Intensive Care Med (2006) 32:1075–1079
DOI 10.1007/s00134-006-0154-1

BRIEF REPORT

**Ilkka Parviainen**
**Ari Uusaro**
**Reetta Kälviäinen**
**Esa Mervaala**
**Esko Ruokonen**

# Propofol in the treatment of refractory status epilepticus

Received: 23 September 2005
Accepted: 10 March 2006
Published online: 6 May 2006


I. Parviainen (✉) · A. Uusaro · E. Ruokonen
Kuopio University Hospital,
Department of Anesthesiology
and Intensive Care,
Puijonlaaksontie 2, FIN-70211 Kuopio,
Finland
e-mail: ilkka.parviainen@kuh.fi
Tel.: +358-17-173423
Fax: +358-17-173443

R. Kälviäinen
Kuopio University Hospital,
Department of Neurology,
Kuopio, Finland

E. Mervaala
Kuopio University Hospital,
Department of Clinical Neurophysiology,
Kuopio, Finland

**Abstract** *Objectives:* To study prospectively the effects of propofol anesthesia on seizure control, hemodynamics and course of intensive care in patients with refractory status epilepticus. *Design and setting:* Prospective observational study in the general intensive care unit in a tertiary university hospital. *Patients:* Ten patients with refractory status epilepticus. *Interventions:* Patients received propofol anesthesia aiming to burst suppression EEG pattern for 12 h. *Measurements and results:* Dose of propofol, quality of burst suppression EEG, hemodynamics and the course of intensive care were recorded. Clinical and electrophysiological seizures terminated quickly, but maintaining burst suppression EEG pattern required incremental doses of propofol. Despite high doses of propofol, recovery from anesthesia was fast. *Conclusions:* High doses of propofol are needed in the treatment of refractory status epilepticus. The maintenance of continuous-burst suppression is difficult, and vigilant titrating of dosage of propofol is necessary under continuous EEG monitoring.

## Introduction

Thiopental, midazolam and propofol have been used for treatment of refractory status epilepticus, but there are no randomized studies comparing the different drugs. After high doses, thiopental accumulates in tissues and prolongs recovery [1]. It also may be immunosuppressive and may predispose patients to infections [1]. Propofol is a short-acting agent and has been considered as a promising drug in the treatment of refractory status epilepticus (SE). On the other hand, its use has been challenged because it may induce excitation of CNS, predispose to seizures and even increase risk of mortality [2, 3]. There is limited data of the effects of propofol in the treatment of refractory status epilepticus, and all the data is based on retrospective case reports and small case series. We conducted a prospective study, in which we used a predefined treatment protocol for the administration of propofol and for the hemodynamic treatment. The purposes of this study were to describe the effects of propofol on termination of SE, hemodynamics and recovery after anesthesia.

## Patients and methods

We studied ten consecutive adult patients with refractory SE. The ethics committee of the hospital approved the study. Informed written consent was obtained from the next of kin. After admission into the intensive care unit, arterial and pulmonary artery catheters were inserted. EEG was recorded with a continuous digital EEG device (Grass-Telefactor, West Conshohocken, PA, USA) during

the 24-h treatment period. Scalp Ag-AgCl-electrodes of 10–20 system were attached with Ten20 electrode jelly. The EEG recording unit was connected to a laptop, which provided online monitoring option as well. An experienced clinical neurophysiologist (E.M.) analyzed the EEGs later. Before admission to ICU, patients received serial boluses of 0.2–0.5 mg $kg^{-1}$ of diazepam and a loading dose of 15–20 mg $kg^{-1}$ of fosphenytoin. During the period from admission to the ICU and the start of EEG monitoring, patients received boluses of 1–2 mg $kg^{-1}$ of propofol aiming to terminate clinical seizures. After starting continuous EEG monitoring, anesthesia was induced with a bolus of 2–3 mg $kg^{-1}$ of propofol, and boluses of 1–2 mg $kg^{-1}$ of propofol were given every 3–5 min until a burst-suppression EEG pattern with suppression phases of 5–10 s was achieved. Thereafter, an infusion of 4 mg $kg^{-1}$ $h^{-1}$ of propofol was started, and EEG was recorded continuously. If a burst-suppression pattern was achieved, the dose of propofol was maintained. If a burst-suppression pattern was not maintained, a bolus of 1 mg $kg^{-1}$ was given, and the rate of propofol infusion was increased by 1 mg $kg^{-1}$ $h^{-1}$. Maintenance infusion of propofol was continued for 12 h after achieving satisfactory burst-suppression EEG pattern. Thereafter, the propofol infusion was tapered during the next 12 h: the rate of propofol infusion was decreased every third hour by 20%.

