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Invited review

Propofol and the electroencephalogram

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ABSTRACT

Propofol is an emulsion formulation of 2,6 diisopropylphenol developed in 1975. Widely recognized, it offers beneficial effects compared with other sedative drugs. Propofol is used in several clinical situations including multiple surgical procedures and critical-care medical conditions. Since technological advances over recent years have allowed an ever-increasing number of patients undergoing propofol therapy to be monitored by using continuous digital EEG, it is important to have a complete understanding of the effects of propofol on EEG in diverse clinical scenarios. This paper presents a review of the effects of propofol in electroencephalograms and discusses proconvulsive, anticonvulsive proprieties and the EEG findings in different medical conditions.

Contents

1. Introduction

Propofol, an emulsion formulation of 2,6 diisopropylphenol, is a short acting hypnotic drug available for parenteral administration which was developed in 1975 (Gepts et al., 1985). It is highly lipid-soluble and readily permeating biomembranes such as the blood–brain barrier and rapidly getting to target sites in the brain. Thus, the time of the onset of anesthetic effect is equivalent to the circulation time from the arm to the brain. Furthermore, it can quickly be redistributed from the brain into other tissues so that patients can readily recover from the anesthetic state. Its fast onset and offset features make propofol ideal for ambulatory surgeries or anesthesia maintenance. In comparison with isoflurane and desflurane, propofol also has some antiemetic and euphoric effects (Gepts et al., 1985; Tramer et al., 1997; Gupta et al., 2004).

The use of propofol in intensive care units is widely recognized and offers beneficial effects as compared with thiopentone, thiopental or etomidate, including decreased airway reactivity and intraocular pressure, anti emesis, without the danger of drug dependence, or change in adrenal function. There are, as well, several potential advantages for sedation and seizure control in the neurological and neurosurgical critically ill (Mirakhur et al., 1987; Eames et al., 1996).

Technological advances over recent years have allowed an ever-increasing number of critically ill patients to be monitored by using continuous digital EEG, and it has become clear that ictal activity is common in this environment (Niermeijer et al., 2003; Nuwer, 2007). The continuous EEG monitoring techniques can greatly enhance the neurological assessment and care of critically ill patients to detect early signs of cortical instability, seizures

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and epileptiform activity; moreover, it can influence decisions to be made concerning therapy and prognosis (Scheuer, 2002; Kilbride et al., 2009).

Propofol is rapidly gaining popularity in patients as an anticonvulsant in status epilepticus (Claassen et al., 2002) as well as a sedative for respirator resistance. Over the past decade, cost has become quite on important factor in choosing a sedative agent; nevertheless, propofol has demonstrated a cost advantage over midazolam in several cost analyses because of faster time to extubation and, in most cases, an earlier discharge from the intensive care units (ICUs). Despite the higher acquisition cost of propofol, the shorter time spent in the ICU reduces total costs over the short term (approximately <3 days) compared with midazolam (Hall, et al., 2001; Crippen, 2002); hence it is important for EEG interpretation to have a complete understanding of propofol effects in the EEG in different scenarios.

2. Anticonvulsive effects of propofol and EEG

Propofol is a γ-aminobutyric acid (GABA) agonist that suppresses seizure activity via GABA-mediated inhibition of neuronal firing. Other mechanisms of action include inhibition of the *N*-methyl-D-aspartate (NMDA) receptor and the modulation of calcium influx through slow calcium ion channels (Kanai et al., 1999; Rossetti et al., 2005; Hayashi et al., 2007). Previous studies that compare propofol with methohexital have consistently demonstrated that propofol (0.75–2.0 mg/kg) reduces seizure duration as compared with methohexital (1.0–1.4 mg/kg) during electroconvulsive therapy (Simpson et al., 1988; Rouse, 1988; Dwyer et al., 1988; Rampton et al., 1989; Mårtensson et al., 1994; Fredman et al., 1994a; Avramov et al., 1995). Currently, continuous intravenous (IV) infusion of midazolam or propofol, together with continuous EEG monitoring, is a common mode of treatment of refractory status epilepticus in children and adults (van Gestel et al., 2005; Parviainen et al., 2006; Holtkamp, 2007). However, there is no prospectively collected evidence that a burst-suppression (BS) EEG pattern is required or is efficacious for the termination of status epilepticus. Many patients can achieve complete seizure control with a background of continuous slow activity and do not incur the greater risks associated with higher doses of medication required to achieve a BS pattern (Marik and Varon, 2004) (Fig. 1).

