Benzo Versus Benzo: And the Winner Is…

Intranasal Versus Intravenous Lorazepam for Control of Acute Seizures in Children: A Randomized Open-Label Study.

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PURPOSE: Intravenous lorazepam is considered the drug of first choice for control of acute convulsive seizures. However, resource or personnel constraints necessitate the study of alternative routes and medications. This study compared the efficacy and adverse effects of intranasal versus intravenous lorazepam in children aged 6–14 years who presented with acute seizures. METHODS: This was a randomized open-label study conducted at an Indian hospital from August 2008 to April 2009. One hundred forty-one consecutive children aged 6–14 years who presented convulsing to the emergency room were included. After stabilization, the children were randomized to receive either intravenous or intranasal lorazepam (0.1 mg/kg, maximum 4 mg). The primary outcome measure was clinical seizure remission within 10 min of drug administration. The study was registered with clinicaltrials.gov (NCT00735527). KEY FINDINGS: Seventy patients were randomized to receive intravenous and 71 to receive intranasal lorazepam. The patients in the two groups were comparable at baseline. Clinical seizure remission within 10 min of drug administration was found in 80% of the intravenous group as compared to 83.1% of intranasal group. The lower limit of 95% confidence interval for effect size was approximately −9.7%, with an a priori cutoff for noninferiority of −10%. SIGNIFICANCE: Intranasal administration of lorazepam is not found to be inferior to intravenous administration for termination of acute convulsive seizures in children.

Recently there has been a renewed interest in optimizing the use of benzodiazepines for acute treatment of seizure clusters, status epilepticus, or both in either the inpatient or outpatient setting. A number of different benzodiazepines as well as different routes of administration have been pitted against each other. Studies have compared rectal diazepam versus intranasal and buccal midazolam, intravenous lorazepam versus intravenous diazepam, and buccal midazolam versus intravenous diazepam, to name a few (1–4). The current study takes a slightly different tack, as it compares two different routes of administration of the same benzodiazepine, namely, lorazepam. The authors selected lorazepam for their study based on results from the Veterans Affairs status epilepticus study, which demonstrated that lorazepam was significantly superior to phenytoin in stopping status epilepticus, as well as the study of intravenous lorazepam versus diazepam, which showed that lorazepam was superior in the out-of-hospital setting (4, 5). The present study shows no difference between intravenous and intranasal administration in the ability to stop seizures within 10 minutes.

There are a few issues with the present study that need to be taken into account when assessing the outcome. First, the authors made the interesting choice of using time of administration rather than time of decision to treat as the starting point. In a recent study comparing intravenous diazepam with intranasal midazolam, the time of emergency room admission was used to highlight the point that intravenous access may take time to achieve; therefore, seizures may continue for a longer time (6). In the current study, not only did it take a median of 4 minutes and up to 25 minutes to achieve peripheral venous access, but one child was considered to have a "protocol violation" because venous access could not be achieved within 10 minutes. The decision of whether to count this time or not depends on the intent of the study. Pragmatically, to a treating physician, the most important number would be the time from when the patient enters the emergency room to when seizures cease, and it would seem that in this study in particular, when two routes of administration of the same drug were compared, the above might be the most relevant outcome.

Why compare two routes of administration of the same drug? There are many things to consider when addressing which benzodiazepine would be optimal when treating acute seizures. The first, as indicated above, is the time necessary to actually deliver a drug to the patient. The second, is the amount of time it takes for the drug, once delivered, to reach its intended target in the central nervous system. Notably, this time depends on both the benzodiazepine selected, as well as its route of administration. What many people do not realize, is that benzodiazepines differ in their physiochemical characteristics, and these differences may make one benzodiazepine optimal under some circumstances but less optimal under others. Lorazepam is an excellent case in point. Lorazepam

Epilepsy Currents, Vol. 11, No. 5 (September/October) 2011 pp. 143–144
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is preferred for the treatment of status epilepticus because of its ability to suppress seizures over a relatively extended period, which reduces the likelihood of relapse. Compared with the other benzodiazepines, diazepam and midazolam, lorazepam has a slower redistribution from the brain owing to lower lipid solubility and also has a reasonably long half-life (7). Thus, with intravenous administration, it is an excellent choice for treatment of status epilepticus. However, the very characteristics that make it the champion under these circumstances (its lower lipid solubility) may make it a less optimal choice for intranasal administration. It is likely that, since lipid solubility is an important characteristic for getting a drug across a mucous membrane such as the nasal cavity, intranasal lorazepam would have a slower rate of absorption and onset of action than its cousins, midazolam and diazepam. Yet, in this study, the time to seizure cessation after intranasal administration was similar to the intravenous route. Is this "proof" that lorazepam is indeed a good choice for intranasal administration? While this study is promising, there are some important reasons why the results may not be definitive. First, the study selected children who "presented convulsing to the emergency room or develop a seizure during an ER stay." Since patients were not required to be in status epilepticus to be enrolled in the study, it is possible (or maybe even likely) that their seizures would have ceased even without administration of a benzodiazepine. In the absence of a placebo arm, this cannot be known. Second, fully half of the children in this study, which was performed in India, were having seizures as a result of neurocysticercosis. Thus, it is unclear whether the results would be generalizable to other populations.

The choice of the ideal benzodiazepine will depend on the speed at which therapy must be initiated, the necessity for prolonged protection against seizures, the use in the emergency room versus by patients or caregivers at home, and the ease of use of a given formulation. It is quite likely that the optimal benzodiazepine may differ depending on situation and user. Thus, it is to be hoped that different formulations of a number of benzodiazepines will be available in the future.

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