*, 176.
[26] Loop, T.; Liu, Z.; Humar, M.; Hoetzel, A.; Benzing, A.; Pahl, H.L.; Geiger, K.K.; Pannen, B.H.j. *Anesthesiology*, **2002**, *96*, 1202.
[27] Ichiyama, T.; Nishikawa, M.; Lipton, J.M.; Matsubara, T.; Takashi, H.; Furukawa, S. *Brain Res*., **2001**, *911*, 56.
[28] Malacrida, R.; Fritz, M.E.; Suter, P.M.; Crevoisier, C.H. *Crit. Care Med*., **1991**, *20*, 1123.
[29] Greenblatt, D.J.; Shader, R.I.; Abernethy, D.R. *N. Engl. J. Med*., **1983**, *309*, 354.
[30] Taupin, V.; Jayais, P.; Descamps-Latscha, B.; Cazalaa, J.B.; Barrier, G.; Bach, J.F.; Zavala, F. *J. Neuroimmunol*., **1991**, *35*, 13.
[31] Galley, H.F.; Dubbels, A.M.; Webster, N.R. *Anesth. Analg*., **1998**, *86*, 1289.
[32] Bidri, M.; Royer, B.; Averlant, G.; Bismuth, G.; Guillosson, J.J.; Arock, M. *Immunopharmacolgy*, **1999**, *43*, 75.
[33] Miyawaki, T.; Sogawa, N.; Maeda, S.; Kohjitani, A.; Shimada, M. *Cytokine*, **2001**, *15*, 320.
[34] Helmy, S.A.K.; Ai-Attiyah, R.J. *Anaesthesia*, **2001**, *56*, 4.
[35] White, P.F.; Way, W.L.; Trevor A.J. *Anesthesiology*, **1982**, *56*, 119.
[36] Slogoff, S.; Allen, G.W. *Anesth. Analg*., **1974**, *53*, 704.
[37] Dowdy, E.G., Kaya, K. *Anesthesiology*, **1968**, *29*, 931.
[38] Chodoff, P. *Anesth. Analg*., **1972**, *51*, 247.
[39] Wong, D.H.W.; Jenkins, L.C. *Can. J. Anaesth*., **1974**, *21*, 57.
[40] Ivankovich, A.D.; Miletich, D.J.; Reimann, C.; Albrecht, R.F.; Zahed, B. *Anesth. Analg*., **1974**, *53*, 924.
[41] Kawasaki, T.; Ogata, M.; Kawasaki, C.; Ogata, J.; Inoue, Y.; Shigematsu, A. *Anesth. Analg*., **1999**, *89*, 665.
[42] Weigand, M.A.; Schmidt, H.; Zhao, Q.; Plaschke, K.; Martin, E.; Bardenheuer, H.J. *Anesth. Analg*., **2000**, *90*, 206.
[43] Li, C.Y.; Chou, T.C.; Wong, C.S.; Ho, S.T.; Wu, C.C.; Yen, M.H.; Ding, Y.A. *Can. J. Anaesth*., **1997**, *44*, 989.
[44] Takenaka, I.; Ogata, M.; Koga, K.; Matsumoto, T.; Shigematsu, A. *Anesthesiology*, **1994**, *80*, 402.
[45] Koga, K.; Ogata, M.; Takenaka, I.; Matsumoto, T.; Shigematsu, A. *Circ. Shock*, **1995**, *44*, 160.
[46] Taniguchi, T.; Shibata, K.; Yamamoto, K. *Anesthesiology*, **2001**, *94*, 928.

[47] Roytblat, L; Talmor, D.; Rachinsky, M.; Greemberg, L.; Pekar, A.; Appelbaum, A.; Gurman, G.M.; Shapira, Y.; Duvdenani, A. *Anesth. Analg*., **1998**, *87*, 266.
[48] Royblat, L.; Roy-Shapira, A.; Greemberg,L.; Appelbaum, A.; Shapira Y. *Pain Clin.*, **1996**, *9*, 327.
[49] Zilberstein, G.; Levy, R.; Rachinsky, M.; Fisher, A.; Greemberg, L.; Shapira, Y.; Appelbaum, A. Royblat, L. *Anesth. Analg*., **2002**, *95*, 531.
[50] Sakai, T.; Ichiyama, T.; Whitten, C.W.; Giesecke, A.H.; Lipton, J.M. *Can. J. Anesth*., **2000**, *47*, 1019.
[51] Hoff, G.; Bauer, I.; Larsen, B.; Bauer, M. *Anaesthesist*, **2001**, *50*, 494.
[52] James, R.; Glen, J.B. *J. Med. Chem*., **1980**, *23*, 1350.
[53] Carrasco, G.; Molina, R.; Costa, J.; Soler, J.M.; Cabre, L. *Chest*, **1993**, *103*, 557.
[54] Sanchez-Izquierdo-Riera, J.A.; Cabellero-Cubedo, R.E.; Perez-Vela, J.L.; Ambros-Checa, A.; Cantalapiedra-Santiago, J.A.; Alted-Lopez, E. *Anesth. Analg*., **1998**, *86*, 1219.
[55] Mikawa, K.; Akamatsu, H.; Nishina, K.; Shiga, M.; Maekawa, N.; Obara, H.; Niwa, Y. *Anesth. Analg*., **1998**, *87*, 695.
[56] Weiss, M.; Buhl, R.; Medve, M.; Schneider, E.M. *Crit. Care Med*., **1997**, *25*, 128.
[57] Taniguchi, T.; Yamamoto, K.; Ohmoto, N.; Ohta, K.; Kobayshi, T. *Crit. Care Med*., **2000**, *28*, 1101.
[58] Taniguchi, T.; Kanakura, H.; Yamamoto, K. *Crit. Care Med*., **2002**, *29*, 904.
[59] Crozier, T.A.; Muller, J.E.; Quittkat, D.; Sydow, M.; Wuttke, W.; Kettler, D. *Br. J. Anasth*., **1994**, *72*, 280.
[60] Janssen, P.A.J.; Niemegeers, C.J.E.; Schellekens, K.H.L.; Lenaerts, F.M. *Arzneimittelforschung*, **1971**, *21*, 1234.
[61] Nimmo, W.S.; Miller, M. *Contemp. Anesth. Pract*., **1983**, *7*, 83.
[62] Maze, M.; Tranquilli, W. *Anesthesiology*, **1991**, *74*, 581.

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