The patients were mechanically ventilated, aiming for normoventilation. The target of core temperature was normothermia. We used a predefined protocol for the treatment of hemodynamics to maintain sufficient blood pressure and tissue perfusion (Fig. 1) [1]. Hemodynamics was recorded after admission into the ICU, and after 4 h, 8 h, 12 h and 24 h from the beginning of burst-suppression EEG pattern. Antiepileptic drugs used prior to admission and during ICU stay, total dose of propofol during the first 24 h and maximal rate of propofol infusion during treatment were recorded. Serum triglyceride concentrations were measured at the beginning and at the end of anesthesia. Plasma propofol concentrations were measured when burst-suppression EEG pattern was initially achieved and after 12 h from the beginning of burst-suppression EEG pattern, when the rate of propofol infusion was at maximum. The analysis was performed with a Hewlett-Packard (Hewlett-Packard, Palo Alto, CA, USA) G1800A GC/MS (EI, positive ions, 70,eV). Duration of mechanical ventilation, Glasgow Coma Scale (GCS) at discharge from ICU, length of intensive care and hospital stay were recorded.

Hemodynamic changes during the first 24 h were analyzed with Friedman's test. Findings were considered significant if $p < 0.05$. Results are presented as median and interquartile range.

## Results

Etiology and treatment of status epilepticus are presented in Tables 1 and 2. Median duration from the onset of seizures to burst-suppression EEG pattern was 6 h (5–11 h). Period between ICU admission and the start of propofol anesthesia under continuous EEG monitoring was 103 min (34–134 min). The period from the beginning of propofol anesthesia to burst suppression was 35 min (18–40 min). Median rate of the highest propofol infusion was 9.5 (8.2–11.0) mg $kg^{-1}$ $h^{-1}$ (Table 2), and median total dose of propofol was 195 (173–204) mg $kg^{-1}$ during 24 h.

Clinical seizures terminated in each patient, but the duration of optimal burst suppression was variable (Table 2). In three patients, burst suppression was maintained for the total 12 h. In three patients, epileptic seizures reoccurred when tapering propofol infusion, and two of them received thiopental anesthesia thereafter. Two patients died early in hospital; one had hypoglycemic brain injury due to self-inflicted insulin overdose, and the other had wide cerebral infarction (Table 3). Three additional patients died later, one due to degenerative brain disease and two due to sequelae of subdural hemorrhage.

Each patient needed fluid resuscitation; the amount of crystalloids was 2,250 ml (2,000–3,000 ml) and colloids 1,000 ml (625–1,500 ml) during the first 24 h. Seven patients received norepinephrine to maintain mean arterial pressure, with the median dose of 0.058 (0.038–0.078) μg $kg^{-1}$ $min^{-1}$. One of these patients also received dobutamine, with a dose of 5.1 μg $kg^{-1}$ $min^{-1}$. Serum lactate

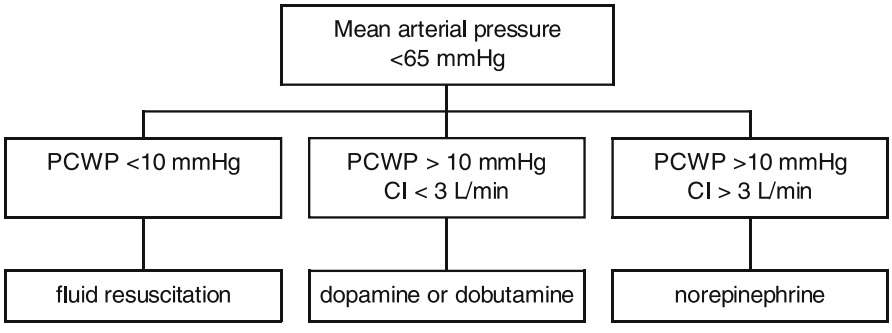


**Fig. 1** Protocol for hemodynamic treatment

**Table 1** Data of previous epilepsy and etiology of status epilepticus (*CBZ* carbamazepine, *CLN* clonazepam, *LTG* lamotrigine, *OXC* oxcarbazepine, *TPM* topiramate, *SE* status epilepticus, *VPA* valproate)

