

A protocol for the in-hospital emergency drug management of convulsive status epilepticus in adults

Shelley Jones,¹ Clemens Pahl,² Eugen Trinkka,³ Lina Nashef⁴

► The protocol is free to download online. Please visit the journal online (<http://dx.doi.org/10.1136/practneurol-2013-000712>).

¹Pharmacy Department, Kings College Hospital NHS Foundation Trust, London, UK

²Department of Neuroscience Intensive Care, Kings College Hospital NHS Foundation Trust, London, UK

³Department of Neurology, Paracelsus Medical University, Salzburg, Austria

⁴Department of Neurology, Kings College Hospital NHS Foundation Trust, London, UK

Correspondence to

Shelley Jones, Clinical Pharmacy Teamleader, Neurosciences, Pharmacy Department, Kings College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, UK; shelley.jones1@nhs.net

INTRODUCTION

There are many options for treating convulsive status epilepticus but one thing is clear: success is closely associated with timely intervention and adherence to a treatment protocol.¹ Delayed intervention leads to treatment resistance and refractory status. There is little evidence from randomised controlled trials, especially for agents used after benzodiazepines.² Therefore, for now, the choices are mostly based not on Class 1 evidence but on accumulated and published experience.

Management protocols are mandatory if patients with status epilepticus are to receive prompt and appropriate treatment. Yet many hospitals do not have these or do not review them regularly. This protocol is adapted from that of King's College Hospital, London, UK, and is in line with the European consensus workshop.² We aim to provide sufficient detail to satisfy the treating physician's practical requirements, while keeping the protocol simple and easily accessible. It should be used with precalculated dose/weight charts.

The treatment pathway comprises first benzodiazepine (first line), then an intravenous antiepileptic agent (second line) followed by, where necessary, general anaesthesia (third line). The choice of benzodiazepine and the route used remains open to discussion. While intravenous lorazepam remains the first choice in hospital, it is not always available and intravenous access is not always possible. Furthermore, the choice of benzodiazepine and its route of administration need revising as new evidence emerges, particularly given the success of intramuscular midazolam in the prehospital setting.³

To allow for different circumstances, drug availability and access, we list several options for stage 1 treatment with benzodiazepines.

With regards to choice of intravenous antiepileptic drug in the second stage, the limited available evidence prevents us from categorically choosing one over another. *We have, however, suggested an order of preference; this is influenced more by local availability and familiarity with use in the emergency department rather than evidence of superiority.* The order should be reviewed as further evidence emerges. Irrespective of the drug chosen, we stress the importance of giving adequate loading doses. We have selected doses in the middle of the usual ranges, recognising that these may need to change with time. Where there is a clear response but not full control of seizures, in a stable patient, it may be appropriate to optimise the antiepileptic drug dose, as well as to consider another second stage agent. Otherwise, treatment should promptly move to the general anaesthesia stage. We have not listed lacosamide—available intravenously and occasionally used in status epilepticus—among the second-stage agents: this needs reassessing as more evidence emerges. It is uncertain whether the doses need capping, depending on weight. This need probably varies with different drugs and also depends on the doses per kg body weight used. There is limited information using loading doses above 2500 mg for phenytoin, 4000 mg for levetiracetam and 3000 mg for valproate: we suggest that their doses should be capped—as is usual clinical practice—though we acknowledge the lack of clear evidence.



CrossMark

To cite: Jones S, Pahl C, Trinkka E, et al. *Pract Neurol* 2014;**14**:194–197.

This protocol will hopefully fulfil requirements for most cases of status epilepticus and readers are welcome to download and adapt it for local use along with the precalculated dose-weight charts. It does not address cases *where seizures continue despite adequate and appropriate general anaesthesia (refractory status epilepticus)*,⁴ which need specialised input, with several other possible treatment options considered, including other antiepileptic drugs, ketamine, corticosteroids, magnesium, intravenous immunoglobulin, ketogenic diet, neurostimulation and, for lesional cases, surgery.

See the next 2 pages for the Protocol.

Contributors LN conceived the protocol, and LN and SJ initiated the protocol design and content. CP provided expert information regarding neuroanaesthetic management of status epilepticus. ET provided expert review and comments during protocol development. LN produced the introductory manuscript presented with the protocol after discussion with ET. All authors contributed to refinement of the protocol and manuscript and approved the final copy.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed. This paper was reviewed by Aiden Neligan, London, UK and Eelco Wijdicks, Rochester, USA.

