Status Epilepticus

Tom Heaps
Consultant Acute Physician
Case Scenario

- 76-year-old male
- no PMHx
- witnessed generalized seizure at home ~2min
- further seizure in ambulance terminated after 5min with IV diazepam 10mg
- GCS 8 on arrival in ED
- further generalized seizure in RESUS
- persisting after 2min

IS THIS STATUS EPILEPTICUS?
Status Epilepticus (SE): Definitions

any seizure that exceeds its usual time course and becomes unlikely to end spontaneously because self-sustaining processes prevail over self-terminating mechanisms
What are the different types of SE?

- tonic-clonic SE
  - generalized convulsive status

- simple partial or focal motor SE
  - epilepsia partialis continua

- complex partial SE
  - non-convulsive status

- myoclonic and absence SE
SE: some useful facts

- more common in;
  - learning disability
  - frontal lobe epilepsy
  - structural cerebral pathology
  - children

- 65% have no preceding history of epilepsy

- up to 50% admitted to ITU with ‘status epilepticus’ actually have *pseudostatus*
What is the prognosis in convulsive SE?

- Mortality 10-20%
- Mortality 20-50% in refractory status (defined as resistance to adequate doses of benzodiazepine plus a 2nd line drug)
- Permanent neurocognitive sequelae in further 5-10%
- Poor prognosis if:
  - Underlying structural pathology (anoxic brain injury, encephalitis)
  - Seizures lasting >1h
  - Older age
  - Coma with non-convulsive SE develops
# STESS Score

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<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td><strong>Consciousness</strong></td>
<td></td>
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<tr>
<td>Alert or somnolent/confused</td>
<td>0</td>
</tr>
<tr>
<td>Stuporous or comatose</td>
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<tr>
<td><strong>Worst seizure type</strong></td>
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<tr>
<td>Simple-partial, complex-partial, absence, myoclonic</td>
<td>0</td>
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<tr>
<td>Generalized-convulsive</td>
<td>1</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus in coma</td>
<td>2</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td></td>
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<tr>
<td>&lt;65 years</td>
<td>0</td>
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<tr>
<td>&gt;65 years</td>
<td>2</td>
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<tr>
<td><strong>History of previous seizures</strong></td>
<td></td>
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<tr>
<td>Yes</td>
<td>0</td>
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<tr>
<td>No or unknown</td>
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- score >2 associated with worse prognosis
What may have caused our patient’s SE?

- cerebral tumour
- intracranial infection
- hypoglycaemia
- head injury or neurosurgery
- electrolyte disturbance (low Na\(^+\), Ca\(^{2+}\) or Mg\(^{2+}\), acidosis)
- pre-eclampsia
- first presentation of idiopathic epilepsy
- drug overdose (e.g. TCA)
- drug withdrawal (e.g. alcohol, benzodiazepines)
- cerebral hypoxia/anoxia
- acute stroke or ICH
- hypertensive encephalopathy
- AED non-compliance or withdrawal
Febrile Infection-Related Epilepsy Syndrome (FIRES)

Acute Encephalitis with Refractory Repetitive Partial Seizures (AERRPS)

- young females
- prodromal febrile illness
- prolonged partial and secondarily generalized seizures
- poor response to AEDs
- high morbidity and mortality
- CSF lymphocytosis but no infectious agent isolated
- aetiology may be viral or heterogenous e.g. genetic, immunological
seizure activity still persisting at 5min

nurse concerned because patient sweating ++, BP 170/112, HR 140 regular, T 37.9°C

VBG shows pH 7.22, lactate 7.3, glucose 12.1

IS THIS NORMAL IN STATUS EPILEPTICUS?
SE: Compensatory Phase 0-60 minutes

- initial autonomic hyperactivity and catecholamine release
- elevated BP, HR and blood glucose
- increased cerebral blood flow and glucose delivery to meet metabolic needs
- sweating, hyperthermia, mydriasis, hypersalivation, bronchial hypersecretion
- arterial pH falls due to lactic acidosis
SE: Decompensation Phase >60 minutes

