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 2 or 3 antiepileptic drugs 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 who were refractory to other antiepileptic drugs.

Design, Setting, and Participants: Retrospective review during a 4-year period of patients with RSE treated with isoflurane and/or desflurane.

Main Outcome Measure: Efficacy of IA on therapy in terminating RSE.

Results: Seven patients (4 male) aged 17 to 71 years received 7 to 15 (mean, 10) antiepileptic drugs in addition to IAs. The IAs were initiated after 1 to 103 (mean, 19) days of RSE and were used for a mean±SD 11±8.9 days. All patients received isoflurane, and 1 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, 3 died (1 of acute hemorrhagic leukoencephalitis, 1 of bowel infarction, and 1 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 (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7), and deep venous thrombosis (2/7). No patient developed renal or hepatic dysfunction.

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.

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Refractory status epilepticus (RSE) is usually defined as seizure activity that continues after first- and second-line therapy has failed.¹ Definitions differ primarily in the number of antiepileptic drugs (AEDs) that have been used (eg, 2⁵,6 or 3⁶-¹⁰) or the duration of seizures (eg, ranging from <1 to ≥1⁵,6,8,10 at least 1 or ≥2 days). Despite the varied definitions, RSE represents a medical emergency with a mortality rate of approximately 50% and a significant morbidity; only about one third of patients return to their premorbid state.⁶ Refractory status epilepticus can occur in 9% to 40% of the patients with status epilepticus.¹¹,¹² Barbiturate anesthesia with pentobarbital or thiopental sodium is commonly recommended as the ultimate treatment of choice for RSE,⁶,¹³-¹⁵ although its effectiveness has not been studied systematically. Among 109 adult patients with RSE who were treated with pentobarbital between 1970 and 2001, 8% experienced acute failure; 12%, breakthrough seizures; 43%, withdrawal seizures within 48 hours; and 8%, refractory hypotension during the therapy.¹¹ Its use is also often accompanied by prolonged sedation and life-threatening infections.¹⁶ Midazolam and propofol have been used more recently in an attempt to overcome these limitations.³ Neither agent is uniformly successful in stopping RSE, and each has its own complications.⁵,⁶ Inhalational anesthesia (IA) represents an alternative approach to the treatment of RSE. Its attractive features include efficacy, rapid onset of action, and the ability to titrate the dose according to the effects demonstrated on the electroencephalogram (EEG).¹⁷,¹⁸ Of the various IA agents, isoflurane and desflurane are the 2 agents that have been administered for RSE because of their safety...
profile associated with long-term administration. This article is a review of our overall experience with IA as a management strategy for RSE.

METHODS

We conducted a retrospective medical record review of all patients with RSE treated with isoflurane or desflurane IA at London Health Sciences Centre, London, Ontario, from 1996 to 2001. We included all cases of convulsive and nonconvulsive, partial, or generalized RSE with the exception of epilepsy partialis continua or RSE secondary to metabolically reversible causes such as hypoglycemia. We defined RSE as clinical and/or electrographic seizures refractory to loading or protracted maintenance doses of at least 3 AEDs. All patients had either continuous EEG monitoring before and during IA or a minimum of 2 EEGs per day for a minimum of 2 h/d. The following EEG features were documented: background activity, interictal epileptic activities, clinical and electrographic seizures, and periods of burst suppression. Burst suppression was considered adequate if the suppression lasted longer than 10 seconds with epileptic bursts lasting less than 1 second. A sustained burst suppression referred to recordings that contained greater than 90% of a sustained burst-suppression pattern. The EEG recording was classified as a partial burst-suppression pattern if suppression lasted less than 10 seconds in more than 90% of the record. Inadequate burst suppression referred to records with frequent seizures and epileptic bursts lasting longer than 10 seconds. All patients underwent detailed investigations including cranial magnetic resonance imaging and computed tomography, cerebrospinal fluid sampling, and connective tissue disease, microbial, and toxicology screens. Patients 4 and 5 were investigated for Hashimoto thyroiditis with antithyroglobulin antibodies and antimicrosomal antibodies. Patient 4 had a detailed survey performed for a potential source of malignancy, which included serum anti-Hu antibody. Patient 5 underwent cerebral angiogram, brain, muscle, and nerve biopsies. Patients 4, 6, and 7 had extensive postmortem examinations.

