

CURRENT TOPIC

Emergency treatment of acute seizures and status epilepticus

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This article discusses some of the issues related to protocols for emergency anticonvulsant treatment of acute seizures and status epilepticus with particular emphasis on the use of benzodiazepines in children presenting to accident and emergency departments.

Definitions

Infants and children can have both convulsive and non-convulsive forms of prolonged seizures. This article addresses only convulsive episodes of status epilepticus, which is strictly defined as two or more seizures occurring consecutively without an intervening period of full recovery of consciousness, or as recurrent epileptic seizures lasting for more than 30 minutes.¹ Unfortunately, such a precise definition of status epilepticus, although useful for epidemiological analysis and evaluation of therapeutic interventions, conceals a sometimes frenetic approach to acute care and the urgency experienced by clinicians when confronted with a convulsing child, irrespective of how long the episode has lasted. It therefore seems more appropriate to take a pragmatic view and consider status epilepticus as the severe end of a continuum encountered during the progressive evolution of an unrelenting seizure, which heralds a potentially life threatening sequence of complications in central, metabolic, and systemic physiology (table 1).²⁻⁵ This somewhat looser approach is reflected in the paediatric literature where seizure episodes of considerably less than 30 minutes have been considered as status epilepticus.^{6,7}

Clinical perspective

Both the clinical context and natural history of acute seizures and status epilepticus are very important considerations when evaluating choice of anticonvulsant treatment. In many parts of the world status epilepticus in childhood is often associated with fever, although there is wide variation in the proportion of patients who have this symptom (25-50%).⁸⁻¹⁰

In the UK, status epilepticus (defined as a 30 minute episode) is an infrequent occurrence. For example, Verity *et al* reported in 1993⁹ that only 37 of 14 676 children from a long term cohort study had an episode of status epilepticus by their 10th birthday. Similarly, Smith *et al* reported in 1996¹⁰ only 12 episodes of status

epilepticus (lasting longer than 30 minutes) in 254 seizure episodes occurring in children presenting to an accident and emergency department over one year; this was from a surrounding population of 70 000 children.

Clinical strategy

Smith *et al*'s district general hospital study¹⁰ also illustrated another important feature of acute seizures in children: 80% of them did not require any anticonvulsant treatment in the emergency department. Therefore, given that most acute seizures in children stop spontaneously, usually during transit to hospital, we should assume that if a child is still convulsing on arrival in the emergency department the seizure will continue unless treated. How rapidly such treatment should be carried out then becomes an important issue. Status epilepticus in the 1990s has a relatively low morbidity and mortality directly attributable to the seizure itself,^{8,9} and an overexuberant approach with anticonvulsants may expose patients to the unnecessary iatrogenic risks of respiratory depression and hypotension. One commentator has raised the important question "Does the morbidity of the treatment of seizures in the emergency room to prevent status now exceed the morbidity of the status epilepticus itself?".¹¹ In the absence of any clear clinical data to answer this question fully, the onus on those involved with acute seizure treatment is to ensure that it is administered safely and in a standardised fashion that is understood by all emergency personnel involved.

Emergency supportive treatment

Anyone who is still convulsing on arrival in the emergency department should receive immediate, basic, supportive treatment.

AIRWAY AND OXYGENATION

Hypoxaemia can be both the cause and the consequence of a seizure. In severe episodes bradycardia and hypotension may complicate the seizure. To begin with, the head and neck should be positioned to keep the airway open and, if necessary, the airway should be suctioned to ensure patency. If feasible, an oral airway can be inserted—although this should only be done if there is no likelihood of trauma to the mouth and teeth—and oxygen should be

Table 1 Systemic physiology, metabolic, as well as central changes, and derangements during prolonged seizures²⁻⁵

