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Commentary

Commentary on 'Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children', with a response from the review authors

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This is a commentary on a Cochrane review, published in this issue of EBCH, first published as: Appleton R, Macleod S, Martland T. Drug management for acute tonic-clonic convulsions including convulsive status epilepticus in children. *Cochrane Database of Systematic Reviews* 2008, Issue 3. Art. No.: CD001905. DOI: 10.1002/14651858.CD001905.pub2.

Further information for this Cochrane review is available in this issue of EBCH in the accompanying Summary article.

Commentary by David McGillivray, Peter Dayan and Martin Pusic

The treatment of an acute convulsion can be a life-saving intervention, especially in cases where the convulsion is likely to be prolonged or leaves the patient susceptible to aspiration or permanent neurologic damage (1). There is wide practice variation in the medications used to abort persistent tonic-clonic convulsions (we leave aside the treatment of partial complex status epilepticus).

The ambitious Cochrane review completed by Appleton *et al*. starts out by stating that 'benzodiazepines (midazolam, diazepam, lorazepam), phenobarbitone, phenytoin and paraldehyde may all be regarded as drugs of first choice in the management of acute tonic-clonic convulsions in children' (2). The task is then to determine which medication and route of administration leads to seizure cessation most rapidly without adverse side effects. The question is complicated given that six medications are considered along with multiple routes of administration that can change the pharmacokinetics of the medication. Further complicating study design is that fact that seizures with different clinical features may respond differently to medications. An investigator must consider whether to include patients with a narrow spectrum of seizure etiologies (e.g. febrile seizures) as opposed to including 'all-comers'. Additionally, efficacy and adverse event outcomes are not well standardized.

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The Appleton review assessed clinical trials in which different drug treatments for acute tonic-clonic convulsions in children were compared. They specifically excluded neonatal seizures but did not distinguish between seizure etiologies or aspects of prior seizure history, including whether the seizure was a first presentation or the latest of ongoing refractory seizures. The review is an update of an earlier Cochrane review carried out by the same group in 2002 (2). At that time, the only study identified was their own 102 patient quasi-randomized trial comparing lorazepam and diazepam. In the present update, they also include three recent studies, all randomized trials. This brings the total number of patients in the review up to 483, a relatively small number considering the frequency of this presentation.

The review has much to recommend it. The authors developed a review protocol *a priori* that defined well the types of participants, interventions and outcome measures they would include. The search was comprehensive and two investigators independently decided on which studies to include of the six their search identified. They do not report whether the two investigators agreed on all studies to include but they resolved any disagreements by discussion. While no quantitative validity criteria were used, the risks of bias are described for each trial including the type of randomization and blinding.

The authors found that: (a) lorazepam was more effective than diazepam both intravenously and rectally for stopping seizures (total $n = 86$ patients) and the use of lorazepam resulted in less respiratory

depression; (b) mucosal (intranasal or buccal) midazolam was as effective as intravenous diazepam [again, small number (52 seizure episodes) in the analysis] and is possibly more effective than rectal diazepam ($n = 219$ seizure episodes); and (c) that intranasal lorazepam is more effective than intramuscular paraldehyde ($n = 160$ seizure episodes). In comparing the medications, the main outcome used was 'seizure cessation'.

The Appleton review did not include several potentially noteworthy studies. Chamberlain *et al*. compared intramuscular midazolam with intravenous diazepam for treatment of 'motor' seizures lasting more than 10 min, with their main outcome variable being time to seizure cessation (3). They found that clinicians could administer the midazolam more quickly, which likely accounted for a decreased time to seizure cessation (7.8 min *vs* 11.2 min for diazepam). This study was excluded as it could not be determined if seizures were tonic, clonic, myoclonic or tonic-clonic. A randomized controlled trial by Shah *et al*. found similar results when they compared the same medications and routes (4). In a study of African patients published after the Cochrane update, Mpimbaza *et al*. randomized 330 patients to receive either rectal diazepam or buccal midazolam to patients who had convulsed for more than 5 min. Importantly, two-thirds of the patients had positive malaria smears (5). They found that buccal midazolam was appreciably more effective at stopping the seizure within 10 min in both the patients with and without malaria. As the optimal medication and route of administration remains uncertain, it is encouraging that investigators continue to conduct randomized trials that compare medications and routes of administration for the treatment of convulsions in children.

