Drug Review

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Propofol in Neurotrauma

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Abstract : Propofol (2,6-diisopropylphenol) is one of the most popular agents used for induction of anesthesia and long-term sedation, owing to its favorable pharmacokinetic profile, which ensures a rapid recovery even after prolonged administration. Propofol is used widely as a sedative agent in neurosurgical critical care because it is generally assumed that it has properties that are advantageous to the injured brain. Propofol is believed to maintain, or even improve, cerebral autoregulation, indeed even high doses of this drug do not obtund autoregulation or carbon dioxide reactivity. A neuroprotective effect, beyond that related to the decrease in cerebral metabolic rate for oxygen, has been shown to play an important role in the so-called multimodal neuroprotection, a global strategy for the treatment of acute injury of the brain that includes preservation of cerebral perfusion, temperature control, prevention of infections, and tight glycaemic control.

Keywords: propofol, neuroprotection, traumatic brain injury

INTRODUCTION

Propofol, like many other inhalational and intravenous anesthetics shares some properties such as the reduction in the cerebral metabolic rate for oxygen ($CMRO_2$), the inhibition of glutamate release, and the positive modulation of GABA-A receptor function, which are known to mitigate the detrimental effects of acute brain injury and thus are typical of the ideal neuroprotective drug[1,2]. Propofol is chemically unrelated to other clinically used general anesthetics[3]. It has a structural analogy with the antioxidant vitamin E, a fact that can partly explain its antioxidant properties.

CLINICAL APPLICATION

The first report on the clinical use of Propofol dates back to 1977 as an anesthesia induction agent[4]. Subsequently, Propofol has been extensively employed also for short-term sedation, as well as for long-term sedation in intensive care unit patients [5].

Propofol exerts its sedative, hypnotic, and amnesic effects by interacting with an allosteric site on the GABA-A receptor, potentiating currents elicited by low concentrations of GABA, increasing agonist efficacy, and at higher concentrations, directly opening the GABA-A receptor Cl" channel in the absence of GABA[6]. It also inhibits excitatory glutamate release by a presynaptic mechanism[7]. Interestingly, some of propofol's effects such as ant emesis, post recovery mood alterations, and postoperative dreaming[8], might rely on inhibition of the cannabinoid degrading enzyme, with consequent increases in anandamide (AEA) and 2-arachidonylglycerol in the brain [9]. Propofol is characterized by rapid distribution from blood to tissues, an equally rapid clearance of the molecule from the blood, and a slow return of the drug from the deep compartments[10], which is responsible for the rapid onset, clear emergence, and lack of cumulative effects observed in clinical use.

Adverse properties of Propofol include pain on injection, apnea after induction, hypotension, and bradycardia (especially when used with other vagotonic drugs and in hypovolaemic patients). Decreases in blood pressure induced by Propofol are generally dose and infusion rate-dependent, and the effect is related to its vagotonic activity and to decreases in peripheral vascular resistance[11]. Other limitations and adverse effects of Propofol include the risk of extraneous microbial contamination of the emulsion formulation and lipidemia induced by repeated administration of the agent over time (infusions for periods exceeding 3 days produce progressive increases in levels of serum lipids, particularly triglycerides). The so-called propofol infusion syndrome, characterized by metabolic acidosis and/or rhabdomyolysis associated with progressive myocardial failure, although rare, has been increasingly reported over

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the years[12]. The syndrome appears to be duration- and dose-related (usually, doses >5 mg/kg/h for >48 h) and more frequent in the pediatric population than in adults. Hence, presently propofol is not indicated for long-lasting sedation in children.

NEUROPROTECTION

The neuroprotective effects of propofol have been investigated. Propofol has proved to be an efficacious neuroprotective agent, but the results have not always been consistent. Propofol has been postulated to be a possible beneficial agent against cerebral ischemia based on the assumption that it decreases cerebral blood flow (CBF) (with a parallel reduction in CMRO2 and EEG activity) and mitigates intracranial pressure (ICP), all effects that are similar to those observed for barbiturates and other intravenous neuroprotective anesthetic agents[1,2].

The effects on glucose metabolism have been addressed in a study (13), who have shown that high doses of propofol (60 mg/kg/h) attenuates both edema formation and lactate accumulation . One recent study have demonstrated neuroprotection with propofol also in a rat model of permanent middle cerebral artery occlusion, in which a short exposure to oxygen glucose deprivation (OGD) induced selective neuronal injury, propofol reduced pyramidal cell death, possibly by preventing an increase in neuronal mitochondrial swelling[14]. Hence, it appears that propofol may block early necrosis in vitro but not subsequent apoptosis, which is in agreement with the lack of long-term histological protection in vivo, particularly if the ischemic insult is severe. However, this postponement of neuronal death afforded by propofol may be of importance to permit intervention with other decisive pharmacologic strategies.

