SHORT COMMUNICATION

Ketamine successfully terminates malignant status epilepticus

Harald Prüss, Martin Holtkamp*

Department of Neurology, Charité – Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany

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Summary  A 22-year-old woman with mitochondriopathy and pre-existing epilepsy developed status epilepticus (SE) not responding to benzodiazepines, phenytoin, thiopental, and propofol. SE was terminated within days after supplemental administration of continuous ketamine infusion to midazolam. The case suggests strong anticonvulsant properties of ketamine even after failure of GABAergic anesthetics, likely due to increased NMDA receptor expression with ongoing seizure activity. Thus, ketamine should be incorporated into therapeutic regimens for difficult-to-treat SE.

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Introduction

Status epilepticus (SE) is a common neurological emergency and incidence figures of 10–41 per 100,000 per year have been reported (Coeytaux et al., 2000; DeLorenzo et al., 1996). Unfortunately, SE is refractory to first-line anticonvulsants such as benzodiazepines and phenytoin in every third patient (Holtkamp et al., 2005b; Rossetti et al., 2005). Further intensive care management of these patients presents an interdisciplinary challenge. Commonly, general anesthesia is induced including administration of barbiturates, midazolam, or propofol which all act predominantly via enhancement of GABAergic inhibition. However, even aggressive treatment aiming at electroencephalogram (EEG) background suppression may not result in permanent termination of SE (Claassen et al., 2002). Furthermore, under those anesthetics vasopressor-requiring arterial hypotension is commonly observed. We recently suggested the term malignant SE for this condition because of its poor prognosis (Holtkamp et al., 2005a).

A malignant course of SE most likely depends on the underlying cause rather than representing a distinct clinical entity (Holtkamp et al., 2005a; Rossetti et al., 2005). An example for disorders predisposing to SE highly resistant to treatment is mitochondrial disease with mutations in the mitochondrial DNA polymerase (POLG) gene. In a series of 26 patients suffering from this progressive neurological disorder, SE occurred in 20, and patients are at high risk of death from malignant SE (Tzoulis et al., 2006).

Termination of SE using GABAergic anesthetics is limited by the progressive erosion of GABAergic inhibition after repeated seizures (Kapur and Macdonald, 1997; Lowenstein and Aldredge, 1993). However, in animal experiments blockade of excitatory NMDA receptors remains highly efficient to terminate SE, even in late stages (Borris et al., 2000; Mazarati and Wasterlain, 1999). Although NMDA antagonists...
were advocated as promising compounds in refractory SE (Bleck, 2002), clinical experiences are very limited (Bleck et al., 2002; Sheth and Gidal, 1998) and concerns exist regarding potential neurotoxicity (Ubogu et al., 2003).

Case report

A 22-year-old Vietnamese woman presented with clusters of left focal motor and generalized tonic–clonic seizures. She suffered from mitochondrial disease with a mutation in the mitochondrial polymerase gene. The neurological symptoms started at the age of 6 years with partial epilepsy, progressive neuropathy, ataxia, and tetraparesis. She was seizure-free for 4 years under primidone and valproate. After admission, seizures initially responded to intravenous (IV) 4 mg lorazepam and loading with 15 mg/kg phenytoin. Two days later, epileptic activity reoccurred and the patient developed SE characterized by generalized motor activity. Other causes of SE like stroke, encephalitis, or intracranial masses were ruled out by MRI and CSF analysis. Thiopental was continuously infused with an average dose of 4 mg/(kg h) until a burst suppression pattern was obtained. Infusion was stopped after 4 days, however, due to barbiturate accumulation in lipid tissue burst suppression pattern persisted for another 3 days. Thereafter, clinical seizure activity reoccurred manifesting as subtle SE with generalized myoclonus. EEG revealed continuous generalized epileptiform discharges (Fig. 1a). A bolus of IV levetiracetam (3000 mg/15 min) did not have any effect on seizure activity. Thereupon, continuous IV propofol was administered for 4 days with a maximum dose of 8 mg/(kg h). Clinical and electrographic seizure activity was not controlled, but severe vasopressor-requiring arterial hypotension impeded

Figure 1  Electroencephalographic recordings obtained during the treatment course of status epilepticus (SE). (a) Four days after discontinuation of thiopental that had been titrated to a burst suppression pattern generalized epileptiform discharges and flat periods are observed indicating recurrence of electrographic seizure activity and thus malignant SE. (b) After 12 days of continuous IV ketamine in combination with midazolam, epileptiform discharges have completely disappeared. EEG shows normal background activity superimposed by beta activity presumably caused by low-dose midazolam infusion and mild intermittent bi-frontal slowing.
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Further increase in dose. Due to persistence of subtle SE, a trial with IV ketamine in combination with midazolam (0.6 mg/(kg h)) was performed. With ketamine bolus administration (0.5 mg/kg) over 1 min, systolic blood pressure immediately raised to 220 mmHg, returning to normal within 10 min. No immediate effect was detectable in continuous EEG recording, and discrete generalized myocloni persisted. Subsequently, the patient was treated with ketamine infusion that was started with 0.4 mg/(kg h) and gradually increased within 3 h to 1.6 mg/(kg h). As clinical and electrographic SE sustained after 48 h of ketamine treatment, the dose was increased to 2.4—3.2 mg/(kg h) for another 8 days. With gradual decline and eventually disappearance of both continuous subtle motor phenomena and EEG epileptiform discharges (Fig. 1b), the ketamine infusion was titrated down over a period of 4 days without clinical or electrographic SE recurrence. The cumulative dose of ketamine over 14 days was 32 g. As sympathomimetic properties of ketamine caused stable blood pressure, noradrenaline infusion became gradually unnecessary and was ceased 5 days after ketamine treatment initiation. No significant acute side effects of ketamine use were noted, and deep tendon reflexes reoccurred after tapering of anesthetics.

