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When benzodiazepines fail: How effective is second line therapy for status epilepticus in children?

Stuart Lewena and Simon Young
Department of Emergency Medicine, Royal Children's Hospital, Flemington Road, Parkville, Victoria, Australia

Abstract

Objectives:	To define the characteristics and management of children presenting to the ED of a major tertiary paediatric hospital with convulsive status epilepticus (CSE). To determine the timing and efficacy of therapeutic interventions in this group and to identify factors that influence the effectiveness of treatment.
Method:	A retrospective audit of all children who presented to an ED of a tertiary paediatric hospital in CSE over a 3 year period.
Results:	Thirty-seven cases were identified. Prehospital treatment had been administered in 51%. Uncomplicated seizure control was achieved in 30% with the combination of first and second line therapy. Rapid sequence induction (RSI) of anaesthesia was required in 70% for the control of ongoing seizure activity (21 cases) or to support severe respiratory depression (five cases). This requirement for RSI was increased to 85% in those with seizure duration in excess of 30 min and 89% of those who received prehospital treatment. Of those who required RSI, 35% were treated for periods in excess of 60 min before this intervention was performed.
Conclusions:	Standard second line anticonvulsant treatment was relatively ineffective in terminating seizures in children who presented in CSE not responsive to benzodiazepines. Failure to respond to prehospital treatment and prolonged seizure duration at presentation both predict poor therapeutic response. Third line treatment with RSI of anaesthesia is often delayed while waiting for second line treatment to work.
Key words:	*benzodiazepine*, *prehospital*, *status epilepticus*, *treatment*.

Introduction

Seizures represent a common medical emergency in paediatric practice. Fortunately, most childhood seizures terminate spontaneously within a few minutes without the need for specific medical intervention.[1] Of those that continue, the majority of seizures can be controlled with initial treatment comprising attention to the child's

Correspondence: Dr Stuart Lewena, Emergency Physician, Department of Emergency Medicine, Royal Children's Hospital, Flemington Road, Parkville, Vic. 3052, Australia. Email: stuart.lewena@rch.org.au

Stuart Lewena, MBBS(Hons), BMedSci, FRACP, Paediatric Emergency Physician; Simon Young, MBBS, Dip Crim, FACEM, Director of Emergency Services.

airway and breathing and the administration of a benzodiazepine. Protocols to standardize this treatment have been developed by various groups including the Advanced Pediatric Life Support Group,[2] The Status Epilepticus Working Party[3] in the UK and The Epilepsy Foundation of America Working Group on Status Epilepticus.[4]

In a recent Australian study examining prehospital treatment of paediatric seizures, 92% did not require treatment in the prehospital setting.[5] Of the small group who did warrant treatment, 43% achieved seizure control within 5 min of prehospital drug administration. Those children who present to the ED with ongoing seizure activity therefore represent a minority.

Infrequently, seizures will persist despite first line treatment with benzodiazepines and such children are at increased risk of progressing to status epilepticus. The formal definition of convulsive status epilepticus (CSE) is a generalized convulsion lasting at least 30 min or repeated convulsions occurring over a 30 min period without recovery of consciousness between each seizure. However, for practical purposes, a child who is not responding to initial drug treatment can be considered to be in CSE earlier.[6,7] For a continuing seizure, management protocols recommend a second dose of benzodiazepine followed by administration of phenytoin or phenobarbitone as a second line agent.[2–4]

Although the termination of seizure activity either spontaneously or after first line drug therapy is highly likely at the onset of a seizure, the same degree of confidence does not exist after 30 min of seizure activity or by the time second line agents are required. A proportion of children with CSE requiring second line therapy do not respond. Treatment protocols then recommend third line management with thiopentone and RSI of anaesthesia which although highly effective, is accompanied by obvious disadvantages and risks including the requirement for a period of mechanical ventilation and potential complications from the procedure.[8–10]

In order to better manage and minimize these risks, second line therapy should ideally be highly effective and have a predictable time of onset to allow for more definitive progression to third line agents in the event of failure. Alternatively, if situations were identified in which standard second line therapy was unlikely to be effective, third line therapy could be instituted earlier in a more controlled way. Unfortunately, our current knowledge regarding the efficacy of second line treatment in paediatric CSE and the factors associated with its failure is limited.

Objectives

The primary aim of this study was to define the characteristics and management of children presenting to a paediatric ED with CSE and determine the effectiveness of second line treatment in this group. Second, we sought to define the time taken to achieve seizure control with RSI in refractory cases and to identify factors at presentation associated with failure of standard second line therapy.