Once it was determined by the attending care team that the patient warranted a trial of IA therapy for RSE, an end-ictal anesthetic monitor connector (Datex Gas analyzer bench, model G-A:OV; Datex-Ohmeda, Helsinki, Finland) was placed into the ventilator circuit near the end of the endotracheal tube. This monitor determined the end-tidal concentration of the IA to indicate the dose the patient was receiving. During the initial administration, the concentration of the anesthetic agent was gradually increased until an adequate suppression of the seizure and background activity was achieved on the continuous EEG recording, and this dose was maintained. Therapy with the IA was reassessed every 12 to 24 hours by gradually reducing the concentration of the anesthetic agent while observing the continuous EEG monitor. This allowed adjustment of the patient’s parenteral anticonvulsant therapy as guided by drug levels or titration paradigms. For example, standard AEDs initiated before the anesthetic agent were maintained in therapeutic doses, and additional agents were administered as indicated clinically. The minimum dose of anesthetic agent to achieve suppression of EEG seizures was determined daily, and the anesthetic agent was gradually discontinued once it was determined that the patient’s current parenteral anticonvulsant regimen was achieving adequate suppression of seizures. The total IA administered to each patient was calculated by dividing the percentage concentration of IA per hour × the total number of hours by the IA’s minimal alveolar concentration (MAC) (1.15% for isoflurane and 6.0% for desflurane).

To demonstrate the safety profile of the IA, we reviewed all medical complications encountered during the course of therapy. Patients who survived RSE were followed up for a minimum of 6 months using the Glasgow Outcome Scale.

RESULTS

Seven patients (4 male, 3 female) met our inclusion criteria. Mean ± SD age at the time of RSE was 42 ± 20 years (range, 17–71 years). Four patients had epilepsy prior to RSE, and presumed causes of RSE are listed in Table 1.

Analysis of EEG features revealed adequate and sustained burst-suppression pattern with isoflurane, which was dose dependent, easy to achieve, and rapidly reversible. This robust effect of both IAs was not seen consistently with the other agents (Table 2).

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Table 1. Clinical Profile of Patients With Refractory Status Epilepticus (RSE)

