Treatment of Refractory and Super-Refractory Status Epilepticus

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Introduction

Refractory and super-refractory status epilepticus (SE) are acute neurologic emergencies with mortality rates of 18–26% [1–4] and 23–48% [5–10], respectively. Over half of survivors have poor functional outcomes [10–12], but excellent outcomes are reported even after prolonged SE lasting weeks or months [13, 14]. The pharmacologic treatment itself portends additional risk of morbidity and mortality, and recent evidence highlights these concerns [15–17]. Although there are risks of treatment, uncontrolled convulsive SE may be fatal or lead to permanent multi-organ failure [18, 19]; therefore, aggressive control of seizures is critical. When nonconvulsive SE, whether focal or generalized, leads to a reduction in the level of consciousness and significant compromise of function, seizures must also be controlled aggressively, despite the inherent treatment risks. Predictors of refractoriness include severity of consciousness impairment at onset, de novo episodes, and encephalitis [7, 9], but SE of any cause can become refractory if initial therapies are delayed or inadequate, or if the underlying cause is not reversed.

If SE is refractory to initial therapies including benzodiazepines and a second line intravenous (IV) anti-seizure drug (ASD) such as fosphenytoin, valproic acid, or phenobarbital, the patient is said to be in refractory status epilepticus (RSE) and treatment with an anesthetic drug is frequently initiated. When SE continues or recurs 24 h or more after the initiation of anesthetic treatment, it is termed super-refractory status epilepticus (SRSE), or alternatively, 'malignant status epilepticus.' The pharmacologic treatment of this very refractory group of patients is not well determined or supported by strong evidence [20, 21].

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This chapter provides a comprehensive overview of the pharmacologic treatment of refractory and super-refractory status epilepticus. Treatment aggressiveness, drug selection, and dosing are discussed, including both anesthetic and non-anesthetic ASDs. An in depth review of commonly used anesthetic drugs including propofol, midazolam, ketamine, and barbiturates including thiopental, phenobarbital, and pentobarbital, is provided. Mirroring the daily care of patients with refractory and super-refractory status epilepticus, the chapter emphasizes the complications of anesthetic therapies and when possible, how to prevent them. Less frequently discussed aspects of treatment, including the electroencephalography (EEG) suppression target, principles of weaning anesthetic drugs, and what to do in between weaning attempts, are addressed. Also included is a section on when and how to initiate a trial of immunotherapy for cryptogenic or antibody-mediated RSE.

Refractory Status Epilepticus

Selection of Third Line Therapy

After failure of an adequate dose of first line (i.e., a benzodiazepine) and a second line ASD (e.g., fosphenytoin), SE is considered refractory. The main decision point at this stage is whether to treat with a third line non-anesthetic ASD or to initiate a continuous anesthetic infusion. Numerous options and little data exist to guide this decision. The only randomized controlled trial designed to evaluate this phase of SE was stopped prematurely due to poor enrollment [22]. Continuous infusion IV anesthetic drugs are often employed to control RSE, especially in convulsive SE. Purported reasons for this aggressive approach include; (1) prevention of systemic injury or death from uncontrolled convulsive SE, (2) prevention of seizure-induced neuronal loss, (3) reduction of cerebral metabolism, and (4) the assumption of lower efficacy of third or fourth line non-anesthetic ASDs. Undoubtedly, uncontrolled convulsive seizures cause

neuronal injury and may lead to severe and permanent systemic and neurologic morbidity [19, 23]. Neuronal injury may well also occur with uncontrolled nonconvulsive seizures [24–26], and the decline in neurologic function appears to be directly proportional to the duration of nonconvulsive seizures [27]. Nevertheless, the use of anesthetic drugs in the doses required to control RSE is associated with serious side effects, some of which can also result in death [19].

Given the limited evidence supporting the use of anesthetic drugs and the relatively unfavorable side effect profiles, multiple recent retrospective observational studies were performed to assess the association between anesthetic drug use and outcome in RSE [15–17], the results suggesting an independent association with mortality and worse functional outcomes. The first of these studies did not adequately control for known outcome predictors [15]. Sutter and colleagues then reviewed 171 consecutive patients with non-anoxic SE of whom 63 (37%) were treated with an anesthetic drug [16]. They controlled for known outcome predictors including duration of SE, critical comorbid medical conditions, SE severity (graded by the Status Epilepticus Severity Score [STESS]), and administration of non-anesthetic third line ASDs. The STESS includes patient age, worst seizure type, level of consciousness at presentation, and whether or not the patient has a history of seizures [28]. The authors found that the use of an anesthetic drug was associated with increased mortality (relative risk 2.88) and worse functional outcomes (relative risk 1.25), but the difference in outcomes was most pronounced in those with focal seizure types, as opposed to convulsive or nonconvulsive SE in coma [16]. The patients who received anesthetic drugs were more likely to have a depressed level of consciousness prior to treatment, an acute symptomatic etiology, and a longer duration of SE. After adjusting for refractoriness, the association of anesthetic drug use with mortality and functional outcome disappeared [16]. Marchi et al. [17] reviewed 467 consecutive episodes of SE lasting longer than 30 min, among whom 50 (10.7%), were managed with an anesthetic drug. After adjusting for etiology, severity of SE (using the SESS), and comorbid conditions, the use of an anesthetic drug was associated with new disability at hospital discharge (relative risk of 4.6) and mortality (relative risk 5.5). Similar to the results of Sutter and colleagues, the effect was most pronounced for those with milder seizure types, and patients treated with anesthetic drugs were more likely to have severe seizure types (convulsive or nonconvulsive SE in coma) [17].

What is clear from these studies is that patients who require anesthetic drugs for control of RSE have more severe and refractory forms of SE, and that in this patient subgroup of patients outcomes are often poor. It remains unknown how much brain function is being saved in survivors by aggressively controlling the seizures and whether this justifies the risks of anesthetic drug use. In fact, one paper showed that a higher dose anesthetic drug infusion was superior to a lower dose of the same drug (midazolam), resulting in fewer withdrawal seizures and lower mortality [29].

