Effect of propofol on the electrocorticogram in epileptic patients undergoing cortical resection†‡‡

P. B. Hewitt1*, D. L. K. Chu1,3, C. E. Polkey2 and C. D. Binnie2

1GKT Department of Anaesthetics, UMDS, Guy's Hospital, London SE1 9RT, UK. 2Department of Clinical Neurosciences, King’s, Guy’s and St Thomas’ School of Medicine and Dentistry, Denmark Hill, London SE5 9RS, UK
3Present address: Intensive Care Unit, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia

*To whom correspondence should be addressed

We have compared the effect of clinical doses of propofol with thiopental on epileptiform activity in the electrocorticograms (ECoG) of 20 epileptic patients undergoing temporal lobe resection. After baseline ECoG had been obtained, with inspired concentrations of 0.5–1% isoflurane and 70% nitrous oxide to provide background anaesthesia, subjects were allocated randomly to receive boluses of either thiopental 25 mg or propofol 20 mg i.v. every 30 s to a maximum of 5 mg kg–1 or until burst suppression was seen. The ECoG was recorded throughout administration and for 10 min thereafter. After return of baseline ECoG tracings, the alternate agent was administered. The amount of epileptiform activity was recorded on an ordinal rating scale, an increase being indicated by either a rise of at least one category on the scale or discharges occurring at a minimum of one new site. Activation occurred more frequently with thiopental but the difference was not significant. This study suggests that propofol has no greater proconvulsive effect than thiopental, a drug commonly used in managing status epilepticus.

Keywords: anaesthetics i.v., propofol; anaesthetics i.v., thiopental; monitoring, electrocorticography; complications, epilepsy

Accepted for publication: September 7, 1998

Propofol has gained worldwide acceptance as an agent for induction and maintenance of anaesthesia since its launch in 1986. However, the use of propofol for anaesthesia in patients with epilepsy, especially for ambulatory surgery, is controversial as various case reports have claimed a potential proconvulsant effect. This is despite contradictory evidence which has shown that propofol reduces the duration of convulsion during electroconvulsive therapy used for psychiatric treatment1 and that it has anticonvulsant properties.2

Although initial animal and clinical data suggested that propofol is devoid of proconvulsant and anticonvulsant properties, animal data3 suggest that propofol possesses intrinsic subcortical glycine antagonist activity which may contribute to excitatory phenomena.

Patients and methods

All patients undergoing temporal cortical resection for intractable epilepsy were invited to participate. Acute electrocorticography (ECoG), including recording after pharmacological activation, has been used routinely as an aid to localization during temporal lobectomy in this unit for more than 50 yr; written informed consent was obtained for the additional recording after administration of propofol. Patients continued their routine anticonvulsant therapy up to the time of surgery. Standard premedication with papaveretum 0.2–0.3 mg kg–1 and scopolamine 0.4–0.6 µg kg–1 was administered i.m., 1 h before anaesthesia.

Anaesthesia was induced with thiopental 3–7 mg kg–1 and tracheal intubation was facilitated with atracurium 0.5–0.6 mg kg–1. Controlled ventilation of the lungs was started using a Penlon Nuffield 200 ventilator via a Bain coaxial breathing system with a fresh gas flow rate of 70–100 ml kg–1, adjusted to maintain end-tidal carbon dioxide partial pressure at approximately 4 kPa (monitored using a Datex Cardiocap 2 or AS/3 sidestream capnograph). Anaes-
Intraoperative heat loss was minimized with the aid of a forced-air warming system (Bair Hugger) and nasopharyngeal temperature was monitored throughout operation (Datex thermistor). Neuromuscular block was produced with an atracurium infusion starting at 0.5 mg kg$^{-1}$ h$^{-1}$ and adjusted to 0.3–0.7 mg kg$^{-1}$ h$^{-1}$ according to the response of the extensor hallucis muscle to stimulation of the common peroneal nerve using a Rutter transcutaneous peripheral nerve stimulator. Haemodynamic stability was maintained so that systolic arterial pressure was greater than 100 mm Hg and mean arterial pressure greater than 60 mm Hg (measured using a 20-gauge intra-arterial cannula with transducer to a Datex Cardiocap or AS/3 monitor) by adjustment of inspired isoflurane concentration and i.v. fluid administration.