| Patient/ gender/age | Etiology of epilepsy | Seizure type | Duration of epilepsy (years) | Antiepileptic medication | Etiology of SE | Type of SE | MRI/CT |
|---|---|---|---|---|---|---|---|
| 1/M/42 | Cerebral contusion | Partial complex + secondary generalized | 9 | TPM, VPA | Epilepsy | Partial complex | Normal |
| 2/F/47 | Unknown syndrome of ataxia | Partial complex + secondary generalized | 13 | CBZ | Epilepsy | Partial simple | Cerebellar atrophy, edema |
| 3/M/52 | Encephalitis | Partial complex + secondary generalized | 5 | VPA, LTG, CBZ, CLN | Epilepsy | Generalized | Normal |
| 4/F/21 | Unknown | Partial complex + secondary generalized | 17 | TPM, LTG, CLB, OXC | Epilepsy | Partial complex | Normal |
| 5/F/21 | No epilepsy | — | — | — | Insulin intoxication | Generalized | Severe edema |
| 6/M/50 | No epilepsy | — | — | — | Subdural hemorrhage | Partial complex | Subdural hemorrhage |
| 7/F/83 | No epilepsy | — | — | — | Infarction | Partial complex | Left hypodense infarct |
| 8/F/35 | Unknown | Partial complex + secondary generalized | 10 | TPM, CBZ, LTG | Epilepsy | Partial complex | Normal |
| 9/F/47 | No epilepsy | — | — | — | Subdural hemorrhage | Partial complex | Operated subdural hemorrhage |
| 10/M/53 | Contusion | Secondary generalized | 1 | CBZ | Epilepsy | Partial complex | Old frontal contusion |

**Table 2** Treatment data of SE (*CBZ* carbamazepine, *CLB* clobazam, *CLN* clonazepam, *CT* computerized tomography, *FT* fosphenytoin, *LTG* lamotrigine, LVT levetiracetam, *MRI* magnetic resonance imaging, *TPM* topiramate, *SE* status epilepticus, *VPA* valproate)

| Patient | Duration of SE (h) | Antiepileptic drugs in ICU | Maximal rate of propofol infusion ($mg\,kg^{-1}\,h^{-1}$) | Mean propofol dose during 24 hours ($mg\,kg^{-1}\,h^{-1}$) | Plasma propofol concentration (mg/l) at 12 h of infusion | Proportion of burst-suppression time of active treatment time (0–12 h) (%) | Epileptic seizures in EEG during tapering anesthesia (12–24 h) | Thiopental anesthesia after propofol anesthesia |
|---|---|---|---|---|---|---|---|---|
| 1 | 2 | TPM, VPA, LVT | 5.8 | 4.6 | 1.43 | 100 | − | No |
| 2 | 6 | FT, VPA, TPM | 11.0 | 8.5 | 2.34 | 100 | + | Yes |
| 3 | 5 | FT, VPA, LTG, CBZ, CLN | 9.0 | 7.0 | 3.04 | 4 | − | No |
| 4 | 36 | FT, TPM, LTG, CLB | 10.9 | 8.4 | 1.74 | 14 | + | Yes |
| 5 | 20 | FT, CBZ | 19.7 | 15.1 | 2.24 | 22 | − | No |
| 6 | 5 | FT, VPA, CBZ | 9.2 | 8.2 | 1.63 | 73 | − | No |
| 7 | 7 | FT, VPA, CBZ | 9.9 | 7.8 | 1.03 | 78 | − | No |
| 8 | 12 | FT, TPM, CBZ | 8.0 | 8.0 | 1.97 | 36 | + | No |
| 9 | 6 | FT, VPA, CLB | 6.2 | 5.0 | 2.70 | 100 | − | No |
| 10 | 5 | FT, CBZ | 12.2 | 9.4 | 4.48 | 65 | − | No |

and triglyceride concentrations maintained at the normal level during treatment (Table 4).

