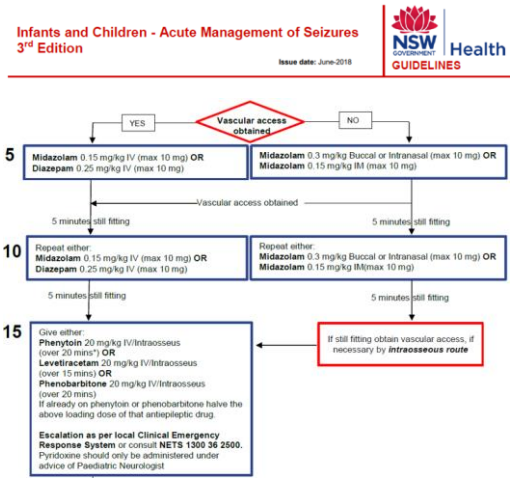
Clinical update no. 545
18 September 2019

Case vignette: 4yr girl presents by ambulance after call for a generalised seizure. There is no past history of note, and she is fully immunised. She was given midazolam IMI prehospital, but at 45 minutes from onset has not recovered and has a further seizure on arrival to ED. Temp 38.7 C, HR 175 bpm RR 18, BP 90/ 60 mm Hg BSL 4.2 mmol/L. She is given a second dose midazolam IMI but after a further 5 minutes is still seizing. What should be given next to control status?

seizure
European Journal of Epilepsy - The Official Journal of epilepsy action May 2019

The most common cause of status epilepticus in children is febrile SE, seen primarily in early childhood. SE is not uncommon and carries significant morbidity, mortality, and cost.



The algorithm is 2 doses benzodiazepines at 5 and 10 minutes, with a dose prehospital <1hr prior to ED arrival counted as a dose already given. Midazolam 0.15 mg/kg IMI is practical, with other alternatives described.

At 15 minutes a 2nd line agent is given. Anecdotally levetiracetam is increasingly used in preference to phenytoin, though supporting evidence is limited. The dose in the Guideline is 20 mg/kg, and its use is off label.

Levetiracetam 20 mg/kg IV/Intraosseous

Levetiracetam use in status epilepticus is "off label".

There are 2 new studies, from Australia and the UK, comparing phenytoin and levetiracetum in paediatric status. The data is informative as to efficacy and other aspects.

The Skeptics' Guide to EM

http://thesgem.com/2019/09/sgem265-total-eclipse-of-the-seizure-what-a-consept/ - link to discussion and papers

CLINICAL QUESTION: IS LEVETIRACETAM SUPERIOR TO PHENYTOIN AS A SECOND-LINE TREATMENT FOR CONVULSIVE STATUS EPILEPTICUS IN CHILDREN?

Articles

Levetiracetam versus phenytoin for second-line treatment of convulsive status epilepticus in children (ConSEPT): an open-label, multicentre, randomised controlled trial

the PREDICT research network

www.thelancet.com Vol 393 May 25, 2019

An Australian study, the ConSEPT trial, randomised 233 children 3mth – 16yr to

- 20 mg/kg phenytoin (IV/IO) over 20 min
- 40 mg/kg levetiracetam (IV/IO) - 5 min

The primary outcome was clinical cessation of seizure activity 5 min after the completion of infusion of the study drug; this happened in 60% given phenytoin group and 50% given levetiracetam group (p=016).

LEVETIRACETAM WAS FOUND NOT TO BE SUPERIOR TO PHENYTOIN.

Research in context

Implications of all the available evidence

This study provides the first robustly powered randomised comparison of phenytoin with levetiracetam in second-line management of paediatric convulsive status epilepticus. Although both drugs when given by themselves were associated with considerable failure rates, treatment with one drug followed by the other reduced the failure rate by more than 50%, adding only an additional 10 min to treatment time (compared with giving phenytoin alone). On the basis of the results of this study, and of earlier studies, clinicians should consider sequential use of phenytoin and levetiracetam, or levetiracetam and phenytoin, for second-line management of paediatric convulsive status epilepticus before moving on to the next standard of care, intubation.

Pheynotin and levetiracetam had similar efficacy, both controlling status in about half. However using one after the other gave seizure control in >70%, and using both may obviate the need for intubation which is the next step on the algorithm.

40 Rapid sequence induction

"*… Clinicians should consider sequential use of phenytoin and levetiracetam … before moving on to … intubation*".