	< 30 mins (phase I)	≥ 30 mins (phase II)	Hours (refractory)
<i>Systemic physiology</i>			
Blood pressure	Increase	Decrease	Hypotension
Arterial oxygen	Decrease	Decrease	Hypoxaemia
Arterial carbon dioxide	Increase	Variable	Hypercapnia
Lung fluid	Increase	Increase	Pulmonary oedema
Autonomic activity	Increase	Increase	Arrhythmias
Temperature	Increase by 1°C	Increase by 2°C	Fever, hyperpyrexia
<i>Metabolic (serum)</i>			
pH	Decrease	Variable	Acidosis
Lactate	Increase	Increase	Lactic acidosis
Glucose	Increase	Normal or raised	Hypoglycaemia
Potassium	Increase or normal	Increase	Hyperkalaemia
Creatine phosphokinase	Normal	Increase	Renal failure
<i>Central</i>			
Cerebral blood flow	Increase 900%	Increase 200%	Cerebral oedema
Cerebral oxygen consumption	Increase 300%	Increase 300%	Cerebral ischaemia
Cerebral energy state	Compensated	Failing	Deficit, ischaemia

administered by nasal cannula or mask and bag-valve-mask ventilation. If the need for respiratory assistance persists after the patient has been supported by bag-valve-mask, endotracheal intubation should be considered. However, administering an anticonvulsant is a top priority because managing the airway and assisting respiration are much easier after the convulsion has stopped. If persistent convulsive activity causes hypoventilation necessitating endotracheal intubation, seizure activity can be stopped temporarily with a high dose of a short acting barbiturate or midazolam, and patient ventilation dysynchrony can be abolished with a neuromuscular blocking agent.

GLUCOSE

Hypoglycaemia is a rare cause of prolonged seizures in children. However, all patients should have prompt measurement of blood glucose. If hypoglycaemia (blood glucose < 3 mmol/l) is documented or if it is impossible to obtain the measurement, intravenous glucose (5 ml/kg) should be administered as 10% glucose.

BLOOD PRESSURE

Hypotension can potentiate or exacerbate any derangement in cerebral physiology and function. Systolic blood pressure should be maintained at normal levels. If there is no evidence of shock, minimal isotonic fluids of 2–3 ml/kg/h should be given initially.

Anticonvulsant treatment

In the convulsing patient, initial supportive, therapeutic, and diagnostic measures need to be conducted simultaneously. The goal of anticonvulsant treatment is the rapid termination of clinical and electrical seizure activity by the prompt administration of appropriate drugs in adequate doses, with attention to the possibility of complicating apnoea, hypoventilation, and other metabolic abnormalities.

PROLONGED SEIZURES AND ANTICONVULSANT RESPONSIVENESS

The concept of acute seizures and status epilepticus being on a continuum is useful in regards to administering anticonvulsant treat-

ment. For example, using diazepam in controlled experimental studies of prolonged seizures has established that the longer the duration of a seizure episode before treatment (ranging from 7–130 minutes) the more difficult it is to stop, and the more likely it is that diazepam will convert an overt motor episode into another subtle or electroencephalographic form of seizure activity.¹² As similar findings have been reported in man,¹³ the need for rapid, definitive treatment of acute seizures, irrespective of whether 30 minutes has elapsed, is underscored.

ANTICONVULSANT PROTOCOL

There is a dearth of evidence in children that one particular anticonvulsant protocol is best for treating acute seizures. There is need for a formal systematic review of the literature to identify what would be the appropriate strategy for future investigation. A clear path or treatment plan however is necessary now, and indeed has been recommended for effective and consistent management.¹⁴ One such approach is that used by the “Advanced Life Support Group” in their recommendations for advanced paediatric life support (fig 1).¹⁵ While endorsing wholly this specific approach, not least because it is taught widely and has been adopted as a national standard of care, the main problem with this approach is the time it might take to stop a seizure if official recommendations are adhered to. For example, 25 to 30 minutes of seizure activity may have elapsed before either phenytoin or phenobarbitone is given: five minutes before the first dose of diazepam, then five minutes to see if diazepam is effective, then the second dose of diazepam, then five minutes to see if this dose is effective, then a dose of paraldehyde, then 15 to 20 minutes to see if this is effective, etc. We shall therefore consider other emerging strategies using only benzodiazepine agents (figs 1 and 2),¹⁶ which may simplify our approach to acute emergency seizure treatment.

