

The treatment of convulsive status epilepticus in children

The Status Epilepticus Working Party

Abstract

There is currently little agreement between hospital protocols when treating convulsive status epilepticus in children, and a working party has been set up to produce a national evidence based guideline for treating this condition. This four step guideline is presented in this paper. Its effectiveness will be highlighted and its use audited in a number of centres.

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Keywords: convulsive status epilepticus; guideline; working party

Generalised convulsive (tonic-clonic) status epilepticus (CSE) is currently defined as a generalised convulsion lasting 30 minutes or longer, or repeated tonic-clonic convulsions occurring over a 30 minute period without recovery of consciousness between each convulsion.^{1–4} Most tonic-clonic convulsions stop spontaneously, often within five minutes, and usually before a child arrives in an accident and emergency department.⁵ However, tonic-clonic convulsions which persist beyond four or five minutes may not stop spontaneously and can become prolonged, lasting 30 minutes or longer, thereby meeting the definition for convulsive status epilepticus.

Convulsive status epilepticus (CSE) in childhood is a life threatening condition with serious risk of neurological sequelae,^{2 4 6} and constitutes a medical emergency. Although the outcome from an episode of CSE is mainly determined by its cause, the duration of CSE is also important. In addition, the longer the duration of the episode, the more difficult it is to terminate.^{6 7} Therefore for practical purposes, the approach to the child who presents with a tonic-clonic convulsion lasting more than five minutes should be the same as with the child who is in “established” status—to stop the seizure and prevent the development of status epilepticus.

Background

There is no precise estimate of the incidence or frequency of CSE at any age. Data from epidemiological studies suggest that four to eight children per 1000 may be expected to experience an episode of CSE before the age of 15 years,⁸ and in children with first seizures, 12% present with CSE as their first unprovoked seizure.⁹ CSE in children has a mortality of approximately 4%.¹⁰ Neurological sequelae of CSE (epilepsy, motor deficits, learning difficulties, and behaviour problems) are age dependent, occurring in 6% of those over 3 years but in 29% of those under 1 year.¹⁰

There is little agreement between hospital protocols when treating CSE in children.¹¹ In a recent study of published guidelines none used the same three initial drugs in the same order.¹¹ Many hospitals use the Advanced Paediatric Life Support (APLS) guidelines, although these are primarily practice based, rather than evidence based.¹² A paper presented to the annual scientific meeting of the British Paediatric Neurology Association in Southampton in 1997 highlighted these differences in treatment and proposed that a multidisciplinary working party be established to produce a national evidence based guideline for treating CSE. It has been shown that the provision of standardised guidelines or protocols, similar to treating cardiac arrest, improve the quality of emergency care and therefore outcome.¹³ The working party was represented by the specialties of paediatric neurology, paediatric A&E medicine, general paediatrics, and paediatric clinical pharmacology.

Method and discussion

A comprehensive computer based literature search was performed using Cochrane group methods. Searches were limited to the English language. All paediatric status epilepticus papers were then hand searched to ensure no articles were overlooked. Over 1100 papers were identified of which 371 included original (non-review) data relevant to the guidelines. Over the course of 12 months the working party met to analyse the published evidence from these papers. A consensus guideline was consequently produced. It is important to emphasise that only two paediatric randomised controlled trials were identified in the systematic review. Therefore the final guideline is based on both evidence (paediatric and where appropriate, adult) and clinical experience. The letters in brackets within the text refer to the strength of recommendations (see Appendix). The working party also prospectively collected audit data on all children presenting with and requiring treatment for an acute tonic-clonic convulsion over a 12 month period in three large children's accident and emergency (A&E) departments. These departments all had an identified protocol for the treatment of CSE, although minor variations existed between the protocols. The results of this 12 month prospective audit will be the subject of a separate paper.

Figure 1 shows the consensus guideline drawn up by the working party. There are many different clinical situations in which CSE can occur. It was felt that a guideline that would cover all possible circumstances and clinical situations would be impractical and lead to

