Prehospital Treatment of Status Epilepticus with Benzodiazepines Is Effective and Safe

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Benzodiazepines are an effective and safe treatment of status epilepticus and serial seizures when used in an out-of-hospital setting. Intravenously administered lorazepam is somewhat superior to diazepam for the treatment of status epilepticus. Treatment of status epilepticus should be initiated when seizures have lasted 5–7 minutes.

Introduction

Emergency medical service (EMS) personnel [note that EMS personnel include EMTs (Emergency Medical Technicians), paramedics, and firemen (who can be EMTs or paramedics)] are often the first medical professionals to encounter patients in status epilepticus. In many jurisdictions, the paramedics are permitted to administer intravenous benzodiazepines to treat status epilepticus while in other places treatment is deferred until arrival in the emergency department due to concern over the potential risks of out-of-hospital therapy. Administration of intravenous benzodiazepines to patients in status epilepticus carries a risk of hypotension and respiratory depression. Intravenously administered lorazepam was reported to cause hypotension in 25–59% of patients and respiratory depression in 10–12% of patients in a Veteran's Administration cooperative study of treatment of status epilepticus (1). In addition, one retrospective study suggested that 43% of seizures lasting 5–29 minutes end spontaneously without treatment (2). If seizures are likely to end spontaneously, patients treated early may be exposed to an unnecessary risk due to medications. Out-of-hospital treatment of status epilepticus carries additional risks because paramedics operate in an environment that lacks many of the diagnostic, treatment, and monitoring facilities frequently used to manage status epilepticus (3). Several out-of-hospital interventions and therapies with rational bases have either failed to show benefit or caused harm to patients in carefully designed clinical trials (4).

There are potential benefits of out-of-hospital treatment of status epilepticus. If the duration of status epilepticus can be shortened by early treatment, systemic and neurological complications of prolonged seizures may be prevented. Status epilepticus can cause pulmonary congestion and edema, cardiac arrhythmias, hypotension, elevation of body temperature, hypoglycemia, acidosis, and rhabdomyolysis. These systemic complications tend to worsen as the duration of status epilepticus lengthens (5,6). Prolonged status epilepticus can also lead to neuronal damage and loss (7). There is growing evidence from experimental animals that the extent of neuronal injury due to status epilepticus is linked to the duration of the seizures (8,9). A delay in treatment may also contribute to the refractoriness of status epilepticus (1,10,11). Mortality associated with status epilepticus also correlates with the duration of the seizures (12).

PHTSE Study

The pre-hospital treatment of status epilepticus (PHTSE) study was designed to determine whether intravenous administration of benzodiazepines by paramedics in the out-of-hospital setting is safe; and whether control of status epilepticus prior to arrival in the emergency department influences the patient's subsequent course (3). Patients, 18 years or older, reliably witnessed to have continuous or repetitive seizure activity without regaining consciousness for five minutes, and who were still seizing or unconscious between seizures at the time of paramedic arrival, were randomized to intravenous placebo, lorazepam (2 mg), or diazepam (5 mg). All medication doses were repeated once if necessary. The patients randomized to the three groups were similar with regard to age distribution, gender, or cause of status epilepticus. However, race or ethnic group were unevenly distributed and the time interval between seizure onset and administration of study drug was significantly longer in the placebo group than in the active treatment groups. In subsequent regression analysis these variables did not significantly affect the outcome.

The PHTSE study clearly establishes that the benefits of out-of-hospital treatment of status epilepticus with intravenous benzodiazepines outweigh its risks (4). Status epilepticus was terminated by the time of arrival at the emergency department

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in 50.7% (68 of 134) of the patients treated with either intravenous diazepam or lorazepam compared to 21.1% (15 of 71) of the patients given placebo. There was a trend toward a lower rate of cardiorespiratory complications in the patients treated with benzodiazepines (10.4%, 14 of 134 patients) than those receiving placebo (22.5%, 16 of 71 patients). The study also emphasizes the importance of terminating status epilepticus as soon as possible. Patients in status epilepticus on arrival at the emergency department were more likely to be admitted to an intensive care unit than those whose seizures were terminated prior to hospital arrival (73% versus 32% likelihood odds ratio chi-square < 0.001). Since the causes of status epilepticus were similar for these two groups, it is likely that the higher rate of admission to intensive care units in patients who were in status epilepticus at the time of arrival at the emergency department was related to ongoing seizures.

Definition of Status Epilepticus

The results of the PHTSE trial and a recent prospective study of new-onset seizures in children (13) strongly emphasize that seizures lasting more than 5–10 minutes need to be treated as status epilepticus. The definition of status epilepticus used in the PHTSE study—continuous or repetitive seizure activity without regaining consciousness for five minutes—called for a shorter duration of seizures than the 30-minute definition employed in epidemiological studies (2). A proposal to change the definition of status epilepticus (14) has generated debate (15) and new studies. In the PHTSE study, 79% (55 of 71) of patients given placebo were still seizing at the time of arrival at the emergency department. These observations suggest that, in adult patients, seizures lasting more than five minutes are unlikely to end spontaneously.