Benzodiazepine agents

PREHOSPITAL TREATMENT

The efficacy of intravenous diazepam for the treatment of status epilepticus is well recognised with termination of episodes in some 80% of cases.¹⁷ However, safety is a significant concern as apnoea and respiratory depression are common complications.¹⁸ Therefore, except in known cases of recurrent prolonged seizures, drug treatment in the UK has traditionally been reserved for administration after arriving in hospital. If, as already discussed, diazepam is not only effective treatment but also better when administered earlier, why not give it before arriving at hospital—providing it can be carried out safely? In support of this argument is a recent American retrospective, case-control, study by Alldredge *et al.*⁷ Using a definition of status epilepticus as seizures lasting longer than 15 minutes, these authors found (in 45 convulsive episodes) that prehospital treatment with intravenous diazepam (0.2 mg/kg) or rectal diazepam

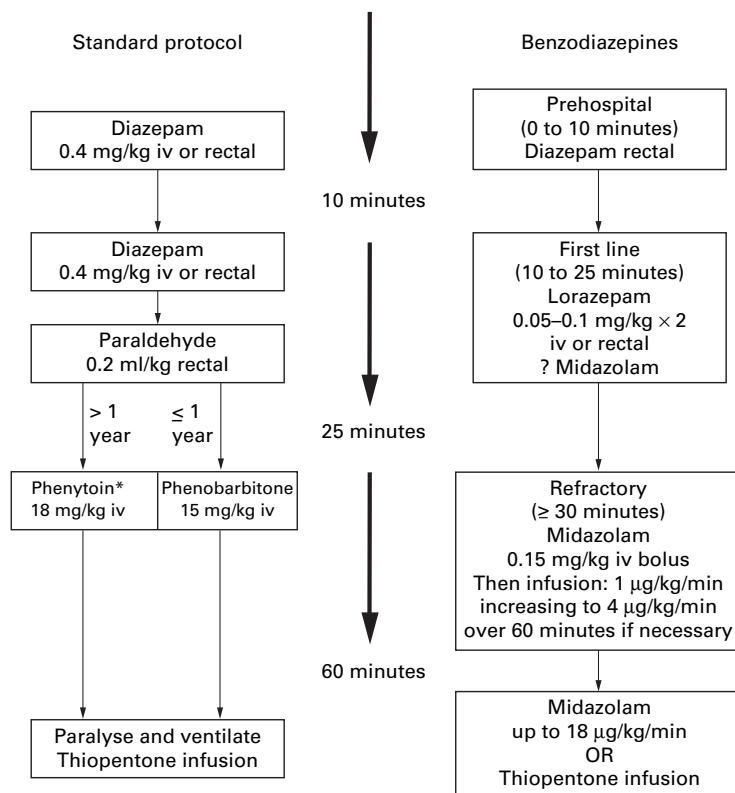


Figure 1 Timing for the Advanced Paediatric Life Support (APLS) "standard" anticonvulsant protocol for status epilepticus¹⁵ alongside a potentially challenging approach using only "benzodiazepines". The time line highlights a problem with the APLS approach: it may be 25 minutes before progressing to phenytoin or phenobarbitone. *Do not use if the child is known to be on regular phenytoin.

(0.6 mg/kg) by paramedical staff significantly shortened the duration of status epilepticus (mean for prehospital 32 minutes *v* mean for emergency department 60 minutes; $p = 0.007$) and reduced the likelihood of recurrent seizures in the emergency department (58% *v* 85%; $p = 0.045$). This study found no difference between the effectiveness of rectal and intravenous diazepam. This experience seems to confirm the experimental data already described,¹³ but is such an approach safe?

The possible complication of respiratory depression from rectal diazepam has been considered in some depth in the treatment of repeated febrile convulsions.¹⁹ Respiratory depression from rectal diazepam (0.2–0.5 mg/kg) is rare among children studied to date, probably because of the slower rise in serum diazepam concentrations compared with that achieved after intravenous administration. The clinical effect from rectal diazepam occurs in approximately five minutes and peak serum concentrations are achieved 6–10 minutes after administration.^{20, 21} Knudsen²² reported no respiratory complications in 376 children treated with rectal diazepam. (The upper limit of the 95% confidence interval for 0/376 is 8 per 1000 cases.) A literature review of 13 papers on rectal diazepam by Siegler in 1990²³ identified only three cases of reversible respiratory depression in 843 cases. Some patients, however, may be at more risk of respiratory depression—for example, those with serious comorbidity and those on regular anticonvul-

sants or with chronic central nervous system abnormalities.²³ In these patients a lower rectal dose of 0.25 mg/kg is advised.