Incorporating the lessons of these studies, Fig. 17.1 depicts a simple algorithmic approach to selection of third line therapy in RSE. As a general principle, refractory generalized convulsive SE should be controlled as rapidly as possible with the use of an anesthetic drug, and control confirmed by continuous electroencephalogram (C-EEG). The decision to initiate an anesthetic drug necessitates admission to an intensive care unit (ICU), endotracheal intubation and mechanical ventilation, continuous hemodynamic monitoring, and initiation of C-EEG monitoring. Nonconvulsive RSE presents less risk to the cardiopulmonary, musculoskeletal and renal systems, and possibly the brain. Thus, in patients who are hemodynamically stable, have preserved airway reflexes and are adequately oxygenating and ventilating, it is reasonable to try one or two

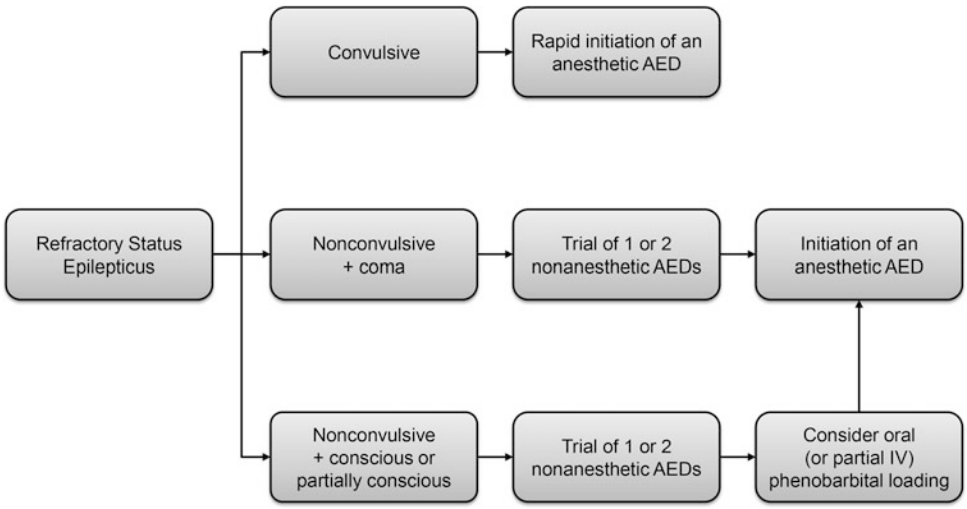

Fig. 17.1 Suggested algorithm for the selection of 3rd–5th *line* anti-seizure drugs for treatment of refractory status epilepticus. *ASD* anti-seizure drug

Table 17.1 Non-anesthetic anti-seizure drug options for the treatment of refractory and super-refractory status epilepticus

Drug	Loading/starting dose	Maintenance dose	Therapeutic level	Adverse effects
Fosphenytoin[d]	18–20 mg PE/kg IV up to 150 mg/min	5–7 PE/kg/day IV, divided every 8 h	Measure phenytoin level	Hypotension, arrhythmia, nonallergic pruritus
Phenytoin[d]	18–20 mg/kg IV, up to 50 mg/min	5–7 mg/kg/day oral/IV, divided every 8 h	Total: 15–20 μg/mL; Free: 1.5–2.5 μg/mL	Hypotension, arrhythmia, metabolic acidosis or tissue injury with extravasation (diluted in propylene glycol)
Valproate[d]	20–40 mg/kg, up to 3 mg/kg/min	30–60 mg/kg/day oral/IV, divided every 6 h	80–140 μg/mL	Hyperammonemia, pancreatitis, thrombocytopenia
Levetiracetam[d]	20–60 mg/kg, up to 500 mg/min	2–12 g/day oral/IV, divided up to every 6 h	25–60 mg/L	Somnolence, rarely agitation
Lacosamide[d]	200–400 mg, over 5 min	400–600 mg/day IV divided every 12 h	Unknown	Mild sedation, allergic skin reactions, prolongation of PR interval
Phenobarbita[a,d]	5–10 mg/kg, up to 60 mg/min	1–4 mg/kg/day oral/IV, divided every 6–8 h	20–50 mg/mL	Sedation, respiratory depression, rare metabolic acidosis due to propylene glycol toxicity
Clonazepam[b,d]	0.015 mg/kg IV	0.5–8 mg/day oral, divided every 6–12 h	Unknown	Mild sedation
Topiramate	200–400 mg oral	400–800 mg/day oral, divided every 8–12 h[c]	Unknown	Metabolic acidosis

IV intravenous; *min* minutes; *PE* phenytoin equivalent
[a]This is a non-anesthetic dose and infusion rate recommendation for the treatment of nonconvulsive SE with some preservation of consciousness. Airway and hemodynamic monitoring including blood pressure and telemetry monitoring are still required
[b]Not available in intravenous form in the United States
[c]Doses up to 1200–1600 mg have been used and are recommended in the Neurocritical Care Society guidelines (Brophy, 2012 [55])
[d]Fast acting intravenous ASD options for the acute control of RSE

additional fast acting non-anesthetic ASDs prior to initiating an anesthetic drug (Table 17.1). When a patient with non-convulsive RSE is comatose, a third line fast acting IV ASD may be administered, followed by a quick assessment of the clinical and electrographic response in order to achieve seizure control as rapidly as possible with escalation to an anesthetic drug if the third line treatment fails. When some preservation of consciousness exists in the setting of non-convulsive seizures, every attempt should be made to avoid the use of anesthetic drugs as long as possible. In these patients, as well as those with a 'do not resuscitate' order, we have had success with loading half or even three-quarters of a full phenobarbital load IV in divided doses, waiting several hours in between. Given the side effect profile of phenobarbital, which includes prolonged sedation, hypotension, and respiratory depression, this is usually considered after failure of multiple non-anesthetic ASDs (i.e., fourth or fifth line treatment). Loading 5 mg/kg of phenobarbital IV followed by another 5 mg/kg load several hours later (if needed) while carefully monitoring the hemodynamic and respiratory status, can be effective and avoid the need for a continuous anesthetic infusion. This should be followed by a maintenance dose of phenobarbital (see Table 17.1).