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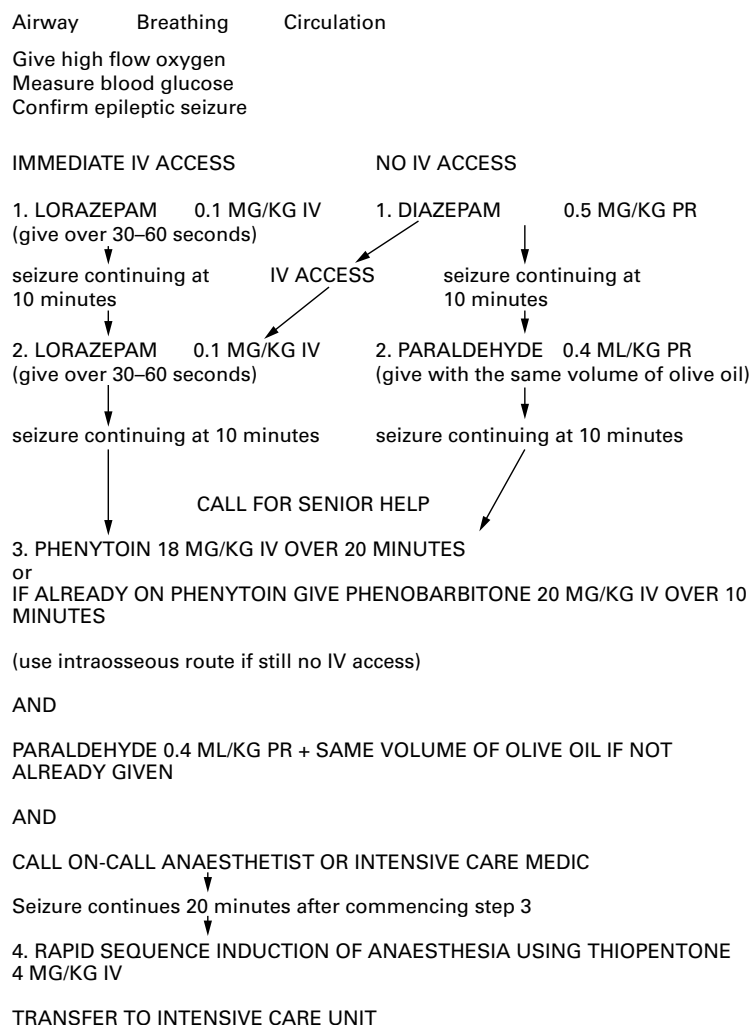


Figure 1 Treatment guideline for an acute tonic-clonic convulsion including established convulsive status epilepticus.

confusion. Specifically, many patients with chronic epilepsy who have had repeated episodes of CSE may be recognised by their usual medical team to respond (or not respond) to certain drugs and in this situation an individual protocol would obviously be more appropriate. Seizures in neonates (less than 28 days old) are usually symptomatic and frequently have a different semiology compared to seizures in older children. This guideline does not therefore address the treatment of seizures in neonates, although many of the principles may still be relevant. This consensus guideline is primarily designed for the A&E department or the ward when a child is first seen for an acute tonic-clonic convulsion. The most common situation in which acute treatment is required is likely to be in young children with a febrile convulsion, those with idiopathic CSE, or in those who have had a recent change in antiepileptic medication. Finally, the investigation of the cause of the status epilepticus is also not addressed by this guideline.

STEP 1

Initial assessment should follow the ABC principle of resuscitation. High flow oxygen should

be given and the blood glucose measured by stick testing. It is important to emphasise that not all episodes that appear to be seizures are epileptic. A brief history and clinical examination should therefore be undertaken to confirm genuine seizure activity and not, for example, a movement disorder (for example, drug induced dystonic reaction or a tonic spasm caused by raised intracranial pressure) or psychogenic (pseudoepileptic) attack.

Most seizures stop within five minutes of onset. Although the definition of CSE implies that the seizure should last 30 minutes, in practice treatment should start within, and certainly no more than 10 minutes of continuous generalised tonic-clonic (GTC) seizure activity. The times of drug administration on the guideline are from the time of arrival in A&E. It must be assumed that the convulsion will have been continuing for at least five minutes prior to arrival. Those treating the child should be aware of the signs of physiological decompensation that occur in prolonged seizures and should consider moving directly to step 4 if systemic compromise is severe with hypotension and metabolic acidosis.

Many children arrive at hospital having received rectal diazepam, or rarely, rectal paraldehyde, from parents or paramedics. It was agreed not to take such treatment into account in drawing up the guidelines as both the drug used and dose given will vary.

For those children in whom intravenous access is immediately established, lorazepam 0.1 mg/kg should be given intravenously. Lorazepam is equally or more effective than diazepam but possibly with less respiratory depression^{14–17} (A). Pharmacokinetic data also suggest a far longer duration of action for lorazepam (12–24 hours) than diazepam (<1 hour).^{15, 18} In those children in whom attempts at immediate intravenous cannulation have failed, rectal diazepam 0.5 mg/kg should be given^{6, 7, 19} (B). Although lorazepam has been administered rectally using the intravenous preparation,^{14, 15} there are doubts about its absorption. Midazolam, administered by either the buccal or nasal route, has been shown to be effective and “safe” in a small number of selected patients.^{20–22} Its role in the accident and emergency department and the effective dose has not yet been completely evaluated, although a multicentre randomised controlled trial (RCT) is currently being designed.