Therefore, the literature supports the use of a single prehospital dose of rectal diazepam, although attendants should be aware of the possibility of respiratory depression and be able to support breathing if necessary.

FIRST LINE HOSPITAL TREATMENT

A child who is still convulsing on arrival in hospital can be assumed to have had a seizure lasting at least 10 minutes and therefore will require emergency treatment. Some children may have already received rectal diazepam. In this phase of management the issues are whether diazepam is the treatment of choice and, if it is, should it be used more than once. Although the precise serum diazepam concentration required for a therapeutic effect is not known, concentrations of 150–336 ng/ml are associated with arrest of seizure activity.²⁴ These are achieved with a single dose of rectal diazepam,^{20, 22} which questions the notion that further doses would be of benefit in those whose seizure has not come under control—unless of course administration of the first dose has been unreliable or if a second episode has occurred. Few studies in children have looked specifically at the effectiveness of serial doses of diazepam when the first dose has failed to control the seizure. However, some information on this question can be learnt indirectly from a recent prospective study reported by Appleton *et al.*²⁵ Of 53 patients presenting with acute seizures to an emergency department, 28 responded to a single dose of rectal or intravenous diazepam (0.3–0.4 mg/kg). In the 25 who required a second dose, 17 also needed additional anticonvulsant drugs. This may have been because of the local protocol, but it does suggest that in those who do not respond to an initial dose of diazepam, the second dose is also likely to be ineffective. Therefore, if giving diazepam twice is questionable, is there a better alternative?

Choices from phenobarbitone, phenytoin, and lorazepam as candidate alternative drugs for status epilepticus have been debated in the literature.^{16, 26, 27} Lorazepam, a hydroxylated benzodiazepine (fig 2), is an effective anticonvulsant with a response latency comparable to that of diazepam, and it has the advantage of a longer duration of anticonvulsant effect than diazepam.²⁷ Although there are few studies comparing lorazepam with established standards, it has been recommended as one of the first line agents for status epilepticus for the above reasons.²⁷ One preliminary study²⁵ compared lorazepam with diazepam for the treatment of acute convulsions and status epilepticus in 102 children in a prospective, open (odd and even dates) trial. Sixteen children had to be excluded and of the remaining 86, convulsions were controlled in 76% of patients treated with a single dose of lorazepam (0.05–0.1 mg/kg) and 51% of patients treated with a single dose of diazepam. Significantly fewer patients treated with lorazepam required additional anticonvulsants to terminate the seizure.