REFERENCES

- 1 Aranda A, Foucart G, Ducassé JL, *et al.* Generalized convulsive status epilepticus management in adults: a cohort study with evaluation of professional practice. *Epilepsia* 2010;51:2159–67.
- 2 Shorvon S, Baulac M, Cross H, *et al.* TaskForce on Status Epilepticus of the ILAE Commission for European Affairs. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. *Epilepsia* 2008;49:1277–85.
- 3 Silbergleit R, Durkalski V, Lowenstein D, *et al.*; NETT Investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. *N Engl J Med* 2012;366:591–600.
- 4 Shorvon S, Ferlisi M. The treatment of super-refractory status epilepticus: a critical review of available therapies and a clinical treatment protocol. *Brain* 2011;134(Pt 10):2802–18.

In-Hospital **Emergency Drug Management of Convulsive Status Epilepticus in Adults**
See page 2 for essential parallel general measures

STEP 1:
benzodiazepine
give if fitting for
> 5 min

First choice:

- **Intravenous lorazepam:** Usual dose bolus **2 to 4 mg** (maximum rate 2 mg/min). If necessary repeat up to a total maximum dose of 0.1 mg/kg.
 - OR Intravenous diazepam:** Usual dose **5 to 10 mg** titrate for effect, up to 20 mg if necessary. Do not give too fast to avoid respiratory depression (maximum rate 5 mg/min). Diazepam is rapidly redistributed and may accumulate with repeated dosing.
 - OR Intravenous clonazepam:** Usual dose 1 mg, if necessary repeat 1 mg dose after 5 minutes (maximum rate 0.5 mg/min).
- If intravenous is difficult or not possible:
- **Buccal midazolam:** Usual dose **10 mg** (caution: Give 5 mg in the elderly or patients less than 50 kg). Repeat dose once after 10 minutes if necessary.¹
If buccal preparation not available, use 10 mg/2 mL injection via buccal route.
 - OR Intramuscular midazolam:** Usual dose 10 mg (Caution: Give 5 mg in the elderly or patients weighing less than 50 kg). Repeat dose once after 10 minutes if necessary.
- If intravenous, buccal and intramuscular are not possible:
- **Rectal diazepam:** Usual dose **10 mg** (caution: give 5 mg in elderly patients or patients weighing less than 50 kg). Repeat dose once after 10 minutes if necessary.

If seizures stop, the recurrence rate is high; most patients need an intravenous stage 2 anti-epileptic drug (see below for doses) to prevent further seizures

STEP 2:
If no response to
step 1 **WITHIN 10**
min, give stage 2
agent
and
**INFORM NEURO-
INTENSIVIST or
EXPERIENCED
ANAESTHETIST**

Second stage antiepileptic drug given **intravenously and inform neurointensivist or experienced anaesthetist**

See loading dose proformas for administration guidance

If there is no specific contraindication or a clear preference for alternative:

Phenytoin; 18 mg/kg (range 15–20); **maximum rate 50 mg/min**. Infuse into large or central vein via filter with ECG and blood pressure monitoring (caution **hypotension, bradycardia**). Check concomitant drugs (phenytoin is an enzyme inducer—its effect on the half-life of affected drugs is not immediate). For patients already on phenytoin, see note on page 2* before administering.

OR

Levetiracetam; 30 mg/kg (range 20–70); **infuse over 10 minutes**; no interactions; good side effect profile in this setting but comparative efficacy remains to be established; renal excretion.^{2,3}

OR

Sodium Valproate; 30 mg/kg (range 15–30); **infuse over 5 minutes**

Contraindicated in mitochondrial disease. Avoid in status of unknown cause in young people. Caution: in pregnancy or acute liver failure, where an alternative is preferable. Check concomitant drugs (valproate is an enzyme inhibitor, with immediate effect on half-life of affected drugs).^{4,5}

OR

Phenobarbital; 10 mg/kg (range 10–15); **maximum rate 100 mg/min**. Monitor blood pressure, ECG and respiratory function (Caution: **respiratory depression** may occur—only give if ventilatory support can be provided). Check concomitant drugs (phenobarbital is an enzyme inducer—its effect on the half-life of affected drugs is not immediate).

ENSURE NEUROINTENSIVIST/EXPERIENCED ANAESTHETIST IS AWARE OF THE PATIENT

If seizures recur in patients who are haemodynamically stable, optimise dose of initial second stage intravenous antiepileptic drug and then consider another second stage intravenous antiepileptic drug.

