



NEW TREATMENTS FOR REFRACTORY STATUS EPILEPTICUS

Propofol Treatment of Refractory Status Epilepticus: A Study of 31 Episodes

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PURPOSE: Refractory status epilepticus (RSE) is a critical medical condition with high mortality. Although propofol (PRO) is considered an alternative treatment to barbiturates for the management of RSE, only limited data are available. The aim of this study was to assess PRO effectiveness in patients with RSE.

METHODS: We retrospectively considered all consecutive patients with RSE admitted to the medical intensive care unit (ICU) between 1997 and 2002 treated with PRO for induction of EEG-monitored burst suppression. Subjects with anoxic encephalopathy showing pathologic N20 on somatosensory evoked potentials were excluded.

RESULTS: We studied 31 RSE episodes in 27 adults (16 men, 11 women; median age, 41.5 years). All patients received PRO, and six also subsequently received thiopental (THP). Clonazepam (CZP) was administered with PRO, and other antiepileptic drugs (AEDs), concomitant with PRO

and THP. RSE was successfully treated with PRO in 21 (67%) episodes and with THP after PRO in three (10%). Median PRO injection rate was 4.8 mg/kg/h (range, 2.1-13); median duration of PRO treatment was 3 days (range, 1-9), and median duration of ICU stay was 7 days (range, 2-42). In 24 episodes in which the patient survived, shivering after general anesthesia was seen in 10 episodes, transient dystonia and hyperlipemia in one each, and mild neuropsychological impairment in five. The seven deaths were not directly related to PRO use.

CONCLUSIONS: PRO administered with CZP was effective in controlling most of RSE episodes, without major adverse effects. In this setting, PRO may therefore represent a valuable alternative to barbiturates. A randomized trial with these drug classes could definitively assess their respective roles in RSE treatment.

Treatment of Refractory Status Epilepticus with Inhalational Anesthetic Agents Isoflurane and Desflurane

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BACKGROUND: Refractory status epilepticus (RSE) is defined as continued seizures after two or three antiepileptic drugs (AEDs) have failed. Several intravenous agents have been used for RSE; however, problems occur with their toxicity and/or effectiveness.

OBJECTIVE: To report our experience with inhalational anesthesia (IA) in patients whose seizures were refractory to other AEDs.

METHODS: Retrospective review during a 4-year period of patients with RSE treated with isoflurane and/or desflurane. The main outcome measure was efficacy of IA on therapy in terminating RSE.

RESULTS: Seven patients (four men) aged 17 to 71 years received 7 to 15 (mean, 10) AEDs in addition to IAs. The IAs were initiated after 1 to 103 (mean, 19) days of RSE and were used for a mean \pm SD of 11 ± 8.9 days. All patients received isoflurane, and one patient in addition received desflurane anesthesia 21 days after the onset of RSE for a total of 19 days. Regardless of seizure type, isoflurane and desflurane consistently stopped epileptic discharges with adequate, sustained electroencephalographic burst suppression within minutes of initiating IA therapy. Four patients had good outcomes, three died (one of acute hemorrhagic leukoencephalitis, one of bowel infarction,

and one of toxic encephalopathy, who remained in a persistent vegetative state until death 5.5 months after the onset of seizures). Complications during IA therapy included hypotension (all seven), atelectasis (all seven), infections (five of seven), paralytic ileus (three of seven), and deep venous thrombosis (two of seven). In no patient did renal or hepatic dysfunction develop.

CONCLUSIONS: Isoflurane and desflurane adequately suppressed RSE in all cases. Complications were common, but mortality and long-term morbidity were related to the underlying disease and duration of RSE. Prolonged use of isoflurane and desflurane is well tolerated.

COMMENTARY

Refractory status epilepticus (RSE) is a common problem in intensive care units and emergency departments. Despite aggressive treatment, it is associated with a high mortality rate. Although the entity of RSE is widely recognized and discussed, a standard definition has not yet been accepted. Proposed criteria vary in the number of antiepileptic drugs (AEDs) failed and in the duration of seizure activity required (1). Rossetti et al. defined RSE as status epilepticus (SE) that is clinically or electroencephalographically refractory after the administration of first- and second-line treatment within 60 min of SE onset. Mirsattari et al. defined RSE as clinical and/or electrographic seizures that are refractory to loading or protracted maintenance doses of at least three AEDs.

A surprisingly high proportion of SE patients fail to respond to conventional treatment, usually consisting of a benzodiazepine (BZD) followed by a loading dose of phenytoin (PHT) or fosphenytoin. A prospective, randomized, double-blinded study comparing treatments for generalized convulsive SE found that 44% of cases treated with diazepam followed by PHT were refractory (2). Timely initial treatment of SE is crucial, as delayed treatment results in longer SE duration and a higher mortality (3). Thus the definition provided by Rossetti et al., which stipulates treatment within 60 min of SE onset, is significant because it excludes patients likely to have worse outcomes.

