

Literature Review and Recommendations
Administration of Benzodiazepines by EMT -I in the pre-hospital setting
EMS Bureau Protocol Review Steering Committee

Background

Status epilepticus is a recognized public health problem in the United States: it is associated with a high mortality rate related to age of the patient, etiology of the condition, and duration of the condition before initial treatment is begun. Status epilepticus is considered a medical neurologic emergency. Immediate diagnosis and treatment are felt to be necessary to reduce morbidity and mortality associated with status epilepticus. EMTs (Emergency Medical Technicians) and Paramedics are often the first medical professionals to encounter patients in status epilepticus. In many jurisdictions, the paramedics are permitted to administer intravenous (IV) benzodiazepines to treat status epilepticus while in other jurisdictions treatment is deferred until arrival in the emergency department due to concern over the potential risks of out-of-hospital benzodiazepine therapy. Administration of intravenous benzodiazepines to patients in status epilepticus carries risks of hypotension and respiratory depression. Out-of-hospital treatment of status epilepticus carries risks because paramedics operate in settings that lack many of the diagnostic, treatment, and monitoring modalities frequently used to manage patients in status epilepticus. If the duration of status epilepticus can be shortened by early and appropriate treatment, some systemic and neurological complications of prolonged seizures may be prevented. Currently there is no evidence available supporting the administration of benzodiazepines in the pre-hospital setting by EMT- Intermediates in other jurisdictions; however, it may prove beneficial to allow EMT – Intermediates to administer benzodiazepines in the pre-hospital setting to avoid adverse outcomes related to delays in treatment.

Question

Do the benefits of intravenous administration of benzodiazepines for seizures in the out-of-hospital setting outweigh the risks and should this skill be added to the New Mexico EMT Intermediate scope of practice? Which medication and route of administration should be used for the safest delivery by the EMT Intermediate?

Methods

NMDOH digital library; keywords searched: pre-hospital, benzodiazepine, emergency medical technician, treatment of seizures, status epilepticus.

Search engine used: PubMed, Clinical Trials, Cochrane Library

Review process: A review of the literature was conducted using two electronic medical literature databases. Medical subject headings, keywords and a pre-hospital search filter were used to yield relevant literature. Also screened were reference lists of included trials and relevant reviews.

Number of articles reviewed: Twelve

Number of articles deemed to be relevant: Seven

Types of Articles: Articles reviewed and cited included: a randomized, double-blind trial to evaluate intravenous benzodiazepines administered by paramedics for the treatment of out-of-hospital status epilepticus; a meta-analysis using individual patient data of a subpopulation of patients emerging from the three randomized, double-blind, placebo-controlled, phase III trials; a five-year randomized, double-blind, multicenter trial of four intravenous regimens of benzodiazepines; a retrospective cohort study of all patients younger than 18 years treated for a seizure with a benzodiazepine by emergency medical services; and a double-blind randomized non-inferiority clinical trial of the efficacy of IM midazolam versus IV lorazepam in the prehospital treatment of status epilepticus.

Articles cited to draw conclusions and formulate recommendations: Seven

Results

The Prehospital Treatment of Status Epilepticus (PHTSE) trial compared diazepam, lorazepam, and placebo given intravenously by paramedics to treat subjects with prolonged convulsive seizures. The trial showed that both these benzodiazepines were an effective prehospital treatment for seizures, as compared with placebo. The proportion of subjects whose seizures were terminated at the time of arrival in the emergency department was 59.1% in the group receiving intravenous lorazepam, 42.6% in the group receiving intravenous diazepam, and 21.1% in the group receiving intravenous placebo. It was uncertain whether any anticonvulsant therapy was better than another in terms of adverse effects. (1)

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%). (1) 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. 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.

In another study, early treatment of status epilepticus (SE) with benzodiazepines by paramedics was shown to reduce the number of patients with persistent seizures on emergency department (ED) arrival and the number admitted to the intensive care unit (ICU). (2)

Leppik et al. compared intravenous lorazepam (4 mg) with diazepam (10 mg) given to hospitalized patients in status epilepticus in a randomized, double-blind fashion. (3) The results suggested the difference in efficacy between lorazepam and diazepam was not statistically significant.

The Veterans Administration Cooperative Study compared the efficacy of four initial treatments of generalized convulsive status epilepticus in a hospital setting: lorazepam (0.10 mg/Kg), diazepam (0.15 mg/Kg) followed by phenytoin (18mg/Kg), phenobarbital (15 mg/Kg), and phenytoin (18mg/Kg) alone. The difference was not statistically significant and there were no differences in adverse effects between the two regimens. (4)

Rectal diazepam is currently approved for out-of-hospital treatment of acute repetitive seizures in children. Warden and Frederick demonstrated that rectal diazepam effectively controlled acute recurrent seizures; however, more recently midazolam has been adopted in a limited number of EMS systems for its more rapid absorption by intramuscular (IM) and trans mucosal routes than diazepam or lorazepam, and has excellent stability. Diazepam and midazolam appear to be equivalent in treating seizures and causing adverse events. Paramedics appear to be administering midazolam intramuscularly more often than they use diazepam rectally. (5)