## Discussion

Propofol terminated clinical seizures, but the quality of burst suppression was unsatisfactory in most patients. Initially, burst suppression was achieved quickly, but efforts to maintain burst suppression required incremental doses of propofol. Despite high doses, propofol plasma concentrations remained at the same level as has been detected during total intravenous anesthesia in patients undergoing operations [4]. Our results demonstrate that the adjustment of propofol treatment warrants continuous vigilance and EEG monitoring to maintain burst suppression, due to the short elimination half-time of propofol. Obviously, unlike thiopental, propofol cannot be stopped immediately after

**Table 3** Clinical data of the patients (*ICU* intensive care unit, *GCS* Glasgow Coma Score, *IQ* interquartile)

| Patient | Apache II | Ventilator treatment (days) | Length of ICU stay (days) | GCS at discharge from ICU | Length of hospital stay (days) | Early/long-term outcome |
|---|---|---|---|---|---|---|
| 1 | 11 | 5 | 5 | 13 | 22 | Baseline/baseline |
| 2 | 19 | 13 | 18 | 12 | 49 | Baseline/late death |
| 3 | 13 | 3 | 3 | 15 | 10 | Baseline/baseline |
| 4 | 13 | 13 | 15 | 15 | 7 | Baseline/baseline |
| 5 | 28 | 5 | 5 | 5 | 8 | Early death |
| 6 | 28 | 3 | 6 | 4 | 13 | Neurological deficits/ late death |
| 7 | 22 | 7 | 8 | 5 | 13 | Early death |
| 8 | 12 | 2 | 3 | 14 | 11 | Baseline/baseline |
| 9 | 27 | 2 | 3 | 13 | 10 | Neurological deficits/ late death |
| 10 | 23 | 2 | 3 | 13 | 16 | Cognitive deficits/ cognitive deficits |
| Median (IQ range) | 20 (13–26) | 4 (2.2–6.5) | 5 (3–7.5) | 12 (6.5–13) | 12 (10–15) | — |

**Table 4** Hemodynamics, $SvO_2$, serum lactate and triglyceride concentrations (median (interquartile range) (*CI* cardiac index, *CVP mean* mean central venous pressure, *HR* heart rate, *MAP* mean arterial pressure, *PCWP* pulmonary capillary wedge pressure, $SvO_2$ mixed venous oxygen saturation, *SVRI* systemic vascular resistance index)

| | Baseline | 4 h | 8 h | 12 h | 24 h | Friedman test $p$ |
|---|---|---|---|---|---|---|
| HR ($1\,min^{-1}$) | 88 (75–98) | 68 (62–82) | 75 (67–85) | 74 (65–82) | 78 (73–96) | 0.097 |
| MAP (mmHg) | 72 (68–91) | 71 (68–80) | 71 (67–76) | 72 (67–74) | 93 (72–105) | 0.062 |
| CVP mean (mmHg) | 6 (4–6) | 6 (4–7) | 6 (3–8) | 6 (4–8) | 5 (4–7) | 0.682 |
| PCWP (mmHg) | 8 (3–9) | 8 (6–10) | 7 (6–11) | 9 (6–10) | 8 (7–9) | 0.675 |
| CI ($l\,min^{-1}$) | 4.0 (3.3–4.6) | 3.2 (2.4–4.0) | 3.0 (2.7–4.0) | 3.0 (2.7–3.7) | 4.0 (3.1–4.8) | 0.188 |
| SVRI ($dyn\,s\,cm^{-5}\,m^2$) | 1,560 (1,150–1,790) | 1,710 (1,330–1,880) | 1,790 (1,290–2,010) | 1,800 (1,400–1,950) | 1,820 (1,500–2,340) | 0.825 |
| $SvO_2$% | 74 (70–80) | 79 (74–82) | 79 (77–82) | 78 (76–83) | 78 (75–79 | 0.218 |
| Serum lactate concentration ($mmol\,l^{-1}$) | 2.3 (1.5–2.8) | 2.2 (1.4–2.9) | 1.9 (1.3–2.6) | 1.8 (0.9–2.1) | 1.1 (1.0–1.7) | 0.001 |
| Serum triglyceride concentration ($mmol\,l^{-1}$) | 1.2 (0.7–1.5) | — | — | — | 1.2 (0.5–1.6) | 0.705 |
| Norepinephrine (μg/kg/min) | — | ($n=4$) 0.04 (0.028–0.06) | ($n=5$) 0.03 (0.03–0.09) | ($n=7$) 0.04 (0.03–0.06) | ($n=3$) 0.02 (0.015–0.025) | — |

