Activation of the electrocorticogram by propofol during surgery for epilepsy

M. SMITH, S. J. SMITH, C. A. SCOTT AND W. F. J. HARKNESS

Summary

Propofol is used widely during general anaesthesia but there has been concern that it may be implicated in provoking seizure activity. We have investigated the effects of low-dose propofol on the electrocorticogram of anaesthetized patients undergoing surgery for medically intractable epilepsy. During continuous peroperative recording of the electrocorticogram, propofol was administered in 25 mg increments until burst suppression occurred. Activation of the electrocorticogram occurred in 17 of 20 patients. There was an increase in mean spike frequency in 16, extension of spike distribution in 15 and polyphasis in 13 patients. The mean dose of propofol required to cause burst suppression was 88.2 (range 25–175) mg. We conclude that at low doses, propofol caused activation of the electrocorticogram in epileptic patients but at higher doses burst suppression was induced. (Br. J. Anaesth. 1996; 76: 499–502)

Key words
Anaesthetics. i.v., propofol. Epilepsy. Monitoring, electrocorticography.

Propofol is used widely during general anaesthesia and for sedation in the intensive care unit. It is gaining popularity for neurosurgical anaesthesia [1] in part because it causes a dose-dependent decrease in intracranial pressure and cerebral metabolic rate and, at modest doses, cerebral perfusion pressure is maintained [2, 3]. It has a favourable pharmacokinetic profile which allows easy control of depth of sedation and rapid and predictable arousal. However, recently there has been concern that propofol may be implicated in provoking seizure activity and some avoid its use in epileptic patients. In contrast, it has been used successfully in the treatment of status epilepticus and appears to have no adverse effect in neurosurgical patients who are at "high risk" of developing seizure activity.

We have investigated the effect of propofol on the electrocorticogram (ECoG) of anaesthetized patients undergoing surgery for medically intractable epilepsy.

Patients and methods

The study was carried out with the approval of the Joint Medical Ethics Committee of the National Hospital for Neurology and Neurosurgery and Institute of Neurology. We studied 20 patients with medically intractable epilepsy. Premedication was omitted but anticonvulsant medication was continued into the perioperative period and administered on the morning of surgery. Anaesthesia was induced with thiopentone 4–5 mg kg⁻¹, fentanyl 1–3 µg kg⁻¹ and vecuronium 0.15 mg kg⁻¹. The trachea was intubated and ventilation controlled to maintain P_{\text{a}}\text{CO}_{2} at 3.8–4.2 kPa. Anaesthesia was maintained with isoflurane and 50% nitrous oxide in oxygen, and neuromuscular block was continued with infusion of vecuronium. Before recording the ECoG, the inspired isoflurane concentration was maintained at <1 MAC to minimize anaesthetic-induced changes in the cortical EEG. Arterial pressure was controlled with incremental fentanyl (to a maximum of 8 µg kg⁻¹) and labetolol, and after ECoG recording by deepening anaesthesia with increased inspired isoflurane concentrations.

Heart rate, invasive arterial pressure (radial artery), oxygen saturation and end-tidal carbon dioxide and isoflurane concentrations were monitored continuously. Arterial blood-gas analysis was used to confirm arterial carbon dioxide tensions.

It is a standard part of the epilepsy surgical procedure at the National Hospital to carry out peroperative recording of epileptiform spiking with ECoG to determine the margins of surgical resection. Intraoperative ECoG for temporal lobectomy was recorded using a 25-contact (5 × 5) plate with an inter-contact spacing of 1 cm. The ECoG was recorded as an analogue signal using an 18-channel EEG machine (Nihon-Kohden). Two standard recording positions over the lateral convexity of the temporal lobe are used: anteriorly, with the first row of contacts approximately 1–2 cm behind the pole of the temporal lobe, and posteriorly, with the plate approximately 4 cm from the pole.

After diagnostic corticography, a 3-min period of baseline recording was obtained. Propofol was then administered i.v. in 25-mg increments, at 3-min intervals, until burst suppression occurred.