Drug selection is determined on a case-by-case basis, but important considerations exist. Patients with known epilepsy may respond well to an IV bolus of their chronic maintenance ASD, if available, even if recent levels had been therapeutic in the outpatient setting. Consideration should also be given to common adverse effects and drug interactions. For example, phenytoin and fosphenytoin are best avoided in hemodynamically unstable patients, as they cause clinically significant hypotension in up to 50% of patients during infusion of the loading dose [30, 31]. Valproate may not be the best option in patients previously loaded with fosphenytoin or phenytoin as a second line therapy, because valproate will initially displace the protein bound portion of phenytoin and inhibit its metabolism, thereby increasing the free levels of phenytoin and decreasing the free valproate concentrations [32]. While free phenytoin and valproate concentrations will eventually be normalized when steady state is reached, this interaction may defeat the purpose of attempting rapid control of seizures, avoidance of intubation, and initiation of anesthesia. For a thorough review of the pharmacologic properties, efficacy and safety data for each ASD, see Trinka and colleagues, 2015 [33].

Anesthetic Anti-seizure Drugs

In generalized convulsive status epilepticus, early escalation to anesthetic drugs is justified because rapid seizure control is imperative to avoid the development of pharmacoresistance, neuronal injury, and systemic complications. Commonly used anesthetic ASDs are listed in Table 17.2. There is insufficient evidence to recommend one anesthetic ASD over another [20, 21]. There are three conventional choices —barbiturates (thiopental or its main metabolite, pentobarbital), midazolam, and propofol—although ketamine has become an alternative choice as experience with it has increased. One randomized controlled trial was attempted comparing thiopental and midazolam, but the trial was powered for 150 patients and recruited only 24 [22]. A systematic review of published (primarily uncontrolled) case series reported control of RSE without breakthrough seizures to be 42, 66, and 60%, respectively, for midazolam, propofol, and barbiturates [6].

As there are no randomized or controlled comparative data upon which to differentiate these choices, selection is based primarily on the advantages and adverse effect profile of each drug in relation to the comorbidities of the patient. It should be stated that all anesthetic ASDs are associated with high rates of infection [16, 17]. If an anesthetic ASD is initiated and titrated to typically adequate doses without achieving electrographic seizure control, an alternative anesthetic drug is usually added or substituted. According to recently published data from the global audit of treatment of refractory SE, the most widely used initial anesthetic ASD is midazolam (59%), followed by propofol (32%), and barbiturates (8%) [12].

Midazolam. Midazolam is a benzodiazepine administered via IV infusion which acts by binding to and enhancing the action of the $GABA_A$ receptor. Onset of action occurs within minutes and it is relatively short-acting in non-obese patients with normal renal function (elimination half-life of 1.8–6.4 h). These properties make it ideally suited to prolonged use without accumulation, but accumulation may occur in adipose tissue and with renal insufficiency. Tachyphylaxis may develop, sometimes after only one day of use, necessitating gradually increasing doses to maintain seizure control. The propensity for breakthrough seizures to develop during treatment with midazolam has been shown in multiple studies [34, 35]. As midazolam is a strong respiratory depressant, mechanical ventilation is required, and hypotension requiring pressors occurs in 30–50% of patients [6, 29, 34]. In a systematic review of 28 studies describing 193 patients with RSE, 54 of whom were treated with midazolam, seizures recurred acutely after the loading dose in 20% of cases. Breakthrough seizures occurred after the

Table 17.2 Anesthetic anti-seizure drug options for the treatment of refractory status epilepticus

Drug	Loading dose	Infusion rate	Adverse effects	Special considerations
Midazolam	0.2 mg/kg IV every 5 min until seizures controlled; maximum dose of 2 mg/kg	0.1–2.0 mg/kg/h	Respiratory depression, hypotension	Tachyphylaxis, requires mechanical ventilation, accumulates in adipose tissue and renal insufficiency
Propofol	2 mg/kg IV every 5 min until seizures controlled; maximum dose 10 mg/kg	30–200 mcg/kg/min; Avoid use $\geq$80 mcg/kg/min for $\geq$48 h	Hypotension, propofol infusion syndrome (potentially fatal myocardial failure, lactic acidosis, hypertriglyceridemia, & rhabdomyolysis)	Requires adjustment of daily caloric intake by 1.1 kcal/ml, requires mechanical ventilation
Ketamine	1–2 mg/kg IV every 5 min until seizures controlled; maximum dose 4.5 mg/kg	1.2–7.5 mg/kg/h	Hypertension, hypotension, supraventricular tachycardia, bradyarrhythmias	Requires mechanical ventilation
Pentobarbital	5 mg/kg IV up to 50 mg/min every 5 min until seizures controlled or maximum 15 mg/kg	0.5–5 mg/kg/h	Hypotension, paralytic ileus, respiratory depression, rare hepatotoxicity, rare metabolic acidosis due to propylene glycol toxicity, prolonged sedation	Complete loss of neurological function at high doses, requires mechanical ventilation
Phenobarbital[a]	20 mg/kg IV up to 100 mg/min	1–4 mg/kg/day oral/IV, divided every 6–8 h	Prolonged sedation, respiratory depression, rare metabolic acidosis due to propylene glycol toxicity	Requires mechanical ventilation
Thiopental[b]	2–7 mg/kg IV up to 50 mg/min	0.5–5 mg/kg/h	Hypotension, respiratory depression, paralytic ileus, prolonged sedation	Accumulates in adipose tissue, metabolized to pentobarbital

[a]Included here despite the absence of a continuous infusion as it requires intubation and mechanical ventilation
[b]Not available in the United States

first six hours of treatment in 51%, and withdrawal seizures occurred during weaning of midazolam in 63% [6]. More recently, a study compared 100 patients treated with a high-dose continuous midazolam infusion (median maximum dose 0.4 mg/kg/h, interquartile range (IQR) 0.2–1.0) to 29 historical controls at the same center treated with a lower dose midazolam protocol (median maximum dose 0.2 mg/kg/h, IQR 0.1–0.3) [29]. Withdrawal seizures, occurring within 48 h of drug discontinuation, were less frequent in the high-dose group (15 vs. 64%; odds ratio (OR) 0.10; 95% CI 0.03–0.27) and mortality was lower (40 vs. 62%; OR 0.34; 95% CI 0.13–0.92) compared with those in the low-dose group, despite a higher incidence of hypotension, and similar baseline patient characteristics and duration of midazolam infusion. The results of this study suggest that high doses of midazolam are safe and associated with fewer withdrawal seizures. The implications of the lower mortality are unclear given the historical controls and inability to account for other practice changes.

