Intramuscular versus Intravenous Benzodiazepines for Prehospital Treatment of Status Epilepticus

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Acute seizures account for 1% of adult and 2% of pediatric emergency department visits, at an annual cost of $1 billion (in U.S. dollars). When seizures are prolonged or repetitive without recovery between episodes, the condition is termed status epilepticus, and it occurs in approximately 6% of visits to the emergency department for seizures. The cost for inpatient care of patients in status epilepticus has been estimated to be $4 billion (in U.S. dollars) annually. Although the term “prolonged” was previously used to refer to seizures lasting 30 minutes or longer, this interval has been shortened to 5 to 10 minutes in recent studies. This change occurred for several reasons. First, almost all convulsive seizures in adults cease in less than 5 minutes without treatment; seizures lasting longer than this are more likely to be self-sustained and to require intervention. Second, the longer seizures persist, the harder they are to terminate pharmacologically. Third, outcome tends to correlate with seizure duration even after one controls for other factors. Mortality among patients who present in status epilepticus is 15 to 22%; among those who survive, functional ability will decline in 25% of cases.

A little more than half the cases of epilepsy have an acute, symptomatic cause (e.g., acute brain injury, metabolic dysfunction, or ethanol withdrawal). About 25% of patients in status epilepticus will not respond to initial treatments. After convulsive movements cease, seizure activity will continue to appear on electroencephalography over the subsequent 24 hours in 48% of patients. Thus, if patients do not wake up shortly after their convulsive movements cease, nonconvulsive seizures should be considered, and an electroencephalogram should be obtained as soon as possible.

The first-line treatment for convulsive status epilepticus is a benzodiazepine, typically intravenous lorazepam, a choice based largely on the results of the 1998 Veterans Affairs Cooperative Status Epilepticus Study. In 2001, a landmark study on prehospital treatment of status epilepticus was published in which patients were randomly assigned to treatment with lorazepam, diazepam, or placebo administered intravenously while they were en route to the hospital. Successful termination was much more common in the two groups that received benzodiazepines (59% with lorazepam, 43% with diazepam, and 21% with placebo). Since respiratory distress was twice as common in the group given placebo as in either of the groups given a benzodiazepine, the best way to avoid the need for intubation is to stop seizure activity.

In this issue of the Journal, Silbergleit et al. present the results of the RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial). This study involved 79 hospitals and more than 4000 paramedics, as well as the use of intramuscular autoinjectors and automatic time-stamped voice recorders, and the subjects were excepted from informed consent. Ultimately, 893 subjects with convulsive seizures lasting longer than 5 minutes were randomly assigned to either intravenous lorazepam plus intramuscular placebo or intravenous placebo plus intramuscular midazolam. Success was defined as cessation of clinical seizure activity and lack of additional rescue medication before arrival in the emergency department. The goal was to show noninferiority of intramuscular midazolam.

Results showed that intramuscular midazolam not only was noninferior but was superior to intravenous lorazepam, with successful ter-
mination of seizures in 73.4% subjects in the intramuscular-midazolam group versus 63.4% in the intravenous-lorazepam group (P<0.001 for both noninferiority and superiority). This difference was due to the more rapid administration of the intramuscular medication (1.2 minutes, vs. 4.8 minutes with the intravenous route). This more rapid administration outweighed the faster cessation of seizures with intravenous administration once it was given (1.6 minutes, vs. 3.3 minutes with the intramuscular route). In those for whom seizures ceased prior to arrival in the emergency department, the overall median time to cessation of convulsions was not significantly shorter in the intramuscular-midazolam group (about 5 minutes, vs. 7 minutes with the intravenous route). Intubation was required in 14% of both groups, and other adverse events were also similar. The rate of hospitalization was lower in the intramuscular-midazolam group, as compared with the intravenous-lorazepam group (57.6%, vs. 65.6%; relative risk, 0.88).

Other trials have shown a more rapid response with nonintravenous administration of benzodiazepines than with intravenous administration. In a small trial of children with prolonged motor seizures, cessation was achieved more quickly with intramuscular midazolam than with intravenous diazepam (8 minutes vs. 11 minutes, P=0.047).12 Multiple studies have shown that nasal or buccal midazolam stops seizures faster than rectal or intravenous diazepam13 and is absorbed faster than intramuscular midazolam.13-15 However, there may be issues with reliable and consistent delivery or absorption with the buccal and nasal routes, as compared with the intramuscular route. For this reason the intramuscular route was chosen for RAMPART, in addition to paramedics’ familiarity with the use of intramuscular medication.

What’s next in this field? Home treatment with nasal or buccal benzodiazepines will soon be widely available and may help prevent status epilepticus and visits to the emergency department for patients who are at risk for prolonged or repetitive seizures (“clusters”). A comparison between the intramuscular and nasal or buccal routes for administering midazolam is needed, as is more research to determine the next step when first-line treatment fails, including the possible usefulness of combinations of medications and neuroprotective agents. Finally, seizure anticipation or warning systems are under development that may allow abortive treatment — perhaps in an automated manner — even before clinical seizure activity occurs. Thus, the future of care for seizure emergencies is quite bright. The study reported by Silbergleit and colleagues is an important step in this direction. As soon as a practical intramuscular autoinjector for midazolam becomes widely available, the findings in this study should lead to a systematic change in the way patients in status epilepticus are treated en route to the hospital.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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