EEG spike analysis was performed manually before and after administration of propofol by one of the authors (S.J.S.). Activation of the ECoG was...
defined as: increase in the frequency of spiking; more extensive spike distribution; or polyphasic spikes. The frequency of spiking was taken as the average number of spikes in three randomly selected 20-s periods. The extent of spiking was assessed by counting the number of contacts at which spiking was seen. Extension was deemed to have occurred if spiking was present at two or more additional contacts after propofol. The Wilcoxon test for paired data was used to compare the frequency and extent of spike activity before and after administration of propofol.

Results
We studied seven males and 13 females, mean age 25.6 (range 18–38) yr and mean weight 71.1 (51–97) kg. The pathological diagnosis was hippocampal sclerosis ($n = 16$) or dysembryoplastic neuroepithelial tumour ($n = 4$) and the surgical procedures consisted of tailored temporal lobectomy (including excision of mesial temporal structures) or lesionectomy.

There were no changes in heart rate, arterial pressure, oxygen saturation or end-tidal carbon dioxide tension during the study. The mean dose of propofol required to cause burst suppression was 88.2 (range 25.0–175.0) mg and individual doses are shown in table 1.

Activation of the ECoG by propofol occurred in 17 of 20 patients (table 1). Examples of ECoG recordings with activation are shown in figure 1. Increase in mean spike numbers from 3.6 to 6.7 occurred in 16 patients ($P < 0.005$). There was extension of spike distribution from 3 to 10 contacts in 15 patients ($P < 0.005$) with marked extension

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Weight (kg)</th>
<th>Propofol dose (mg)</th>
<th>Increased in spike numbers</th>
<th>Extension of spike distribution</th>
<th>Development of polyphasia</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>65</td>
<td>75</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>2</td>
<td>73</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>3</td>
<td>53</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>4</td>
<td>72</td>
<td>75</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>54</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>82</td>
<td>25</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>79</td>
<td>50</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>81</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>9</td>
<td>71</td>
<td>50</td>
<td>–</td>
<td>Burst suppression by 20 s</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>63</td>
<td>100</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>11</td>
<td>78</td>
<td>150</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>88</td>
<td>150</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>97</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>74</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>68</td>
<td>50</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>16</td>
<td>68</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>17</td>
<td>51</td>
<td>50</td>
<td>–</td>
<td>No spike activity</td>
<td>–</td>
</tr>
<tr>
<td>18</td>
<td>88</td>
<td>175</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>19</td>
<td>58</td>
<td>75</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>20</td>
<td>59</td>
<td>100</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

*Figure 1* ECoG recording before and after administration of propofol. Before propofol, one epileptiform spike is noted at contact 16 (a). After propofol 25 mg, the epileptiform discharges become more widespread (b) and runs of spikes occur with polyphasia (c). The recording was common referential; same gain and filter settings were used before and after administration of propofol.
Effect of propofol on the ECoG

(1 s⁻¹) before and after administration of propofol but there was no change in spike morphology after propofol. In another, burst suppression occurred within 20 s of the initial 25-mg bolus of propofol and in the third there was no spiking before or after propofol administration.

Discussion

Activation of the ECoG by propofol was noted first by Hodkinson, Frith and Mee in 1987 [4]. They described an increase in the frequency of epileptiform spikes and the development of polyspikes, both within and beyond a previously mapped epileptogenic focus, after a bolus of propofol 2 mg kg⁻¹. At the clinical level, generalized seizures and opisthotonos have been attributed to propofol anaesthesia in patients with no previous neurological history and also in those with a history of epilepsy [5–8]. However, several of these case reports did not include EEG conformation of seizure activity and in one with contemporary EEG recording, a subcortical origin of the abnormal movements was postulated [8]. Other causes of seizure activity cannot be excluded in many of the reports. For example, propofol has been implicated as the cause of a grand mal seizure in a patient after termination of propofol sedation 5 days after deep hypothermic circulatory arrest [9]. The validity of implicating propofol as the cause of seizures in a case involving so many other factors has already been questioned [10]. There has however, been sufficient concern to cause the Committee on Safety of Medicine to issue a Safety Action Bulletin in 1992, drawing attention to the possible link between propofol and provocation of seizures [11].

Our results confirmed that, at low doses, propofol caused activation of the ECoG in epileptic patients. The activating effect may be dose related. In a study of propofol in 20 patients with indwelling subdural strip electrodes undergoing chronic monitoring as part of pre-surgical evaluation [12], only five showed induction of epileptiform activity. However, patients in this study received a minimum dose of propofol 50 mg followed by 70- or 140-mg increments, and spike induction occurred most frequently in those patients receiving the lower doses.

