REVIEW

CNS Neuroscience & Therapeutics

The Experimental and Clinical Pharmacology of Propofol, an Anesthetic Agent with Neuroprotective Properties

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Propofol (2,6-diisopropylphenol) is a versatile, short-acting, intravenous (i.v.) sedative-hypnotic agent initially marketed as an anesthetic, and now also widely used for the sedation of patients in the intensive care unit (ICU). At the room temperature propofol is an oil and is insoluble in water. It has a remarkable safety profile. Its most common side effects are dose-dependent hypotension and cardiorespiratory depression. Propofol is a global central nervous system (CNS) depressant. It activates γ-aminobutyric acid ($GABA_A$) receptors directly, inhibits the *N*-methyl-D-aspartate (NMDA) receptor and modulates calcium influx through slow calcium-ion channels. Furthermore, at doses that do not produce sedation, propofol has an anxiolytic effect. It has also immunomodulatory activity, and may, therefore, diminish the systemic inflammatory response believed to be responsible for organ dysfunction. Propofol has been reported to have neuroprotective effects. It reduces cerebral blood flow and intracranial pressure (ICP), is a potent antioxidant, and has antiinflammatory properties. Laboratory investigations revealed that it might also protect brain from ischemic injury. Propofol formulations contain either disodium edetate (EDTA) or sodium metabisulfite, which have antibacterial and antifungal properties. EDTA is also a chelator of divalent ions such as calcium, magnesium, and zinc. Recently, EDTA has been reported to exert a neuroprotective effect itself by chelating surplus intracerebral zinc in an ischemia model. This article reviews the neuroprotective effects of propofol and its mechanism of action.

Introduction

Propofol is an intravenous (i.v.) agent that is widely used for the induction and maintenance of anesthesia, as well as for sedation in intensive care units (ICUs). Laboratory investigations revealed that propofol might also protect brain from ischemic injury. Propofol has been reported to have many pharmacological effects: (a) it reduces cerebral blood flow, cerebral metabolic rate, and intracranial pressure (ICP) (Murphy et al. 1992), (b) it acts as an antioxidant: it scavenges free radicals, and decreases lipid peroxidation (Sagara et al. 1999; Wilson and Gelb 2002), (c) it activates γ-aminobutyric acid ($GABA_A$) receptors (Ito et al. 1998), inhibits glutamate receptors (Zhan et al. 2001), and reduces extracellular glutamate levels by either inhibiting Na^+ channel-dependent glutamate release or by enhancing glutamate uptake (Sitar et al. 1999), and (d) it reduces ischemic neuronal injury in animal models of transient global or focal cerebral ischemia (Young et al. 1997).

Disodium edetate (EDTA) or metabisulfite is added to propofol preparations to retard bacterial and fungal growth. As EDTA is a chelator of divalent ions such as calcium, magnesium, and zinc, we recently hypothesized that chelation of excessive neuronal zinc by EDTA might ameliorate zinc-induced neurotoxicity and reduce subsequent neuronal injury. In this article, we review the literature on the neuroprotective effects of propofol, including the most recent reports, and discuss whether EDTA has indeed a neuroprotective effect.

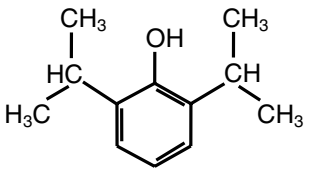

Figure 1 The chemical structure of propofol.

Chemistry

The empirical formula of propofol (2,6-diisopropylphenol, Fig. 1) is $C_{12}H_{18}O$, and its molecular weight is 178.27. The octanol/water partition coefficient for propofol is 6,761:1 at a pH of 6–8.5, and its pK_a is 11. As propofol is only very slightly soluble in water, it is formulated in a white, oil-in-water emulsion. Current formulations consist of 1% or 2% (w/v) propofol, 10% soya bean oil, 1.2% egg phosphatide, and 2.25% glycerol. To this, 0.005% disodium edetate (EDTA) or metabisulfite is added to retard bacterial and fungal growth.

Pharmacology

Propofol is an i.v. sedative-hypnotic agent with amnestic properties, it causes rapid and reliable loss of consciousness (Godambe et al. 2003). In addition, because of its easy titration, it is widely used as a sedative for intensive care patients. Induction of anesthesia can be achieved by administering propofol at doses of 40 mg every 10 second, until the clinical signs indicate the onset of anesthesia (Langley and Heel 1988). The dose of propofol required to induce anesthesia in adults is normally between 2 and 2.5 mg/kg i.v. (Bryson et al. 1995), although older patients may require a lower dose. Propofol anesthesia can be maintained either with a continuous infusion (approximately 6–12 mg/kg/h) or with intermittent bolus injections (20–50 mg). Among the favorable characteristics of propofol are the lack of accumulation and the short recovery time, both of which are essential for neurological examination after the operative procedure (Mirski et al. 1995). Propofol is lipophilic, it easily crosses the blood–brain barrier, and has been shown to depress electroencephalographic activity (Kochs et al. 1992). It decreases cerebral metabolic rate dose-dependently (Dam et al. 1990; Ridenour et al. 1992), and reduces cerebral blood flow (Ergun et al. 2002). Propofol may, therefore, be viewed as a global central nervous system (CNS) depressant.