STEP 3:
If no response to
step 2 within 30
minutes of onset
anaesthesia and
ICU admission

General anaesthesia with intubation and ventilation

Consider if haemodynamically unstable at any stage or if respiratory support is needed

- These drugs must be **administered by a neurointensivist/experienced anaesthetist in an intensive care unit (ICU) setting** as per local protocols to control clinical/EEG seizures
- **Induction:** usually propofol (1.5–3 mg/kg bolus); caution: hypotension, bradycardia **OR**
 - thiopentone (usually 3–5 mg/kg bolus, additional boluses of 50 mg every 3 minutes until seizures terminated may be given if blood pressure remains stable)
- **Maintenance:** Propofol 1–5 mg/kg/hour titrated to effect; prolonged use may lead to propofol infusion syndrome **OR**
 - midazolam if patient already ventilated, initial bolus 1 mg intravenously and titrate to effect then 0.05–0.20 mg/kg/hour titrated to effect **OR** consider propofol with midazolam **OR**
 - thiopentone 3–5 mg/kg/hour titrated to effect. Caution: hypotension, cardiac suppression, immunosuppression, hypokalaemia, pancreatitis and drug accumulation
- **EEG monitoring is indicated (continuous or minimum every 24 hours) to assess level of anaesthesia and abolition of ictal discharges.**

Over next 24–48 hours, optimise doses and levels of non-anaesthetic anti-epileptic drugs and, if no electrical or clinical evidence of ongoing seizures, withdraw anaesthesia to assess response.

General Management - In Parallel to Drug Management

General Medical Measures

Secure airway and resuscitate

Administer oxygen

Assess cardiorespiratory function

Establish intravenous access (large veins if possible)

Measure capillary blood glucose and immediately correct hypoglycaemia.

Give 75 mL 20% glucose intravenously over 5 minutes

If no intravenous access 1 mg intramuscular glucagon

Re-check blood glucose after 15 minutes

Check temperature

Check blood gases

If poor nutrition/alcohol abuse suspected give:

Pabrinex[®] (thiamine, riboflavin, pyridoxine, ascorbic acid, nicotinamide) ONE PAIR intravenously

OR

over 10 minutes

Thiamine 100 mg intravenously in 100 mL 0.9% sodium chloride over 30 minutes

If woman of child bearing age—consider pregnancy test

Take blood for:

electrolytes

glucose

calcium

magnesium

full blood count

liver function tests and INR

anti-epileptic drug levels

creatinine kinase

alcohol and toxicology screen

culture as appropriate

CAUTION: Not all seizures are epileptic

In psychogenic non-epileptic seizures 'pseudostatus' **OR**, treatment with sedation or anti-epileptic drugs is not indicated

Consider urgent EEG and seek senior opinion

Mandatory Seizure Related Measures

- Investigate the cause of status and treat accordingly
- Consider reinstating any recently withdrawn anti-epileptic drug
- Continue existing anti-epileptic drugs
- Start maintenance anti-epileptic drug therapy promptly
- Refer to local specialist services

*For those on phenytoin, full loading is not appropriate but 'top-up' dose is given as per **clinical decision** or using the following formula:

$$\text{DOSE} = (\text{target level (mg/L)} - \text{actual level obtained urgently (mg/L)}) \times 0.7 \times \text{weight in kg}$$

Example: If desired level is 20 mg/L, actual level is 5 mg/L and weight is 70 kg, then
Dose = 20 – 5 = 15; 15 × 0.7 × 70 = 735 mg, rounded up to 750 mg

References:

1. Sibergleit R, Lowenstein D, Durbalski V, Conwit R and NETT investigators; RAMPART (Rapid Anticonvulsant Medication Prior to Arrival Trial): A double-blind randomized trial of the efficacy of intramuscular midazolam versus intravenous lorazepam in the prehospital treatment of status epilepticus by paramedics; *Epilepsia*; 2011; 52 (Suppl 8): 45-7.
2. Uges JW, Huizen MD, Engelsman J, Wilms EB, Touw DJ, Peeters E, Vecht CJ; Safety and pharmacokinetics of intravenous levetiracetam as add-on in status epilepticus; *Epilepsia*; 2009; Mar; 50 (3): 415-21.
3. Navararro V, Dagron C, De-meret S, An K, Baulac M, Carli P; Comparison of add-on levetiracetam versus placebo in a prehospital randomized trial in convulsive status epilepticus; Abstract at The 4th London-Innsbruck Colloquium on status epilepticus and acute seizures; Salzburg 4-6 April 2013.
4. Misra UK, Kalita J, Patel R; Sodium valproate vs phenytoin in status epilepticus: a pilot study; *Neurology*; 2006; Jul 25; 67 (2): 340-2.
5. Morton L, O'Hara KA, Coots BP, Pellock JM; Safety of Rapid Intravenous Valproate Infusion in Pediatric Patients; *Paediatr Neurol*; 2007; 36: 81-3.