Method

A retrospective audit of children presenting with CSE to the ED of the Royal Children's Hospital in Melbourne, Victoria, Australia was performed. The computerized ED database (HAS Solutions Pty Ltd, version 8) was searched for all seizure related diagnoses (febrile convulsion, afebrile convulsion, status epilepticus and seizure) over a 36 month period from January 2000 to December 2002. The selection was then limited to cases presenting with Australasian Triage Scale[11] category one or two, indicating the need for immediate or urgent resuscitation and to exclude seizure presentations that had terminated spontaneously or with prehospital treatment and arrived in a stable post-ictal state.

All charts and ambulance records were then individually reviewed by one of the authors (SL) to ensure they met the study criteria and to collate data using a standardized pro forma. Patients with seizure activity exceeding 10 min duration prior to treatment were eligible. Data collected included demographics, details of seizure onset, duration of seizure, prehospital treatment given and the subsequent course of hospital emergency management including the time over which this treatment occurred.

This study was approved as a clinical audit by the Royal Children's Hospital, Melbourne.

Results

Thirty-seven cases of CSE satisfying the entry criteria were identified. Ages ranged from 2 months to 7 years (mean 3.7 years) with a balanced sex distribution (43% male). A history of prior seizures was present in 65%. Prehospital treatment in the form of i.v., rectal (PR), i.m. or nasal benzodiazepine was administered to 51% (19). Average seizure duration at the time of hospital presentation was 48 min with a median of 45 min. Duration at

presentation exceeded 30 min in 70% (26) whereas only 19% (7) presented with seizures of less than 20 min duration.

First and second line therapy

First line hospital treatment consisted of various combinations of diazepam, midazolam and clonazepam given by i.v., PR or i.m. routes at variable dose. The majority of cases were treated with diazepam (81%). PR or i.m. administration was required after hospital presentation in four patients due to difficult i.v. access. Initial dose of i.v. diazepam ranged from 0.1 to 0.2 mg/kg with a tendency to give smaller doses repeated several times. The average cumulative dose of i.v. diazepam was 0.3 mg/kg in addition to any prehospital treatment or other benzodiazepine used. Control of seizures with benzodiazepine alone was achieved in only 14% (5) of cases (Fig. 1).

The remaining 86% (32) had seizures resistant to first line therapy. Second line treatment, consisting of phenytoin and/or phenobarbitone was administered to 88% (28) of this group with the remaining four patients undergoing RSI to facilitate more rapid seizure control due to accompanying severe airway or breathing compromise. Phenytoin was used in 18 patients, phenobarbitone in 17, and both agents in combination were used on seven occasions. Average time from hospital presentation to administration of a second line agent was

24 min. The administration of a second line agent resulted in termination of CSE without the need for subsequent third line therapy in a further six patients (Fig. 1). Therefore, a total of 30% (11) had successful treatment of CSE with first and second line agents. On all of these occasions, CSE was terminated within 40 min of hospital presentation (Fig. 2).

Failure of first and second line therapy

Seventy per cent (26) had convulsions refractory to standard first and second line therapy (21 cases) or developed significant and persistent airway or respiratory compromise as a consequence of drug therapy and/or seizure activity (five cases). These patients required RSI to facilitate seizure control or to support airway and respiratory function and are considered to represent failure of first and second line therapy. It could not be determined retrospectively whether any of the five patients in whom RSI was performed primarily for respiratory support also had ongoing seizure activity.

RSI was achieved with thiopentone and suxamethonium on all occasions. Subsequent drug therapy consisted of midazolam infusion or administration of a second line agent if not already given. Clinically evident CSE was terminated in 96% (25) after RSI. One patient had continuous CSE culminating in death after 11 h.

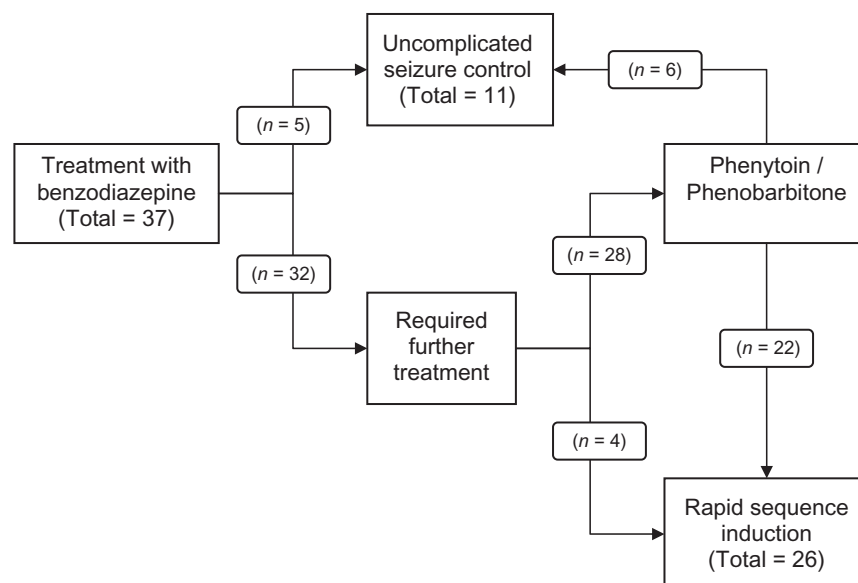Seizure duration beyond 30 min at presentation was associated with an 85% RSI rate (22/26) compared with

