Title: The Use of Lorazepam for Febrile Seizures in Children

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Context and policy issues:

Febrile seizures are the most common form of childhood seizures, affecting approximately 2 to 5% of children. They usually occur between the age of 3 months and 5 years, with a peak incidence at 18 months. Febrile seizures are defined as “an epileptic seizure occurring in childhood after the age of 1 month, associated with a febrile illness not caused by an infection of the central nervous system, without previous neonatal seizures or a previous unprovoked seizure, and not meeting criteria for other acute symptomatic seizures”.

Lorazepam is a benzodiazepine with anticonvulsant properties. The injectable formulation (Ativan®) is approved in Canada for the initial management of status epilepticus. Given intravenous (IV) diazepam is an established benzodiazepine treatment for febrile seizures, information on the comparative efficacy of IV lorazepam in this population is required to determine which benzodiazepine can be stocked in community health centres providing urgent care to rural populations. Information on the efficacy of other routes of administration for lorazepam (e.g. nasal, rectal), as well as guidelines on the management of seizures before drug administration, would be useful in developing an initial management plan for children under age 12 years presenting with febrile seizures.

Research questions:

1. What is the comparative efficacy of IV lorazepam and IV diazepam for the treatment of febrile seizures in children (less than 12 years of age)?

2. Is there evidence that IV lorazepam may be administered by another route of administration (e.g. rectally, nasally) when there is no IV access to treat febrile seizures in children (less than 12 years of age)?

3. What are the guidelines for the treatment of febrile seizures before drug administration?
Methods:

A limited literature search was conducted on key health technology assessment (HTA) resources, including PubMed, OVID MedLine, OVID Embase, The Cochrane Library (Issue 4, 2007), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results are limited to English language publications only. A filter was used to search for guidelines for the treatment of febrile seizures in order to limit the retrieval to clinical practice guidelines. No other filters were applied to limit the retrieval by study type or start date. The end date of the literature search was January 2008. In addition to the evidence retrieved from the literature search, the lists of references of review articles identified through the literature search were reviewed to identify relevant studies.

Summary of findings:

Two relevant systematic reviews were identified from the literature search. The first systematic review retrieved was published in January 2008 by Fetveit. It addressed questions related to the overall assessment of febrile seizures in children. A small section of this systematic review addressed issues related to pharmacological treatment. Concerning lorazepam, Fetveit only cited findings from the Cochrane review published in 2002 by Appleton et al (and updated in 2005). Their conclusion was that there is no evidence to suggest that initial treatment with lorazepam is better than diazepam in treating acute tonic-clonic convulsions including status epilepticus. Given the lack of information on lorazepam in the review by Fetveit, findings from the Appleton et al review will be discussed.

The Cochrane review by Appleton et al searched three databases [CENTRAL – Epilepsy Group register], MEDLINE and EMBASE]. In addition, relevant reports were identified by hand searching selected journals and conference proceedings. Key criteria for considering studies included study types [randomized, quasi-randomized, and non-randomized design (blinded or unblinded)] and types of participants (children aged one month to 16 years presenting to the hospital with an acute tonic-clonic convulsion, regardless of the cause). Two of the authors independently assessed trials for inclusion and extracted data. Disagreements were resolved by discussion. Using the checklist for review articles from Oxman, the quality score of the systematic review by Appleton et al was 4/7, that is minor flaws are likely to be present.

Only one trial met the inclusion criteria of this systematic review. It was a one year, unblinded quasi-randomized study comparing lorazepam to diazepam (either given intravenously or rectally). A total of 102 participants were enrolled. Of the 86 participants who were included in the analysis, 19 had febrile seizures. Therefore a limitation of this review is that findings may not be directly generalizable to the febrile seizure population. In the original article, authors conducted the statistical analysis grouping both the IV and rectal routes of administration. Overall, more patients using diazepam [17 out of 53 (31%)] required the use of another antiepileptic drug to abate the initial seizure than those using lorazepam [1 out of 33], p < 0.001. Differences in the other outcome measures (i.e., multiple doses of benzodiazepine, recurring seizures within 24 hours) did not reach statistical significance. In the Cochrane review, statistical analyses were conducted for individual routes of administration. Statistical significance was not reached for any of the individual outcome comparisons except for the cessation of the presenting seizure. For this particular comparison, a single dose of rectal lorazepam stopped the initial seizure in six of six participants, compared to six of 19 participants treated with rectal diazepam [relative risk (RR) = 3.17, 95% confidence intervals (CI) = 1.63, 6.14]. However, given the limitations of this study (unblinded and quasi-randomized design, unbalanced number of patients between the lorazepam and diazepam treatment groups),
authors of the Cochrane review concluded that there is no definitive evidence supporting the use of IV or rectal lorazepam as first-line treatment for status epilepticus in children, compared to using IV or rectal diazepam.⁴