The RAMPART (the Rapid Anticonvulsant Medication Prior to Arrival Trial) hypothesized that in the prehospital treatment of SE, the efficacy of intramuscular midazolam would be not be inferior to that of intravenous lorazepam, as determined by the proportion of subjects with termination of a clinically evident seizure at arrival in the ED after a single dose of study medication and without use of rescue medication. The time interval data in RAMPART are consistent with the expectation that the medication given by the IM route is administered more rapidly after arrival than medication given IV, but that the onset of action after IV administration is more rapid than after IM administration. The administration time saved by using the IM route appears to more than offset the delay in onset of action. (6)

The superiority of IM midazolam over IV lorazepam demonstrated in RAMPART indicates that early administration of IM midazolam is the best option for the prehospital treatment of SE by paramedics. The ability to use an IM route with midazolam allows more reliable and rapid administration and ultimately leads to better clinical outcomes as reflected in lower rates of hospital admission, and lower rates of intensive care unit (ICU) admission.

Some EMS systems that use midazolam for the prehospital treatment of SE use transmucosal routes of administration (buccal, nasal, or rectal) as an alternative to IM administration. Such routes are less invasive and are potentially similarly rapid (McMullan et al.). (7) In the context of status epilepticus, the clinical importance of avoiding the invasiveness of an IM or IV injection is unclear, and there are potential limitations to each trans-mucosal route. The potential limitations of trans-mucosal routes include: a) concentrations of midazolam available for these routes are relatively lower than for those administered IM or IV; b) these formulations have most often

been studied via nasal administration only; and c) the occasional problem of seizing patients spitting or blowing out medication during administration. On the other hand, trans-mucosal administration offers the advantage of patient and provider safety by avoiding the challenges of administering benzodiazepines either IM or IV.

Regarding mechanism, the time interval data in RAMPART are consistent with the expectation that the medication given by the IM route is administered more rapidly after arrival than medication given IV, but that the onset of action after IV administration is more rapid than after IM administration. The administration time saved by using the IM route appears to more than offset the delay in onset of action.

Discussion

Status epilepticus can cause pulmonary congestion and edema, pneumonia, cardiac arrhythmias, hypotension, hypoxia, vomiting, incontinence, elevation of body temperature, hypoglycemia, acidosis, and rhabdomyolysis, rarely with associated acute renal failure, to name a few systemic complications of generalized convulsive status epilepticus. These systemic complications tend to worsen as the duration of status epilepticus lengthens, though the literature does suggest that in childhood convulsive status epilepticus, the major predictor of outcomes is etiology. (8) Prolonged status epilepticus can also lead to neuronal damage and loss. There is growing evidence from experimental animals that the extent of neuronal injury due to status epilepticus is linked to the duration of the seizure. A delay in treatment may also contribute to the refractoriness of status epilepticus. Mortality associated with status epilepticus also correlates with the duration of the seizures

If the duration of status epilepticus can be shortened by early initiation of treatment, systemic and neurological complications of prolonged seizures may be decreased or prevented. There is some evidence that administration of benzodiazepines in the pre-hospital setting for status epilepticus has an acceptable safety and effectiveness profile. Midazolam seems to be the benzodiazepine of choice by EMS because of its safety, effectiveness, and options of delivery.

Benzodiazepines are commonly used to terminate acute seizures because they are effective against a variety of seizure types, have rapid onset of action, and are relatively safe. Studies showed that midazolam may be considered the best choice for the out-of-hospital treatment of status epilepticus and can safely be administered at the EMT I level due to several acceptable delivery methods.

Traditionally, diazepam has been the agent used most frequently by emergency medical services (EMS) to treat patients with seizures despite evidence that intravenous lorazepam may be more effective. However, lorazepam has proven impractical for EMS use because of its short shelf life without refrigeration. Hence, the use by EMS systems of intramuscular midazolam for status epilepticus has been increasing because small studies have indicated its effectiveness and because this drug is rapidly absorbed intra-muscularly. According to a meta-analysis of small

trials, the use of non-intravenous midazolam in the hospital setting compared favorably with intravenous diazepam in the emergency treatment of status epilepticus. Furthermore, unlike lorazepam, midazolam does not have the problem of poor stability when not refrigerated and midazolam can be administered by non- intravenous routes as well. The intramuscular route is more consistently effective than the intranasal or buccal routes because the drug cannot be blown or spat out by the convulsing patient.

Recommendations

While there is good evidence that benzodiazepines are generally safe and effective when administered by paramedics, there is nothing in the literature that supports or opposes the administration of benzodiazepines by caregivers who are not paramedics.

Adding this as an approved drug and skill would add hours to an already packed intermediate life support (ILS) curriculum. While we have heard of two agencies in New Mexico with particular interest in this being added to the ILS scope, we have not heard a general need expressed by the majority of ILS providers. It is not clear that this need exists statewide.

The EMS Bureau recommends that ILS agencies desiring to administer this medication utilize the special skill process, and work with the EMS Bureau to develop data regarding ILS administration of benzodiazepines.

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