After craniotomy, exposure of the brain surface and application of surface electrodes to the cerebral cortex, approximately 1.5–2.5 h after induction of anaesthesia, an ECoG of at least 5 min duration was recorded. Background anaesthesia was continued with 0.5–1% isoflurane and 70% nitrous oxide in oxygen, and other conditions, as stated above. Subjects were allocated randomly to one of two groups to receive thiopental 25 mg or propofol 20 mg i.v. every 30 s to a maximum of 5 mg kg$^{-1}$ or until burst suppression. The ECoG was recorded throughout administration and for 10 min thereafter. After return of baseline ECoG, which took 10–20 min, the alternate drug was administered and the ECoG recording continued.

When the study terminated, the intraoperative ECoG recordings were assessed and compared for evidence of epileptiform activity (spikes, sharp waves, or spike-and-wave discharges). Sites of epileptiform activity were noted, and the rate of discharge at each site quantified on the following ordinal rating scale: 0 = no discharge; 1 =<1 discharge per 10 s; 2 = 1–3 discharges per 10 s; 3 = 4–10 discharges per 10 s; 4=more than 10 discharges per 10 s; and 5 = continuous epileptiform activity.

This scale had been validated previously on more than 100 ECoG, against pathology, outcome, etc., and in 40 subjects against a computerized discharge recognition algorithm, with which there was close agreement. Activation was defined as an increase of at least one grade on the rating scale and/or extension of the ‘irritative zone’ (i.e. occurrence of discharges at a new site). It was not possible to carry out the ECoG assessment blind, as the effects of propofol were recognizably different from those of thiopental.

Statistical analysis was performed using the chi-square test to compare the incidence of epileptiform activity with propofol and thiopental. $P<0.05$ was taken as significant.

Results

We studied 20 patients. Mean age was 26.6 (range 12–39) yr and mean weight 68.3 (range 52–105) kg. All had a diagnosis of intractable complex partial seizures and were undergoing temporal lobectomy or amygdalo–hippocampectomy. They received a mean dose of 101 (range 40–200) mg of propofol and 242.5 (150–350) mg of thiopental. Burst suppression was produced in the ECoG in all but two subjects with propofol but in only 11 of 20 with thiopental.

There was an increased rate of discharge after administration of propofol in 12 of 20 patients and in 16 of 20 patients after thiopental (Table 1). There was extension of the irritative zone in eight patients after propofol and in 11 patients after thiopental. All patients showing extension of the irritative zone after either drug also showed an increased discharge rate. Neither activation nor extension was observed on the ECoG in eight patients after propofol and in four patients after thiopental, usually because burst suppression was reached without activation or extension, but in one patient there were no ECoG changes or burst suppression after either thiopental or propofol administration. The order of administration of the two drugs had no effect on activation.

There was no significant difference between propofol and thiopental in causing activation (chi-square = 1.07, $P=0.30$) or extension (chi-square = 0.4, 0.80 < $P < 0.70$) on the ECoG. There was a trend in favour of thiopental to increase rate and extent of discharge more than propofol, but this was not statistically significant.

Discussion

Hodkinson, Frith and Mee\textsuperscript{6} reported the first incidence of propofol-induced activation of the ECoG. After an epileptic patient undergoing cortical resection was given a bolus dose of propofol 2 mg kg$^{-1}$ to deepen anaesthesia, he observed frequent discharge of spikes, polyspikes and slow wave complexes. A wide range of propofol-related reactions have subsequently been reported, ranging from twitching, truncal shaking,\textsuperscript{7} hypertonia, myoclonus, dystonia, choreoathetosis\textsuperscript{8} and opisthotonos\textsuperscript{9,10} to grand mal convulsions. The significance of these case reports as confirmation of the proconvulsant properties of propofol is limited because they do not have simultaneous electroencephalographic recordings to confirm true cortical epileptic activity. Alternative mechanisms related to pharmacological interaction,\textsuperscript{11,12} metabolic
events\textsuperscript{16} or cardiac arrhythmias\textsuperscript{17} may contribute to these neurological phenomena.

We have carried out more than 500 insertions of foramen ovale electrodes for the purpose of preoperative assessment of patients with intractable epilepsy using propofol to induce and maintain anaesthesia for approximately 20–30 min.\textsuperscript{18} During this procedure no patient has suffered a seizure.