<table>
<thead>
<tr>
<th>Patient/Age, y/M</th>
<th>History of Seizures</th>
<th>Etiology of RSE</th>
<th>Seizure Type During RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/19/F</td>
<td>Cryptogenic RSE with multiple seizure types (GTC, CPS, atypical absences, drop attacks); onset at age 1 y</td>
<td>Cryptogenic, preceded by increased frequency of seizures (especially drop attacks), precipitated by corpus callosumotomy and right frontal resection</td>
<td>NCSE (generalized, maximum left hemisphere)</td>
</tr>
<tr>
<td>2/51/M</td>
<td>Cryptogenic epilepsy with GTC for 3 y</td>
<td>Poor compliance with AEDs (serum PHT level &lt;0.5 µg/mL)</td>
<td>GCS and NCSE</td>
</tr>
<tr>
<td>3/51/M</td>
<td>Symptomatic epilepsy with partial motor (rolandic) seizures due to a low-grade oligodendroglioma of left frontal lobe for 3 y</td>
<td>Oligodendroglioma (left frontal)</td>
<td>Partial motor (rolandic) and secondary generalized convulsive status epilepticus and NCSE</td>
</tr>
<tr>
<td>4/71/M</td>
<td>None</td>
<td>Silver toxicity</td>
<td>Multifocal and general myoclonus; stimulus-sensitive myoclonus; partial motor with secondary GCS and NCSE</td>
</tr>
<tr>
<td>5/17/F</td>
<td>None</td>
<td>Encephalitis of unknown cause</td>
<td>GCS and NCSE (multifocal, generalized)</td>
</tr>
<tr>
<td>6/56/F</td>
<td>Cryptogenic epilepsy with GTC and absences from age 4-38 y; then seizure free while taking PB and CBZ</td>
<td>Acute hemorrhagic leukencephalitis</td>
<td>GCS and NCSE (generalized, multifocal)</td>
</tr>
<tr>
<td>7/32/M</td>
<td>Seizures with meningitis as an infant</td>
<td>Cryptogenic</td>
<td>NCSE (partial)</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; CPS, complex partial seizure; GCS, generalized convulsive status; GTC, generalized tonic-clonic seizure; NCSE, nonconvulsive status epilepticus; PB, phenobarbital; PHT, phenyltoin; SI conversion factor: To convert phenytoin to micromoles per liter, multiply by 3.96.
Mean ± SD hospital stay, intensive care unit stay, and days receiving ventilatory care were 42 ± 29 days (range, 9-84 days), 31 ± 23 days (range, 9-67 days), and 28 ± 20 days (range, 9-56 days), respectively (Table 3). Prior to IA use, RSE continued for a mean of 19 days (range, 1-102 days). Patients received a mean of 10 AEDs (range, 7-15) in addition to the IA. One patient received desflurane anesthesia 21 days after RSE for a total of 19 days. Isoflurane treatment was then instituted for 7 days with equal efficacy. The other patients had isoflurane as the only anesthetic. The IA was initiated after a median of 3 days of RSE (range, 1-103 days), and it was used for a mean ± SD of 11 ± 9 days (range, 2-26 days). Maximal end-tidal isoflurane concentration ranged from 1.2% to 5.0% with a mean ± SD isoflurane dose of 173 ± 159 MAC-hours (range, 12-277 MAC-hours). Regardless of the pre-existing pattern of the EEG, all patients achieved an adequate burst-suppression EEG pattern within minutes of initiating IA (Table 3) (Figure 1). Although patients 1, 2, and 5 had adequate and sustained burst suppression with thiopental, this was replaced with IA because of the concerns for toxic effects on organs and prolongation of action with the large doses of thiopental required to maintain burst suppression.

All patients required volume resuscitation and vaso-pressors/inotropes before, during, and after IA; how-
ever, the doses required were higher during isoflurane or desflurane administration. Atelectasis was also present in all patients before, during, and after IA. All patients developed an infection while in the intensive care unit; however, infections occurred in 5 of 7 patients during IA therapy. These infections were successfully managed: respiratory tract in 5, urinary tract in 2, and fungal catheter sepsis in 1 patient. Paralytic ileus occurred in 3 patients, necessitating total parenteral nutrition in 2 patients. Deep venous thrombosis and decubitus ulcers occurred in 2 and 3 patients, respectively; however, these conditions were present prior to the initiation of IA therapy. Indices of renal and hepatic function did not alter significantly during and following IA therapy.

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COMMENT

The IAIs, isoflurane and desflurane, effectively stopped seizures in all 7 cases of RSE. Adequately sustained burst-suppression EEG patterns were obtained in all patients within minutes of initiation of IA therapy in a dose-dependent manner during administration of IA.

Most currently available anticonvulsant drugs in the treatment of RSE have GABAergic (\( \gamma \)-aminobutyric acid) properties except for phenytoin, which affects the rapid neuronal firings. Experimental studies suggest that