Propofol. Propofol is an anesthetic with ill-defined anti-seizure properties, which is thought to act by modulation of the $GABA_A$ receptor, and possibly N-methyl-D-aspartate (NMDA) antagonism, at least in vitro [36]. Like midazolam, propofol is very short-acting and has a rapid onset of action. Other advantages include its intracranial pressure and cerebral metabolism lowering properties [37]. Pressors are required for treatment of hypotension in 22–55% of patients [6, 22, 38]. Apnea occurs in 50–84% of patients, and mechanical ventilation is required [39]. The most feared complication of propofol is the propofol infusion syndrome (PRIS), a syndrome of metabolic acidosis, rhabdomyolysis, renal failure, hyperkalemia, hypertriglyceridemia, and rapid cardiovascular collapse which results from a toxic effect on mitochondrial and cellular metabolic function. The incidence of PRIS is unknown, and estimates vary widely with the dose and duration of use [38, 40]. Risk factors include young age, high fat and low carbohydrate intake, concomitant catecholamine infusion or corticosteroid use, and prolonged high-dose infusions ($\geq$80 mcg/kg/min, for $\geq$3 days) [40, 41]. In a study of 31 patients with RSE treated with propofol for a median 67 (range 2–391) hours with median cumulative doses of 12,850 (range 336–57,545) mg, three sudden cardiorespiratory arrests occurred without clear explanation. Two patients died and 11 additional patients exhibited features of PRIS despite careful monitoring for metabolic and cardiac changes [40]. It is therefore likely that the only way to avoid this potentially lethal complication is with the use of a protocol limiting its use to no more than 2 or 3 days at doses not higher than 80 mcg/kg/min. Treatment of PRIS is primarily supportive and includes stopping propofol, supporting the cardiopulmonary and renal systems, sometimes with cardiac pacing, renal replacement therapy, and extracorporal membrane oxygenation [42].

While significant clinical experience exists with propofol, data about efficacy is limited. One study examined the use of propofol in 27 consecutive episodes of RSE retrospectively, and found that breakthrough seizures occurred in 9/27 (33%) episodes, but in only two cases were the seizures severe enough to prompt substitution of an alternative anesthetic ASD [38]. In a systematic review of 28 studies describing 193 patients with RSE, 33 of whom were treated with propofol, seizures recurred acutely after the loading dose in 27% of cases. Breakthrough seizures occurred after the first six hours of treatment in 15%, and withdrawal seizures occurred during weaning in 46% of cases [6].

Barbiturates. Thiopental and its metabolite, pentobarbital, are barbiturate anesthetic drugs with strong anti-epileptic action. Their primary mechanism of action is to enhance transmission at the $GABA_A$ receptor but they also lower the core body temperature and may have neuroprotective effects. The barbiturates have a strong sedative effect and are respiratory depressants, necessitating mechanical ventilation. At high doses, they can result in loss of all brainstem reflexes and an isoelectric EEG, mimicking brain death [43].

Barbiturates are virtually always effective in achieving initial seizure control. Nevertheless, because of their prolonged duration of action, it is this author's opinion that they are not an ideal choice for first-line anesthetic therapy. There is a subset of patients with RSE who require only 24 h of anesthetic therapy and, upon correction of the etiology, are easily weaned from anesthesia, extubated, and discharged from the ICU within a 12–24 h period. If thiopental or pentobarbital is chosen as the first-line anesthetic therapy, the likelihood of the patient awakening and liberation from mechanical ventilation within that time frame is significantly reduced. This is due to their zero order kinetics, rapid redistribution, and resultant accumulation leading to a long half-life, prolonged recovery times [44], and longer duration of mechanical ventilation [22]. The barbiturates are metabolized by the liver, undergo autoinduction, and have many drug–drug interactions. Hypotension requiring pressors occurs in 29–77% [6, 45] of patients [22]. While less common, several other potentially serious systemic complications are specific to barbiturate. A relatively common complication of barbiturate infusions is adynamic ileus (Fig. 17.2), reported in 10% of patients [45]. When severe, bowel ischemia, and even perforation can result [22, 46]. Rarely, lingual edema (Fig. 17.3) can develop risking airway obstruction [47]. This gradually resolves after discontinua-

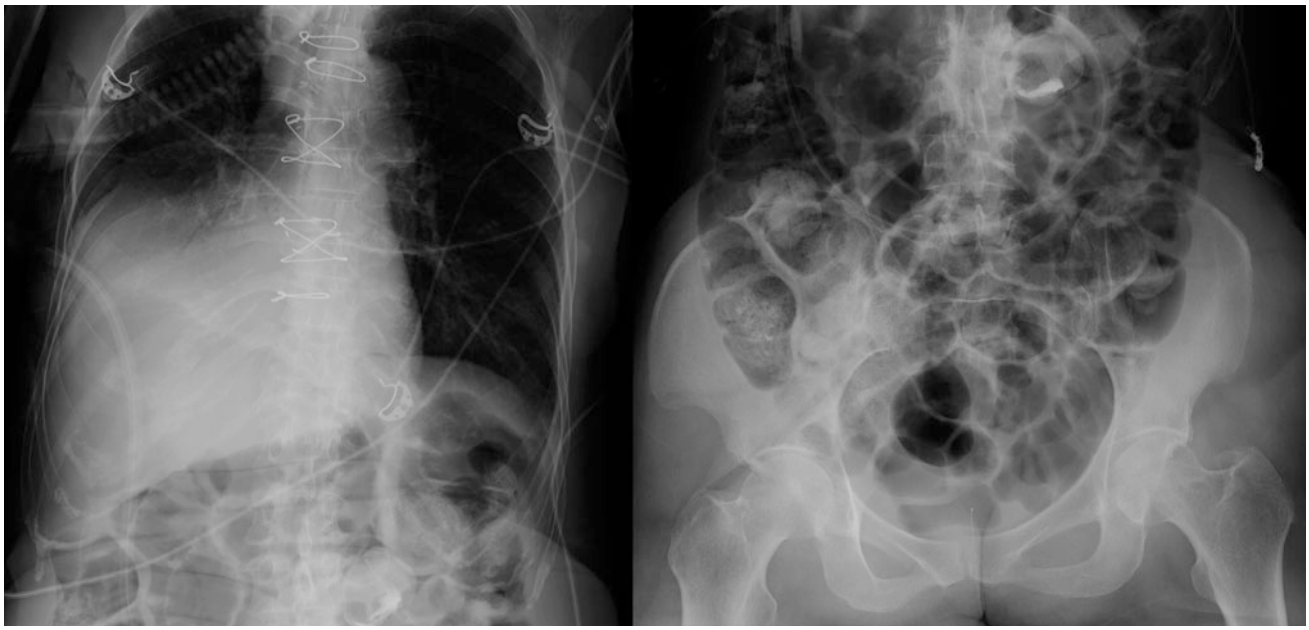

Fig. 17.2 Large amount of small bowel and colonic gas consistent with ileus in a patient treated with a continuous pentobarbital infusion for 17 days at a maximum dose of 5 mg/kg/h

tion of the drug. In <1% of patients, propylene glycol toxicity may develop which manifests as a progressive acidosis that resolves after drug discontinuation [45]. Rarely, pancreatic, gastric, or hepatic injury may develop due to systemic and splanchnic hypoperfusion, complications which more commonly occur in elderly patients [48].