STEP 2

If after 10 minutes the initial convulsion has not stopped or another convulsion has begun, then a second dose of lorazepam (0.1 mg/kg) should be given (C).

Children who do not respond to rectal diazepam after 10 minutes should then have one dose of intravenous lorazepam 0.1 mg/kg, assuming intravenous access is established.

If following the first dose of rectal diazepam no intravenous access is established and assuming that the child is still convulsing, rectal paraldehyde 0.4 ml/kg mixed with an equal volume of olive oil should be given (C). Arachis oil should now be avoided because of the theo-

retical risk of peanut allergy. There are limited published data on the use of rectal paraldehyde^{6,23}; however, a large amount of clinical experience in children supports its effectiveness. At the time of writing, paraldehyde for rectal administration is difficult to obtain. A sterile injection (Faulding DBL) suitable for rectal use is, at the time of writing, difficult to acquire but available. Paraldehyde can be obtained as a chemical and tested to ensure compliance with pharmacopoeia standards. Supplies of the drug should therefore be available. Further information can be obtained from IDIS World Medicines (020 8410 0700), the national paediatric Drug Information Advisory Line (DIAL; 0151 252 5837), or from "special order" manufacturers (*British National Formulary* 38:709). Intramuscular paraldehyde should be avoided because the injection is painful, and there are risks of damaging the sciatic nerve and causing sterile abscesses.⁶ The working party considered whether a second dose of rectal diazepam should be given in preference to rectal paraldehyde, but the risk of accumulation resulting in respiratory depression (particularly if the child had been given prehospital diazepam), was felt to be greater than with paraldehyde.

In the majority of children, either of the treatments in Step 2 (a second dose of intravenous lorazepam or rectal paraldehyde) should be effective within 10 minutes,^{15,24} and should therefore obviate the need for progressing to step 3 and giving a longer acting anticonvulsant such as phenytoin or phenobarbitone.

STEP 3

At this stage a further assessment of the child is also needed by senior and experienced staff to confirm that the convulsion is a genuine epileptic seizure and that no treatable cause, such as hypoglycaemia, is being overlooked. In the unlikely event that intravenous access is still not possible, then an intraosseous needle should be inserted.

Continuing convulsive activity dictates that a longer acting anticonvulsant is required. Phenytoin (PHT) and phenobarbitone (PHB) are often used intravenously to treat CSE because of their relatively rapid onset of action.^{6,16} There have been no reported studies directly comparing the two drugs in children. A recent adult RCT suggested that phenobarbitone was more effective than phenytoin alone but equally as effective as diazepam plus phenytoin.¹⁶ The opinion of the working party was that PHT causes less respiratory and central nervous system depression and is therefore the preferred drug (B). A dose of 18 mg/kg given through a peripheral line intravenously over 20 minutes is recommended.¹⁶ The infusion can only be made up in 0.9% saline, at a maximum concentration of 10 mg in 1 ml, and infused at no more than 1 mg/kg/min. Heart rate, ECG, and blood pressure monitoring during infusion are recommended.

The use of infusions of clonazepam or midazolam was considered for step 3. The increased time to adjust the rate of infusion and monitor

the effects were considered detrimental. The likelihood of respiratory depression and the difficulty of assessing a heavily sedated child are major drawbacks.

Fosphenytoin (FOS) manufactured by Parke-Davis, is a recently produced prodrug of phenytoin.^{25,26} Although FOS has no known anticonvulsant action, the drug is 100% bioavailable and is rapidly converted to phenytoin after either intravenous or intramuscular administration. Importantly, FOS is freely soluble in aqueous solutions, does not require organic solvents, has a pH of 8 in solution, and does not precipitate in commonly used intravenous diluents. Because of its solubility in aqueous solutions and absence of the propylene glycol solvent (which is used with phenytoin), FOS may be infused up to three times more rapidly than phenytoin, over a period of 7–10 minutes, although the time to peak concentration is almost identical. Potential practical benefits with FOS include a reduced risk and incidence of both serious extravasation reactions, hypotension, and inducing cardiac dysrhythmias. The principal if only potential disadvantage of using FOS is that this drug is prescribed in phenytoin equivalents (PE), which could cause confusion and errors in prescribing (75 mg of FOS is equivalent to 50 mg of PHT). There are limited adult, and no paediatric efficacy data on the use of fosphenytoin in treating CSE.^{27,28} Although further paediatric data are obviously required, it is the opinion of the working party that FOS should eventually replace PHT as the long acting anticonvulsant of choice, based primarily on the practical advantages with FOS. At the time of writing this guideline, the cost effectiveness of fosphenytoin has not yet been fully evaluated by many Trusts (it is more expensive) and it is not routinely available in most hospitals in the UK; phenytoin was therefore chosen for this guideline.

