PROPOFOL ANTICONVULSANT ACTIVITY IN EXPERIMENTAL EPILEPTIC STATUS

P. L. DE Riu, V. PETRUZZI, C. TESTA, M. MULAS, F. MELIS, M. A. CARIA AND O. MAMELI

SUMMARY
We have examined the anticonvulsant properties of propofol in high doses in two experimental models of status epilepticus: generalized pentyleneetetrazol (PTZ)-induced seizures and partial, cortically applied penicillin G-induced seizures. Propofol was administered either as a single bolus injection or as a bolus injection followed by an infusion for 1 h. When administered as a single bolus injection, propofol 12 mg kg\(^{-1}\) suppressed electrical and clinical seizures in PTZ generalized epileptic status, and an infusion of 50 mg kg\(^{-1}\) h\(^{-1}\) prevented the reappearance of electrical and clinical signs. In focal epileptic status, the single dose stopped paroxysmal activity and the associated clonic jerks for a few seconds. When the bolus dose was followed by an infusion, the firing bursts were replaced by isolated spikes, and contralateral jerks became sporadic and feeble. The greater efficacy of propofol against PTZ convulsions may be a reflection of the opposite action of the two drugs on neural membrane conductance: PTZ induces paroxysmal neural discharge by enhancing membrane conductance while propofol appears to decrease membrane conductance, thus suppressing paroxysmal discharge. There was no close relationship between blood concentration of the anaesthetic and its clinical effects, at least after a short-term infusion, as used in the present experiments. We suggest that propofol may be a potentially useful drug in status epilepticus in patients in whom benzodiazepines, clonazepam and thiopentone have failed.

KEY WORDS

Status epilepticus is not a single condition and several types have been identified [1]. Consequently, several different anticonvulsants have been suggested for treatment but there is still controversy regarding their efficacy. Diazepam is considered the first choice, followed by phenytoin, clonazepam, thiopentone and, finally, halothane and neuromuscular blocking drugs [2]. Nevertheless, status epilepticus is sometimes unresponsive to treatment.

Several years ago, Althesin was used successfully in patients suffering from status epilepticus where benzodiazepines, clonazepam and thiopentone had failed [3-5]. Unfortunately, this anaesthetic agent is no longer available, but its success suggests that other i.v. anaesthetics, even of different classes, may be useful in this condition. There are reports that propofol shortens seizures during electroconvulsive therapy [6] and that it shows stronger anticonvulsant properties than thiopentone in laboratory tests in mice [7]. These characteristics may make it useful in status epilepticus. However, electroencephalogram epileptiform patterns were seen after propofol was used in patients suffering from intractable epilepsy and selected for temporal lobectomy [8], and a recent warning was issued by the Committee on Safety of Medicines on the possible risk of seizures after the administration of propofol [9].

The aim of the present study was to test the potential anticonvulsant properties of propofol in two experimental models of status epilepticus: continuous generalized seizures and continuous focal seizures.

METHODS
We studied 25 adult male New Zealand rabbits weighing 3-4 kg allocated to five groups of five animals each. The left and right marginal ear veins were cannulated and the animals were anaesthetized with pentobarbitone 30 mg kg\(^{-1}\) i.v. A catheter was inserted into the left femoral artery and connected to a Statham transducer to allow continuous measurement of mean arterial pressure (MAP) and withdrawal of blood. A large craniectomy was performed in all rabbits to expose the cerebral hemispheres. Pairs of silver ball electrodes applied to the pia, connected to a Model 7 Grass polygraph were used for EEG recordings.

In group I (controls), the rabbits were allocated to two subgroups: in the first (n = 2), propofol 12 mg kg\(^{-1}\) i.v. was given as a single bolus in 20 s; in the second subgroup (n = 3), propofol 12 mg kg\(^{-1}\) was injected as a bolus in 20 s followed after 5 min by an infusion of propofol 50 mg kg\(^{-1}\) h\(^{-1}\) for 1 h.

P. L. De Riu*, M.D., Department of Neurological Rehabilitation, University of Turin, Italy. C. Testa, B.Sc., Sardinian Zoon prophylaxis Institute, Italy. V. Petruzzl, V.D. (Institute of Veterinary Surgery); M. Mulas, M.D. (Institute of Anaesthesiology); F. Melis, M.D., M. A. Caria, M.D., O. Mamel, B.Sc., Ph.D. (Institute of Human Physiology); University of Sassari, Italy. Accepted for Publication: January 14, 1992.
In group II, continuous epileptic generalized seizures were induced with pentylenetetrazol (PTZ) 1 ml kg\(^{-1}\) (10% sterile solution, G. Streuli & Co., AG Uznach). When status epilepticus was clinically and electrically well established, propofol 12 mg kg\(^{-1}\) i.v. was given as a single bolus in 20 s. This dose was chosen because it induces sedation in mice [7].