3. Proconvulsive effects of propofol and EEG

Many drugs used in anesthesia may induce cerebral excitation during administration or withdrawal. Although the precise underlying mechanisms of the proconvulsant effects of propofol, especially in seizure-prone individuals, remains to be elucidated (Modica et al., 1990; Bevan, 1993; Mäkelä et al., 1993; Walder et al., 2002), a potential mechanism for the proconvulsant properties of propofol may be due to intrinsic subcortical glycine antagonism or GABAergic agonism as suggested by animal data (Albertson et al., 1991; Dolin et al., 1992; Hadipour-Jahromy and Daniels, 2003). Today it is recognized that glycine receptors are widely distributed throughout the CNS in humans (Tao and Ye, 2002.) and the antagonism of glycine receptors for strychnine to the cerebral cortex in animals evokes epileptiform phenomena such as high-voltage waves in the EEG with concomitant paroxysmal depolarization shifts at the cellular level (Straub et al., 1997; Deudeck et al., 2003). Furthermore, propofol increases the inhibition of GABAergic thalamopetal inputs to the thalamus, generates thalamo-cortical oscillations and promotes high-voltage spike and wave spindles and clinical seizures in animal models (Hadipour-Jahromy and Daniels, 2003).

Propofol can induce clinical seizures and seizure like phenomena (SLP) during induction, maintenance or emergence; it may even be delayed after anesthesia and sedation in epileptic and non-epileptic patients (Bevan, 1993; Walder et al., 2002). SLP are defined in five clinical presentation categories: (1) generalized tonic–clonic seizures (GTCS); (2) focal motor seizures; (3) events present such as increased tone with twitching and rhythmic movements not perceived as generalized tonic–clonic seizures; (4) opisthotonus; and (5) involuntary movements. From a semiological point of view, categories 1–3 are most suggestive of an epileptic origin (Walder et al., 2002).

In a recent systematic review study that included 70 patients without known epilepsy who received a propofol induction dose between 0.5 and 5.2 mg/kg, and between 3.0 and 13.2 mg/kg/h during the entire intervention (combined with different analgesics) showed SLP during the induction of anesthesia or sedation (24 patients; 34%), during emergence (28; 40%), or delayed (16; 23%). Delayed SLP were 33 min to 6 days after anesthesia or sedation. Two SLP (3%) occurred only during maintenance. SLP were generalized tonic–clonic seizures in 30 patients (43%); the events presented were increased tone with twitching and rhythmic movements

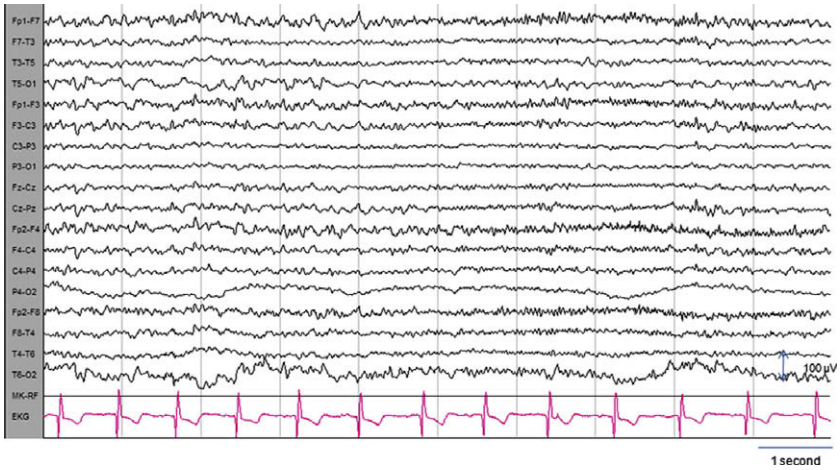

Fig. 1. Male, 23 years old with a history of long standing of frontal lobe epilepsy, intractable and cryptogenic etiology. He was admitted to the emergency room in a generalized convulsive status epilepticus which started 12 h before. He has been undergoing propofol infusion at 2.5 mg/kg/h for 24 h. This EEG was carrying out during the first 24 h while the patient is a comate state induced by propofol. EEG shows a generalized slowing, focal bi-frontal slowing, fast rhythms in beta range mixed and occasional spike-waves on the bi-frontal regions. Then, the patient was seizure free for 72 h. A BS pattern was not a necessary to the control of the status epilepticus. Low-pass filter (LFF) 0.3 Hz, High-pass filter (HFF) 70 Hz. Sensitivity 10 μV/mm.

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not perceived as GTCS in 20 (29%), involuntary movements in 11 (16%), opisthotonus in six (9%) and focal motor seizures in three (4%). An EEG was performed during the next 24–48 h on 24 patients (34%), after the SLP had stopped (Walder et al., 2002). Five patients had an abnormal EEG (generalized spikes in two, generalized slowing in three) (Hopkins, 1988; Bevan, 1993; Mäkelä et al., 1993; Borgeat et al., 1993; Mangan and Perala, 1995; Bragonier et al., 2000). Since the seizures generated by propofol appear to be induced with low doses (Nadstawek et al., 1993), the rapid changes of propofol concentration in the brain at the beginning or end of anesthesia may be crucial for the generation of seizures. In rats, propofol increases inhibition in the evoked potential measurements from the dentate gyrus in a manner attributed to GABAergic agonists (Albertson et al., 1991). GABAergic thalamopetal inputs to the thalamus generate thalamo-cortical oscillations and promote high-voltage spike and wave spindles in some genetically defined rat strains; these spindles are associated with unresponsiveness, eye blinking, and myoclonic jerks resembling human nonconvulsive generalized epilepsy (Hadipour-Jahromy and Daniels, 2003). Propofol may also cause the inhibition of mechanisms that dampen epileptic activity, thus inducing seizures (Cochran et al., 1996).