In a retrospective review of 31 patients with SRSE treated with pentobarbital infusions, seizure control was achieved in 90% of patients but recurred in 48% upon weaning of the drug [45]. A systematic review of 28 studies describing 193 patients with RSE, 106 of whom were treated with pentobarbital, seizures recurred acutely after the loading dose in only 8% of cases. Breakthrough seizures occurred after the first six hours of treatment in 12%, and withdrawal seizures occurred during weaning in 43% of cases [6].

Ketamine. Ketamine is an NMDA antagonist—a potential advantage over the other anesthetic ASDs, as prolonged seizures are accompanied by pharmacoresistance to GABA agonists [49] but not to NMDA antagonists [50]. An additional advantage is its lack of respiratory depressant effects. Onset of action occurs within seconds, and it is relatively short-acting (elimination half-life of 2–3 h). Metabolism is hepatic and excretion is largely renal. Efficacy has been demonstrated in animal models, even in late stages of RSE [50, 51]. Experience in humans with RSE has been increasing in recent years. The largest published series is a multicenter retrospective review of 46 adults and 12 children totaling 60 episodes of RSE treated with ketamine [52]. In this series, ketamine was thought to have contributed to permanent control of RSE in 32% of cases, and transient control in an additional 13%, similar to the reported efficacy of the other anesthetic ASDs [6]. Interestingly, response rate was highest when ketamine was introduced early (as a third or fourth line agent). Still, an assessment of efficacy in a retrospective fashion, without controlling for the effects of other ASDs, treatment of the cause of RSE, and other factors, is questionable. The true value of this study lies in its confirmation of relative safety at the reported doses. Infusions of up to 10 mg/kg/h for up to 27 days were not associated with increased complications or mortality compared to patients receiving lower doses for fewer days [52]. Two patients in this series developed supraventricular tachycardia that resolved after drug discontinuation. One developed atrial fibrillation requiring amiodarone, and there was one incident of severe acidosis during coadministration of both high-dose midazolam and ketamine leading to discontinuation of the drug. Despite a call for earlier use [53], it is generally reserved for the most severe cases, usually after more than one anesthetic ASD has failed [50], a practice which is in line with current guidelines [54].

Treatment Goals

Once an anesthetic ASD has been initiated, the primary treatment goals are clinical and electrographic seizure suppression, and reversal of the cause of seizures. It is a common practice to titrate anesthetic ASDs to a predetermined EEG endpoint. Endpoints are controversial, and available evidence is conflicting [8, 10, 29, 55]. Options include

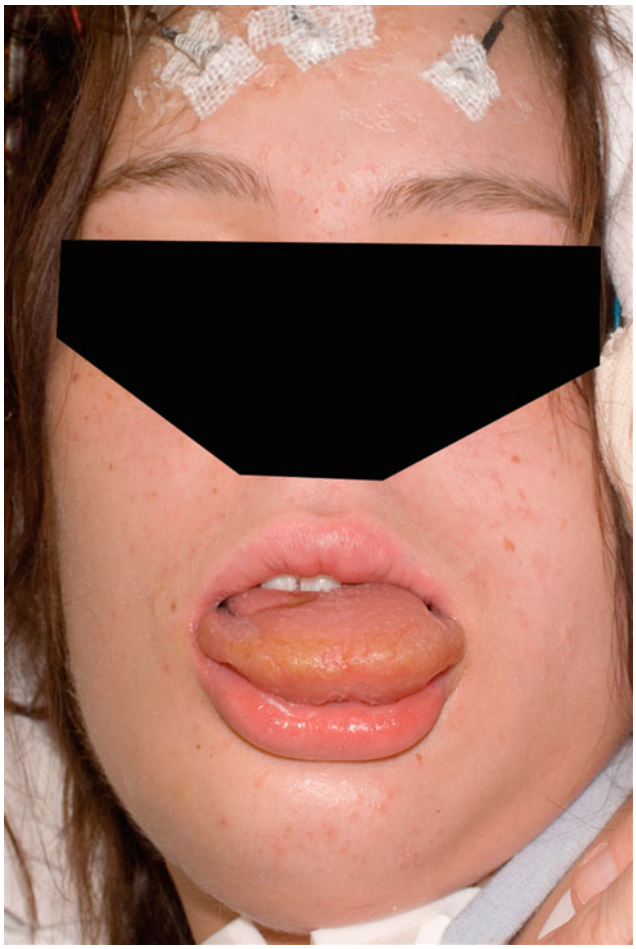

Fig. 17.3 Photograph of an enlarged tongue in a 20-year-old woman with refractory status epilepticus treated with continuous pentobarbital infusion for two weeks with a maximum dose of 9 mg/kg/h. From Ji et al. [48] with permission

complete background suppression (sometimes referred to as 'isoelectric' or 'flat'), burst suppression, or seizure suppression. Determining how much to suppress requires a clinical judgement that balances the risks of increased suppression (very high doses of anesthetic ASDs are sometimes required to achieve a burst suppression or isoelectric EEG background, risking increased hypotension, and other systemic complications), with the benefit of increased seizure suppression. Continuous EEG monitoring has shown that seizures may still emerge from a burst suppression pattern, so it follows that greater suppression should confer better seizure control [56].