In group III, status epilepticus was induced as in group II. Propofol 12 mg kg\(^{-1}\) was administered as a bolus and after 5 min, before the reappearance of the paroxysmal activity, as an infusion (50 mg kg\(^{-1}\) h\(^{-1}\)) lasting 1 h.

In group IV, acute focal epileptic status was obtained by applying a small swab soaked in penicillin G 40 000 u. ml\(^{-1}\) to the left fronto—parietal area. EEG was recorded via two pairs of silver ball electrodes applied to the pia surface in the perifocal area and in the contralateral symmetric area. When the firing bursts in the cortical focus were well established and clonic jerks of face and limbs were continuous in the right side, propofol 12 mg kg\(^{-1}\) i.v. was given as a bolus dose.

In group V, continuous focal seizures were induced as in group IV, and propofol 12 mg kg\(^{-1}\) was administered as a bolus and after 2 min, before the reappearance of the firing bursts, as a 1-h infusion of 50 mg kg\(^{-1}\) h\(^{-1}\).

In all groups, the electrocorticographic and clinical observations were continued for 10 min after administration of propofol ended.

Blood samples were obtained for blood-gas analysis and measurement of plasma concentrations of propofol before and 20 s after the bolus injection, 10 and 20 min after the onset of the infusion, at the end of the infusion and 10 min later. The concentration of propofol in blood was measured by high pressure liquid chromatography (HPLC). At the end of the experiment the rabbits were killed with pento-barbitone.

RESULTS

In group I there was a marked decrease in electrocorticographic activity immediately after the bolus injection; after about 70 s the EEG tracing approached the baseline pattern, although there was more low voltage fast activity. The infusion maintained and increased the low voltage fast activity induced by the drug. Figure 1 shows a typical EEG pattern of response to propofol in the control animals. There were no paroxysmal EEG patterns or critical signs in the control group after administration of propofol.

In group II, PTZ i.v. induced low voltage isolated spikes and sharp waves in less than 30 s. The voltage of the spikes increased gradually and they appeared in a series of bursts. Approximately 4 min after administration of PTZ, the cortical electrical activity was characterized exclusively by generalized high voltage (≈ 250 μV), high frequency spikes. This EEG pattern remained stable whilst clinically there were successive tonic-clonic attacks. The propofol bolus suppressed paroxysmal activity and clinical signs but isolated bursts reappeared 6 min later. Approximately 8 min after the bolus dose of PTZ, tonic-clonic attacks reappeared, accompanied by generalized high voltage, high frequency spike activity.

In group III, the propofol bolus suppressed the PTZ generalized seizures and the infusion prevented the reappearance of critical signs and paroxysmal EEG patterns. However, medium voltage fast activity intermingled with sporadic slow waves was present during the first part of the infusion and, as it proceeded, the fast activity disappeared gradually giving way to slow polymorphic activity which persisted during the 10-min observation period at the end of the infusion.

In all animals in groups IV and V, penicillin G, applied to the pia of the left fronto—parietal area, after a transitory focal depression of the electrical activity, induced the appearance of isolated spikes with increasing voltage and frequency. Approximately 3 to 4 min after the administration of penicillin G, high voltage spikes (more than 250 μV) and spike wave paroxysmal bursts occurred in the focal area, associated with clonic jerks of the contralateral face and limbs. Subsequently, clinical and electrical patterns of the penicillin G partial epileptic status remained stable.

In group IV rabbits, a single bolus of propofol suppressed electrical and clinical focal seizures for about 20 s, then low voltage isolated spikes reappeared. Three minutes after the bolus injection, focal bursts reappeared, followed quickly by contralateral jerks (fig. 2).

In group V, the infusion of propofol after the
bolus dose prevented the occurrence of firing bursts in the focal area although intense spiking activity persisted during the infusion, together with sporadic mild contralateral jerks (fig. 3).

In PTZ generalized epileptic status, all rabbits showed an increase in MAP of 44.4% compared with basal values, and respiratory failure as indicated by blood-gas values.
In group II, propofol induced an immediate decrease in MAP of 59% compared with an arterial pressure peak caused by PTZ convulsions. Five minutes after the bolus, arterial pressure returned to initial values. A further reduction in Po2 and increase in Pco2 occurred after administration of propofol.

In group III, the infusion of propofol caused a decrease in MAP of 22% compared with baseline values. There was no further decrease in arterial pressure during the infusion and MAP returned to baseline values 10 min after the infusion. Blood-gas variables improved, despite the presence of the drug, and returned to the normal range 10 min after the infusion.