There are several case reports of patients with epilepsy who received anesthesia with propofol (Cameron, 1987; Jones et al., 1988; Strowbridge, 1989; Bredahl, 1990; Paech and Storey, 1990; Collier and Kelly, 1991; Borgeat et al., 1991; Mäkelä et al., 1993; Karadimov et al., 1994; Slater, 1995; Bellver-Romero et al., 1997). SLP occurred mainly during the emergence from anesthesia. The induction dose of propofol was between 1.5 and 2.5 mg/kg. GTCS occurred in 82% of the patients (Walder et al., 2002). Electroencephalographic correlation was available only in two cases, which showed generalized slowing and spikes in one patient and focal spikes in the temporal region in another (Bredahl, 1990; Mäkelä et al., 1993). The general consensus among anesthesiologists is that propofol should be avoided in patients with epilepsy (Paech and Storey, 1990; Collier and Kelly, 1991; Borgeat et al., 1991; Mäkelä et al., 1993). This recommendation, however, is changing because an increasing number of patients have manifested good outcomes during epilepsy surgery (Hufnagel et al., 1990; Ebrahim et al., 1994; Cheng et al., 1996; Hewitt et al., 1999; Soriano et al., 2000).

4. Relationship between propofol doses and electroencephalographic findings

There are several studies that show the relation between propofol doses and EEG changes during induction. A study in the pediatric population (21 children, 7–8 yrs) randomized children to receive propofol at 3 mg/kg and 5 mg/kg or thiopental at 5–7 mg/kg. The baseline EEG was normal in all the patients. The induction EEG sequences were similar for the three groups: after a mean latency of 12 s, the tracing showed an increase in frequency from 9 to 10 Hz (alpha waves) to more than 14 Hz (beta waves). This transition lasted approximately 2 s, followed by delta waves (2–3 Hz) that continued for 1–2 min. Finally, beta waves reappeared progressively but incompletely replaced delta waves during the next 5 min (Borgeat et al., 1993). Delta waves are more common in orbitofrontal regions (Johnson et al., 2003; Sonkajärvi et al., 2008). Besides, induction EEG sequences are similar using 2.5 mg/kg (Saint-Maurice et al., 1987).

Immediately following the induction of anesthesia there is a marked depression of neuronal activity in the EEG. Subsequently, out of the almost flat EEG, a spindle-shaped, rhythmic series of waves emerge, to be later joined by typical BS patterns. These 14 Hz spindles waves with waxing and waning amplitudes appeared simultaneously over several channels (Huotari et al., 2004). It resembles spindle-waves of sleep and barbiturates, which generate in the thalamus and exclusively distributed to neocortex along thalamo-cortical axons (Steriade et al., 1990; Mackenzie et al., 2004; Feshchenko et al., 2004; Sonkajärvi et al., 2008). The main components of propofol burst are the slow waves, which are positive at all scalp or neck electrodes referred to the depth electrodes and show a the highest amplitude in the frontopolar electrodes and the lowest in the central and parietal electrodes when refer to the depth electrodes. Furthermore, the sharp waves of the BS resemble the vertex waves of physiological sleep and their distribution similar to that of the spindles. These similarities with slow wave sleep could be explained by the effect of propofol on the aurosal system (Sonkajärvi et al., 2008). Clinically the patients develop unconsciousness, which is secondary to the suppression of cortical activity (Velly et al., 2007) and the 50% effective dose for propofol to induce loss of consciousness is 0.97 mg/kg (Iwakiri et al., 2005; Kodaka et al., 2006).

A propofol dose range of 40–200 mg produces burst-suppression in all patients, (Hopkins, 1988; Nadstawek et al., 1993; Mangan and Perala, 1995) except during refractory status epilepticus, in which case BS is initially achieved quickly but efforts to maintain BS require incremental doses of propofol (9.5 (8.2–11.0) mg/kg/h). Despite high doses, propofol plasma concentrations remain at the same level as has been measured during total IV intraoperative anesthesia (van Gestel et al., 2005; Parviainen et al., 2006) (Fig. 2). Animal experiments have shown that during BS EEG approximately 95% of cortical cells switch over to alternating sequences of phasic depolarizing events (bursts) and electrical silence (flat periods), whereas 30–40% of thalamic cells continue to discharge rhythmic spike bursts during flat periods in neocortical neurons. However, this occurs only when the flat periods are limited to approximately 30 s (Steriade et al., 1994). The anesthetic-induced neocortical BS activity appear to involve action sites which are intrinsic to neocortex, requiring intact glutamatergic transmission; the transition from BS to isoelectric EEG activity appears to result from an anesthetic-induced depression of glutamate-mediated excitatory synaptic transmission (Lukatch et al., 2005). Besides, animal studies using rats have shown that the electrophysiological characteristics of BS induced by propofol vary among BS induced by isofluorane or thiopental, the BS induced by propofol showing shorter duration and lower amplitude (Akrawi et al., 1996).