Prospective studies in children also suggest that if a seizure continues for more than seven minutes, it is unlikely to end soon spontaneously. Shinnar and colleagues (13) studied the duration of first unprovoked, afebrile seizures in 407 children. The group included children who had suffered from neonatal seizures, febrile seizures, posttraumatic seizures, or other provoked seizures. The total seizure duration was measured and a study of the distribution of seizure duration suggested two populations of patients. One group constituted 76% of the total study population and had a mean seizure duration of 3.6 minutes; the second group constituted 24% of the population and had a mean seizure duration of 31 minutes. The data were further analyzed to define the likelihood that a seizure was likely to terminate in next several minutes after it had lasted certain time by hazard analysis (see the study for details). This analysis demonstrated that the longer a seizure lasted, the less likely it is to spontaneously end. Analyzed in a different fashion, these data suggested that once a seizure had lasted more than seven minutes, it was highly likely (95% probability) that the patient belonged in the second group and would have a prolonged seizure. In addition, the longer a seizure lasted, the less likely it was to terminate in the next few minutes. These prospective studies strongly emphasize the need for initiating treatment if seizures have lasted five minutes or longer, and support the proposal to change the definition of status epilepticus.

Diazepam versus Lorazepam for Prehospital Treatment

The second major goal of the PHTSE study was to determine whether lorazepam is superior to diazepam for the prehospital treatment of status epilepticus (4). Benzodiazepines are commonly used to terminate acute seizures because they are effective against a variety of seizure types, have rapid onset of action on entering the brain, and are relatively safe. However, it is unclear whether out-of-hospital status epilepticus should be treated with diazepam or lorazepam. Rectal diazepam is currently approved for out-of-hospital treatment of acute repetitive seizures in children. Two randomized, double-blind, placebo controlled studies (16,17) have demonstrated that rectal diazepam administered by caregivers at home is an effective and safe treatment for acute recurrent seizures. In these two studies, 185 children who had at least one episode of multiple seizures (partial complex, generalized tonic-clonic, atypical absence or myoclonic) within a 12-hour period that were recognized by their caregivers as an unusual pattern, were randomized to placebo or rectal diazepam (the dose was adjusted according to the child's age). In these studies, etiology, age, seizure frequency, monthly frequency of acute recurrent seizures, and race of the patients randomized to placebo or control were similar. However, more males were randomized to treatment than placebo (18).

Rectal diazepam effectively controlled acute recurrent seizures. The median number of seizures per hour in diazepam-treated children was 0 while that in the placebo-treated group was 0.25. During the 12-hour observation period, significantly more diazepam-treated children remained seizure free compared with those given placebo (59% versus 31%, $p = 0.001$). Fewer diazepam-treated children needed emergency medical care than placebo-treated children (4.4% versus 15.4%, $p = 0.042$). Furthermore, rectal diazepam proved to be safe. Somnolence was the only adverse effect observed more often in diazepam-treated children than in placebo-treated children, and no child suffered from serious respiratory compromise. These results suggest that rectal diazepam is effective and safe for out-of–hospital treatment of acute recurrent seizures. As yet, rectal diazepam has not been compared with other benzodiazepines for out-of -hospital treatment of acute recurrent seizures.

Studies conducted in hospital settings suggest intravenous lorazepam is somewhat more effective than intravenous diaz-

epam in terminating status epilepticus in adults. Leppik et al. (19) compared intravenous lorazepam (4 mg) with diazepam (10 mg) given to hospitalized patients in status epilepticus in a randomized, double-blind fashion. The dose was repeated in 10 minutes if the seizures persisted. A total of 37 episodes of status epilepticus were treated with lorazepam—78% were terminated by the first dose and 89% following the second injection. In 33 episodes, diazepam terminated status epilepticus in 58% following the first injection and in 76% following the second dose. This difference in efficacy between lorazepam and diazepam was not statistically significant.

The Veteran's Administration Cooperative Study (1) compared the efficacy of four initial treatments of generalized convulsive status epilepticus: lorazepam (0.10 mg/Kg), diazepam (0.15 mg/Kg) followed by phenytoin (18mg/Kg), phenobarbital (15 mg/Kg), and phenytoin (18mg/Kg) alone. Overt status epilepticus was diagnosed if more than 10 minutes of continuous generalized convulsions or intermittent convulsions without recovery of consciousness occurred. Treatment was considered successful if clinical and electrographic seizures stopped within 20 minutes and did not return within 60 minutes of initiation of treatment. Lorazepam controlled status epilepticus in 64.9% (62 of 95 patients) with confirmed overt status epilepticus while diazepam followed by phenytoin was effective in 55.8% (51 of 91 patients). The difference was not statistically significant. There were no differences in adverse effects between the two regimens.

The PHTSE study also found no statistically significant difference between the effectiveness of intravenously administered lorazepam versus diazepam for pre-hospital treatment of status epilepticus. However, it is important to note that status epilepticus was terminated in more lorazepam-treated patients (59.1%) than in diazepam-treated patients (42.6%). The odds of terminating status epilepticus on arrival at the emergency department were 1.9 times higher for the lorazepam group compared to the diazepam group (95% confidence interval, 0.8 to 4.4). It is also noteworthy that evidence from open trials suggests that the recurrence rate of status epilepticus is higher in patients treated with diazepam than in those treated with lorazepam (20).

There are pharmacological reasons for the superiority of lorazepam over diazepam in the treatment of status epilepticus. Both diazepam and lorazepam are benzodiazepines that share common mechanisms of action: they bind to the $GABA_A$ receptor and increase its affinity for GABA. The *in vivo* level of occupancy of $GABA_A$ receptors by benzodiazepines depends largely on benzodiazepine brain concentration rather than the affinity for the receptor (21). Diazepam is highly lipohilic while lorazepam is a hydroxylated derivative and is less lipophilic. Diazepam enters the brain rapidly but is rapidly redistributed to fat stores throughout the body, resulting in a lower brain concentration, larger volume distribution, and shorter duration of action compared to lorazepam (22). These pharmacological considerations and clinical studies support current recommendations to initiate the treatment of status epilepticus with intravenous lorazepam (23).

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