Activation of $GABA_A$ or $GABA_B$ Receptors

It is thought that propofol directly activates $GABA_A$ receptors. Ito et al. (1998) found that pharmacological agents that either act directly on $GABA_A$ receptors or modulate $GABA_A$ receptor activity (such as propofol, midazolam, and muscimol) are capable of reducing the severity of brain injury following ischemia in gerbils. It has been reported that at clinically relevant concentrations, propofol inhibits glutamate release by blocking current through sodium channels or by activating $GABA_A$ receptors (Ratnakumari and Hemmings 1997; Rehberg and Duch 1999; Buggy et al. 2000). Excessive glutamate accumulation in the extracellular space due to ischemia within the CNS is believed to initiate a cascade toward irreversible neuronal damage. Following an ischemic insult, there is a massive release of glutamate, which acts on both ionotropic and metabotropic glutamate receptors. In the pathophysiology of cerebral ischemia, such an uncontrolled release of glutamate during the ischemia and the consequent excessive stimulation of postsynaptic glutamate receptors (excitotoxicity), play a major role in the initiation of neuronal injury (Kawaguchi et al. 2005). Furthermore, glutamate receptor antagonists protect rodents from cerebral injury in both focal (Park et al. 1988; Dezsi et al. 1992; Sarraf-Yazdi et al. 1998) and transient global ischemia (Gill et al. 1988) models.

Some studies assessed whether propofol has the potential to modify glutamate dynamics during cerebral ischemia. Yano et al. (2000) examined the hypothesis that by intracerebroventricular (i.c.v.) administration propofol, 3 or 10 mg/kg, would reduce the extracellular glutamate levels during global ischemia leading to neuroprotection. They concluded that, although i.c.v. propofol exhibits neuroprotection in transient global forebrain ischemia, the extracellular glutamate level during ischemia is not a major determinant of the neuroprotective activity of propofol. Using rat synaptosomes Bianchi et al. (1991) showed that the propofol (with an approximate IC_{50} of 3.0×10^{-5} M), slightly inhibited glutamate release, glutamate-dependent Ca^{2+} entry, and voltage-gated calcium channels. According to Feiner et al. (2005), propofol (10–100 μM) lacks the glutamate-receptor antagonist potency required for neuroprotection by an antiexcitotoxicity mechanism. Amorim et al. (1995) reported that in hippocampal slices during hyperthermal anoxia, propofol (20 μg/mL) attenuated the increase in intracellular Ca^{2+}, but did not depress the release of glutamate. Further examination of these findings is needed.

Using a different approach Schwieler et al. (2003) analyzed whether propofol (1–16 mg/kg i.v.) might, by activating somatodendritic $GABA_B$ receptors, decrease the firing rate and the burst firing activity of nigral dopamine neurons. They concluded that an activation of central $GABA_B$ receptors may, at least partially, contribute to the anesthetic properties of propofol.

Inhibition of *N*-Methyl-D-Aspartate (NMDA) Receptors

Stimulation of the NMDA receptors leads to Ca^{2+} and Na^{2+} influx into the cells. The subsequent excessive accumulation of intracellular calcium activates enzymes such as proteases, lipases, and endonucleases (Kawaguchi et al. 2005). Propofol inhibits the NMDA receptor and reduces calcium influx through slow calcium channels. As calcium influx into the tissues is believed to be responsible for cellular dysfunction and tissue injury, propofol may have organ protective activity. Indeed, antagonists of either NMDA or α-amino-3hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors have been shown to be neuroprotective in global and focal cerebral ischemia (Kawasaki-Yatsugi et al. 1998; Sarraf-Yazdi et al. 1998). Zhan et al. (2001) used an *in vitro* cerebral ischemic model to examine the relation between the effects of i.v. anesthetics on neurotransmission and their effects on the NMDA receptors during ischemia. They reported that propofol (100 μM), rather than inhibiting NMDA receptors, slightly augments the NMDA-mediated effect on the intracellular calcium. In contrast, Hans et al. (1994) showed that in cultured hippocampal neurons, propofol attenuates the neurotoxic effect of glutamate exerted via NMDA receptors. Other reports suggested that the neuroprotective efficacy of propofol might not be sustained. For example, an NMDA antagonist dizocilpine maleate (MK-801), at 0.5 mg/kg i.v., reduced neuronal injury when the injury was evaluated after a short recovery period (3 days), but not when it was evaluated at 4 weeks after initiation of ischemia (Valtysson et al. 1994). Moreover, Zhu et al. (1997), using the recovery of the population spike amplitude as an indicator of neuronal viability, demonstrated that propofol (112 μM) may enhance NMDA-induced neuronal damage. Taking all these data together, it appears that propofol may, at best, weakly and incompletely inhibit NMDA receptors.