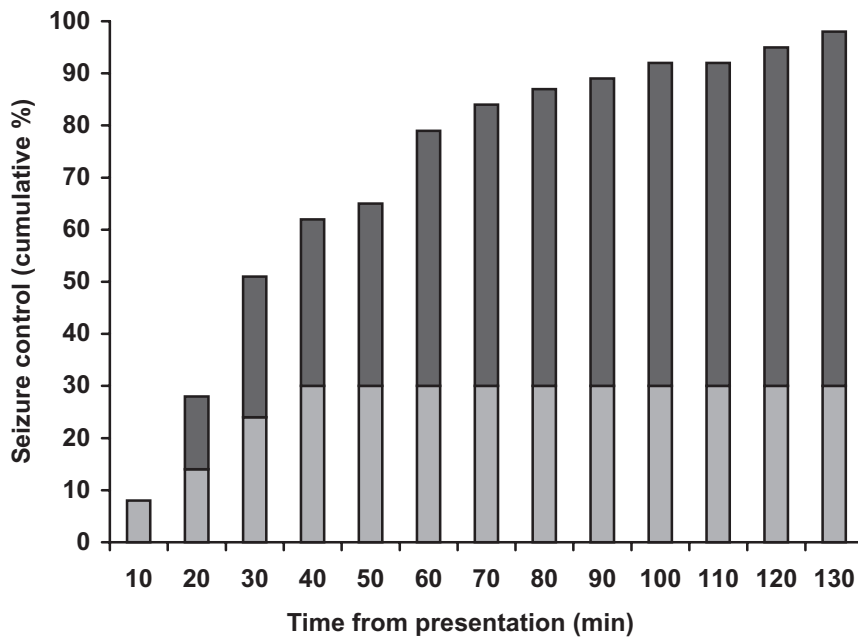**Figure 1.** Response to treatment in 37 cases of convulsive status epilepticus.

Figure 2. Time from presentation to seizure control. (▢) First and second line, (▩) RSI.
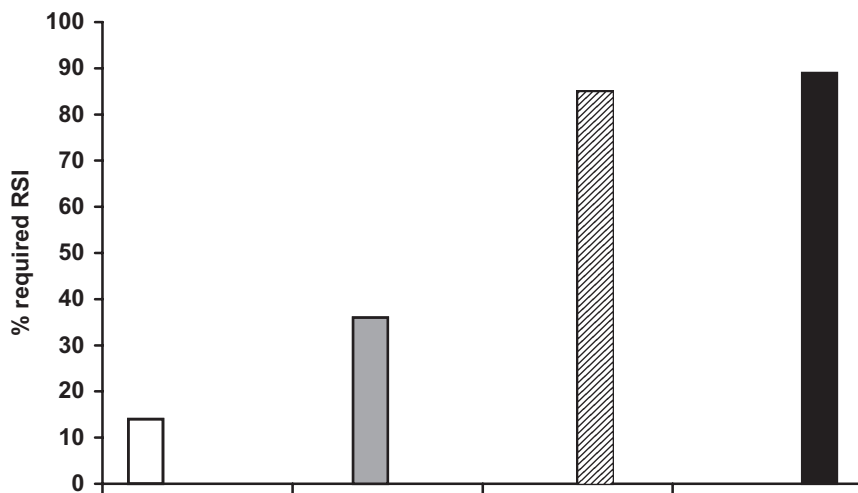

Figure 3. Effect of prehospital treatment and duration of seizure on need for RSI. (▢) Prehospital seizure duration less than 20 min, (▩) prehospital seizure duration less than 30 min, (▨) prehospital seizure duration more than 30 min, and (■) ongoing seizure despite prehospital treatment.

a 14% rate (1/7) for seizures of less than 20 min duration (Fig. 3). Furthermore, of those patients presenting in CSE despite prehospital treatment, 89% (17/19) required RSI to facilitate management versus 50% (9/18) of those who did not receive any prehospital treatment (Fig. 3). This relationship was independent of the effect of seizure duration which was similar in the group

given prehospital treatment compared with the study population overall (56 *vs* 48 min).

Delay to RSI

The mean and median time from hospital presentation to perform RSI was 50 min. Time to RSI exceeded 1 h

in 35% (9) of patients. Persistent seizure activity was the indication for RSI in eight of these nine patients with the remaining case intubated for recurrent apnoeas after apparent seizure termination. Longer delays to RSI were frequently associated with discontinuous seizure activity. RSI performed early in the course of management was generally in response to significant airway or respiratory compromise in the context of ongoing CSE.