Levetiracetam, topiramate, and phenytoin were started as adjunctive oral antiepileptics and the patient was weaned off midazolam. She remained comatose and displayed intermittent left focal motor seizures until transferring to a rehabilitation clinic 4 weeks after ketamine cessation. On follow-up 6 weeks later, she was able to ventilate without mechanical assistance, was still comatose, tetraplegic and exhibited several isolated focal motor seizures per day. Clinical or electrographic signs of status epilepticus did not reoccur.

Discussion

In a number of patients with refractory status epilepticus (RSE), the condition can be terminated by GABAergic anesthetics like barbiturates, midazolam, and propofol. Unfortunately, in some patients recurrence of seizures occurs with tapering, and serious side effects including arterial hypotension and immunosuppression are common. Alternative pharmacological approaches are therefore desirable. We report the case of a young woman with SE refractory to first-line anticonvulsants and to anesthesia with thiopental and propofol. While various ictal-like EEG patterns in coma only reflect severe brain damage, in our patient, the electroclinical evolution of the condition clearly indicates subtle SE (Meierkord and Holtkamp, 2007; Treiman et al., 1990). Control of both clinical and electrographic continuous seizures was achieved by ketamine coadministered with midazolam. After failure of two high-dose GABAergic anesthetics, the anticonvulsant effect is unlikely referred to the benzodiazepine alone. Furthermore, SE was terminated only after doubling the initial ketamine dose while midazolam infusion rate remained unchanged. Experimental data show that NMDA receptor activation regulates SE refractoriness to benzodiazepines (Rice and De Lorenzo, 1999). Ketamine coadministered with benzodiazepines in rats has recently been demonstrated to have strong synergistic anticonvulsant effects (Martin and Kapur, 2008) that may explain resolution of SE in the current case.

The patient suffered from mitochondrial disease with genetically confirmed POLG mutation. In this progressive disorder, SE is common and highly resistant to treatment including generalized anesthesia. In a recent series, 11 out of 26 patients with POLG mitochondrial disease died, and in over 80% malignant SE was the recorded cause of death (Tzoulis et al., 2006). In patients with SE caused by mitochondrialopathy, propofol may be administered with caution as patients are at increased risk to develop propofol infusion syndrome that pathophysiologically is based on impaired mitochondrial activity (Vasile et al., 2003). Keeping in mind that outcome after prolonged SE is mainly determined by the underlying cause (Rossetti et al., 2005), the efficacy of ketamine to control seizures in our patient encourages the use of ketamine as a promising additional drug in the treatment of malignant SE.

In animal experiments, the NMDA antagonist ketamine is not useful in SE at first, but becomes effective in advanced stages when GABA \(_A\) agonists lose efficacy (Borris et al., 2000; Mazarati and Wasterlain, 1999). Despite some NMDA-antagonistic properties of thiopental and propofol (Kozinn et al., 2006; Liu et al., 2006), in the treatment of SE, barbiturates, midazolam, and propofol mainly act via similar GABAergic mechanisms and lose their potency in a progressive, time-dependent manner. The current "receptor trafficking" hypothesis of GABAergic pharmacoresistance after repeated seizures is based on gradual reduction of GABA \(_A\) receptors at the synaptic membrane following receptor internalization into endocytic vesicles and subsequent degradation (Naylor et al., 2005). By contrast, NMDA blockers remain efficient even in late stages of SE as NMDA receptors are progressively transported to the synaptic membrane during ongoing epileptic activity, resulting in increasing numbers of functional excitatory NMDA receptors per synapse (Wasterlain et al., 2002).

Despite these promising data from animal experiments and the availability of ketamine for decades, only few clinical publications report trials with ketamine in RSE. A series of seven patients treated with ketamine for RSE reported electrographic seizure control in four patients on 0.3—5.8 mg/(kg h) infusion (Bleck et al., 2002). In other patients, 7.5 mg/(kg h) infusion was administered to terminate SE (Sheth and Gidal, 1998; Ubogu et al., 2003). We succeeded with 3.2 mg/(kg h) ketamine infusion at a time when SE already lasted 4 weeks.

We did not observe obvious acute neurotoxicity after ketamine use, and patient follow-up displayed clinical improvement including weaning off mechanical ventilation and recurrence of deep tendon reflexes which do not support marked ketamine-associated neurotoxicity as presumed in a previous case (Ubogu et al., 2003). Persistent coma in the current patient most likely resulted from both long-lasting subtle SE and progression of the underlying mitochondrial disorder. The constantly progressive nature of this disease argues against "burning out" of SE, as rarely proposed for RSE associated with self-limiting conditions like encephalitis. The hemodynamic properties seem to represent a considerable advantage of ketamine. Slow bolus administration is recommended as drastic raise in arterial blood pressure was observed in the present case. However,
stable hemodynamic conditions were seen during continuous infusion that even allowed ceasing catecholamine infusion initiated for anesthesia-induced arterial hypotension.

Based on our present clinical observation, ketamine seems to be useful in controlling malignant SE in patients with disorders particularly predisposing to death from treatment-resistant SE. It is worth speculating whether ketamine administration should even be considered earlier in high-risk patients for malignant SE, like in POLG mitochondrial disease or encephalitis. However, the response to ketamine and absence of obvious adverse effects in our patient need further confirmation.

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References


