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SEIZURE DISORDERS

INTRAMUSCULAR VS INTRAVENOUS BENZODIAZEPINES FOR PREHOSPITAL TREATMENT OF STATUS EPILEPTICUS

Researchers at the Department of Emergency Medicine, University of Michigan, Ann Arbor, and other centers in the US, compared the efficacy of intramuscular (IM) midazolam with that of intravenous (IV) lorazepam for children and adults in status epilepticus treated by paramedics. This so-called RAMPART (Rapid Anticonvulsant Medications Prior to Arrival Trial) involved 79 hospitals and >4000 paramedics, and was funded by NIND & Stroke and others. The trial tested the hypothesis that IM midazolam was not inferior to IV lorazepam by 10% margin. Doses in children weighing 13-40 kg were 5 mg IM midazolam by autoinjector or 2 mg IV lorazepam; children >40 kg received 10 mg IM midazolam or 4 mg IV lorazepam. Subjects included had convulsions that persisted for >5 minutes and who were still convulsing after paramedics arrived. Primary outcome was absence of seizures at time of arrival in ED.

On arrival in the ED seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the IM group and in 282 of 445 (63.4%) in the IV group (P<0.001). The treatment groups were similar in percent in need of endotracheal intubation (14.1% and 14.4%). Intubation was more commonly a sequela of continued seizures than an adverse effect of the benzodiazepine. In patients whose seizures ceased before arrival at ED, the median times to active treatment were 1.2 min in the IM-group and 4.8 min in the IV-group. Convulsions ceased in 3.3 min and 1.6 min after injection, respectively. Adverse-event rates were similar in the 2 groups. IM midazolam is at least as safe and effective as IV lorazepam for prehospital treatment of status epilepticus. (Silbergleit R, Durkalski V, Lowenstein D, et al. for the NETT investigators. Intramuscular versus intravenous therapy for prehospital status epilepticus. **N Engl J Med** February 16, 2012;366:591-600). (Respond: Robert Silbergleit, MD, Dept Emergency Medicine, Ann Arbor, MI. E-mail: Robert.silbergleit@umich.edu).

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COMMENT. In an editorial, Hirsch LJ of Yale University Epilepsy Center notes that the mortality of status epilepticus is 15 to 22% and the outcome correlates with seizure duration. (**N Engl J Med** 2012;366:659-660). The definition of status has been shortened from 30 minutes to 5 to 10 minutes in recent studies. Seizures lasting > 5 minutes are likely to be self-sustained and require intervention. The RAMPAR Trial reported above found that the more rapid administration of the IM midazolam (1.2 min) than the IV lorazepam (4.8 min) outweighed the faster cessation of seizures with intravenous administration (1.6 min IV vs 3.3 min via IM route). The rate of hospitalization was lower in the IM-midazolam group, as compared with the IV-lorazepam group (57.6% vs 65.6%). Dr Hirsch comments that home treatment for status epilepticus may be found more satisfactory in the future, using the nasal or buccal routes for administering midazolam.

COMBINATION DRUG THERAPY IN REFRACTORY EPILEPSY

Researchers from University of Washington, Seattle, WA analyzed the treatment records from 148 developmentally disabled adults with refractory epilepsy cared for in 2 state-run institutions. Records charted monthly convulsive seizure occurrence and AED regimen over 30 years. Patients had a predominance of focal over generalized EEG abnormalities. The effects of 8 commonly used AEDs alone and in combination on seizure frequency were studied in within-patient comparisons. In decreasing order of frequency, the drugs compared were lamotrigine, valproate, carbamazepine, phenytoin, topiramate, levetiracetam, gabapentin, and zonisamide; phenobarbital and oxcarbazine were used at only one institution and were excluded from calculations. Individual AED combinations were first compared to an aggregate measure of all other combinations to which a patient had been exposed. This allowed greater statistical power to assess efficacy of individual combinations.

Out of the most frequently used AED combinations, only lamotrigine (LTG) and valproate (VPA) combination had superior efficacy; seizure frequency was reduced by 50% or more in comparison to other regimens. The LTG/VPA combination was superior to VPA or LTG monotherapy, and CBZ/VPA, VPA/GBP, or CBZ/VPA/PHT combinations. While 2 concurrent AEDs provided improved efficacy over monotherapy, use of 3 AEDs at a time provided no further benefit over two AEDs combined. AEDs should be used no more than 2 at a time for optimal response. (Poolos NP, Warner LN, Humphreys SZ, Williams S. Comparative efficacy of combination drug therapy in refractory epilepsy. **Neurology** Jan 3, 2012;78:62-68). (Response and reprints: Dr Poolos. E-mail: npoolos@uw.edu).

COMMENT. The superior efficacy of LTG/VPA combination compared to other AED combinations is reported previously (Brodie MJ et al. **Epilepsy Res** 1997;26:423-432)(Pisani F et al. **Epilepsia** 1999;40:1141-1146) (Refs cited by authors). Synergism between the 2 drugs may explain the improved seizure control by a valproate-induced reduction in hepatic clearance of lamotrigine. However, the present study found no VPA effect on LTG serum concentrations, and the mechanism of synergism is unexplained.