Review: Lorazepam provides the best control for status epilepticus

Prasad K, Al-Roomi K, Krishnan P, Sequeira R. **Anticonvulsant therapy for status epilepticus.** Cochrane Database Syst Rev. 2005;(4):CD003723.

Clinical impact ratings: Emergency Med ★★★★★★☆ GIM/FP/GP ★★★★☆☆☆ Hospitalists ★★★★★★☆ Neurology ★★★★★★☆

QUESTION

In patients with status epilepticus (SE), which anticonvulsant drugs are most effective?

METHODS

Data sources: Cochrane Epilepsy Group Specialized Register, Cochrane Central Database of Controlled Trials, MEDLINE, EMBASE/Excerpta Medica, and bibliographies of relevant studies.

Study selection and assessment: Randomized or quasi-randomized controlled trials (RCTs) that compared any anticonvulsant drug with placebo or another anticonvulsant drug in patients with premonitory, early stage, established, or refractory SE. Quality assessment of individual studies included randomization method, baseline comparability of groups, blinding, and intention-to-treat analysis.

Outcomes: Depending on SE stage, outcomes included development of SE, death, continuation of seizures, continuation of SE requiring use of a different drug or general anesthesia for control, long-term disabling sequelae, and need for ventilatory support.

MAIN RESULTS

11 RCTs (n = 2017) met the selection criteria. Patients had premonitory (5 RCTs), established (1 RCT), refractory (1 RCT), and mixed SE (2 RCTs), and 2 RCTs did not define the status. Superior results were seen with intravenous (IV) lorazepam for cessation of seizures and reducing risk for SE that required a second drug (Table). IV diazepam was better than placebo for reducing death, continuation of seizures, SE, and ventilatory support (Table). Diazepam gel was better than placebo, and 30 mg of diazepam gel was superior to 20 mg for reducing continuation of seizures (Table). No differences were seen for comparisons of lorazepam with diazepam plus phenytoin, phenobarbital, or midazolam; diazepam with midazolam (IV or intramuscular); diazepam plus phenytoin with phenobarbital or phenytoin alone; or phenobarbital with phenytoin.

CONCLUSIONS

In patients with status epilepticus, lorazepam is better than diazepam, phenytoin, or placebo for cessation of seizures, and diazepam is better than placebo. Lorazepam is better than placebo or diazepam for preventing status epilepticus requiring a different drug or general anesthesia, and diazepam is better than placebo.

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Anticonvulsant drugs for status epilepticus to hospital discharge*

Outcomes	Number of trials (n)	Comparisons	Weighted event rates	RRR (95% CI)	NNT (CI)
Continuation of seizures	3 (264)	Lorazepam vs diazepam	24% vs 38%	36% (10 to 55)	8 (5 to 25)
	1 (137)	Lorazepam vs placebo	41% vs 79%	48% (29 to 62)	3 (2 to 5)
	1 (198)	Lorazepam vs phenytoin	35% vs 56%	38% (14 to 55)	5 (3 to 13)
	1 (139)	Diazepam vs placebo	57% vs 79%	27% (8 to 43)	5 (3 to 17)
	2 (165)	Intrarectal diazepam gel vs placebo	32% vs 72%	57% (38 to 70)	3 (2 to 4)
	1 (39)	Intrarectal diazepam gel 30 mg vs 20 mg	28% vs 71%	61% (14 to 82)	3 (2 to 7)
Continuation of status epilepticus requiring a different drug	3 (264)	Lorazepam vs diazepam	24% vs 39%	37% (12 to 55)	7 (4 to 25)
	1 (137)	Lorazepam vs placebo	41% vs 79%	48% (29 to 62)	3 (2 to 5)
	1 (139)	Diazepam vs placebo	57% vs 79%	27% (8 to 43)	5 (3 to 17)
Death	1 (139)	Diazepam vs placebo	4.4% vs 15%	72% (2 to 92)	10 (5 to 100)
Ventilatory support	1 (139)	Diazepam vs placebo	8.8% vs 23%	61% (6 to 84)	8 (4 to 50)

*Abbreviations defined in Glossary; weighted event rates, RRR, NNT, and CI calculated from data in article using a fixed-effects model. All drugs given intravenously unless otherwise noted. Event rates with 1 trial are unweighted.

COMMENTARY

SE is a neurologic emergency with a 30-day mortality rate of about 22%, contingent on duration before treatment, underlying cause, and patient age (1). Prasad and colleagues have attempted to determine which initial pharmacologic treatment for SE is best in terms of rapidity of action, maintenance of efficacy, and incidence of adverse events. Most of the studies enrolled patients with "premonitory SE," which, while not meeting the criteria for "established SE," is generally thought to be a condition best addressed early and aggressively.

Their results affirm the consensus of standard clinical practice, but underscore the diversity that exists among investigator definitions of SE and outcome measures. Their strongest conclusion, that lorazepam is more effective than diazepam or phenytoin, reinforces guidelines published > 10 years ago (2), matches the preferences of surveyed neurologists (3), and is in turn buttressed by the theoretical pharmacokinetic advantages of lorazepam.

The review shows that any of the agents investigated perform better than placebo regardless of administration route, although routes were not a focus of study. Despite this lack of comparative data, we recommend IV formulations when available, and rectal formulations when IV is not feasible—reserving the intramuscular route as a last resort. This review also does not address what to do when initial treatments fail, but a related review concludes that continuous IV pentobarbital, titrated to electroencephalographic background suppression, produces the most favorable results (4).

Prasad and colleagues highlight the need for further RCTs that use a standardized approach to the classification of SE, the dosing and route of compared agents, and common outcome measures.

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