Antioxidant Activity

Propofol is a lipophilic and phenolic antioxidant, it scavenges free radicals, reduces lipid peroxidation, inhibits cellular oxidative damage, and increases glutathione levels in the tissues. Its chemical structure has some similarity with that of phenol-based free-radical scavengers, such as vitamin E (Murphy et al. 1992; Kahraman and Demiryurek 1997). Murphy et al. (1992) demonstrated that propofol (10^{-6}–10^{-5} M) has an antioxidant capacity equal to that to "Trolox C" (Sigma-Aldrich, St Louis, MO, USA) a water-soluble analogue of vitamin E and a known antioxidant. They also reported that Trolox C and propofol are equipotent in reducing the rate of oxygen consumption and lipid peroxidation. Further, Hans et al. (1996) noted that in isolated cell membranes propofol and vitamin E produce qualitatively similar improvements in cell function and that their effects can be correlated with the measurements of lipid peroxidation, so that propofol can replace vitamin E as an antioxidant. Vincenti et al. (1991) examined the antioxidant and antiglutamatergic activities of propofol and found that it inhibits lipid peroxidation in rat liver microsomes and mitochondria, inhibits glutamatergic responses in rat brain synaptosomes, and interfers with the glutamic acid-mediated calcium entry. Navapurkar et al. (1998) further proposed that propofol (28 μM) may exert a protective action against the oxidative stress caused by free radicals in the liver. Scavenging of free radicals by propofol may, in presence of Ca^{2+}, contribute to the stabilization of the mitochondrial membrane during oxidative stress (Eriksson 1991). Taken together, these results indicate that propofol is a free radical scavenger with a significant antioxidant activity.

Immunomodulatory Activity

Propofol possesses immunomodulatory activity, and may thus diminish the systemic inflammatory response believed to be responsible for organ dysfunction (Crozier et al. 1994; Matsushita et al. 1996; Helmy et al. 1999). The lipid component of propofol EDTA is based on soybean oil, and contains a variety of triglycerides, phospholipids, glycerol, vitamins, and minerals. The primary lipid in soybean oil is linoleic acid, an omega-6 long-chain polyunsaturated fatty acid, and there are smaller amounts of omega-3 long-chain fatty acids. Long-chain fatty acids are bioactive and affect the synthesis and secretion of cytokines, free radicals, and other inflammatory mediators (Herr et al. 2000). These lipids integrate into cellular membranes altering membrane structure and function, as well as ion-channel flow, second-messenger generation, and production of eicosanoids.

Anxiolytic Effects

Propofol, like benzodiazepines, has anxiolytic effect at doses that do not induce sedation. Smith et al. (1994) found that by i.v. infusion at 0.2, 0.4, 0.5, or 0.7 mg/kg propofol decreases anxiety scores in patients undergoing urologic surgery under regional anesthesia. The mechanism of its anxiolytic action is likely to involve a positive modulation of the inhibitory function of GABA through $GABA_A$ receptors (Ito et al. 1999).

Analgesic Effects

Anwar and Abdel-Rahman (1998) reported that at 25 or 50 mg/kg i.p. propofol may control pain via an opioid

system, with the onset of action of 5 up to 20 min. The analgesic effect of propofol was also reported by other investigators (Briggs et al. 1982; Anker-Moller et al. 1991; Jewett et al. 1992).

In contrast, Godambe et al. (2003) found that at 1 mg/kg i.v. propofol is a poor analgesic, and that it usually requires an adjunctive analgesic agent, and Ewen et al. (1995) found that propofol (340 or 680 μg/kg/min, 20 min, i.v.) may produce a hyperalgesic effect. Overall, these results suggest that pain control by propofol may be weak and incomplete.

Anticonvulsant Activity

The anticonvulsant properties of propofol were examined some years ago in two experimental models of status epilepticus in rabbits (de Riu et al. 1992). In that study, it was found that propofol (12 mg/kg) suppressed electroencephalographic and pharmacological seizures in a pentylenetetrazole-induced generalized epileptic status. It also reduced focal epilepsy induced by cortically applied penicillin G, although its efficacy was low and the effect was short-lasting. In a later *in vitro* study, Rasmussen et al. (1996) showed that in rat hippocampal slices propofol markedly reduces epileptiform activity induced by picrotoxin, bicuculline, pilocarpine, K^+, or by omission of Mg^{2+} from the medium (1.7, 50, 16.9–56.2, 168, 337 μM propofol, respectively). Furthermore, in humans propofol is well known to be effective against status epilepticus that was refractory to standard anticonvulsants (Marik 2004).

Neuroprotective Properties

The reports that propofol depresses electroencephalographic activity (at 0.8–1.2 mg/kg/min i.v., Kochs et al. 1992), decreases cerebral metabolic rate (at 20 mg/kg i.v., Dam et al. 1990), and reduces cerebral blood flow (at 50 mg/kg i.p., Ergun et al. 2002) suggested that it may have a neuroprotective effect against brain ischemia. Actually, it has certain properties that might well be neuroprotective, including free-radical scavenging (Grasshoff and Gillessen 2002), augmentation of aminobutyric acid (GABA)-receptor currents, and inhibition of NMDA-type glutamate receptor currents (Orser et al. 1995; Yamakura et al. 1995; Wakasugi et al. 1999). Indeed, the neuroprotective effect of propofol has been attributed to its antioxidant properties, potentiation of $GABA_A$-mediated inhibition of synaptic transmission, and inhibition of glutamate release in cerebral ventricles (at 3 or 10 mg/kg, Yano et al. 2000).