Next Steps

Once achieved, it is standard practice to maintain the desired EEG endpoint for 24–48 h prior to a slow withdrawal of anesthetic ASDs [54]. Prior to attempting the first anesthetic wean, 2–3 non-anesthetic ASDs (usually including the drug selected as second line therapy) should be initiated at high doses and titrated to achieve therapeutic levels. In patients at risk for development of adynamic ileus (i.e., patients receiving opiates or barbiturates), the IV route of administration is preferred to ensure reliable absorption. In other patients, ASDs may be administered enterally via a nasogastric or orogastric tube. No evidence exists to guide optimal ASD combinations in this setting. General considerations for drug selection include seizure type, systemic comorbidities, drug–drug interaction profiles, and avoidance of polypharmacy (>3 ASDs may add morbidity by increasing the risk of adverse effects without evidence of benefit).

In addition, the clinician must ensure that the underlying etiology has been addressed. By this time patients will have undergone at a minimum, a thorough history, noncontrast head computed tomography (CT) scan, comprehensive laboratory evaluation, and lumbar puncture for cerebrospinal fluid (CSF) analysis. If an etiology is identified, attempts are made to correct the etiology (e.g., reverse hypoglycemia), or at least initiate appropriate treatment when the etiology is not expected to resolve rapidly (e.g., fulminant bacterial meningitis). If an etiology has not yet been identified at this stage, this is the time to begin the search for more unusual causes of SE (e.g., complete autoimmune encephalopathy panels including NMDA receptor, and voltage gated potassium channel antibodies) and to consider initiation of empiric immunotherapy. (See also Chap. 8, "Unusual Causes of Status Epilepticus.")

Weaning of Anesthesia

There is no evidence to guide the weaning of an anesthetic ASD. This author's practice is to wean anesthetic drugs one at a time by 10% per hour. For example, if the desired EEG endpoint is achieved with midazolam 20 mg/h and propofol 50 mcg/kg/min, and maintained for 24–48 h, the midazolam dose would be decreased by 2 mg/h each hour until off, while carefully monitoring the EEG for seizure recurrence. When midazolam is successfully discontinued, the propofol wean would begin, decreasing the dose by 5 mcg/kg/min every hour until off. Deciding which anesthetic drug to wean first is somewhat arbitrary but clinical circumstances may dictate which drug to wean first. Patients exposed to prolonged barbiturate infusions are at higher risk for withdrawal seizures; this may be avoided by utilizing phenobarbital as one of the 2 or 3 non-anesthetic ASDs [57].

If seizures recur, usual practice is to resume anesthesia and reestablish EEG suppression. Occasionally breakthrough seizures that occur upon weaning of anesthesia will subside spontaneously. How long to observe, if at all, remains a clinical judgment. It is probably reasonable to

observe and allow some electrographic seizures during an anesthetic wean, but if the frequency of breakthrough seizures does not decline gradually over time, anesthesia should be resumed. The same principle applies to other patterns that do not meet criteria for electrographic seizures, but are on the ictal–interictal continuum. As long as the EEG background continues to improve, and seizures are infrequent and declining in frequency, this author's practice is to continue weaning. During this time, bolus doses of benzodiazepines and further optimization of the patient's non-anesthetic ASD regimen may increase the likelihood of successful weaning.

Super-Refractory Status Epilepticus

If seizures continue or recur 24 h or more after the initiation of anesthetic therapy, the patient is considered to have reached the stage of 'super-refractory status epilepticus.' The majority of recommendations to guide treatment of this stage come from expert consensus. Issues that remain unresolved include what anesthetic drug to choose after failure of a weaning attempt and when to attempt weaning again. Barbiturates are often used as second line anesthetic ASDs [12]. They are reasonably well suited for long term use and are not prone to tachyphylaxis. Over time, the time between weaning attempts is increased, and after failure of several attempted weans, anesthesia is often continued for 5–7 days between weaning attempts.

Between Weaning Attempts

If not already accomplished, the primary focus between weaning attempts must be on identification and treatment of the seizure etiology. Additional tasks include careful temperature control, continued optimization of the non-anesthetic ASD regimen, and meticulous daily screening for complications of critical illness and anesthetic ASD use. Common complications in this setting include infections (especially pneumonia), venous thromboembolism, skin breakdown with formation of decubitus ulcers, adynamic ileus, and anasarca. Cardiac complications are not infrequent and include arrhythmias and stress-induced cardiomyopathy [58]. Excellent nursing and use of a 'checklist mentality' can aide in early recognition (or even prevention) of these complications.

Treatment of Antibody-Mediated or Cryptogenic Refractory Status Epilepticus

When a patient presents with a history suggestive of autoimmune or paraneoplastic disease (e.g., delirium, mood change, memory and personality disturbance, and focal seizures with or without secondary generalization), initiation of immunotherapy is indicated as soon as metabolic, toxic, infectious, and structural etiologies have been excluded (by basic laboratory evaluation and noncontrast CT scan), *and* the CSF cell count, chemistry, and gram stain are not suggestive of infection, whether or not an antibody has been identified. In the absence of such a history or other markers of inflammation or autoimmunity, it is appropriate to await negative CSF cultures and serologies prior to a trial of immunotherapy.

Clinical features supportive of immune mediated SE include: (1) a well-defined clinical syndrome (e.g., limbic encephalitis or faciobrachial dystonic seizures), (2) subacute onset (maximal seizure frequency <3 months) of cryptogenic epilepsy, (3) cryptogenic RSE or new onset refractory status epilepticus (NORSE), (4) a viral prodrome, (5) antecedent psychiatric symptoms, (6) history of systemic autoimmunity, or (7) history of neoplasia. Supportive paraclinical features include: (1) evidence of central nervous system inflammation (e.g., CSF pleocytosis, elevated CSF protein, CSF oligoclonal bands, elevated CSF IgG index or synthesis rate, mesial temporal or parenchymal T2-weighted or fluid-attenuated inversion recovery sequence hyperintensities, or hypermetabolism on functional imaging), (2) extreme delta brush pattern on EEG, or serologic markers of systemic autoimmunity (e.g., antinuclear antibody or thyroid peroxidase antibody positivity) [59]. These patients should undergo comprehensive evaluation for neural-specific autoantibodies in the serum and CSF.

Multiple arguments in favor of early empiric initiation of immunotherapy in SRSE can be made. First, earlier initiation of immunotherapy confers a better outcome in autoimmune central nervous system diseases when compared with delayed initiation of therapy [60–62]. Second, autoimmune and paraneoplastic syndromes are the most common cause of cryptogenic RSE [63], also known as NORSE [64]. Finally, there is increasing evidence that inflammation plays an important role in epileptogenesis and activation of specific inflammatory signaling pathways (e.g., interleukin-1 receptor/toll-like receptor (IL-1R/TLR) pathway) [65–68].

A trial of immunotherapy usually consists of high-dose IV steroids alone or combined with either plasma exchange or IV immunoglobulin [69]. If an antibody is identified, or the patient responds favorably to the trial of immunotherapy as evidenced by fewer breakthrough seizures or reduction in the dose of anesthesia required to maintain the desired EEG suppression target, immunosuppression should be continued (Table 17.3). If there is no objective favorable response to the trial of immunotherapy but an antibody-mediated syndrome is proven or strongly suspected, consider a second immunotherapy trial with an alternative agent. In patients where an antibody is identified, and patients in whom the etiology remains unknown even after an exhaustive evaluation, escalation of immunotherapy to rituximab or cyclophosphamide can be considered when there is either no, or incomplete, response to first-line treatments [59].

While this approach remains unproven in undifferentiated NORSE, experience with 501 patients with anti-NMDA receptor encephalitis demonstrated that rituximab and cyclophosphamide are usually effective in patients who do not respond to first-line immunotherapies [70]. A series of five patients with NORSE reported better outcomes with earlier initiation of immunotherapy compared with delayed initiation [71]. Recognizing the limitations inherent in case reports and series, this further supports the notion that early immunotherapy may be beneficial in cases of SRSE where no cause has been identified.

Finding a neural-specific autoantibody should prompt a targeted search for malignancies associated with the specific antibody [72]. When no antibody is identified, but an antibody-mediated syndrome is suspected, it is appropriate to screen broadly for malignancy by obtaining a CT scan of the chest, abdomen, and pelvis and if negative, proceed to fluorodeoxyglucose positron-emission tomography (FDG PET)-CT [73]. FDG PET is not sufficient in women with NMDA receptor encephalitis or in any patient suspected of having a germ-cell tumor. In these situations, ultrasound and MRI are the preferred modalities [59]. When initial malignancy screening is negative, ongoing surveillance may be required.

'Hail Mary' Pharmacologic Therapies

A number of other pharmacologic options have been reported and can be considered 'when all else fails' (Table 17.4). Experience with these drugs in the setting of SRSE is limited to case reports and small case series. Each of these therapies has limited evidence of benefit and either unknown, or at least moderate risk. They should therefore be

Table 17.3 Acute immunotherapy options in antibody mediated or cryptogenic refractory status epilepticus

Drug	Route	Dose	Schedule
Methylprednisolone	Intravenous	1000 mg	Daily for 3–5 days; then weekly for 4–6 weeks
Immune globulin	Intravenous	0.4 g/kg	Daily for 5 days; then weekly for 4–6 weeks
Plasma exchange	Intravenous	1 exchange	Every other day for 10–14 days
Rituximab	Intravenous	375 mg/m^2	Weekly for 4 doses
Cyclophosphamide	Intravenous	500–1000 mg/m^2	Monthly for 3–6 months
	Oral	1–2 mg/kg	Daily

Table 17.4 'Hail Mary' pharmacologic options for the treatment of super-refractory status epilepticus

Drug	Route	Dose	Level	Adverse effects
Magnesium	IV	LD: 2–4 g over 2 h; Maintenance: 2 g every 8 h or 0.5–2 g/h infusion	2.0–3.5 mEq/L (up to 7.0 mEq/L)	Respiratory depression at levels of 5.0–6.5 mEq/L; Cardiac conduction abnormalities at levels >7.5 mEq/L
Lidocaine	IV	LD: 1–5 mg/kg every 5 min until seizures controlled; Maintenance: up to 6 mg/kg/h	<5 mg/L	Mild hypotension
Etomidate	IV	LD: 0.3 mg/kg every 5 min until seizures controlled; Maintenance: 1.2–7.2 mg/kg/h	Unknown	Tachyphylaxis, adrenal insufficiency, hypotension
Isoflurane	Inhaled gas	End tidal anesthetic concentration titrated to desired suppression of the seizure and EEG background activity	MAC 1.2–5.0%	Hypotension, adynamic ileus, possible neurotoxicity with prolonged use
Felbamate	Oral	LD: 400 mg every 8 h; Maintenance: up to 1200 mg every 8 h	40–100 2 g/mL	Aplastic anemia, hepatic failure

