Intravenous Clonazepam in Status Epilepticus

Practice Variability and Efficacy of Clonazepam, Lorazepam, and Midazolam in Status Epilepticus: A Multicenter Comparison.

Alvarez V, Lee JW, Drislane FW, Westover MB, Novy J, Dworetzky BA, Rossetti AO. *Epilepsia* 2015;56:1275–1285.

OBJECTIVE: Benzodiazepines (BZD) are recommended as first-line treatment for status epilepticus (SE), with lorazepam (LZP) and midazolam (MDZ) being the most widely used drugs and part of current treatment guidelines. Clonazepam (CLZ) is also utilized in many countries; however, there is no systematic comparison of these agents for treatment of SE to date. METHODS: We identified all patients treated with CLZ, LZP, or MDZ as a first-line agent from a prospectively collected observational cohort of adult patients treated for SE in four tertiary care centers. Relative efficacies of CLZ, LZP, and MDZ were compared by assessing the risk of developing refractory SE and the number of antiseizure drugs (ASDs) required to control SE. RESULTS: Among 177 patients, 72 patients (40.62%) received CLZ, 82 patients (46.33%) LZP, and 23 (12.99%) MDZ; groups were similar in demographics and SE characteristics. Loading dose was considered insufficient in the majority of cases for LZP, with a similar rate (84%, 95%, and 87.5%) in the centers involved, and CLZ was used as recommended in 52% of patients. After adjustment for relevant variables, LZP was associated with an increased risk of refractoriness as compared to CLZ (odds ratio [OR] 6.4, 95% confidence interval [CI] 2.66-15.5) and with an increased number of ASDs needed for SE control (OR 4.35, 95% CI 1.8-10.49). SIGNIFICANCE: CLZ seems to be an effective alternative to LZP and MDZ. LZP is frequently underdosed in this setting. These findings are highly relevant, since they may impact daily practice.

Commentary

Status epilepticus (SE) is a major neurologic emergency that is associated with case-fatality rates ranging from 3% to 39% across studies (1), leading to 55,000 deaths per year in the United States (2). Prompt treatment of SE correlates with better outcome (3), and numerous studies have led to the recommendation that benzodiazepines (BZD) should be administered as a first-line treatment. However, there is little agreement as to which benzodiazepine and route of administration are best. Different studies have compared different BZDs and routes of administration, with notable heterogeneity in the utilized methodology and major paucity of data about clonazepam (CLZ). The RAMPART study, for example, compared midazolam (MDZ), given through an intramuscular autoinjector, with intravenous lorazepam (LZP) given by the paramedics prior to arrival to the emergency department, concluding superiority of MDZ (4). Other studies analyze similarly collected data to either evaluate a particular benzodiazepine, a particular route of administration, or both. A recent such study performed a network meta-analysis of nonvenous drugs used in randomized controlled trials for treatment of SE (5). The authors aimed at ranking in one network the efficacy in seizure cessation within 10 minutes of sublingual LZP, buccal MDZ, intrananasal MDZ, rectal diazepam, and IV diazepam; they concluded that IM and intranasal MDZ resulted in the fastest and most persistent seizure termination. Obviously, the study did not include CLZ due to lack of data.

As such, many studies have offered a number of potential choices of BZD and routes of delivery as first lines in SE. MDZ is commonly used in Britain, while LZP continues to be very commonly used, though notoriously underdosed, in the United States. Class I evidence exists for LZP and MDZ but not CLZ. Nevertheless, the continental Europeans commonly use CLZ in SE. CLZ has many attributes that make it an excellent alternative for initial treatment of SE. Although it has less affinity to the $GABA_A$ receptor than LZP (6), it is lipophilic and has a rapid onset of action, with evidence of more rapid entry to the brain after intravenous administration than LZP (7). In addition, its long elimination half-life (typically 30 to 40 hours) is particularly important for rapid initial treatment of SE and for reducing the chances of recurrence in the acute setting. CLZ (0.015 mg/Kg) can also be administered as a rapid bolus over 30 seconds or less, which is faster than the rate of LZP demonstration (2 mg/min). While these are attractive attributes, there are no randomized clinical trials to support the use of CLZ in SE.

Alvarez et al. conducted a prospective observational study at one center in Lausanne, Switzerland, and three centers in Boston (7). Intravenous CLZ was the first-line treatment for SE in Switzerland, and intravenous LZP was first line in the Boston hospitals. In all centers, MDZ was an alternative treatment. The authors defined SE as continued seizures or repetitive

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seizures without intervening recovery of consciousness for five minutes or longer, and outcome measures included the risks of developing refractory SE, and the number of antiseizure medication (ASM) needed to control SE. The authors included 177 patients in this study, 72 (41%) of whom received CLZ, 82 (46%) received LZP, and 23 (13%) received MDZ as first line. Some of the strengths of this study include the fact that the patients were consecutive, continuous EEG was obtained for all subjects in the United States and for some subjects in Switzerland, and all three groups were similar in terms of the characteristics of SE, postanoxic SE excluded. In particular, the etiology and severity of SE were comparable across the three groups, as was the median time to treatment.

Interestingly, the authors found that only 75% of patients received a benzodiazepine as a first-line treatment for SE; among these, 59% received insufficient doses. The adequacy of the loading dose of the first-line benzodiazepine was different among the three groups. The loading dose was considered sufficient more frequently in the CLZ group than in the other two groups ($p < 0.001$). Subjects in the LZP group had longer duration of SE ($p = 0.003$), and were significantly more likely to become refractory ($p < 0.001$), requiring more ASMs to control SE than did the other two groups. Even after adjustment for the loading dose, the risk of SE refractoriness continued to be higher with LZP than with CLZ (OR 6.4, 95% CI 2.66–15.5, $p < 0.001$), with no difference between CLZ and MDZ. In a subgroup analysis of generalized convulsive SE, similar results were obtained with LZP resulting in more refractoriness and higher number of ASMs needed to control SE. Mortality was related to the etiology and severity of SE but was neither different among the three groups nor influenced by second-line treatments.

This study is particularly helpful for a number of reasons. Importantly, it alerts regarding inconsistent adherence to treatment guidelines by administering a BZD as first line and to the commonness of underdosing BZDs when used. Additionally, it suggests that CLZ may be an appropriate first-line treatment in SE and may even be superior to LZP, for which a huge body of data exists. Instead of the recommended 0.15 mg/Kg initial dose of LZP, physicians commonly administer smaller (e.g., 2-mg) boluses to adults with SE, planning to repeat if no seizure cessation is achieved. Obviously, this deviation from the recommended dose is likely to compromise the outcome, and it may be driven by the fear of respiratory depression, especially in the elderly. With CLZ, the recommended dose of 0.015 mg/Kg may be easier to adhere to as it is highly unlikely to result in respiratory depression. This dose amounts to only 1 mg in an average adult. In the placebo-controlled clinical trials of CLZ, done over 6 to 9 weeks and including doses of 3 mg or more, there was no respiratory depression (7). In these trials, the route of administration was oral, but CLZ has oral bioavailability of 80 to 90 percent. Although a class I evidence remains lacking to prove that IV CLZ is better than good enough in SE, the current study should encourage the design and conduction of a randomized trial and may herald the debut of CLZ as a first-line treatment in SE in the United States.

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