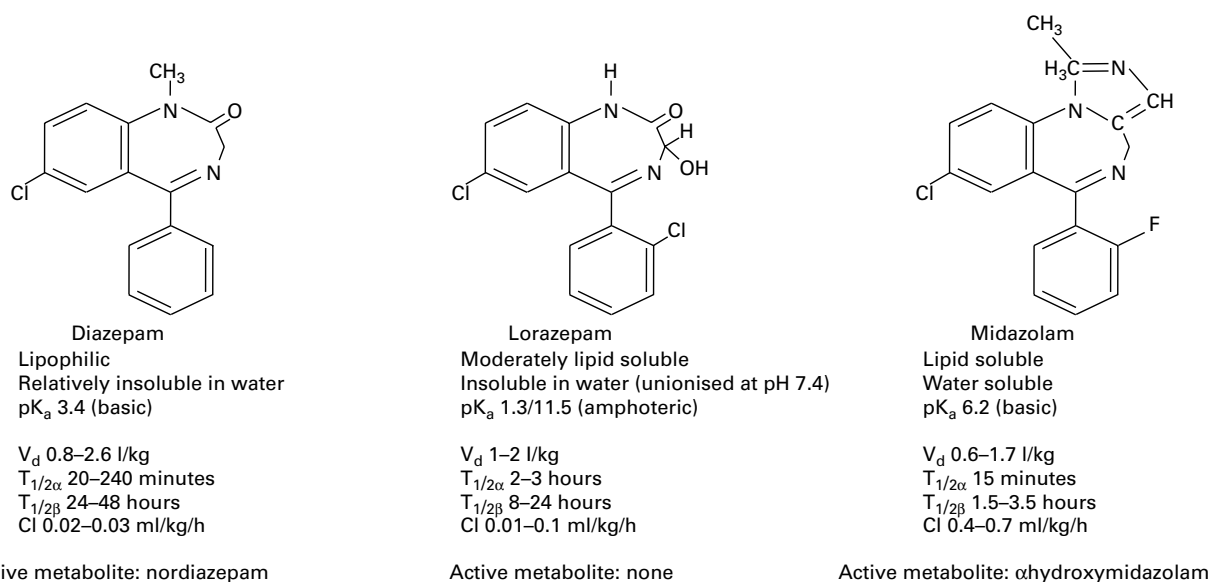


Figure 2 Chemical structure and pharmacokinetic properties of diazepam, lorazepam, and midazolam illustrating some of the similarities between these benzodiazepine GABA_A agonists. Adult pharmacokinetics¹⁶: V_d, volume of distribution; T_{1/2α}, distribution half life; T_{1/2β}, elimination half life; Cl, clearance. All three drugs are metabolised in the liver and excreted via the kidney. All three have significant protein binding (> 88%).

Respiratory depression occurred in 3% of lorazepam treated patients and 15% of diazepam treated patients. No patient who received lorazepam required admission to the intensive care unit for either respiratory depression or refractory status epilepticus, whereas all eight of the patients with diazepam related respiratory depression were admitted for intensive care. Importantly, rectal and parenteral lorazepam were equally efficacious.

Despite these favourable aspects of lorazepam, there are still indications for the other agents. Lorazepam appears to be less effective in patients chronically treated with other benzodiazepine anticonvulsants and in those who will need the drug more than once.²⁷ In both of these instances phenobarbitone appears to be superior,^{26, 28} although there is little comparative clinical data for these agents and phenytoin. In practice, choice between anticonvulsants appears to relate to age and aetiology. In infants, the metabolism of phenobarbitone is more predictable than the metabolism of phenytoin. Phenytoin has a role when there is concern about impaired cerebral function and the need for clinical assessment of neurology.

REFRACTORY SEIZURES

Refractory status epilepticus has been defined as a seizure that is unresponsive to an adequate dose of a first line parenteral anticonvulsant²⁸; or a seizure that is unresponsive to at least two doses of diazepam intravenously or rectally in succession followed by phenytoin/phenobarbitone or both (20 mg/kg) given over 30 minutes as an infusion, or failure to respond to the latter alone or in combination^{15, 28–30}; or a seizure that continues for 60 to 90 minutes after the initiation of treatment.¹ This lack of consistency in definition is important when one considers the treatment and its consequences. Traditionally, for the most severe cases of status epilepticus induction of general anaesthesia has

been recommended using a short acting barbiturate such as thiopentone (4–8 mg/kg bolus followed by infusion of up to 10 mg/kg/h) along with supportive endotracheal intubation and mechanical ventilation.^{15, 29} An alternative, effective approach has been to use, if necessary, repeated bolus doses of intravenous phenobarbitone (10 mg/kg) every 30 minutes, without reference to a predetermined maximum level or dose, after one dose of intravenous diazepam has failed to control a seizure.²⁸ A number of questions arise—for example, at what point is induction of anaesthesia overexuberant? Is it really necessary to wait 60 to 90 minutes before deciding that standard anticonvulsants are ineffective? When is it inevitable that standard anticonvulsants are unlikely to work—after the second dose of diazepam, after the second drug, or after the third drug? Some of these issues have been addressed already. The main disadvantage of thiopentone relates to its high lipid solubility and slow metabolism, which results in a prolonged period of intensive care support before a child is completely awake and cooperative once treatment has been stopped.²⁹ Similarly, prolonged intensive care will be necessary when using the very high dose phenobarbitone strategy.²⁸