- cerebral metabolic demands can no longer be met
- excitotoxic neuronal damage
  - glutamate-mediated calcium influx
  - elevated neuron-specific enolase (NSE)
  - temporal lobe and hippocampus (visible on MRI as T2 hyperintensities)
- physiological decompensation
  - hypotension, hypoxia, arrhythmias, profound acidosis
  - neurogenic pulmonary oedema
  - loss of cerebral autoregulation, intracranial hypertension, cerebral oedema
SE: Mechanisms of Drug Refractoriness

- progressive reduction in effectiveness of Rx with time
- endocytosis of GABA$_A$ receptors into neuronal cytoplasm
- efficacy of benzodiazepines decreases by 20x within first 30min
- efficacy of PHT declines more slowly (resistance due to differential expression of Na channel subunits during SE)
- overexpression of multidrug transporter P-glycoprotein (Pgp) causing efflux of AEDs from neurones
- increased activity of excitatory neurotransmitters e.g. glutamate at NMDAr
What basic management should you institute in a patient with SE?

- Open airway, consider Guedel or nasopharyngeal airway
- Give high-concentration oxygen
- Correct hypotension with fluids
- Correct electrolyte abnormalities
- IV thiamine (Pabrinex®) if malnourished/alcoholic
- IV glucose 100ml 10% (give thiamine first if alcoholic)
- IV dexamethasone 10mg if known cerebral tumour/vasculitis
What Investigations does he need?

**All Patients**
- FBC
- U&E
- LFTs
- glucose
- Ca\(^{2+}\)
- Mg\(^{2+}\)
- VBG or ABG
- ECG
- CXR

**Some Patients**
- CT/MRI
- blood cultures
- urine culture
- AED levels
- toxicology screen
- EEG
- LP
What drug therapy will you give first?

- **IV diazepam** 10-20mg bolus in 2-5mg increments repeated once after 10min
  - rapid onset (10-20s) but short duration of action (15-30min)
  - risk of sudden CNS/respiratory depression and cardiovascular collapse
  - may also be given PR

- **IV lorazepam** 1-4mg bolus in 1mg increments repeated once after 10min
  - takes longer to work (up to 2min)
  - longer duration of action (4-6h)
  - strong cerebral binding and does not accumulate in lipid stores as much

- **IV midazolam** 2.5-10mg bolus
  - may also be given as buccal liquid preparation

- **PO clobazam** 10-30mg
  - useful in focal motor or complex partial status
Case Scenario cont.

- further 10mg diazepam given in 2mg increments
- persistent seizure activity 5min later

WHAT DRUG ARE YOU GOING TO GIVE NEXT?

WHAT DOSE?

HOW FAST?
2\textsuperscript{nd} Line Drug Therapy: Phenytoin

- Give usual AED IV if known epileptic.
- Phenytoin infusion 18-20 mg/kg.
- Not just 1G for everyone.
- Dilute in 100-250 ml 0.9% NaCl (final concentration ≤10 mg/ml).
- Give at ≤50 mg/min with continuous ECG monitoring.
- SE, hypotension, cardiac arrhythmia, respiratory depression, thrombophlebitis, purple glove syndrome.
- Avoid if severe cardiovascular disease or AVB.
- Maintenance dose 100 mg IV TDS- QDS.
- Effective in 30% after 10 min and 80% after 20 min.
- Consider additional dose of phenytoin 5-10 mg/kg if first dose ineffective.
2nd Line Drug Therapy: Alternatives

- **IV fosphenytoin** 18-20mg/kg phenytoin equivalents (fosphenytoin 1.5mg ≡ PHT 1mg)
  - given faster than PHT at ≤100-150mg PE/min
  - supposedly less thrombophlebitis and cardiovascular effects than PHT

- **IV phenobarbital** 10-20mg/kg IV at ≤100mg/min then 45-90mg BD
  - very effective, more rapid action and fewer cardiac SE than PHT
  - not used long-term and high risk of respiratory depression/arrest