Table 3. Course of Therapy for Patients With Refractory Status Epilepticus (RSE)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Hospital Stay, d</th>
<th>ICU Stay, d</th>
<th>Ventilatory Support, d</th>
<th>MAC-Hours of Isoflurane (d)</th>
<th>RSE Prior to Isoflurane, d</th>
<th>Other AEDs Tried During RSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>53</td>
<td>30</td>
<td>27</td>
<td>33.8 (2)</td>
<td>3</td>
<td>LZP, diazepam, MDL, PHT, PB, TS, PRO, VPA, LMT</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>12</td>
<td>11</td>
<td>43.9 (3)</td>
<td>4</td>
<td>LZP, diazepam, MDL, PHT, PB, TS, PRO</td>
</tr>
<tr>
<td>3</td>
<td>49</td>
<td>27</td>
<td>18</td>
<td>151.4 (6)</td>
<td>1</td>
<td>LZP, diazepam, clonazepam, MDL, PRO, CBZ, VPA, GBP, TPM</td>
</tr>
<tr>
<td>4</td>
<td>84</td>
<td>58</td>
<td>56</td>
<td>276.9 (26)*</td>
<td>7</td>
<td>LZP, diazepam, clonazepam, MDL, PHT, PB, PTB, TS, PRO, CBZ, VPA</td>
</tr>
<tr>
<td>5</td>
<td>67</td>
<td>67</td>
<td>57</td>
<td>11.6 (19)</td>
<td>103</td>
<td>LZP, diazepam, MDL, PHT, PB, primidone, PTB, TS, PRO, CBZ, VPA, clobazem, LMT, VGB, TPM, paraldehyde</td>
</tr>
<tr>
<td>6</td>
<td>9</td>
<td>9</td>
<td>9</td>
<td>248.2 (8)</td>
<td>2</td>
<td>LZP, MDL, PHT, PB, CBZ, VPA, LMT, fentanyl citrate</td>
</tr>
<tr>
<td>7</td>
<td>18</td>
<td>17</td>
<td>17</td>
<td>444.3 (13)</td>
<td>2</td>
<td>LZP, diazepam, MDL, PHT, PB, CBZ</td>
</tr>
</tbody>
</table>

Abbreviations: AED, antiepileptic drug; CBZ, carbamazepine; GBP, gabapentin; ICU, intensive care unit; LMT, lamotrigine; LZP, lorazepam; MAC, minimal alveolar concentration; MDL, midazolam; PB, phenobarbital; PTB, pentobarbital; PHT, phenytoin; PRO, propofol; TPM, topiramate; TS, thiopental sodium; VGB, vigabatrin; VPA, valproic acid.

*237.9 MAC-hours (19 days) of desflurane and 39 MAC-hours (7 days) of isoflurane.

Figure 1. A, Longitudinal bipolar recording of left hemispheric seizure onset with secondary generalization (not shown). Sensitivity, 15 µV/mm; low-frequency filter (LFF), 0.3 Hz; and high-frequency filter (HFF), 70 Hz; notch filter on. B, Longitudinal bipolar recording of termination not controlled with boluses of lorazepam and continuous infusion of large doses of propofol (patient 3). Sensitivity, 15 µV/mm; LFF, 0.3 Hz; and HFF, 70 Hz; notch filter off. C, Longitudinal bipolar recording of the same patient with sustained, adequate burst suppression while receiving isoflurane. Sensitivity, 7 µV/mm; LFF, 0.3 Hz; and HFF, 70 Hz; notch filter off.

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GABAergic agents lose their efficacy in prolonged seizures, which may account for the refractoriness to treatment that occurs in some patients with status epilepticus. This has been attributed to excess glutamate release, which is associated with ongoing seizure activity lasting longer than 1 hour, resulting in an altered balance of excitation vs inhibition. In addition, the benzodiazepine receptor loses its affinity for its ligands, reducing their potency. Although the mechanism of action of IA is not well understood, the antiepileptic effects of isoflurane are likely due to potentiation of inhibitory postsynaptic GABA<sub>A</sub> receptor-mediated currents; however, its effects on thalamocortical pathways have also been implicated. In our study, although patients received IA therapy late in the course of their illness, they still maintained their responsiveness to these agents. Recurrence of seizures was also high with discontinuation of the IA therapy. Perhaps the early use of IA within the first 2 to 4 hours of RSE would result in a more favorable alteration in the balance of excitation vs inhibition so that conventional agents used in the treatment of RSE would become more efficacious. As such, early and aggressive treatment of RSE with IA agents may alter disease outcome. A randomized controlled trial is therefore needed to determine the efficacy of IA in the “early” management of RSE.