Burst suppression in the EEG is generally considered to be the end-point of the treatment of seizures or status epilepticus with anaesthetic agents. All patients in our study developed burst suppression at higher doses of propofol, except for one, in whom burst suppression occurred soon after the initial dose of propofol. Profound burst suppression after bolus administration of propofol (2 mg kg⁻¹) to patients receiving nitrous oxide in oxygen and sufentanil infusion, during anaesthesia for epilepsy surgery, was also noted in a recent study [13]. This study failed to demonstrate an increase in the frequency of interictal spikes, presumably because of the relatively large doses of propofol and the early onset of burst suppression.

Although an activating effect of propofol was observed in our study, it has been shown previously to have anticonvulsant effects in both animals [14–16] and humans. It has been used successfully in the treatment of status epilepticus resistant to other medical therapies [17, 18] and is known to shorten the duration of seizure activity during electroconvulsive therapy [19]. Additionally, many i.v. anaesthetic agents, which are anticonvulsants when given in the usual clinical dose (e.g. thiopentone), show proconvulsive activity at lower doses [20]. It appears likely from our data, and that of other workers [12], that propofol might also have dose-dependent pro- and anticonvulsant properties. In common with other i.v. anaesthetic agents, proconvulsant activity is seen at lower doses and anticonvulsant activity at higher doses.

In our study, the effects of propofol on the ECoG were evaluated during isoflurane anaesthesia and this may have affected the results. However, during the study the inspired concentration of isoflurane was <1 MAC and it is possible to obtain high quality peroperative ECoG, with little or no apparent anaesthetic interference on the recording, using low-dose isoflurane [21, 22]. However, we are unable to comment on the combined ECoG effects of propofol and isoflurane. Adjuvants, such as opioids and nitrous oxide, cause EEG suppression at lower doses of isoflurane than might otherwise be anticipated [23]. Isoflurane may reduce or suppress background epileptiform activity and has been used successfully in the treatment of status epilepticus [24]. It is possible that isoflurane may in turn suppress the activating effects of propofol and our results may have underestimated the true extent of ECoG activation. The doses of propofol required to produce burst suppression in our patients were lower than normal anaesthetic doses. In one patient, burst suppression occurred within a few seconds of the initial 25-mg bolus of propofol and persisted for almost 15 min. If the presence of isoflurane influences the degree of ECoG change, we believe that its effect would be to reduce rather than enhance the activating effects of propofol.

All patients continued to receive their anticonvulsant medication during and after surgery and drug concentrations were measured before operation to ensure therapeutic concentrations. Although it is possible that the variety of preoperative medication might have altered the effects of propofol on the ECoG, it is again likely that these would minimize the activating effects of propofol. Rapid decreases in plasma concentrations of anticonvulsant medication may result in an increase in epileptiform spiking [25] but it is unlikely that plasma concentrations changed significantly during the study. Furthermore, activation of the ECoG was linked temporally to the administration of propofol. We believe, therefore, that activation of the ECoG observed during our study was related directly to the introduction of propofol.

Whether or not our findings are of clinical
significance is a matter for debate. It is also uncertain if similar effects would be noted after administration of propofol to non-epileptic patients. It is conceivable however, that during induction or recovery from propofol anaesthesia or sedation, a stage of activation is passed as blood propofol concentrations increase or decrease through a critical plasma concentration. This may increase the risk of epileptiform activity, particularly in those already predisposed to seizures.

Propofol is often used for intracranial surgery during general anaesthesia and has become the agent of choice for sedation during awake craniotomy [22, 26]. Awake resection of epileptic foci is now commonplace in the USA and gaining popularity in the UK. Cortical mapping of epileptiform activity in awake and anaesthetized patients, and stimulation testing to identify eloquent areas in awake patients, allows careful identification of surgical resection margins. In view of the apparent activation of the ECoG by low doses of propofol, we would not recommend the use of propofol during general anaesthesia for epilepsy when the ECoG is used to guide tailored resection. When propofol is used as an adjunct to sedation during awake procedures, the infusion should be discontinued at least 30 min before cortical mapping with the ECoG.

References