The propofol infusion syndrome, characterized by cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure may be associated with a high-dose infusion of propofol (Bauer et al., 2004). The dose of 4 mg/kg/h has been considered as the upper limit in the sedation of critically ill patients for longer than 48 h. The syndrome has been reported mainly in patients with acute neurological illnesses including status epilepticus (Hanna and Ramundo, 1998; Vasile et al., 2003).

Status epilepticus patients frequently use a broad range of doses of propofol (0.1–24 mg/kg/h) to achieve a cessation of status epilepticus. However, propofol therapy achieves just 64% of complete clinical seizure suppression, 78% of electrographic seizure suppression and 29% of the elimination of all epileptiform discharges (Prasad et al., 2001).

Propofol can inhibit the interictal epileptiform activity in vitro (Rasmussen et al., 1996; Ohmori et al., 2004). However, data on propofol-induced EEG changes in epilepsy patients are limited to a few small size studies in adults, and it is not conclusive as to whether propofol activates or depresses EEG seizure activity in this patient cohort (Hufnagel et al., 1990; Oei-Lim et al., 1992). A study on the pediatric population has analyzed the propofol effects (bolus; mean (SD) 2.4 (1.0) mg/kg) and the continuous infusion rate (mean (SD) 0.4 (0.2) mg/kg/h) in the EEG in 25 epilepsy patients during sedation to carry out MRI studies. In 16 out of 18 patients

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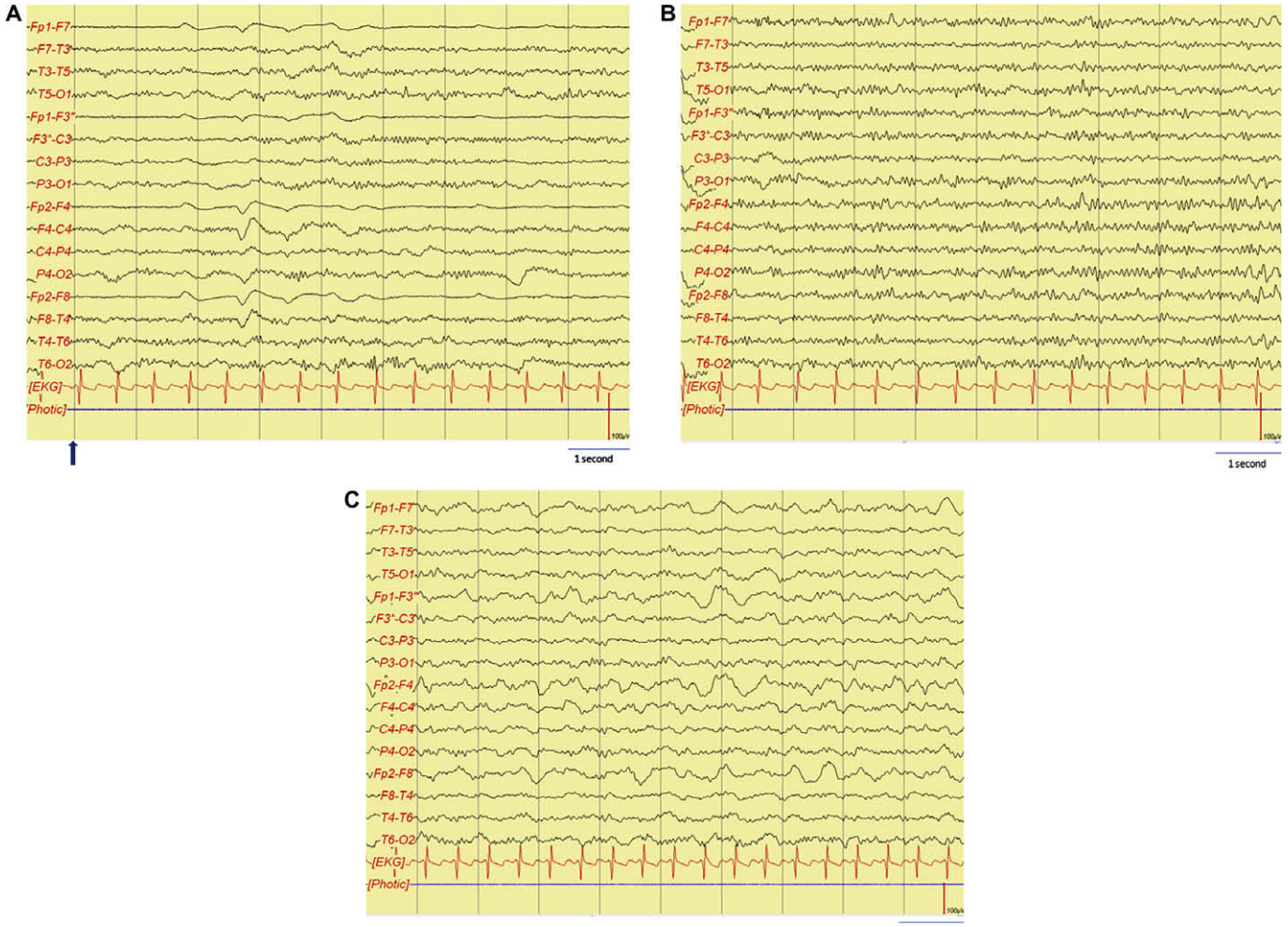