Both isoflurane and desflurane produce dose-dependent changes in the EEG. Initially, an increase in frequency and lowering of voltage occurs with sub-MAC concentrations, and as the concentration increases, there is a gradual decrease in voltage with increasing periods of electrical silence (burst suppression). Upon initiation of the IA in our group of patients, the concentration was gradually increased to obtain adequate burst suppression. This dose was gradually decreased on a daily basis and eventually weaned off, if a parenteral therapeutic regimen became effective in adequately controlling the patient’s seizures.

The pharmacokinetic and pharmacodynamic properties of isoflurane and desflurane make them effective agents in producing burst-suppression EEG patterns that are easily titratable. Other advantages, including rapid onset of action and elimination and the reduced potential for toxic effects on organs owing to their relative resistance to bio-transformation, make them an ideal choice of therapy for RSE. Halothane was the first IA to be used for RSE, however, the potential toxic effect on organs associated with its toxic metabolites is a concern, particularly during prolonged administration. Isoflurane and desflurane, on the other hand, undergo significantly less metabolism (0.20% and 0.02%, respectively), and their potential to produce organ toxicity is substantially reduced. Other IAs currently available, such as sevoflurane and enflurane, also undergo a significant amount of metabolism, producing potentially toxic metabolites, especially during prolonged administration. Also, sevoflurane under certain conditions may be epileptogenic. Isoflurane and desflurane are therefore among few agents of choice, particularly for anticipated prolonged periods of application.

Isoflurane has been the IA most used by several groups. Kolke et al. reported 9 patients with RSE who were treated with isoflurane for a maximum of 55 hours. To our knowledge, our series is the first study that demonstrates the safety of isoflurane and desflurane in the treatment of RSE for up to 26 days. Although significant increases in plasma organic fluoride have been reported in patients receiving isoflurane for prolonged periods, no renal toxicity was associated with this observation. During isoflurane and desflurane administration, there was a dose-dependent reduction in systemic vascular resistance due to peripheral vasodilation. As a result, all 7 patients required fluid resuscitation and vasopressor therapy during their administration. Most intravenous agents used to treat RSE are expected to produce a degree of hypotension; therefore, hemodynamic consequences must be considered in choosing any AED. There is no evidence of toxic effects on the central nervous system with isoflurane, and experimental studies have generally shown a favorable effect of isoflurane on cerebral metabolism.

Burst suppression and isoelectric background EEG have been shown to be accompanied by fewer recurrent seizures than simply stopping seizures. This was consistent with our findings. We considered the maintenance of burst suppression for burst duration of less than 1 second and suppression duration of longer than 10 seconds as the goal of therapy. There is, however, no general agreement on what constitutes adequate burst suppression. Van Ness empirically used 3 to 9 bursts per minute during pentobarbital treatment with close attention to the hemo-
dynamic parameters. Koffe et al., on the other hand, used 15 to 30 seconds as an empirical burst-suppression interval. This was based on an animal study that demonstrated maximal depression of cerebral metabolism with barbiturates with burst-suppression intervals of 30 seconds. Bleck advocates a more aggressive approach using isoelectric EEGs as the end point of therapy. However, there is no evidence that what constitutes an optimal burst-suppression interval can optimize patient outcome. Our patients had a dichotomous outcome: good to excellent or death due to underlying illness; the mortality rate was 43%. This is in agreement with previous studies confirming that the underlying etiology of RSE is the major determinant of outcome.

In conclusion, we suggest that isoflurane or desflurane may be used as a single agent for management of patients with RSE while their standard anticonvulsants are being adjusted. These agents were also well tolerated during prolonged administration with no evidence of organ toxicity. We recommend a randomized controlled trial to determine whether IAs or other anticonvulsant regimens offer the best therapy for RSE.

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