Seven previous studies have addressed the action of propofol on the ECoG with markedly different results. The effects of sub-anaesthetic doses of propofol on the ECoG were studied by Samra and colleagues\textsuperscript{19} without evidence of activation of epileptiform discharges. Ebrahim and colleagues\textsuperscript{20} demonstrated no activation of the ECoG with propofol 2 mg kg\textsuperscript{-1}. However, thiopental, sufentanil and scopolamine had been administered previously and the occurrence of burst suppression with propofol 2 mg kg\textsuperscript{-1} suggests that the effects may have been modified by the other medications.

Cheng and colleagues\textsuperscript{21} recorded ECoG activity in seven patients undergoing removal of subdural grid electrodes after induction of anaesthesia with propofol. Propofol was infused at a rate of 0.5 mg kg\textsuperscript{-1} min\textsuperscript{-1} to a total dose of 5 mg kg\textsuperscript{-1}, producing burst suppression in six of the seven subjects and inducing epileptiform discharges in none. The authors suggested that reported proconvulsive effects of propofol anaesthesia might be caused by co-medication. This is supported by the findings of Hufnagel and colleagues\textsuperscript{22} who studied the effects of a bolus dose of propofol 50 mg, with or without fentanyl, during 20 ECoG recordings. Epileptiform activity was induced only in the presence of co-medications. Hodkinson, Frith and Mee\textsuperscript{6} and Makela and colleagues\textsuperscript{23} demonstrated ECoG activation with propofol 2 mg kg\textsuperscript{-1} and 150 mg, respectively, but in both cases in combination with other medications, including fentanyl.

In contrast, Smith and colleagues\textsuperscript{24} reported activation of electrocorticographic discharges by propofol 50–175 mg in 20 subjects. They considered this as evidence of a proconvulsive action of the drug. Anaesthesia was induced with thiopental 4–5 mg kg\textsuperscript{-1}, fentanyl 1–3 µg kg\textsuperscript{-1} and vecuronium 0.15 mg kg\textsuperscript{-1}, and maintained with isoflurane and 50% nitrous oxide. Our findings are in accordance with those of Smith and colleagues but our interpretation is not.

Sleep and hypnotic or anaesthetic agents are used routinely in clinical EEG practice to activate epileptiform discharges. It is an interesting paradox that, for instance, sodium thiopental, which activates GABA\(_A\)-gated chloride currents and which, at higher doses, may reduce glutamatergic transmission\textsuperscript{25} and is used in the treatment of status epilepticus, has for many years also been used to activate the EEG during sphenoidal recording and electrocorticography. The explanation lies most probably in the nature of the epileptiform discharge, which involves not only excessive but also hypersynchronous neuronal activity. Drugs or a physiological state such as sleep which produce partial functional deafferentation of the cortex create conditions which promote synchronization of neuronal activity. The balance between inhibition and suppression of excitation, on the one hand, and promotion of synchrony on the other, determines if the overall effect is to activate or suppress epileptiform EEG discharges. In our study propofol showed a non-significant trend towards lesser activity in activating epileptiform EEG discharges than a known anticonvulsant, sodium thiopental, administered under identical conditions. ECoG activation by propofol cannot therefore be interpreted as evidence for proconvulsive action and indeed is compatible with the drug having an anticonvulsant action, as suggested by some authors who have even advocated its use in status epilepticus.\textsuperscript{26, 27}

References


2 Mackenzie SJ, Kapadia F, Grant IS. Propofol infusion for the control of status epilepticus. Anaesthesia 1990; 45: 1043–5


6 Hodkinson BP, Frith RW, Mee EW. Propofol and the electroencephalogram. Lancet 1987; 2: 1518


8 McHugh P. Acute choreoathetoid reaction to propofol. Anaesthesia 1991; 46: 42


10 Hopkins CS. Recurrent opisthotonus with anaesthesia. Anaesthesia 1988; 43: 904

11 Jones GW, Boykett MM, Flok M. Propofol opisthotonus and epilepsy. Anaesthesia 1988; 43: 905

12 Saunders PRI, Harris MNE. Opisthotonus and other unusual neurological sequelae after outpatient anaesthesia. Anaesthesia 1990; 45: 552–7


17 Dorrington KL. Asystole with convulsion following a sub-anaesthetic dose of propofol plus fentanyl. Anaesthesia 1989; 44: 658–9

18 Ammar T, Towey RM. The laryngeal mask airway. Anaesthesia 1990; 45: 75

19 Samra SK, Sneyd JR, Ross DA, Henry TR. Effects of propofol...
sedation on seizures and intracranially recorded epileptiform activity in patients with partial epilepsy. Anesthesiology 1995; 82: 843–51