Discussion

In this select group of children only 30% were controlled by benzodiazepines, together with phenytoin or phenobarbitone without the need for RSI. First line therapy was effective in 14% and second line treatment in a further 16%. This is considerably lower than other studies. An audit of children presenting with seizures to Royal Liverpool Hospital in the UK showed that 94% were controlled with first and second line treatment in the ED.[12] We propose that our study population has significant and important differences and postulate the following reasons for the observed high failure rate of first and second line therapy.

The average duration of seizures in this study at the time of ED presentation is long (mean 48 min, median 45 min). The efficacy of any specific seizure treatment has been shown to be related to the duration of seizure activity at the time of administration.[13] Drugs given early in the course of the seizure are more likely to be effective in both terminating the seizure and preventing recurrence.[14,15] The impact of seizure duration on treatment efficacy has been supported by this study. Successful first and second line therapy occurred in only 15% of cases where seizure duration exceeded 30 min at presentation. In contrast, 86% of those with seizures of less than 20 min duration at presentation responded. It is difficult to make direct comparison with the Liverpool study which quotes a range (10–210 min) and a mean duration (34 min) but no median. It is possible that a large number of patients in their study presented with relatively brief seizures which would provide some explanation for the higher response to standard first and second line therapy compared with our experience.

Children who presented with CSE and who had been given prehospital treatment were less likely to be controlled with first and second line therapy than those who presented without any treatment. Indeed, 89% of those who had received prehospital treatment required

RSI. We postulate that resistance to prehospital treatment has the effect of presenting a selected cohort of patients to the ED who are more likely to be refractory to standard therapy. This important relationship has not been described previously and is of significance when the high rate of prehospital treatment for children with seizures in our society is appreciated. In this study, 51% of children presenting with CSE had received prehospital treatment. This is in contrast to the findings of Garr et al.[11] where only two children (2%) had received prehospital treatment. Of the remainder, 87% had their seizures terminated with the first dose of benzodiazepine administered in the ED. In our community, a large number of these children would not have presented to the ED with seizures as they would have been controlled with prehospital treatment. Garr et al. acknowledged the low rate of prehospital treatment and conclude that such a group of children need to be evaluated separately in future audits due to the influence that such treatment might have on subsequent management. It is interesting to note that the two patients in their study who did receive prehospital therapy both required intensive care admission.

Our study shows that children presenting to our ED with CSE have frequently had a significant duration of seizure activity and have failed to respond to initial treatment with benzodiazepines. These children can be identified as a high-risk group at presentation and their poor response to further therapy predicted at that time. Failure to do so and persistence with the standard treatment algorithm might contribute to delays in definitive seizure control such as the delays we observed in performing RSI when required. Indeed, the 30 min spent in administering a second line agent such as phenytoin could be put to better use considering the frequent failure of this agent to achieve seizure control in this setting.

There are two main limitations to this study. The first relates to the retrospective design, with all of the information obtained by review of medical records. Although it would have been of interest to record other pertinent information such as an individual's past history of seizures and anticonvulsant medication, unfortunately, the variable and unreliable inclusion of this information in the medical record precluded it from being included. In addition, it is often difficult in a retrospective review to determine the specific reasons for a physician electing to perform a certain intervention. The decision to perform RSI is an example of where this limitation applies. As mentioned, 12% (five

cases) of RSI were documented as being performed primarily for airway and respiratory support and we are uncertain whether seizures had been controlled or were ongoing in these cases. Although we accept that some of these seizures might have been terminated, we do not believe they should be included with cases of successful first and second line therapy. The requirement for RSI and ventilation is never the intention of first and second line anticonvulsant treatment. We have therefore included all patients who needed to progress to RSI as representing failure of first and second line therapy regardless of the relative indications for RSI.

The second limitation of this study is the relatively small sample size, despite being performed in a major tertiary paediatric ED. As with many areas of paediatric emergency medicine research, a multicentre collaborative approach is required if we hope to definitively answer the questions raised by this study. Although having insufficient numbers to make conclusive recommendations, our findings do highlight important issues in current ED management of paediatric CSE that need to be addressed.

Although constrained by these limitations, this study suggests that the existing experience of seizure management in children is not directly applicable to the child that presents to the ED in CSE. These children have important differences including the possibility of an already prolonged seizure that has failed to respond to standard anticonvulsant treatment. Although the standard algorithm is appropriate for the management of an undifferentiated group of children with seizures, it is important to recognize that children presenting to ED in metropolitan Australia are an already selected population. Further collaborative research is required to confirm these findings and explore alternative treatment, particularly for the high-risk group identified in this study.

Competing interests

None identified

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