In rabbits with focal epileptic status penicillin G, applied to the cortex, did not alter MAP or blood-gas variables. In group IV, the bolus dose of propofol induced a sharp decrease in MAP of 39.9% compared with baseline values and mild respiratory acidosis.

In group V, the propofol infusion, started 2 min after the bolus injection when MAP had not yet returned to baseline values, induced a further decrease in MAP; however, the decrease was less (22.2% compared with basal values) than that induced by the bolus dose and arterial pressure remained stable throughout the infusion. MAP returned to normal 10 min after the infusion was stopped. Mild respiratory depression was observed also during the infusion but resolved several minutes after it had been discontinued.

In groups II–III and IV–V, the plasma concentration of propofol 20 s after the bolus injection was 1.2 ng ml−1 and 2.1 ng ml−1, respectively. These values increased progressively to 52.5 and 53.2 ng ml−1, respectively, at the end of the infusion.

DISCUSSION

We have observed that a single bolus injection of propofol suppressed cortical paroxysmal electrical activity in PTZ seizures and also clinical manifestations for about 6 min. Furthermore, an infusion of propofol given after the bolus caused complete resolution of electric epileptic patterns and tonic-clonic attacks during the period of observation. Thus, propofol had a powerful anticonvulsant effect on the acute, continuous, generalized seizure model used [10]. The effect of the anaesthetic agent on the acute focal epileptic model induced by PTZ, a convulant drug that appears to act mainly by enhancing brain excitatory systems [10]. The effect of the anaesthetic agent on the acute focal epileptic model induced by PTZ, a convulant drug that appears to act mainly by enhancing brain excitatory systems [10]. The effect of the anaesthetic agent on the acute focal epileptic model induced by PTZ, a convulant drug that appears to act mainly by enhancing brain excitatory systems [10].

The differing efficacy of propofol in our study may be explained by the partially different mechanisms of action of the two convulsant drugs. PTZ (in addition to its blocking action on gamma-aminobutyric acid (GABA) receptors [11]) has mainly a direct excitatory effect on the neurone membrane by altering ionic conductance [12]. Penicillin G, in common with bicuculline and picrotoxin, produces an indirect excitatory effect by blocking interaction of the inhibitory amino acid GABA with postsynaptic receptors [13]. Thus, the two convulsants have a similar action with regard to GABA, but PTZ is different in its direct enhancing action on membrane conductance. Although some of these observations were made in molluscs and tissue slices, they may be applicable to the human CNS. In common with many general anaesthetic agents, even of different classes [14], propofol reduces membrane conductance and excitability [15]. Thus, propofol may act on PTZ convulsions by decreasing membrane conductance.

In addition to anticonvulsant activity, propofol caused central respiratory depression but paradoxically improved the respiratory state in PTZ convulsions. In generalized epileptic status, respiration may be compromised as a result of three mechanisms [16]: mechanical impairment of respiratory muscle function as a result of clonic contractions; brainstem respiratory centre inhibition as a result of abnormal electrical discharge from the forebrain; and massive autonomic discharges that produce excessive bronchial secretion and constriction with consequent hypoxaemia and hypercapnia [17]. Propofol improves respiratory status in status epilepticus as it suppresses electrical and clinical seizures. However, in the focal model of epileptic status, where convulsions were not accompanied by respiratory failure, propofol depressed respiration after both the bolus and during the infusion. Respiratory depression was not related to the plasma concentration of the drug, as 10 min after the infusion, when blood-gas variables were normal, blood concentrations of propofol were greater than after the bolus and at the beginning of the infusion, when respiratory acidosis was present. Propofol also caused a reduction in mean arterial pressure both in animals with focal epileptic status and in those with generalized status epilepticus. However, MAP in all animals after administration of a bolus or infusion did not decrease to less than 60 mm Hg, a value that still allowed adequate brain perfusion.

We found no evidence to suggest that propofol can induce seizures despite the advice of the Committee on Safety of Medicines [9]. It is possible that the drug intensifies EEG abnormalities in patients suffering from epilepsy, in common with other anaesthetic agents in subnarcotic doses. For example, Athesins causes appearance of bitemporal abnormalities in EEG tracings of epileptic patients [18] but nevertheless has powerful anticonvulsant activity in experimental epilepsy and in epileptic status [4, 5].

In conclusion, the characteristics of propofol make it a putative drug in the treatment of generalized epileptic status when drugs such as benzodiazepines, barbiturates and diphenylhydantoin have failed. Propofol acts quickly, has a short half-life and can be given i.v.—properties of an ideal drug.

REFERENCES