A newer approach, recently delineated in children, has been to use midazolam,^{30, 31} an imidazobenzodiazepine (fig 2). This drug has a relatively short elimination half life of 1.5 to 3.5 hours, and preclinical and clinical analyses indicate that it shares anxiolytic, muscle relaxant, hypnotic, and anticonvulsant actions with other benzodiazepines. Rivera *et al* reported the use of midazolam in 24 children (aged 2 months to 2 years) with status epilepticus failing to respond to three repeated doses of 0.3 mg/kg diazepam, 20 mg/kg of phenobarbitone, and 20 mg/kg phenytoin.³⁰ Intravenous midazolam given as a bolus of 0.15 mg/kg followed by continuous infusion of 1 µg/kg/min (with increasing increments of 1 µg/kg/min

every 15 minutes until seizure control) was successful in all cases. The average time to achieve seizure control was 47 minutes (range 15 minutes to 4.5 hours) with a mean infusion dose of 2.3 µg/kg/min (range 1 to 18). After stopping the infusion, the average time to full consciousness was just over four hours (range 2 to 8.5). Lal Koul *et al* recently reported similar findings in a further 20 children.³¹

Given the structural and pharmacokinetic similarities between diazepam and midazolam (fig 2) and their similar mechanism of action via binding to the γ -aminobutyric acid A (GABA_A) receptor, it is pertinent to question "Why should midazolam be effective when other GABA_A agonists including phenobarbitone and benzodiazepines have failed?" As yet this cannot be answered from the available data, but it may relate to actions and interactions distant to the benzodiazepine binding site on the GABA_A receptor.³² This therapeutic conundrum does however raise another important consideration—if midazolam is effective when all drugs have failed, would it be a better option earlier in acute seizure care? Lal Koul *et al* addressed this question in their report³¹ by using a midazolam infusion as their only treatment in eight patients who had seizure activity for at least 30 minutes. Once this treatment was started, control of the seizure was achieved within 10 to 60 minutes (mean 34). None of their patients required mechanical ventilation or endotracheal intubation.

What about the potential use of midazolam as a first line anticonvulsant for all acute seizures? In the accident and emergency department in predominantly adult series, intravenous³³ and intramuscular³⁴ midazolam as first line treatment for seizures have been used effectively and safely. Galvin and Jelinek³³ reported that intravenous midazolam alone was successful in stopping seizures in all 75 patients they treated. Intramuscular midazolam is also rapidly effective: in 36 of 38 patients undergoing seizures, seven of whom were children, seizures were controlled with a mean of 1 minute and 53 seconds.³⁴ The two patients whose seizures continued despite intramuscular midazolam responded to another benzodiazepine given intravenously.

Conclusion

Devising a protocol for the management of status epilepticus with the optimal selection of anticonvulsant drugs is fraught with problems given the reality of clinical duty rotations and varied expertise of frontline staff. Introducing relatively new agents such as midazolam and lorazepam into an established pattern of practice will need to be justified. Inevitably, factors other than pharmacology and therapeutics will influence the specific approach adopted. What is right for a practice seeing head injury as the major cause of status epilepticus may not be appropriate for those dealing with central nervous system infection as the leading cause. The clinical context, cost, and logistics of delivering effective treatment and care are also important. Finally, diagnostic studies and the

type and timing of investigation are a concern. Some of these aspects are well summarised elsewhere.^{35,36} However, irrespective of regional variance in practice, it is clear that much thought should be given to these issues at a local level. In a recent UK intensive care questionnaire study reported by Walker *et al*,¹⁴ only 12% of the respondents were aware of a local protocol for status epilepticus.

Future direction

Perhaps not surprisingly there is a paucity of clinical data comparing drug regimens for status epilepticus, which means that there is still much to learn about this emergency. As alluded to already, there is a need to formalise and confirm our current ignorance in a systematic review. Building on this knowledge will inevitably require a number of specific studies concentrating on prehospital, first line, and refractory phases of drug treatment. For example: Is prehospital administration of rectal lorazepam by paramedical staff of benefit? Can midazolam be used as monotherapy, intranasal or rectal in the prehospital setting and then parenterally thereafter? Can we predict better those patients who will eventually prove to be refractory to treatment? For the present, standards such as that recommended by the Advanced Paediatric Life Support Group¹⁵ have been rightly adopted on a national level, but that should not detract from a constructive, investigational questioning of alternative or even better, more timely approaches, which have as their goal improved emergency care.

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