Table 1. Anticonvulsant activity and protective index of intraperitoneal AEDs in mice

AED	Rotorod test	MES test		Pentylenetetrazol		Bicuculline		Picrotoxin		Strychnine	
	TD_{50} (95% CI) mg/kg	ED_{50} (95% CI) mg/kg	PI	ED_{50} (95% CI) mg/kg	PI	ED_{50} (95% CI) mg/kg	PI	ED_{50} (95% CI) mg/kg	PI	ED_{50} (95% CI) mg/kg	PI
Rufinamide	>500 <1,000	15.5 (12.5–18.1)	>32.2	54.0 (38.1–74.9)	>9.3	50.5 (23.9–87.8)	>9.9	76.3 (64.0–90.7)	>6.6	125[a]	NA
Phenytoin	65.5 (52.5–72.1)	9.5 (8.1–10.4)	6.9	300 no protection	<0.2	100 no protection	<0.7	100 no protection	<0.7	55–100[b]	<0.7
Phenobarbital	69.0 (62.8–72.9)	21.8 (15.0–25.5)	3.2	13.2 (5.9–15.9)	5.2	37.7 (26.5–47.4)	1.8	27.5 (20.9–34.8)	2.5	95.3 (91.3–99.5)	0.7
Valproate	425.8 (369–450)	272 (247–338)	1.6	148.6 (123–177)	2.9	359.9 (294–439)	1.2	387.2 (341–444)	1.1	292.9 (261–323)	1.5
Ethosuximide	440.8 (383–485)	1,000 no protection	<0.4	130.3 (111–151)	3.4	459.0 (350–633)	1.0	243 (228–255)	1.8	250–1,000[c]	<0.4

[a]Maximum protection, 37.5%.
[b]Maximum protection, 50.0%.
[c]Maximum protection, 62.5%.
AED, antiepileptic drug; MES, maximal electroshock; TD_{50}, the dose eliciting evidence of minimal neurotoxicity in 50% of animals; CI, confidence interval; ED_{50}, the dose of drug required to produce the desired end point in 50% of animals; and PI, protective index (ratio of TD_{50} to ED_{50}).

Pentylenetetrazol-induced seizure test

Rank order for relative potencies of the intraperitoneal administration of AEDs in the pentylenetetrazol-induced clonic seizure test in mice was phenobarbital > rufinamide >> valproate = ethosuximide >> phenytoin (Table 1). Phenytoin was ineffective up to a dose of 300 mg/kg. In slight contrast, the rank order for relative anticonvulsant potency in this test with oral administration in mice was phenobarbital > rufinamide > ethosuximide >> valproate >>> phenytoin (Table 2).

Oral rufinamide (≥1,000 mg/kg) and phenytoin (800 mg/kg) did not inhibit pentylenetetrazol-induced seizures in rats (Table 3). Phenobarbital achieved the best anticonvulsive potency of the remaining three AEDs.

Bicuculline-, picrotoxin-, and strychnine-induced seizure tests in mice

Intraperitoneal rufinamide was effective at nontoxic doses in the bicuculline and picrotoxin clonic seizure tests (ED_{50} ~50–75 mg/kg) and showed partial protection from strychnine-induced tonic seizures (37.5% protection; Table 1). Overall, the general order of potency in these chemically induced seizure tests was phenobarbital ≥ rufinamide >> valproate = ethosuximide > phenytoin (Table 1). In the strychnine-induced tonic seizure test, phenytoin had the lowest ED_{50} value, suggesting the greatest potency. However, it is important to note that 50% protection was the maximum achieved with this AED. Phenytoin failed to provide protection against bicuculline- and picrotoxin-induced clonic seizures in mice.

Evaluation of behavioral toxicity in mice

The median toxic dose of intraperitoneal rufinamide (TD_{50}) in the rotorod test of behavioral impairment was 500–1,000 mg/kg. The TD_{50} for rufinamide was higher than that for comparator AEDs (Table 1), indicating a lower toxicity. Higher doses of rufinamide were not assessed due the low ED_{50} values and high protective index (>40).

Neurological side effects of very high-dose intraperitoneal rufinamide (1,000 mg/kg, n = 2; ED_{50} 15–100 mg/kg) included decreased motor activity, ataxia, muscle relaxation, decreased respiration, and death (one animal died; the other appeared normal). Higher doses of the comparator drugs induced increased side effects (2 × TD_{50}) and resulted in death (all animals) in 3–24 h (4 × TD_{50}). The safety ratio for rufinamide in mice (TD_3/ED_{97} >19.2 [intraperitoneal] and >23.8 [oral]) was consistently greater than for phenytoin, phenobarbital, and valproate (Table 4).

The median dose of intraperitoneal rufinamide required to produce loss of righting reflex in mice (HD_{50}) was >500 and <1,000 mg/kg (Table 5). Rufinamide had a numerically greater HD_{50} value than phenytoin or phenobarbital (HD_{50} values of 178 and 135 mg/kg, respectively). Rufinamide, ethosuximide, and valproate had comparable