NEUROPROTECTION WITH PROPOFOL: MECHANISM

As compared with studies in models of cerebral ischemia, there are relatively fewer reports on the effects of propofol in experimental traumatic brain injury. Most anesthetic agents are neuroprotective because of their ability to reduce the $CMRO_2$, which has a beneficial impact on the balance between brain energy supply and demand, and because they increase neuronal tolerance to hypoxic/ischemic injury. However, propofol has no direct preconditioning effect and that cerebral metabolic depression cannot entirely account for its effects in experimental ischemia, suggesting that there might be other mechanisms playing a key role in propofol-mediated neuroprotection[15].

Propofol has been proposed to attenuate glutamate-mediated excitotoxic mechanisms by either decreasing NMDA receptor activation, reducing glutamate release, or recovering the function of transporters responsible for glutamate uptake into neuronal and glial cells. Propofol has been shown to modulate glutamate release. Propofol does not alter high-affinity glutamate uptake by brain synaptosomes under standard conditions[16] but is able to normalize glutamate transport in astrocytes during oxidative stress[17] and in cortical neurons exposed to OGD[18].

A mechanism that is known to be beneficial against acute neuronal injury is the potentiation of GABAergic neuronal activity, mainly due to its counteracting effects on excitatory neurotoxicity.

Propofol directly activates GABA-A receptors[19], leading to neuronal hyperpolarization and enhancement of inhibitory synaptic transmission[16]. Free radical generation is an important component of neurologic injury. Propofol has been assumed to possess antioxidant activity because it bears a phenolic OH group like the natural lipid peroxidation inhibitor *á*-tocopherol (vitamin E). Indeed, propofol has repeatedly been demonstrated to inhibit free radical generation, prevent the initiation of free radical chain reactions, and terminate their propagation by scavenging highly reactive species and inhibiting lipid peroxidation.

Following acute brain injury, oxidative stress can lead to neuronal death by triggering a number of detrimental cellular responses, including the loss of selective ion permeability in mitochondria, which appears to be one of the regulators of the apoptotic cascade [20].

Propofol has also been demonstrated to prevent mitochondrial swelling caused by acute overload of Ca^{++} in isolated brain mitochondria or by OGD injury in organotypic hippocampal slices[14]. Very recently, propofol has been shown to interact with the endocannabinoid system in the brain. This novel mechanism has been associated with the sedative, psychomimetic, and antiemetic properties of propofol, but there is accumulating evidence that the endocannabinoid system regulates the release of various neurotransmitters and may also be involved in neuroprotection[21].

NEUROPROTECTION IN THE CLINICAL SETTING

Even molecules that have shown to be dramatically neuroprotective under experimental conditions may not have clinical utility if they are endowed with negative effects on cerebral physiology, especially on ICP and on the coupling between CBF and $CMRO_2$. The effects of propofol on cerebral physiology are generally positive.

The effect on CBF is mostly mediated by the reduction of $CMRO_2$, even if a direct vasoconstrictor effect is also thought to contribute, as the decrease in CBF is larger than that in $CMRO_2$. Propofol reduces ICP, a property that is mandatory in case of intracranial hypertension and is always favorable in cases of acute brain injury. Cerebral autoregulation and CO_2 responsiveness are maintained during propofol anesthesia[22], and an anticonvulsant activity comparable to that of thiopental has also been described[23]. Other specific advantages in the use of propofol in neurosurgery include a rapid recovery when intraoperative awake functional evaluation is requested, a lower incidence of nausea and vomiting as compared to volatile anesthetics, a lesser degree of depression of electrophysiological brain activity as compared to all the other anesthetic agents, which allows better intraoperative monitoring[24].

CONCLUSIONS

Taken as a whole, the available data appear to indicate that propofol, has the potential of offering a certain degree of neuroprotection, which is not exclusively due to reduction of the $CMRO_2$ but involves inhibition and/or modulation of specific cellular pathways activated following acute brain injury. At present, however, there are no clinical data available to indicate that propofol may have neuroresuscitative properties, as it occurs with other anesthetic agents with the possible exception of xenon[25]. It is probably quite naïve to imagine that a single anesthetic, given for a limited amount of time, might offer long lasting protection against cerebral injuries for which an evolution over days and months after the primary insult occurs. However, propofol may share a useful role with other anesthetics in the prevention of intraoperative ischemic insults, which tend to be less severe than spontaneous strokes. Undoubtedly, propofol offers advantages during neurosurgery in which intracranial hypertension is a menace, in that it allows the surgeon to operate under safe and optimal conditions.

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