In contrast, propofol failed to protect cells *in vivo* (at 10 mg/kg i.v. bolus or 16 mg/kg/h continuous i.v. infusion for 4 h, Tsai et al. 1994) or in *in vitro* models of cerebral ischemia (at 20 μg/mL, Amorim et al. 1995; or at 100 μM, Zhan et al. 2001). Kawaguchi et al. (2005) suggested that the propofol may be neuroprotective in mild ischemic insults during a long postischemic recovery period, but that its neuroprotective effect is not adequate for sustained protection from moderate to severe insults. They concluded that sustained anesthetic neuroprotection might be limited to brief ischemia. On the other hand, Engelhard et al. (2004) compared the effect of propofol (by i.v. infusion at 0.8–1.2 mg/kg/min) with that of nitrous oxide ($FiO_2 = 0.33$) and fentanyl (i.v. bolus: 10 μg/kg, i.v. infusion: 25 μg/kg/min) and demonstrated that propofol reduces neuronal damage and favorably modulates apoptosis-regulating proteins for at least 28 days, suggesting long-term neuroprotection by this agent. In a permanent middle cerebral arteryocclusion (MCAO) model, we recently demonstrated (Kotani et al. 2008) that propofol (10 mg/kg, i.v.) reduces infarct volume and neuronal damage for 7 days, suggesting a long-term neuroprotection by propofol.

In Vitro Studies

Several researchers reported that propofol reduces cell injury in cellular preparations (1–8 μM, Daskalopoulos et al. 2001; 1,10, or 100 μM, Grasshoff and Gillessen 2002; 20–100 μM, Sagara et al. 1999). Velly et al. (2003) studied the relationship between propofol-induced neuroprotection, glutamate extracellular concentrations, and glutamate transporter activity in a cell-culture model of cortical ischemia. They found that propofol (0.05–10 μM) displayed a neuroprotective effect against oxygen-glucose deprivation (OGD). Adembri et al. (2006) reported that propofol (10–100 μM) attenuated CA1 injury in hippocampal slices *in vitro* when it was present in the incubation medium during both OGD and the subsequent 24 h recovery period. However, Feiner et al. (2005) were unable to demonstrate neuroprotection with 10–100 μM propofol in a similar organotypic hippocampal slice model. We recently examined the *in vitro* effects of propofol and EDTA against OGD-induced cell damage in cultures of PC12 cells (Fig. 2). The results showed that either propofol (20 μM) or EDTA (0.05 μM) protected PC12 cells from OGD-induced damage, and that this effect of propofol was enhanced by EDTA.

In Vivo Studies

Permanent middle cerebral artery occlusion

Adembri et al. (2006) reported that at twenty-four hours after permanent MCAO in rats, infarct size was reduced by approximately 30% when propofol (100 mg/kg, i.p.)

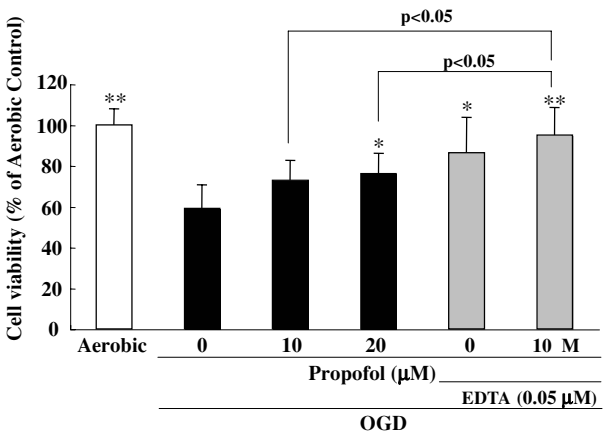

Figure 2 Both propofol and propofol EDTA reduced the cell damage induced by OGD in PC12 culture. Cell viability was assessed following immersion in 10% resazurin solution for 3 h at 37 °C, and fluorescence was recorded at 560/590 nm. OGD induced cell death, and propofol and EDTA each inhibited this OGD-induced cell death. Propofol plus EDTA reduced cell death by more than propofol alone. Data are expressed as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ versus OGD-treatment alone (Dunnett's test or Student's *t*-test); $n = 4$. Data from Kotani et al. (2008).

was administered immediately after or up to 30 min after the occlusion. On the other hand, Tsai et al. (1994) failed to demonstrate a protective action of propofol (10 mg/kg i.v. bolus or 16 mg/kg/h continuous i.v. infusion for 4 h) after permanent MCAO in rats. Recently, we evaluated the neuroprotective properties of propofol by determining whether or not it alters the volume of the infarct resulting from permanent focal cerebral ischemia in mice. By i.v. administration at 5 or 10 mg/kg propofol EDTA or propofol (but not at 1 mg/kg) significantly reduced infarct area, infarct volume, and brain swelling (Fig. 3A, B). Propofol EDTA reduced infarct area and brain swelling significantly better than propofol alone. Likewise, propofol EDTA or propofol, at 5 or 10, but not at 1 mg/kg i.v., 10 min before ischemia, appeared to reduce neurological deficits, although only propofol EDTA reduced them significantly (Fig. 3C). In our study, TUNEL-positive cells were predominantly located in the ischemic core region rather than in the ischemic penumbra, although propofol EDTA significantly reduced the number of TUNEL-positive cells only in the ischemic penumbra (Fig. 4C, D). Thus, our findings suggest that propofol EDTA inhibits apoptosis mainly within ischemic penumbra.

Transient middle cerebral artery occlusion

Lee et al. (2000) reported that pretreatment with propofol (administered at 96 mg/kg/h for 20 min and maintained at 72 mg/kg/h until the initiation of carotid occlusion) could markedly reduce the extent of the 2,3,5-triphenyltetrazolium chloride (TTC)-infarcted area following incomplete global cerebral ischemia and reperfusion. Arcadi et al. (1996) investigated the hippocampal cell death in the gerbil that occurred as a result of transient cerebral ischemia. They concluded that propofol (50 or 100 mg/kg, i.p.) has protective activity against transient forebrain ischemia-induced delayed hippocampal neuronal death without improving overall survival rate. A few years later, Wang et al. (2002) used microdialysis technique to evaluate the effects of propofol infusion on infarct size and the striatal dopamine levels following temporary MCA occlusion in rats. They showed that when propofol (36 mg/kg/h) was infused during ischemia and reperfusion, it reduced the cerebral infarct size and significantly decreased dopamine accumulation in the striatum. They concluded that the neuroprotective effect of propofol might be partially due to its ability to inhibit dopamine accumulation. Engelhard et al. (2004) used rats to investigate the long-term effects of propofol against neuronal damage and apoptosis-related proteins after cerebral ischemia and reperfusion. They analyzed the amounts of the apoptosis-related proteins Bax, p53, Bcl-2, and Mdm-2, and the number of neurons positive for activated caspase-3, and found: (1) that propofol (at 1 mg/kg i.v. bolus, immediately followed by an infusion at 10 mg/kg/h for 10 min, at 8 mg/kg/h for the next 10 min, and thereafter at 6 mg/kg/h) had a sustained neuroprotective effect that was associated with reduced eosinophilic and apoptotic injury, and (2) that activated caspase-3-dependent apoptotic pathways were not affected by propofol, suggesting the presence of activated caspase-3-independent apoptotic pathways.

Some studies failed, however, to detect the neuroprotective effect of propofol. In rat hippocampal slices propofol, at 100 μM, had no protective effect in terms of the recovery of population spikes in the CA-1 pyramidal layer following transient ischemia (Zhan et al. 2001). Thus, opinions are divided as to whether propofol has a neuroprotective effect in transient cerebral ischemia, although most investigators seem to believe that propofol is neuroprotective.

Zinc Chelation

In our recent studies, we focused on zinc because it is one of the most abundant transition metals in the brain, and is essential for development, growth, DNA synthesis, immunity, and a wide array of cellular processes. The physiological significance of neuronal zinc release within the CNS is not clear, and its role in ischemic brain injury is controversial. After brain ischemia, there is a depletion of presynaptic bouton zinc and a concurrent accumulation of zinc in the cell bodies of vulnerable neurons (Koh et al.

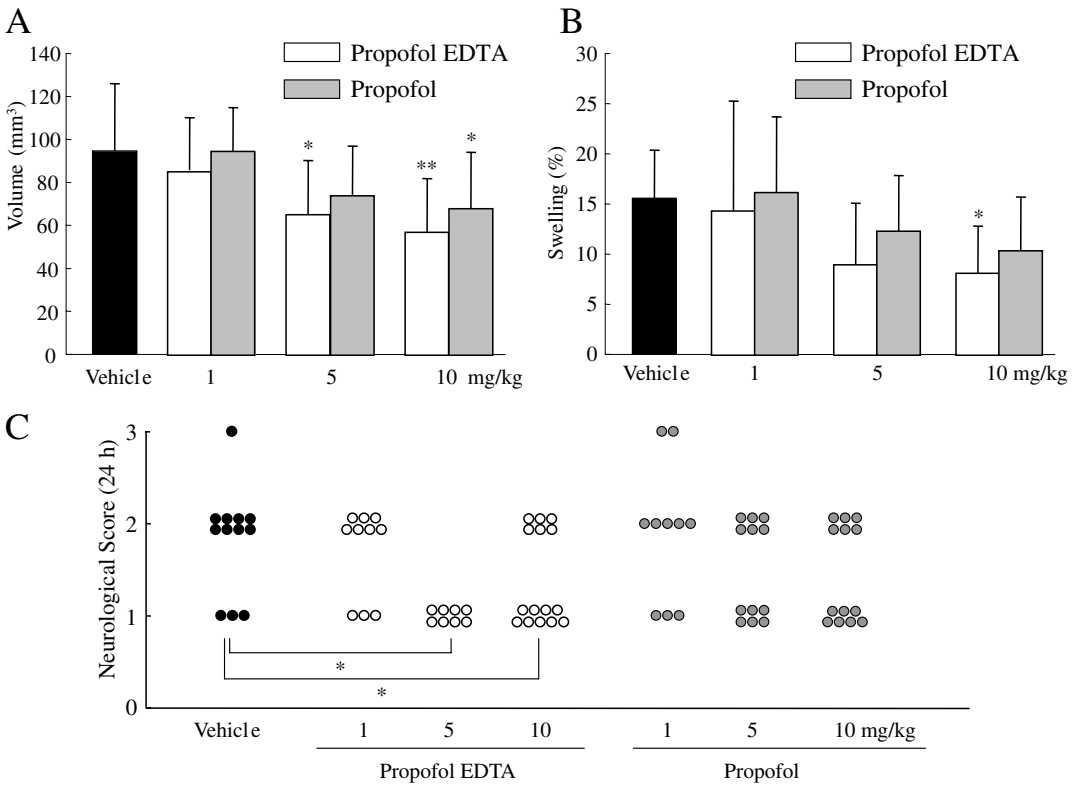

Figure 3 (A) Effects of propofol EDTA and propofol on infarct volume at 24 h after permanent MCA occlusion (each treatment being given intravenously [1, 5, or 10 mg/kg, given over 90 second, at 0.1 mL/10 g] 10 min before MCA occlusion). $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle (Dunnett's test); $n = 10$–14. (B) The effects of propofol EDTA and propofol on brain swelling 24 h after permanent MCA occlusion in mice. $^{*}P < 0.05$ versus vehicle (Dunnett's test); $n = 10$–14. (C) Effects of propofol EDTA and propofol (details as in B) on neurological deficits at 24 h after permanent MCA occlusion. $^{*}P < 0.05$ versus vehicle (Mann-Whitney *U*-test); $n = 10$–14. Values are mean ± SD. Data from Kotani et al. (2008).