Fig. 2. Male 52 years old with intractable, right frontal lobe epilepsy and spinocerebellar ataxia. He was admitted to the emergency room for very frequent hypermotor seizures and underwent EEG long-term monitoring to get a new MRI brain scan using propofol. A. The initial EEG shows a generalized slowing at 7–8 Hz. After propofol bolus (2.0 mg/kg; arrow blue), this EEG pattern was changed by a faster rhythm in alpha range, at 10–12 Hz, mainly over the fronto-central regions after 2 s of the propofol infusion. B. At 10 s later, the EEG shows a generalized faster background activity at 10–12 Hz. C. Then at 12 s a generalized slowing at 5–6 Hz, and a more pronounced focal delta slowing over the frontal areas. LFF 0.3 Hz, HFF 70 Hz. Sensitivity 7 μV/mm (A and B) and 10 μV/mm (C). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with epilepsy and documented spike-wave patterns prior to propofol sedation there was demonstrated a suppression of spike-wave patterns (>90% of baseline seizure activity). In addition, no depression or augmentation of EEG amplitudes, a primary occurrence, or an increase in spike-wave patterns was seen. EEG changes induced for propofol disappeared 4 h after terminating the infusion (Meyer et al., 2006). In a study of 11 mentally handicapped adults with pharmacologically treated epilepsy, propofol (mean (SD); 5.5 (1.1) mg/kg/h) decreased epileptic activity in the EEG in three patients and paroxysmal discharge disappeared in two patients. The EEG was unaffected by propofol in the remaining six patients during conscious sedation (Oei-Lim et al., 1992). Another study on 30 neurosurgical adult patients with or without a history of seizures (control group) showed that spike or sharp waves appeared in 33% of the control patients and in 40% of the epileptic group after propofol 0.5 mg/kg and in 73% of the control and 67% of the epilepsy patients after 1.5 mg/kg. In the majority of patients, the spike-waves disappeared when additional doses of propofol were administered. One patient in the epileptic group had an EEG-recorded and clinical grand mal seizure after propofol (1 mg/kg), but the seizure disappeared after an additional 0.5 mg/kg bolus was administered (Nadstawek et al., 1993). Table 1 summarizes the profolol doses and the main clinical and EEG findings.

An alternative methodology to analyze the anesthetic effects of the propofol doses on the brain activity is the EEG entropy. The electroencephalographic entropy is a combined EEG and electromyographic (EMG) monitor used to measure the degree of brain function and the depth of anesthesia. Entropy calculates two different spectral entropy indicators; (1) the state entropy (SE) is computed over the frequency range from 0.8 to 32 Hz. It includes the EEG-dominant part of the spectrum and (2) the response entropy (RE) is computed over a frequency range from 0.8 to 47 Hz. (Viertiö-Oja et al., 2004; Riad et al., 2007). SE is a stable indicator of the effect of hypnotics on the cortex. RE, on the other hand, reacts rapidly to changes and serves as a nearly immediate indication of frontal EMG activity and the impending awakening of the patient (Davidson et al., 2005). RE ranges from 0 to 100, whereas SE varies between 0 and 91 (Viertiö-Oja et al., 2004). For fully awake and responsive subjects, a value of 100 for RE and 91 SE, respectively, is observed, i.e. the difference between these parameters is usually <10. For clinically meaningful anesthesia and low probability of consciousness, a value between 40 and 60 is considered appropriate (Riad et al., 2007). Some studies indicate that the propofol anesthesia guide by EEG entropy significantly reduces the total dose of propofol (37%) and the induction dose (31.8%) mg/kg used (Vakkuri et al., 2005; Riad et al., 2007). The sensitivity and specific-

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Table 1
Correlations between propofol doses, clinical states and electroencephalographic findings.