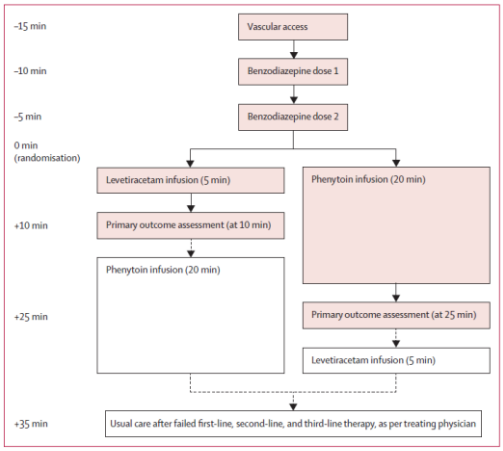


Figure 1: Study protocol

	Phenytoin group (n=114)	Levetiracetam group (n=119)
Age		
Mean age, years	4·0 (3·9)	3·8 (3·8)
≤5 years	82 (72%)	85 (71%)
History of current status epilepticus presentation		
Febrile	82 (72%)	87 (73%)
Focal onset	14 (12%)	14 (12%)
Median length of seizure before first study drug‡, min	74 (54–99)	72 (50–103)

Of note, about ¾ with status were <5yr and over 80% were febrile. There was a median >70 minutes seizure activity (up to100 min) before the study drug was given, a very long time and more than the 10 minutes needed to given 2 doses of benzodiazepines.

	Phenytoin group (n=114)	Levetiracetam group (n=119)
Clinical cessation of seizure activity at 2 h without further seizure management	62 (54%)	61 (51%)
Received alternative study drug in first 2 h	42 (37%)	48 (40%)
Clinical cessation of seizure activity at 2 h (receiving only one or both study drugs)†	89 (78%)	86 (72%)
Median time to clinical seizure cessation‡, min	22 (9–49)	17 (5–30)
Intubation		
Before first study drug	3 (3%)	2 (2%)
Within first 2 h	13 (11%)	21 (18%)
Subsequently during admission	5 (4%)	8 (7%)
Total	21 (18%)	31 (26%)

About 40% received the alternate study drug, with seizure cessation in about ¾ given both. Median time to seizure cessation was about 20 minutes; and about ¼ were intubated.

Adverse events were similar with "purple glove" syndrome in 1 patient given phenytoin.

Discussion

Levetiracetam was not superior to phenytoin as a second-line agent for convulsive status, with no difference in any safety outtcome. Previously reported success with levetiracetam of up to 90% was not confirmed.

Articles

Levetiracetam versus phenytoin for second-line treatment of paediatric convulsive status epilepticus (EcLiPSE): a multicentre, open-label, randomised trial

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https://www.thelancet.com/action/showPdf?pii=S0140-6736%2819%2930724-X

A UK study of 404 patients used a similar protocol and dosing regimen. About 40% were <2yr and 40% had a febrile convulsion; about 5% had CNS infection. The primary outcome was time to cessation of seizure. There was seizure cessation in 70% with levetiracetam group and 64% with phenytoin group with median time to cessation 35 min v 45 min (p=0·20). Levetiracetam could be an alternative to phenytoin though is no better, however has greater ease of administration.

	Levetiracetam (n=152)	Phenytoin (n=134)
Age		
6 months to <2 years	65 (43%)	53 (40%)
2–11 years	81 (53%)	74 (55%)
Seizure cause*		
Febrile convulsion	63 (41%)	58 (43%)
Seizure (pre-existing epilepsy)	46 (30%)	46 (34%)
First afebrile seizure	16 (11%)	12 (9%)
CNS infection	6 (4%)	7 (5%)

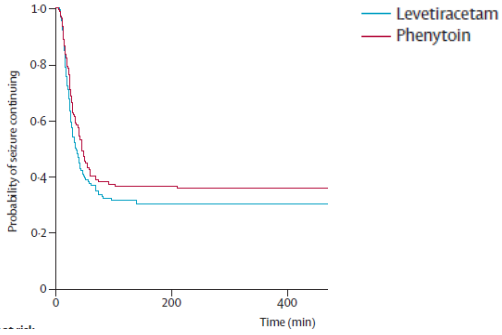

Figure 2: Kaplan-Meier curve for time to seizure cessation

These updates are a review of current literature at the time of writing. They do not replace local treatment protocols and policy. Treating doctors are individually responsible for following standard of care.