1996). In fact, it has been proposed that synaptic zinc or extracellular zinc acts as "the cell-death ion" during neuronal damage, both *in vitro* and *in vivo* (Choi et al. 1998; Canzoniero et al. 1999; Shabanzadeh et al. 2004).

In contrast, some authors believe that zinc may have a protective function (Matsushita et al. 1996; Bancila et al. 2004). Nakatani et al. (2000) reported that Zn^{2+} ions play an important role in free radical metabolism and apoptosis, while Calderone et al. (2004) reported that when the influx of extracellular Zn^{2+} into postsynaptic neurons is blocked by intraventricular injection of a Zn^{2+}-chelating agent, neurodegeneration is prevented.

Disodium edetate (EDTA) or metabisulfite is added to conventional pharmaceutical preparations of propofol to retard bacterial and fungal growth. EDTA is a potent chelator of heavy metals, including zinc, iron, copper, manganese, chromium, cobalt, and lead (Guldager et al. 1996; Powell et al. 1999). In our recent study, we asked whether EDTA could modulate the neuroprotective effect of propofol, and studies the effects of EDTA on intracerebral zinc levels during cerebral ischemia. When propofol EDTA at 10 mg/kg i.v. was injected at 10 min before the onset of cerebral ischemia (permanent MCAO), the zinc levels decreased significantly (vs. vehicle) in the cortical area, but not in the subcortex (Table 1) (Kotani et al. 2008). In contrast, in the propofol EDTA-treated group that did not undergo MCAO, the intracerebral zinc levels in the cortex were not significantly altered (Kotani et al. 2008). This finding indicates that chelation of zinc by EDTA occurs in the cortex during ischemia, possibly leading to neuroprotection. Therefore, the dynamics of microelements (in particular, zinc) at the time of cerebral ischemia should be considered in the future studies, and chelation therapy using EDTA may prove to be a new treatment for cerebral ischemia.

Pharmacokinetics

The pharmacokinetics of propofol can be well described by a three-compartment linear model, with the compartments representing plasma, rapidly and slowly equilibrating tissues (AstraZeneca 2001). Following an i.v. bolus