Authors	Dose ranges (mg/kg)	Clinical effect	EEG findings
Iwakiri et al. (2005), Kodaka et al. (2006)	0.97	50% effective dose for propofol to induce loss of consciousness	Induction sequence, see below
Simpson et al. (1988), Rouse (1988), Dwyer et al. (1988), Rampton et al. (1989), Mårtensson et al. (1994), Fredman et al. (1994a), Avramov et al. (1995), Rosa et al. (2008), Eser et al. (2009), Bauer et al. (2009)	0.75–2.0	Reduces seizure duration compared with methohexital, thiopental, or etomidate during electroconvulsive therapy	Electrographic seizure induced
Walder et al. (2002)	0.5 and 5.2	Propofol can induce clinical seizures and seizure like phenomenon	Non epilepsy patients: Generalized spikes or generalized slowing
Bredahl (1990), Mäkelä et al. (1993), Walder et al. (2002)	1.5 and 2.5	Propofol can induce clinical seizures and seizure like phenomena	Epilepsy patients: Generalized spikes, generalized slowing or focal spikes
Oei-Lim et al. (1992), Meyer et al. (2006)	2.4 or 0.4 to 5.5 mg/kg/h	Loss of consciousness	Epilepsy patients: $\geqslant$90% suppression of spike-wave patterns
Saint-Maurice et al. (1987), Borgeat et al. (1993), Huotari et al. (2004)	2.5, 3 and 5	Loss of consciousness	Induction sequence: 12 s, 9–10 Hz α and 14 Hz β waves; 14 s, delta waves (2–3 Hz);120 s, 14 Hz β waves and delta waves(2–3 Hz); 300 s, spindles and isoelectric EEG; >300 s burst-suppression
Hopkins (1988), Nadstawek et al. (1993), Mangan and Perala (1995)	0.1–5	Coma in all patients	Burst-suppression
Hanna and Ramundo (1998), Vasile et al. (2003)	>4 mg/kg/h for >48 h	Propofol infusion syndrome	Burst-suppression or status epilepticus
van Gestel et al. (2005), Parviainen et al. (2006)	9.5 (8.2–11.0) mg/kg/h	Doses usually required in refractory status epilepticus (RSE)	Burst-suppression or status epilepticus
Prasad et al. (2001)	0.1–24 mg/kg/h	RSE: 64% complete clinical seizure suppression	RSE: BS or status epilepticus 78% electrographic seizure suppression 29% elimination of all epileptiform discharges

ity of the entropy has been demonstrated in previous reports; this indicates that entropy is as efficient as the Bispectral Index (BIS) in predicting changes in the hypnotic component of anesthesia (Bonhomme and Hans, 2004; Vakkuri et al., 2004), and the changes in SE and RE values follow a similar pattern to the BIS values during propofol, thiopental, sevoflurane and desflurane induction in adults (Vakkuri et al., 2004, 2005). However, there is a wide variability in the response of patients to propofol that cannot be detected without the continuous monitoring of cortical electrical activity during the operating period, e.g. an unexpected abnormally low BIS and an almost isoelectric EEG pattern during typical induction of anesthesia with propofol (1.26 mg/kg) (Rudner et al., 2005).

Other authors have suggested, however, that different stages of anesthesia including the burst-suppression phase can easily be distinguished best by both nonconventional spectral measures, and nonlinear measures. A study using scalp and deep hippocampus and anterior parahippocampal gyrus recording simultaneously showed increasing delta and alpha power with the deep structures with increasing depth of anesthesia while scalp spectral entropy and the Lyapunov-exponent in the anterior parahippocampal gyrus decreased, expressing a more concentrated power spectrum at the scalp position (*Cz*) and reduced EEG chaoticity within rhinal cortex during deeper levels of anesthesia (Fell et al., 2005).

5. Relationship between age, propofol and electroencephalographic findings

The number of older people who have to undergo surgical procedures is steadily growing. For these patients the risks of anesthesia are often increased because of their past medical history and their restricted physiological resources. Apart from parameters of the cardiovascular system, the electroencephalogram represents a supplementary method for intraoperative monitoring, because cerebral alterations caused by anesthetics or narcotics are directly reflected in the EEG (Schultz et al., 1995). Older patients differ from younger ones regarding the hypnotic effect of propofol and the spectral patterns in the EEG. During induction, patients older than 70 years reach significantly deeper EEG stages than younger patients, needing a longer time to reach the deepest EEG stage and more time for recovery to a light EEG stage. In patients aged 70 years and older, the total power, mainly in deep EEG stages, is significantly smaller due to a distinctly smaller absolute power of the delta frequency band. During the steady state of anesthesia, older patients need less propofol for the maintenance of a defined stage of brain function than younger patients (Schultz et al., 2004).

Fospropofol disodium (Aquavan® injection; MGI Pharma, Inc., Bloomington, MN, USA) is a water-soluble prodrug of propofol currently under investigation for diagnostic procedures. Fospropofol is rapidly hydrolyzed by endothelial alkaline phosphatases in vivo after intravenous administration, releasing propofol, phosphate and formaldehyde. Fospropofol derived propofol is the active compound that provides sedation and has a slower pharmacokinetic and pharmacodynamic profile than propofol lipid emulsion; it could hence, be a better option in elderly patients or another special population (Fechner et al., 2005; Levitzky and Vargo, 2008).