Traditionally, barbiturates such as pentobarbital or thiopental have been used to terminate RSE, inducing coma and EEG suppression. This treatment requires intubation, mechanical ventilation, and often, prolonged stays in the intensive care unit (ICU), with accompanying risks for infection and other comorbidities. In addition to safely and effectively terminating RSE, the ideal treatment would have rapid onset and short half-life, allowing rapid assessment of EEG and clinical responses. Barbiturates sometimes fail to control SE and are often associated with hypotension, prolonged sedation, and the need for ventilatory support (4). Therefore alternative anesthetic agents have been considered as treatments for RSE. The two articles

discussed here review cases of RSE treated with propofol and isoflurane.

From a neurophysiologic point of view, SE that is refractory to treatment may be the result of several processes. Seizures lasting >1 h are associated with excess glutamate release, shifting the balance toward neuronal excitation (5). In experimental models, resistance to both BZDs and barbiturates develops during prolonged seizures, and it has been hypothesized that prolonged seizure activity alters the structure and/or function of γ -aminobutyric acid (GABA_A) receptors (6). The drugs studied in the articles by Rossetti et al. and Mirsattari et al. are both active at the GABA_A receptor: propofol, at a site distinct from the BZD and barbiturate binding sites, and isoflurane, by potentiation of inhibitory postsynaptic GABA_A receptor-mediated currents, although effects on thalamocortical pathways also have been implicated (5,7–9).

The goal of the study by Rossetti et al. was to determine the efficacy and safety of propofol, a short-acting anesthetic agent in the treatment of RSE. The authors retrospectively reviewed 31 RSE episodes in 27 adults in whom SE treatment was initiated within 60 min of onset. All patients received propofol, 2 mg/kg intravenously (IV), followed by continuous IV infusion and concomitantly clonazepam (CZP) IV infusion. PHT and other AEDs also were continued. Propofol, administered concomitant with CZP, successfully treated RSE in two thirds of the cases. Thiopental, administered to six patients after propofol failure, controlled an additional three episodes of RSE. Seven deaths were due to causes that were not directly related to treatment. The most common side effects were hypotension, occurring in almost half of the episodes, followed by shivering, which occurred in 10 episodes. There was one case each of transient dystonia and reversible hyperlipidemia.

The study by Mirsattari et al. reviewed seven patients who had RSE treated with an inhalational anesthesia (IA). Six patients received isoflurane alone, and one patient received desflurane followed by isoflurane. IA effectively stopped seizures and achieved EEG burst suppression within minutes of initiation of therapy. Patients received a mean of 10 AEDs in addition to the IA. Seizure recurrence was high after discontinuation of

IA therapy. Four patients had good outcomes, and three died. Complications included hypotension and atelectasis in all patients. Other adverse events included infection in five patients, paralytic ileus in three, and deep venous thrombosis in two. Renal and hepatic dysfunction did not occur in association with IA treatment.

Because of differences in methods and data reported, it is difficult to compare the results of these two studies. It is interesting that the application of two definitions of RSE resulted in significantly different patient populations. The patients treated with propofol were less severely affected or less refractory to treatment, or both, than were those who received IA. Whereas propofol was administered immediately after initial unsuccessful treatment with CZP and PHT, IA was initiated later in the course of illness, after a median of 3 days of RSE, in patients who had already been treated with continuous IV infusion of midazolam, propofol, thiopental, or a combination of these. This difference in severity of illness between the two study populations is reflected in other parameters of interest. For propofol cases, the median duration of treatment was 3 days, the median duration of mechanical ventilation was 5 days, and the median duration of ICU stay was 7 days. For the more severely affected IA patients, the average duration of IA therapy was 11 days (median not reported), whereas the median duration of mechanical ventilation was 18 days, and the median ICU stay was 27 days.

Adverse effects were encountered with both therapies. Hypotension can be a limiting factor in the treatment of RSE with barbiturates. Not surprisingly, it also was a significant side effect of treatment with both propofol and IAs. Whereas all patients treated with IA required pressor support, 48% of the propofol cases received pressors. Again, this difference likely reflects the disparity in severity of illness between populations in the two studies.

These case series suggest that propofol and isoflurane, when administered concomitantly with other AEDs, can control SE that is refractory to conventional treatments. With the ability to titrate the dose rapidly according to clinical and EEG effects, these agents have major theoretical advantages over barbiturates, including decreased duration of coma, reduced duration of mechanical ventilation, reduction in associated complica-

tions, shorter ICU and hospital stays, and lower hospitalization costs. However, it is unclear how the appeal of these short-acting anesthetics translates into measurable benefits for critically ill patients, and many questions remain regarding safety and patient outcomes with these agents (10). Clinicians still do not know which therapy is best for RSE. These articles are instructive in generating methodologic questions that should be addressed in the design of a future prospective trial comparing treatments for RSE.

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