In addition to above review, a number of other comparative studies were retrieved. In a prospective study using a before and after design, Qureshi et al compared the efficacy of IV lorazepam and IV diazepam in 48 children presenting to the emergency department in a British hospital.⁷ In the first 6-month period, 17 children were treated with IV diazepam while 33 patients seen in the second 6-month period were treated with IV lorazepam. Of these, a total of 15 children presented with febrile seizures. The primary outcome measure was successful treatment (defined as seizure stopping within 15 minutes of initiating treatment). Overall, the same proportions of patients were successfully treated in both treatment groups (65% for IV lorazepam vs 65% for IV diazepam). Comparison of the other treatment outcomes (duration of seizure, time to seizure cessation after IV cannula inserted, number of patients requiring a second dose, latency to seizure cessation after single IV dose and proportions of patients requiring intensive care treatment) did not reveal any statistically significant differences between the IV lorazepam and the IV diazepam groups.⁷ In interpreting these results, the following limitations should be considered: this was an observational (non-randomized/unblinded) study and the number of participants was small and unbalanced between the treatment groups. Also, given only a third of participants had febrile seizures, generalizability of these findings to the population of interest is limited.

A third comparative study evaluated the efficacy of IV lorazepam versus IV diazepam in children aged 2 weeks to 18 years.⁸ This was a retrospective chart review of 44 patients (45 episodes of status epilepticus) discharged from a US hospital. Of these, 27 episodes were treated with lorazepam and 18 with diazepam. Effectiveness was defined as the cessation of seizure activity within 15 minutes of the benzodiazepine administration. Overall, diazepam terminated status epilepticus in 11 of 16 (69%) episodes (2 episodes excluded from the analysis as a non-benzodiazepine drug was also used). Lorazepam use resulted in 18 of 22 episodes of status epilepticus (82%) ceasing. This difference was not statistically significant. Interpretation of these findings needs to account for a number of limitations: i) the retrospective review design of this study does not demonstrate a direct association between the intervention to observed effect, ii) the number of patients was small and unbalanced between the two treatment groups, which augments the amount of uncertainty relative to the robustness of the findings, iii) fever was the cause of only 12 of the 45 seizure episodes, therefore limiting the generalizability of these findings to the febrile seizure population.

In addition to the efficacy in controlling the seizures, another important clinical parameter to consider in treating children with benzodiazepines is their associated risk of respiratory depression, potentially resulting in the need for endotracheal intubation.⁹ In the publications cited above, lorazepam appeared to have a slight advantage over diazepam. Appleton et al reported a lower incidence of respiratory depression occurred in the lorazepam-treated group [1 out of 27 (4%)] compared to the diazepam-treated group [7 out of 34 (21%)], although this difference did not reach statistical significance (RR = 0.18, 95% CI = 0.02 to 1.37).⁴ The same non-statistically significant trend was also reported by Giang et al; 25% of patients treated with lorazepam required mechanical ventilation following treatment with lorazepam versus 36% for diazepam.⁸ In addition to these two studies, Chiulli et al performed a retrospective chart review of 38 consecutive cases of children (< 16 years of age) admitted to a university hospital emergency department for seizures or status epilepticus.⁹ Among these, 21% were admitted for febrile seizures. Of all children, 45% underwent endotracheal intubation. Excluding patients who received phenobarbital concurrently (because these are at risk of profound respiratory depression), four out of 15 (27%) patients treated with lorazepam alone or with phenytoin had...
endotracheal intubation compared to eight out of 11 (73%) patients treated with diazepam alone or with phenytoin \((p = 0.026)\) demonstrating a greater risk with diazepam. However, in another retrospective review of 40 children treated with either lorazepam or diazepam for seizures (total of 56 prolonged seizures) in the emergency department of a Canadian hospital, Stewart et al reported problems with respiratory depression in 9 children (11 seizures).\(^{10}\) Excluding three cases unrelated to medication use (intracranial hemorrhage, respiratory acidosis prior to medication use), data from six patients showed that eight out of 56 (14%) seizure events were associated with worsening respiratory depression. Of these, there was one out of 19 events treated with diazepam (5%), six out of 30 events treated with lorazepam (20%), and one out of seven events treated with both drugs. In six out of eight events, multiple doses of benzodiazepine were administered. Authors concluded that multiple small doses of lorazepam increases the risk of respiratory depression in the management of prolonged seizures.\(^{10}\) In interpreting the findings from the study by Chiuli et al and the study by Stewart et al, the following limitations need to be considered: the design of both studies is based on a retrospective chart review which does not demonstrate a direct association between interventions and effects, the number of participants was small, 21% of patients in the Chiuli et al study had febrile seizures whereas none had this condition in the Stewart et al study, which limits the generalizability of these findings to the population of interest.