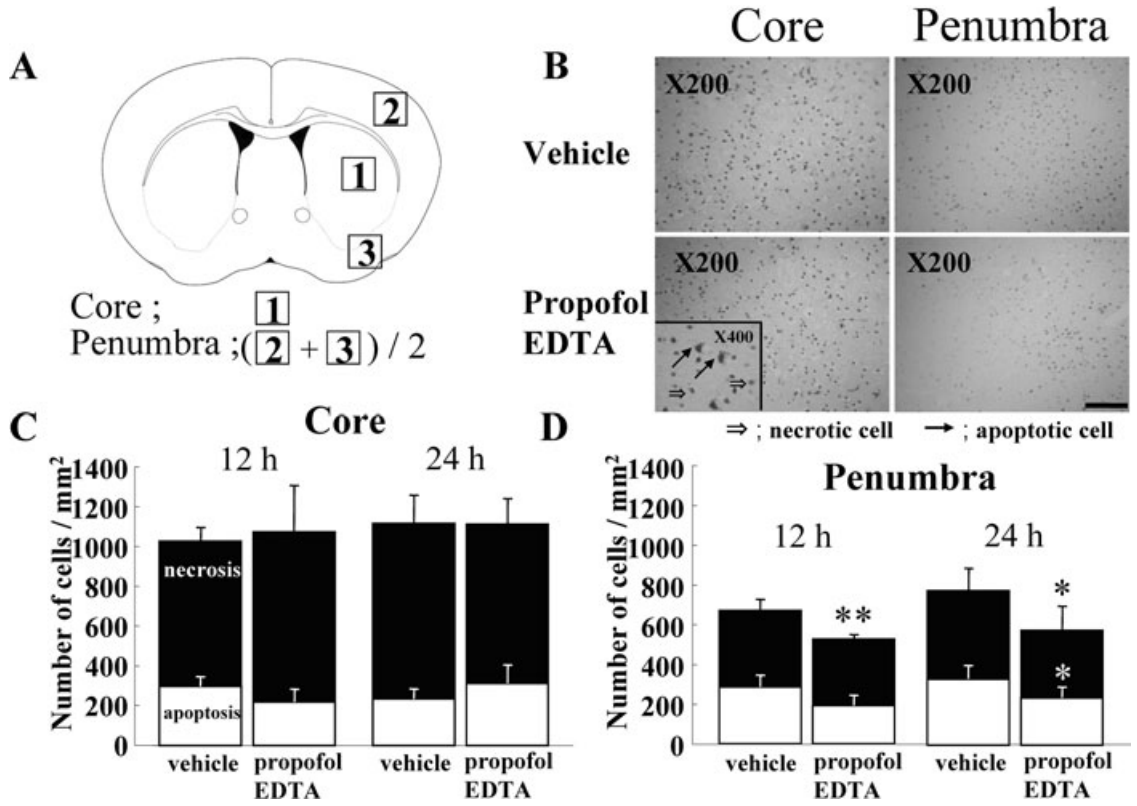

Figure 4 Effect of propofol EDTA on TUNEL staining after MCA occlusion. Propofol EDTA (10 mg/kg i.v.) was administered 10 min before MCA occlusion, and mice were sacrificed at 12 or 24 h after the occlusion. (A) Schematic drawing showing the brain regions at a level 0.4–1.0 mm anterior to bregma (through the anterior commissure); 1, ischemic core; 2 and 3, ischemic penumbra. The number of TUNEL-positive cells was counted in each of these areas, the average for areas 2 and 3 being taken as the number for the ischemic penumbra. (B) Propofol EDTA appeared to reduce the number of TUNEL-positive cells (versus vehicle treatment) in the ischemic penumbra, but not in the ischemic core. (C and D) Quantitative representation of TUNEL-positive cells in ischemic brains treated with propofol EDTA or vehicle. White part of bar shows number of apoptotic cells among all positive cells. Note that at 24 h in the ischemic penumbra, a considerably smaller number of TUNEL-positive cells was observed in mice treated with propofol EDTA than in mice treated with vehicle. However, in the ischemic core no such difference was detected. Data are expressed as mean ± SD. $^{*}P < 0.05$, $^{**}P < 0.01$ versus vehicle (Student's *t*-test); $n = 4$–6. Scale bar = 100 μm. Data from Kotani et al. (2008).

dose, there is rapid equilibration of propofol levels between plasma and highly perfused tissue of the brain, accounting for the rapid onset of anesthesia. Propofol has been shown to be extensively (97–98%) bound to plasma proteins (Altmayer et al. 1995), although the plasma level initially shows a steep decline as a result of both rapid distribution and high metabolic clearance (the latter being from 23 to 50 mL/kg/min [1.6 to 3.4 L/min in a 70 kg adult]). A difference in pharmacokinetics due to gender has not been observed (AstraZeneca 2001). Propofol is mainly eliminated by hepatic conjugation to inactive glucuronide metabolites (Raoof et al. 1996), which are excreted by the kidney, and glucuronide conjugates account for about 50% of the administered dose.

The terminal half-life of propofol after a 10-day infusion is 1–3 days (AstraZeneca 2001). If there are higher than necessary infusion levels of plasma, this return of propofol from the peripheral tissues will delay recovery. In other words, failure to reduce the infusion rate in patients receiving propofol for extended periods may result in excessively high blood concentrations of the drug. Therefore, titration to the clinical response and daily evaluation of sedation levels are important during the use of propofol infusion for ICU sedation, especially if it is of long duration.

Clinical Efficacy

Propofol causes hypotension (particularly in volume-depleted patients), decreases cerebral oxygen consumption, reduces ICP, and has potent anticonvulsant properties. Therefore, propofol is being increasingly used in the

Table 1 Zinc levels in mouse brains

Treatments	Ischemia	Cortex (μg/g)	Subcortex (μg/g)
Vehicle	−	139.9 ± 42.6	110.3 ± 30.1
Propofol EDTA	−	137.0 ± 32.0	108.0 ± 36.5
Vehicle	+	150.2 ± 36.7	107.3 ± 30.4
Propofol EDTA	+	120.8 ± 22.4*	98.6 ± 19.2

Propofol EDTA (10 mg/kg i.v.) or vehicle (Intralipid) was administered 10 min before the onset of ischemia. Mice were anesthetized using 2.0–3.0% isoflurane and maintained using 1.0–1.5% isoflurane in 70% N_2O and 30% O_2. After a midline skin incision, the left external carotid artery was exposed, and its branches were occluded. An 8–0 nylon monofilament (Ethicon, Somerville, NJ) coated with a silicone resin mixture (Xantopren; Bayer Dental, Osaka, Japan) was introduced into the left internal carotid artery through the external carotid artery stump so as to occlude the origin of the middle cerebral artery (MCA). Afterwards, the left common carotid artery was occluded. Mice were killed 1 h after the onset of ischemia. Nonischemic groups were killed 1 h after drug (or vehicle) administration. Values are mean ± SD ($n = 10$). *$P < 0.05$ versus vehicle + ischemia group (Bonferroni correction). Data from Kotani et al. (2008).

management of traumatic head injury, status epilepticus, delirium tremens, status asthmaticus, and in septic patients (Cosmo et al. 2005). In patients with severe head injury, the goal of therapy is to avoid secondary brain damage, with i.v. sedation being an integral part of the therapy. Herregods et al. (1988) investigated the effects of a bolus injection of propofol (2 mg/kg) on mean ICP in six adult, comatose patients who had severe head injuries. They demonstrated that the mean ICP was decreased significantly (from 25 to 11 mmHg; $p < 0.05$) at 30 seconds and at 1 and 2 min, and that the cerebral perfusion pressure was decreased significantly from 92 mmHg at all measurement-point ($p < 0.05$) (Herregods et al. 1988). Merlo et al. (1991) investigated the decrease in ICP in 11 patients who had an ICP above 20 mmHg despite hyperventilation and neurosedation. They observed statistically significant ($p < 0.05$) decreases in ICP and systolic arterial pressure after a bolus of propofol (1.5 mg/kg i.v.). They concluded that propofol could be used to treat intracranial hypertension, but that the hemodynamic effects in hypovolemic patients need to be taken into consideration (Merlo et al. 1991). Thus, the available data permit the conclusion that propofol can be used effectively in patients with an elevated ICP.

Mizuno et al. (2002) reported a case in which propofol (a bolus of 60 mg i.v., followed by continuous i.v. infusion at 2 mg/kg/h) was effective in controlling myoclonus during rewarming of a hypothermic patient. In addition, propofol is frequently used in cardiac surgery. CNS dysfunction is a common consequence of otherwise uncomplicated cardiac surgery. This led Ederberg et al. (1998) to investigate the effects of burst-suppression doses of propofol (a bolus dose of 1 mg/kg immediately followed by an infusion of 10 mg/kg/h for 10 min, 8 mg/kg/h for the next 10 min, and thereafter at 6 mg/kg/h) on cerebral blood flow velocity (CBFV), cerebral oxygen extraction (COE), and dynamic autoregulation in 20 patients undergoing cardiac surgery. They reported that propofol induced 35% and 10% decreases in CBFV and COE, respectively, and concluded that propofol decreases CBFV and improves dynamic autoregulation during moderate hypothermic nonpulsatile cardiopulmonary bypass (Ederberg et al. 1998). Consequently, Souter et al. (1998) prospectively investigated the effects of propofol (at a subanesthetic dose of 30 mg/min, causing a burst-suppression rate of 80%, throughout cardiopulmonary bypass) on cerebral venous oxyhemoglobin saturation (SjO_2) ($SjO_2 < 50\%$). They concluded that, when administered at doses sufficient to produce electroencephalographic burst suppression, propofol did not attenuate either the frequency or extent of the reductions in cerebral venous oxyhemoglobin saturation (Souter et al. 1998). Thus, propofol appears to have a neuroprotective effect only when given at anesthetic doses.

Toxicology

Acute Toxicity

Propofol has a remarkable safety profile. However, the effects of acute hepatic or renal failure on the pharmacokinetics of propofol have not been studied. The i.v. LD_{50} values for propofol, administered as the emulsion formulation, average 53 and 42 mg/kg in mice and rats, respectively, while the oral LD_{50} values for propofol, administered as a solution in soybean oil, are 1,230 and 600 mg/kg in mice and rats, respectively (Stuart Pharmaceuticals 1989). Overdosage with propofol would be expected to produce manifestations that principally represent extensions of the drug's pharmacologic and adverse effects and are associated with cardiorespiratory depression. It is recommended that in the case of an overdose, propofol should be discontinued immediately, and appropriate symptomatic therapy initiated (AstraZeneca 2001).

Adverse Effects

The reported adverse effects of propofol are: pain on injection (Boysen et al. 1989), bradycardia (Tramer et al. 1997), arterial hypotension (Nimmo et al. 1994), bloodstream infection (Bennett et al. 1995), airway obstruction, changes in serum lipids (Barrientos-Vega et al. 1997), and excitation of the CNS (Stark et al. 1985), including seizures in susceptible patients (Bredahl 1990).

Pain on injection is the most frequently observed adverse effect, its incidence varies from 28.5% (for small veins) to 6% (for larger veins) (Mackenzie and Grant 1987), but the incidence of thrombophlebitis is very low (about 0.5%) (Stark et al. 1985). Other uncommon complications include hypertriglyceridemia and pancreatitis.

High-dose propofol infusions may be associated with the "propofol syndrome," a potentially fatal complication characterized by severe metabolic acidosis and circulatory collapse. This is a rare complication first reported in pediatric patients, and believed to be due to a decreased transmembrane electrical potential and alteration in electron transport across the inner mitochondrial membrane (Marik 2004).

Herr et al. (2000) compared the safety of propofol with that of propofol EDTA. Each drug was given initially for sedation of critically ill postsurgical or trauma patients in ICU by continuous infusion at a rate of 5 μg/min, with the rate adjusted, if necessary. The infusion continued till the patients achieved the Modified Ramsay Sedation Scale score. They investigators reported that: (1) the addition of EDTA to propofol appeared to have no effect on calcium or magnesium homeostasis, and (2) because propofol has little effect on renal function, adding EDTA, at a low concentration, to propofol produced no untoward effects on renal function in critically ill patients. In addition, Zaloga and Teres (2000) observed that the most notable abnormality in ICU patients given propofol containing EDTA was a low blood zinc level, although no adverse events indicative of zinc deficiency occurred.

Conclusions

Propofol is a versatile i.v. sedative-hypnotic agent. Many preliminary studies suggest that it may have a neuroprotective effect against brain ischemia. Indeed, it seems to afford neuroprotection against both *in vivo* and *in vitro* ischemic damage. Such effects may be enhanced when EDTA is added, and the addition of EDTA appears to have no detrimental effect on the safety or efficacy of propofol when it is used for sedation in critically ill surgical ICU patients. However, the evidence that propofol may reduce ischemic cerebral damage is inconclusive, and further research is needed.

Conflict of Interest

The authors have no conflict of interest.

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