6. Propofol and epilepsy surgery

Previous studies have addressed the action of propofol on the electrocorticogram (ECoG) during epilepsy surgery with markedly different results (Hewitt et al., 1999). Propofol does not interfere with intraoperative ECoG during awake craniotomies (Soriano et al., 2000; Herrick et al., 1997) and there was no activation of the ECoG with propofol at 0.5–5 mg/kg in children and adults (Hufnagel et al., 1990; Ebrahim et al., 1994; Cheng et al., 1996; Hewitt et al., 1999; Soriano et al., 2000) (Fig. 3).Other authors demonstrated ECoG activation with propofol 2 mg/kg and 150 mg, respectively, in both cases in combination with other medications, including fentanyl (Hodkinson et al., 1987; Mäkelä et al., 1993).

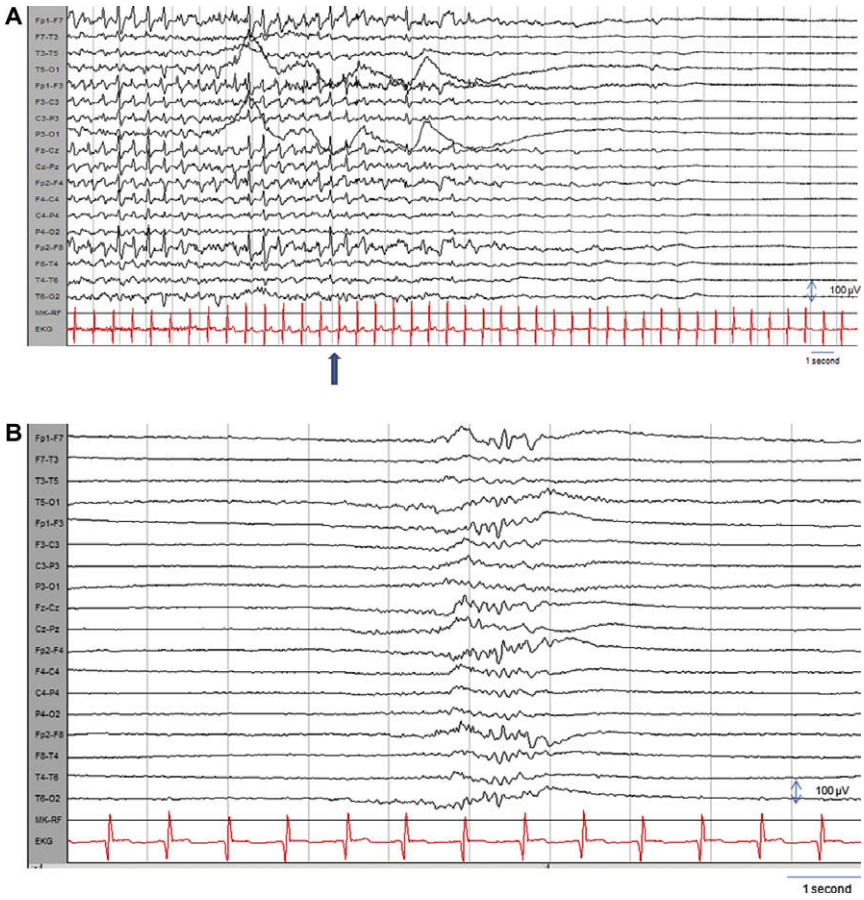

Fig. 3. Female 65 years old with diabetes mellitus type 2. She was admitted to the emergency room in a convulsive generalized status epilepticus, which started 6 h before due to hypoglycemic encephalopathic state, which was secondary to hypoglycemic drug intoxication. A. EEG shows generalized spike-waves complexes at 2 Hz. After propofol bolus (2.5 mg/kg; arrow blue), this EEG pattern was changed by an isoelectric activity in 8 s. B. At 5 min. later, the EEG shows a burst-suppression pattern with fast rhythms in beta range and bi-frontal epileptic activity. LFF 0.3 Hz, HFF 70 Hz. Sensitivity 10 µV/mm. (For interpretation of references to color in this figure legend the reader is referred to web version of this article.)

The authors suggested that reported proconvulsive effects of propofol anesthesia might be caused by co-medication (Cheng et al., 1996). The only finding during epilepsy surgery is a higher frequency background ECoG activity, but this does not interfere with ECoG interpretation (Johnson et al., 2003) (Fig. 4).