In addition to the systematic reviews and individual studies identified above, one recent set of clinical guidelines for the management of febrile seizures was retrieved.\(^3\) These guidelines were published in 2002 by the Hong Kong College of pediatricians. Authors of the guidelines adapted the definition of levels and types of evidence from the US Agency for Health Care Policy and Research 1992 [Level I evidence being the highest level of evidence available (meta-analysis of randomized controlled trials) and Level IV evidence being the lowest level (evidence obtained from expert committee reports or opinions and/or clinical experience of respected authorities)]. Concerning the acute management of febrile seizures, the following recommendations were made:

- Maintain a clear airway*
- Protect the child from injury*
- Place the child in a semi-prone position*
- Loosen clothing or remove excess clothing*
- Give oxygen is available*
- Apply suction for nasal or oral secretions if facility available*
- Treat fever by sponging with tepid water and antipyretics (e.g. acetaminophen)*

* Level 1b recommendations
- Monitor vital signs**
- If convulsion > 5 minutes, administer rectal diazepam**
- If convulsion > 15 minutes, administer IV anticonvulsant (preferably in the following order: diazepam, lorazepam, phenobarbital)**

** Level IV recommendations

With respect to alternative routes of administration, apart from the Appleton et al trial published in 1995, in which rectally administered diazepam was compared to rectally administered lorazepam, most of the evidence available is non-comparative. Prior to the Appleton et al study, Dooley et al evaluated the effect of lorazepam administered rectally to eight children with epilepsy. Authors reported that seizures were controlled in all children after one dose.\(^{11}\) Yager and Seshia evaluated the efficacy of sublingual lorazepam in 10 children with intractable epilepsy.\(^{12}\) The medication was administered at home under the supervision of parents. Authors reported that eight patients had a good response (defined as cessation of seizures) whereas
two had a partial response (defined as a reduction in the frequency or severity of seizures). Limitations of these studies include their non-comparative and unblinded design as well as the small number of participants. Also, it does not appear that any of the enrolled participants had febrile seizures. Finally, Ahmad et al recently compared intranasal lorazepam to intramuscular paraldehyde in 160 children with seizures persisting for more than five minutes.\textsuperscript{13} This was a randomized unblinded prospective trial in a pediatric emergency department of a tertiary care hospital in Malawi, in sub-Saharan Africa. Authors reported that intranasal lorazepam stopped convulsion within 10 minutes in 75\% (60 out of 80) of seizure episodes whereas intramuscular paraldehyde led to seizure cessation in 61\% (49 out of 80) of episodes, \textit{p} = 0.06.\textsuperscript{13} Interpretation of these findings should account for the fact that seizures were exclusively due to acute central nervous system infection (cerebral malaria or bacterial meningitis) in about two-third of the study participants. Patients for whom convulsion was attributed to fever were excluded. Therefore, the generalizability of these findings to patients with febrile seizures may be comprised.

Conclusions and implications for decision or policy making:

Evidence available on the comparative efficacy of IV lorazepam and IV diazepam in children with febrile seizures is limited both in terms of quantity and quality. The total population enrolled in the three studies\textsuperscript{6-8} which compared the efficacy of the two drugs was small (\textit{n}=178) among which only 46 had febrile seizures. The design of these studies does not control for observed effects to be the result of chance alone, as opposed to the drugs. Acknowledging these limitations, the available evidence suggests that there is no important difference in the effect of IV lorazepam, compared to IV diazepam, for the acute management of febrile seizures. It is unclear whether the use of IV lorazepam is associated with a potential advantage or disadvantage in terms of risk of respiratory depression. The 2002 guidelines on the management of febrile seizures published by the Hong Kong College of pediatricians appear to be consistent with these findings as IV lorazepam is recommended as second-line therapy. Evidence available on alternative routes of administration (intranasal, sublingual and rectal) may be considered preliminary at this time.

Overall, there is no conclusive evidence to suggest that IV lorazepam is superior or inferior to IV diazepam for the initial pharmacological treatment of children with febrile seizures. This conclusion applies to both clinical benefit (seizure control) and harm (risk of respiratory depression). In either case, close monitoring of the patient to evaluate the need to repeat the initial dose of benzodiazepine and assess the respiratory status is required. Given the limitations of the currently available evidence, we can not rule out that this conclusion could change, should new comparative studies be published in the future. It should also be noted that convenience (vials of lorazepam injection need to be refrigerated, diazepam for rectal use is available as a commercially available product (Diastat® - Shire BioChem) and economic considerations were not included in this assessment. These may also need to be considered in determining the benzodiazepine of choice for the initial management of children with febrile seizures in a particular practice setting.

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References:


