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Ketamine for Refractory Status Epilepticus

Introduction

1. Status epilepticus (SE)* is characterized by:
    a. ≥5 minutes of continuous clinical and/or electrographic seizure, OR
    b. Recurrent seizure activity without recovery to baseline between seizures.
2. Thirty-day mortality in convulsive SE is 19 to 27%, while non-convulsive SE rates reach 65%.
3. In one study, patients with treated and resolved SE within 10 hours had 10% mortality compared to 85% mortality in those treated within 20 hours. Remember.... **Time is brain!**
4. Definitive SE control should be established within 60 minutes of onset.

Pharmacology of Ketamine	
Rationale	**What happens during SE?** ▪ GABA (inhibitory) receptors are internalized after ~1 hour ▪ NMDA (excitatory) receptors accumulate in the postsynaptic membrane **What are the consequences?** ▪ Pharmaco-resistance to GABAergic drugs, such as benzodiazepines ▪ NMDA receptors facilitate neuronal excitability = ↑ eptileptiform activity & neuronal death
Mechanism of Action	**Noncompetitive NMDA receptor antagonist**
Dosing & Administration	**Loading Dose:** 1.5 mg/kg (0.5 to 3 mg/kg) slow IV push ▪ Administer over 1 minute or rate of 0.5 mg/kg/minute ▪ Repeat 0.5 mg/kg loading dose every 3 to 5 minutes as needed for electrographic/burst suppression, followed by continuous infusion **Maintenance Dose:** 0.3 to 4 mg/kg/h ▪ Titrate as needed for electrographic/burst suppression (usually ≥2 mg/kg/h) ▪ Max: 10 mg/kg/h
GHS Formulations	**Standard concentration:** 500 mg in 250 mL NS; 1,000 mg in 500 mL NS **Double concentration:** 1,000 mg in 250 mL NS; 2,000 mg in 500 mL of NS
PK/PD	**Onset:** within 30 seconds **Metabolism:** hepatic (norketamine metabolite 33% as potent as ketamine) **Elimination:** urine (91% as metabolites) **Half-Life:** 2 to 3 h **Duration:** 5 to 10 minutes (recovery 1 to 2 h)
Adverse Effects	**Emergence reactions** – vivid dreams, hallucinations, and/or delirium **Sympathomimetic effect** – hypertension, tachycardia, ischemia **Airway complications** – increased salivary & tracheobronchial secretions, laryngospasm (0.3%)

*Definitions:
Refractory SE: status epilepticus that continues despite adequate doses of initial benzodiazepines followed by a second acceptable antiepileptic drug
Super-Refractory SE: status epilepticus that continues or recurs ≥24 h after the onset of anesthetic therapy, including cases where SE recurs on the reduction or withdrawal of anesthesia

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Overview of Evidence			
Author, Year	**Design**	**Purpose**	**Outcome**
Alkhachroum 2020	Retrospective study (n=68)	IV ketamine in super-refractory SE	-Average dose of ketamine 2.2 mg/kg/h for 2 days -Associated with ***seizure burden by ≥50% within 24 h*** of starting ketamine in 81% of patients -Associated with ***complete cessation of seizures in 63% of patients*** -Limitation: midazolam 1 mg/kg/h was started 0.4 days before ketamine possibly confounding effects of ketamine
Höfler 2016	Retrospective study (n=42)	IV ketamine in super-refractory SE	-Average dose of ketamine 2.39 mg/kg/h for 4 days -***Ketamine last drug administered in 64% (27/42) of patients before SE cessation*** -***No adverse effects*** -Limitation: only 17% of patients received a loading dose
Sabharwal 2015	Retrospective study (n=67)	IV ketamine in super-refractory SE	-Ketamine ranged from 1.5 to 10.5 mg/kg/h -***SE was controlled in 91% (61/67) of patients*** -***Ketamine was used in the early phase within 24-48 h*** -Infusion duration was 3.6 days, 5.97 days, and 6.5 days for propofol-ketamine, ketamine, and propofol, respectively
Gaspard 2013	Retrospective study (n=60)	IV ketamine in refractory SE	-Average load with1.5 mg/kg, followed by 2.75mg/kg/h -Likely responsible for SE control in 12% (7/60) of cases, and possibly responsible in 20% (12/20) of cases -***Likely response to ketamine if administered within 12 h***
Synowiec 2013	Retrospective study (n=11)	IV ketamine in refractory SE	-Average load with 2 mg/kg, followed by 1.3 mg/kg/h -***45% of cases all co-infusions were weaned within 24 h*** -***27% of cases all co-infusions were discontinued within 72 h*** -Refractory SE was terminated in all 11 patients -***No adverse effects*** -Limitation: ketamine administered at sub-anesthetic doses

Conclusions

1. Ketamine offers advantages over other anesthetics, as it targets a different pathway and has shown to have more favorable hemodynamic effects.
2. Ketamine is most effective when a loading dose is administered and a continuous infusion is provided at anesthetic doses of at least 2 mg/kg/hour.
3. Studies on ketamine for status epilepticus are confounded by many methodological limitations.
4. There is still debate regarding ketamine's place in therapy in SE. However, there are trends to starting ketamine earlier in combination with other anesthetics like propofol or midazolam.

References

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