Both PHT and FOS may take up to 25 minutes from the start of the infusion to be effective, although theoretically, the shorter infusion time with FOS may lead to a more rapid control of the convulsion. Because it is desirable to stop the status epilepticus as soon as possible a faster acting drug could be given at the same time as phenytoin. If paraldehyde has not been given up to now this should be used (in a dose of 0.4 ml/kg with an equal volume of olive oil). The full dose of phenytoin should be given even if the seizure ceases during infusion or with paraldehyde.

The working party considers that it is preferable not to use intravenous phenytoin in those children who are already receiving phenytoin as a maintenance oral anticonvulsant. Although it is possible that the cause of CSE may be a fall in PHT concentrations, it is very unlikely that a blood level taken in the A&E department will be available rapidly enough to either confirm or refute this possibility. Therefore, to avoid potential PHT toxicity (given its pharmacokinetic profile), the working party advises that intravenous phenobarbitone in a dose of 20 mg/kg over 10 minutes,^{6,12} should be given to children on maintenance, oral PHT (B).

Finally it is recommended that during step 3, a consultant paediatrician or senior registrar in paediatric neurology is called if not already present, and that anaesthetic or intensive care advice is sought.

STEP 4

If 20 minutes after step 3 has commenced the child remains in CSE, then rapid sequence induction of anaesthesia is performed using thiopentone^{6 12} (C). If neuromuscular paralysis is used this should be short acting so as not to mask the clinical signs of the convulsion.

At this stage, and possibly earlier (for example, step 3), children under 3 years of age with a prior history of chronic, active epilepsy and who present with an episode of established CSE (lasting at least 30 minutes) should be treated with intravenous pyridoxine in case the child has either pyridoxine dependent or pyridoxine responsive seizures²⁹ (C).

Propofol has been recently proposed for use in this situation,³⁰ but there are concerns that the drug may have a proconvulsant effect in some patients and its use as an infusion in children has been seriously questioned.^{2 31}

The child will subsequently need to be nursed on a paediatric intensive care unit and advice on ongoing management should be sought from a paediatric neurologist.

Unfortunately, the subsequent anticonvulsant management is unclear in those children who continue to convulse and who are in refractory CSE, following the use of thiopentone. A number of regimes using continuous intravenous (for example, midazolam³²) or inhalational anaesthetic agents (for example, isoflurane³³) have been reported, but inadequately evaluated.³ Although refractory CSE is uncommon, it is clearly an important issue, but the working party considered that this was outside the remit of the present guideline.

Despite CSE being a relatively common and serious medical emergency in children, its management has been poorly studied, particularly in randomised controlled trials. The proposed guideline can justifiably be criticised as being based predominantly on clinical experience and practice rather than on evidence. Nevertheless, it was felt important to produce a guideline based on the currently available information, rather than waiting for data from future randomised controlled trials. The working party is proposing to assess the effectiveness of the guideline and to audit its use in a number of centres and, where appropriate, to modify it in the light of experience.

It is clear that further studies are needed to clarify a number of outstanding issues which have been identified by the working party. The group is currently designing two multicentre RCTs, the first comparing rectal diazepam with buccal midazolam (step 1 of the guideline) and the second comparing intravenous phenytoin with intravenous fosphenytoin (step 3 of the guideline). Finally, the management of refractory or persistent CSE on the intensive care unit will be addressed in the near future, through a similar multidisciplinary group approach.

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Appendix: Grading of evidence for recommendation strengths and levels of evidence

LEVEL OF EVIDENCE

- I—Well designed randomised controlled trials, systematic reviews, or meta-analyses
- II—Well designed (but non-randomised), prospective or retrospective controlled studies or other observational studies
- III—Uncontrolled trials or descriptive studies or consensus agreed in reports from expert committees or other respected authorities.

STRENGTH OF RECOMMENDATIONS

- A—Based directly on level I evidence
- B—Based directly on level II evidence or extrapolated from level I evidence
- C—Based directly on level III evidence or extrapolated recommendations from level I or II evidence.

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