active treatment period but must be tapered stepwise. It is also important to monitor EEG during tapering of propofol, in order to detect possible signs of relapsing epileptic activity.

Hypotension is a well known adverse effect of high-dose anesthetics. All of our patients needed fluid resuscitation, and most of them required norepinephrine for hypotension. The volumes of fluids given were quite large, but hemodynamics was monitored using pulmonary artery catheter, and the median pulmonary capillary wedge pressures varied between 7 mmHg and 9 mmHg during the study treatment, suggesting that the patients were normovolemic but not hypervolemic. Propofol infusion syndrome, characterized by cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure, may be associated with high-dose infusion of propofol [5]. The dose of $4\,mg\,kg^{-1}\,h^{-1}$ has been considered as the upper limit in 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 [6, 7]. Therefore, the use of high-dose propofol in the treatment of status epilepticus should be limited to short term treatment (< 48 h). In our study, the mean rate of propofol infusion during 24 h varied from $4.6–15.1\,mg\,kg^{-1}\,h^{-1}$. There were no signs of cardiac failure: cardiac index was normal, metabolic acidosis was not seen and serum lactate concentrations were low. It seems that propofol can be administered at high doses for short-term treatment. Invasive hemodynamic monitoring reveals early signs of propofol infusion syndrome, and it can be recommended.

The major advantage of propofol is fast recovery from anesthesia due to short elimination half-time. In our previous study, ventilator treatment and intensive care in patients treated with thiopental lasted twice as long as in patients of this study [1]. The faster recovery from anesthesia may decrease the costs of care and prevent or de-

crease complications, like ventilator-associated pneumonia and pressure sores.

In conclusion, propofol is needed at high doses in the treatment of refractory status epilepticus. Even if clinical and electrophysiological seizure control can be achieved quickly, the maintenance of continuous-burst suppression is difficult. Vigilant titrating of dosage of propofol is necessary under continuous EEG monitoring. The advantage of propofol is short recovery from anesthesia. However, randomized studies are needed to compare the effect and safety of anesthetic drugs in the treatment of refractory status epilepticus.

## References


1. Parviainen I, Uusaro A, Kälviäinen R, Kaukanen E, Mervaala E, Ruokonen E (2002) High-dose thiopental in the treatment of refractory status epilepticus in intensive care unit. Neurology 59:1249–1251
2. Victory RA, Magee D (1988) A case of convulsion after propofol anesthesia. Anaesthesia 43:904
3. Niermeijer JM, Uiterwaal C, van Donselaar C (2003) Propofol in status epilepticus: little evidence, many dangers? J Neurol 250:1237–1240
4. Bauer M, Wilhelm W, Kraemer T, Kreuer S, Brandt A, Adams HA, Hoff G, Larsen R (2004) Impact of bispectral index monitoring on stress response and propofol consumption in patients undergoing coronary artery bypass surgery. Anesthesiology 101:1096–1104
5. Vasile B, Rasulo F, Candiani A, Latronico N (2003) The pathophysiology of propofol infusion syndrome: a simple name for a complex syndrome. Intensive Care Med 29:1417–1425
6. Hanna JP, Ramundo ML (1998) Rhabdomyolysis and hypoxia associated with prolonged propofol infusion in children. Neurology 50:301–303
7. Friedman JA, Manno E, Fulgham JR (2002) Propofol. J Neurosurg 2002 96:1161–1162