- **IV valproate** 20-30mg/kg IV in 100ml 0.9%NaCl over 15min +/- infusion at 1-6mg/kg/h
  - as effective as PHT with fewer SE (limited studies)
  - risk of pancreatitis and hyperammonaemia (CI in liver disease)

- **IV levetiracetam (Keppra®)** 20-30mg/kg in 100ml 0.9%NaCl over 15-30min
  - particularly effective in partial (secondarily generalized) and myoclonic SE
ongoing seizure activity 20 minutes after PHT given at 20mg/kg

blood pressure now 91/66mmHg

cHEST sounding ‘rattly’ and oxygen requirements increasing

WHAT ARE YOU GOING TO DO NOW?
3\textsuperscript{rd} Line Drug Therapy in SE

- **haemodynamically stable:** thiopental (pentobarbital)
  - 5-10mg/kg IV then 1-10mg/kg/h
  - highly effective but risk of prolonged sedation and severe hypotension
  - may require pressor support

- **haemodynamically unstable:** midazolam
  - 0.05-0.2mg/kg IV bolus then 0.05-0.5mg/kg/h
  - if unsuccessful give propofol or thiopental with pressor support

- **high risk for prolonged ventilation e.g. COPD:** propofol
  - 2mg/kg bolus followed by infusion at 1-2mg/kg/h up to 10-12mg/kg/h
  - titrated until seizure free (or burst suppression seen on EEG) risk of propofol syndrome with prolonged infusion
  - if ineffective use thiopental
Other Drugs for Refractory SE

- lacosamide (amino acid which enhances slow Na channel inactivation)
- lignocaine (sodium channel blocker)
- verapamil (inhibits Pgp reducing efflux of AEDs from brain cells)
- ketamine (NMDA antagonist)
- magnesium (NMDAr blockade)
- topiramate (200-700mg BD via NGT)
Why might we fail to terminate seizure activity in SE?

- use of diazepam rather than lorazepam
- failure to initiate 2nd line agent early enough
- inadequate dosing of phenytoin or other 2\textsuperscript{nd}/3rd line drugs
- aetiology (encephalitis, anoxic brain injury, NORSE)
- failure to correct metabolic factors e.g. hyponatraemia, hypomagnesaemia, hypoglycaemia
- not continuing deep sedation with barbiturates/propofol for $\geq 12h$
- incorrect diagnosis e.g. NEAD
Pseudostatus  
(pseudoseizures, PNES, NEAD)

- females >> males, onset 3rd decade, history of childhood trauma

- tongue biting (tip), urinary incontinence and injury may occur
- normal prolactin level may occur with prolonged SE
- CK, lactate and WBC usually not elevated
What complications is he at risk of?

- urinary retention, rhabdomyolysis and renal failure
- aspiration pneumonitis, hypoxia and respiratory failure
- hypotension, arrhythmias, neurogenic pulmonary oedema
- DIC or VTE including cerebral venous thrombosis
- cerebral oedema and raised ICP
- leucocytosis, fever and hyperpyrexia
- lactic acidosis
- hypoglycaemia, hyponatraemia (SIADH), hypo/hyperkalaemia
Summary of Convulsive SE

- Physiological Compensation
- Drug Refractoriness
- Cardiorespiratory decompensation
- Neuronal Damage

Time (mins) from onset of SE
Summary of Convulsive SE

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Time (mins) from onset of SE
Summary of Convulsive SE

- **Early**
  - Lorazepam
  - Diazepam
  - Midazolam

- **Established**
  - Phenytoin
  - Valproate
  - Levetiracetam
  - Phenobarbital

- **Refractory**
  - Thiopental
  - Propofol
  - Midazolam
  - Ketamine
  - Lacosamide
  - Verapamil
  - Magnesium
  - Topiramate
  - Lignocaine

**Time (mins) from onset of SE**
Summary of Convulsive SE

ACT FAST: TIME IS BRAIN!