Most physicians use a benzodiazepine as their first line agent for tonic-clonic seizures. The Appleton review and others indicates that there is reasonable but not definitive evidence from randomized trials that lorazepam is preferred ahead of diazepam when the intravenous route is used (2,6). This question will be more definitively addressed by the PECARN research network in the US which is conducting a large randomized controlled trial comparing intravenous lorazepam with diazepam. In those individuals in whom intravenous access is not available, buccal or intramuscular midazolam are likely the preferred choices (Appleton, Prasad). The Appleton review points out that randomized controlled trials directly comparing intravenous lorazepam to midazolam are not available. However, the comparisons that are available do suggest that we can begin to simplify and standardize our approach to the acutely seizing child.

Ideally, the clinician could choose a single benzodiazepine to be used as a first line agent whether or not an IV is available. Given the relative heterogeneity of the research evidence, it is not surprising that review articles suggest several different possibilities for the initial treatment of status epilepticus. Standardization and simplicity of seizure protocols are important to allow for rapid treatment, avoidance of medication errors, ease of education of staff (nurses, pharmacists, physicians), and an in-depth familiarity of particular agents. Standardization also facilitates the cohesiveness of the treatment teams, including those in the EMS system, emergency department, and inpatient settings.

Midazalom may become the single agent of choice as it appears to both effectively stop seizures via several routes (intranasal, buccal, intravenous, and intramuscular) and does not have a worse adverse event profile compared to other agents (7,8). Definitive data do not exist, however, comparing midazolam to all other medications via all routes (e.g. intravenous lorazepam has not been compared to intravenous midazolam). The use of midazolam as a single agent has been considered by others (7,9). Brevoord *et al*. have previously suggested a simplified protocol for status epilepticus based on the use of midazolam and phenytoin (9).

Midazolam has other features that make it an excellent first line choice for status epilepticus. It is a medication that is very familiar to emergency medicine physicians, intensivists and anesthesiologists for use in procedural sedation, rapid sequence intubation, and status epilepticus. Intravenous midazolam infusion has been shown to be effective in the most worrisome patients, those with refractory status epilepticus unresponsive to the usual anticonvulsants (diazepam, lorazepam, phenytoin, and phenobarbital) (8,10–13). Midazolam as a single dose, or as an infusion, is able to stop refractory status epilepticus effectively (8,10–13). If midazolam is proposed as the medication to use after all others have failed, it would seem logical that it could be a good choice as a first line agent as long as there are no adverse side effects to its use.

In seizing patients without an intravenous at the time of presentation, the Appleton review and other studies support the choice of intranasal, buccal or intramuscular midazolam in terms of rapidity of seizure cessation. For patients with intravenous access, the current choice would appear to be lorazepam based on the available evidence though we have made an argument that midazolam could be chosen for this indication as well. We agree with the Appleton group that more research is required, with perhaps the most urgent comparison being between intravenous midazolam and intravenous lorazepam in order to confirm that midazolam should be the single agent of choice by any route. In future studies the goal of streamlining the treatment of tonic-clonic convulsions and status epilepticus, ideally with a single first line agent, should be a guiding principle.

Declarations of Interest

None.

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Response from the Review Authors

We appreciate the opportunity to respond to the Commentary on our Cochrane review published in 2008. We consider that this commentary provides a largely accurate interpretation of the Review although we would question the comment that 'several' noteworthy studies were not included, as in fact this was limited to only two [Chamberlain (1997) and Shah (2005)].

We would agree that any protocol or algorithm could (and should) be simplified if this were possible, and specifically to assess the role and use of midazolam as the preferred benzodiazepine primarily because of its multiple routes of administration and well-known (and accepted), effectiveness and safety profiles. However, lorazepam could also be considered as the preferred benzodiazepine based on the evidence of its effectiveness and safety using the intravenous, buccal and nasal routes of administration.

It would also be interesting, if not appropriate, to consider a randomized clinical trial (RCT) of intravenous phenytoin *vs* levetiracetam for those children who continue to seize after receiving a benzodiazepine, in view of the emerging efficacy and safety data of this latter anticonvulsant.

Finally, we are currently involved in reviewing the current protocol and algorithm for treating acute tonic-clonic convulsions (including convulsive status epilepticus) in children in the UK. This review will identify areas where data are limited and will lead to the design of one or more specific RCTs to address these deficiencies. It is important to emphasize that the original work of the UK Status Epilepticus Working Group (1) led directly to the study by McIntyre *et al*., which was subsequently published in 2005 (2).

Richard Appleton, Stewart Macleod and Timothy Martland.

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