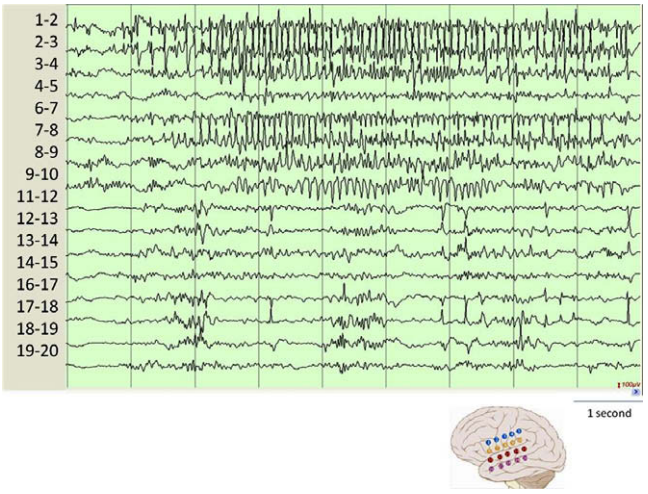

Fig. 4. Female 44 years old with cryptogenic, intractable epilepsy arising from right frontotemporal region. She underwent electrocorticography (ECoG) before the epilepsy surgery. ECoG shows frequent electrographic seizures over the right frontal area, one of this events is shown on the lines 1 and 2 (1–4 and 6–8 contacts) of the grid (5 × 4). Also, often spikes are seen independently over the first and second temporal gyrus. The background shows a 5–14 Hz frequency in range theta and beta. Anesthesia: propofol 3 mg/kg/h and Fentanyl 80 µg/h LFF 0.3 Hz, HFF 70 Hz. Sensitivity 75 µV/mm.

Intracranial monitoring of patients with partial epilepsy using depth electrodes implanted in the hippocampi and temporal neocortex and plasma propofol concentrations of 0.3, 0.6, 0.9 and 1.2 µg/ml during 30 min demonstrated no a significative change in epileptiform activity with sedative doses of propofol (Herrick et al., 1997).

7. Propofol and electroconvulsive therapy

Electroconvulsive therapy (ECT) is still considered the most effective biological treatment strategy in psychiatric disorders (Eser et al., 2009). The most widely studied hypnotic agents for use in ECT are methoxital, etomidate and propofol (Folk et al., 2000; Ding and White, 2002). However, in some countries, propofol is the only hypnotic agent available to the anesthesiologist for ECT (Porter et al., 2008). Propofol has a favorable cardiovascular profile advantages (Rampton et al., 1989), rapid recovery, and reduced agitation (Fredman et al., 1994b; Nguyen et al., 1997). However, it has a major disadvantage in that it is antiepileptic and reduces seizure length if used in traditional anesthesia induction doses of 2 mg/kg (Simpson et al., 1988). The clinical efficacy of ECT may be affected by stimulus variables and the concomitant use of psychopharmacological medication; nevertheless, recent studies comparing propofol with thiopental anesthesia have shown that the clinical effectiveness is similar in both anesthetic

procedures (Eser et al., 2009). These studies also show that propofol significantly decreases seizure duration and offers the best recovery profile compared with thiopental or etomidate (Rosa et al., 2008; Eser et al., 2009; Bauer et al., 2009). However, propofol requires a higher mean electric charge to induce a seizure during the ECT (Rosa et al., 2008).

The EEG is recorded bilaterally from the frontal and mastoid electrodes during the ECT and the EEG seizures length can be measured directly for visual inspection; detection software are even included in some ECT devices (Porter et al., 2008). EEG measures may better predict the clinical efficacy of treatment. For example, the postictal suppression index, shown in several studies to correlate with clinical efficacy is calculated as the ratio of the amplitude of the postictal EEG divided by the amplitude of the baseline EEG (Nobler et al., 1993; Perera et al., 2004; Porter et al., 2008). The application of electroencephalography is recommended in monitoring patients with prolonged confusion following ECT to diagnose nonconvulsive status epilepticus (Povlsen et al., 2003).

8. Conclusions

Propofol is a unique short acting hypnotic with several advantages over other anesthetic drugs. Over the time, the use of propofol is increasing as anticonvulsant and as a sedative agent. Hence, the knowledge of the electroencephalographic changes induced by propofol is relevant to neurologists, anesthesiologists, neurophysiologists or other health care professionals involved in the medical attention of the critical ill patients and other patients undergo anesthesia with propofol.

Propofol can suppress the seizures activity via GABA agonism, inhibition of the NMDA receptor and modulation of the slow calcium ion channels, several range of doses can suppresses the interictal and ictal activity abolish the epileptiform discharges, electrographic seizures, clinical seizures and the status epilepticus inducing the burst-suppression pattern. However, the same GABA agonism and the glycine antagonism can also induce clinical seizures and EEG epileptiform changes, the rapid changes of propofol concentration in the brain at the beginning or end of anesthesia may be crucial for the generation of seizures in both epileptic and nonepileptic patients.

The sequences of the EEG changes induces by propofol is unique between other anesthetic drugs. These EEG changes are more prominent in the fronto-central regions and do not interfere with the interpretation of the routine EEGs and intraoperative ECoG during awake craniotomies.

During the anesthesia the continuous monitoring of cortical electrical activity is used to measure the degree of brain function and the depth of anesthesia. Currently, the entropy is as efficient as the Bispectral Index in predicting changes in the hypnotic component of anesthesia correlated with EEG scalp findings, and these measurements significantly reduces the total dose of propofol and the induction dose used during the surgical procedures. However, during the ECT the sedation with propofol significantly decreases seizure duration and requires a higher mean electric charge to induce a seizure. Although, recently studies have shown that the clinical effectiveness is similar using other anesthetic drugs.

Conflict of interest

The authors report neither disclosures nor any conflict of interests; all coauthors have seen the manuscript and are in agreement concerning its contents. This paper is not under review for any other publication.

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