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SEIZURE DISORDERS

LORAZEPAM VS DIAZEPAM FOR STATUS EPILEPTICUS

Investigators at the Division of Emergency Medicine, Children's National Medical Center, Washington, DC, and ten additional US centers in the Pediatric Emergency Care Applied Research Network (PECARN), conducted a double-blind, randomized clinical trial comparing the efficacy and safety of lorazepam and diazepam in the treatment of generalized convulsive status epilepticus (SE) in children aged 3 months to younger than 18 years. Of a total of 273 patients presenting with SE from 2008-2012, 140 randomized to diazepam (0.2 mg/kg) and 133 to lorazepam (0.1 mg/kg) administered intravenously. Half this dose was repeated at 5 min if necessary, and fosphenytoin was administered if SE continued at 12 minutes.

SE was controlled for 10 min without recurrence within 30 min in 101 of 140 (72.1%) in the diazepam-treated group and 97 of 133 (72.9%) in the lorazepam group. The median time to termination of SE was 2.5 min in the diazepam group and 2 min in the lorazepam group ($p=0.80$). Assisted-ventilation (bag-valve-mask ventilation or endotracheal intubation) was administered in 26 patients in each group (16.0% given diazepam and 17.6% given lorazepam). There were no statistically significant differences in efficacy or safety outcomes in the two groups, except that lorazepam patients were more likely to be sedated (66.9% vs 50%, respectively). There was a significant difference favoring diazepam in time to return to baseline mental status ($p=0.0004$). The estimate for efficacy for febrile SE was lower than for other etiologies (65.2% vs 76.1%, respectively). (Chamberlain JM, Okada P, Holsti M, et al. Lorazepam vs diazepam for pediatric status epilepticus. A randomized clinical trial. *JAMA* 2014 Apr 23-30;311(16):1652-60).

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COMMENTARY. Diazepam is FDA approved for the treatment of pediatric status epilepticus but lorazepam is not approved. Several reports of treatment with lorazepam have suggested superior effectiveness, longer duration of action, and lower incidence of respiratory depression when compared to diazepam, but the evidence to support lorazepam superiority is inconclusive. In one study, intravenously administered lorazepam was compared to rectal diazepam [1]. In a Cochrane Database Review [2], intravenous lorazepam is as effective as intravenous diazepam, has fewer adverse events, and rectal lorazepam may be more effective than rectal diazepam. Where intravenous access is unavailable, buccal midazolam is recommended as the treatment of choice and intranasal lorazepam is as effective as intravenous diazepam. In contrast to these positive lorazepam responses, the results of the present study do not support the preferred use of lorazepam vs diazepam in the treatment of pediatric convulsive status epilepticus [3]. Neither agent is optimal since SE is uncontrolled in 1 in 4 children and severe respiratory depression occurs in approximately 1 in 6.

The FEBSTAT study of the emergency management of febrile status epilepticus finds that the earlier the onset of treatment, the shorter the total seizure duration and better the outcome [4]. A comparison of buccal or intranasal midazolam vs intravenous or rectal diazepam found that non-IV midazolam was as effective as IV diazepam, and buccal midazolam was superior to rectal diazepam in achieving seizure control; and respiratory complications requiring intervention were similar, regardless of administration route [5]. A comparison of midazolam nasal spray and rectal diazepam solution for residential treatment of seizure exacerbations found midazolam was equal in efficacy to diazepam, and drowsiness occurred in more than 50% of administrations for both drugs. The majority of patients and caregivers preferred the nasal spray to rectal formulation [6]. In the UK, an epidemiological study strongly supports prehospital treatment with buccal midazolam as a widely used but unlicensed option in the community [1].

References.

1. Neville BG, et al. *Acta Neurol Scand.* 2007 Apr;115(4 Suppl):21-4.
2. Appleton R, et al. *Cochrane Database Syst Rev.* 2008 Jul 16;(3):CD001905.
3. Chamberlain JM, et al. *JAMA.* 2014 Apr 23-30;311(16):1652-60.
4. Seinfeld S, et al. *Epilepsia.* 2014 Mar;55(3):388-95.
5. McMullan J, et al. *Acad Emerg Med.* 2010 Jun;17(6):575-82.
6. De Haan GJ, et al. *Epilepsia.* 2010 Mar;51(3):478-82.

PYRIDOXINE RESPONSIVENESS AND PNPO GENE MUTATIONS

Investigators at University Hospital, Zurich, Switzerland, and multiple centers in Europe and Canada, sequenced the pyridoxal 5-phosphate oxidase (PNPO) gene in 31 patients with pyridoxine-responsive seizures but normal biomarkers for antiquitin deficiency and normal sequencing of the ALDH7A1 gene. Eleven patients from 7 families carried 3 novel mutations of the PNPO gene. Response to pyridoxine was prompt in 4 patients, delayed in 2, on EEG only in 2, and initially absent in another 2 patients. Earlier and continuous pyridoxine therapy was related to a better prognosis. Two unrelated patients homozygous for the pArg225His mutation developed status epilepticus when switched to pyridoxal 5-phosphate (PLP).