LD loading dose, *IV* intravenous, *MAC* minimum alveolar concentration

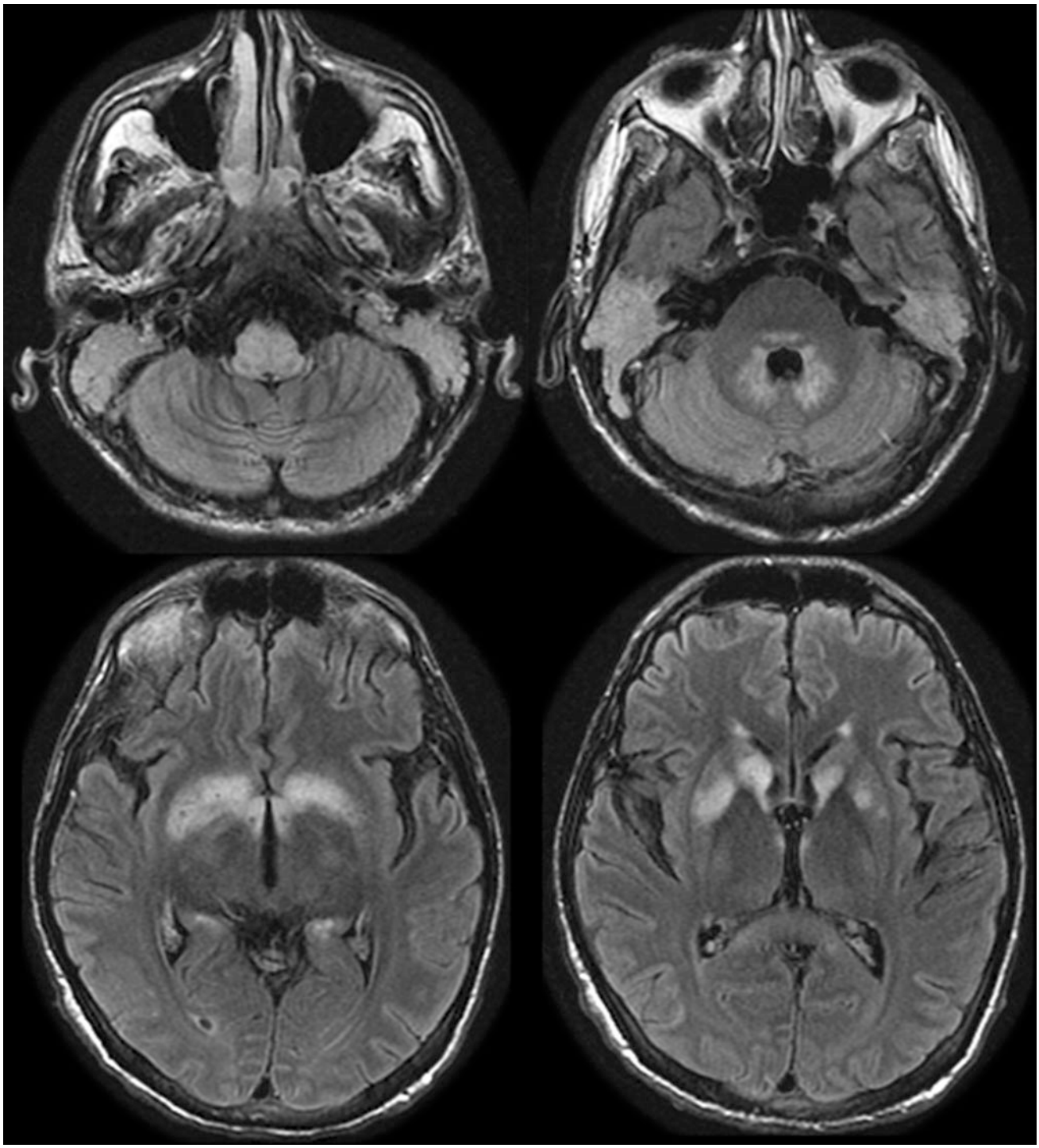

Fig. 17.4 Axial brain magnetic resonance images with fluid-attenuated inversion recovery sequences showing hyperintensities in the medulla, periventricular cerebellum, and basal ganglia after prolonged treatment with isoflurane

considered only in the most refractory cases when other options have proven unsuccessful.

Inhalational Halogenated Anesthetics. The inhalational halogenated anesthetic drugs isoflurane and desflurane have been used to treat RSE, with variable success. A recent literature review reported 13 studies with 28 adult patients treated with inhalational anesthetics in which electrographic seizure control was achieved in 26 (92.9%) patients. Isoflurane was used in the majority of cases, and the most common complication was hypotension requiring

vasopressor support [74]. In one series of 7 patients treated with inhalational anesthetic drugs, anesthesia was maintained for a mean of 11 days (range 2–26), and four patients had good outcomes (Glasgow Outcome Scale score of 4–5) while three patients died [75]. Complications included hypotension (7/7), atelectasis (7/7), infections (5/7), paralytic ileus (3/7), and deep venous thrombosis (2/7). MRI changes in the basal ganglia, cerebellum, and brainstem have been reported after prolonged use of isoflurane in two patients (Fig. 17.4) [76]. These changes were reversible with discontinuation of the drug but cannot be entirely separated from possible brain injury due to the excitotoxic state induced by SRSE.

Lidocaine. Lidocaine has been reported for use in SRSE where it is used as a continuous anesthetic infusion. A recent systematic review reported 11 published manuscripts and two abstracts covering 76 adult patients treated for 82 episodes of SE [77]. Lidocaine doses varied with some receiving only bolus doses and others receiving a combination of boluses and continuous infusion IV lidocaine. Seizure control was reported in 53 of 82 (64.6%) episodes with a >50% reduction in seizure frequency reported in an additional 5 (6.1%) episodes. Seizures recurred upon withdrawal of lidocaine in 13 of 58 (22.4%) of those who were initially responsive to lidocaine. Lidocaine was generally well tolerated, but two patients died from cardiorespiratory arrest during lidocaine infusion.

Magnesium. Experimental evidence for the benefit of IV magnesium in non-eclamptic status epilepticus is contradictory [78, 79]. It has been tried in humans, with favorable responses reported [80]. A recent systematic review of magnesium sulfate for non-eclamptic SE found 19 published papers reporting 28 patients of whom 11 were adults, 9 were children, and 8 were of unknown age. Seizure reduction or control occurred in half of the published cases, but in half of those, seizures recurred upon withdrawal of magnesium therapy. Complications included one patient who developed limb weakness and two who developed heart block [81].

Felbamate. Felbamate was approved by the US FDA for treatment of partial seizures with or without secondary generalization in 1993. While its exact mechanism is not known, it acts as an antagonist at the strychnine-insensitive glycine recognition site of the NMDA receptor–ionophore complex [82].Animal studies have shown that felbamate may increase the seizure threshold and decrease seizure spread [83]. Due to two rare but serious idiosyncratic effects of felbamate, aplastic anemia, and hepatic toxicity, its use has been restricted and a 'Black Box' warning was inserted into packaging. Despite the risks, in cases of SRSE where safer ASDs have failed, felbamate remains an option. If initiation of felbamate is considered, it should be with the guidance of an epileptologist, and with frequent monitoring of blood cell counts and liver function [84]. In a series of 63 consecutive episodes of SRSE, felbamate was the last drug added prior to successful weaning of anesthesia in two cases where it was added as the 9th and 11th attempted ASD (including anesthetic and non-anesthetic drugs) [10].

Allopregnanolone. Allopregnanolone is a neurosteroid metabolite of progesterone with anticonvulsant properties in multiple animal seizure models [85–88]. Infusion of allopregnanolone was reported to be successful in a very refractory case of pediatric SE [89]. A phase II clinical trial of allopregnanolone (SGE-102), has been completed [90] and a multicenter blinded randomized controlled trial is ongoing (ClinicalTrials.gov Identifier: NCT02477618).

Conclusions

Nearly all cases of SRSE can be controlled with anesthetic ASDs, but these drugs are not a panacea. Control of the underlying cause of the seizures and multiple non-anesthetic ASDs at high therapeutic levels are required to achieve liberation from anesthesia. In patients with NORSE or proven antibody-mediated encephalitis, early initiation of immunosuppression is recommended. Equally important is the careful maintenance of normal organ function and early identification and management of systemic complications to decrease the ultimate morbidity for those patients who do survive and often face a difficult and frequently prolonged recovery.

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