COMPARATIVE ANTICONVULSANT ACTIVITY OF CARBAMAZEPINE, LAMOTRIGINE AND VALPROATE IN THE MOUSE AND IN THE RAT

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INTRODUCTION

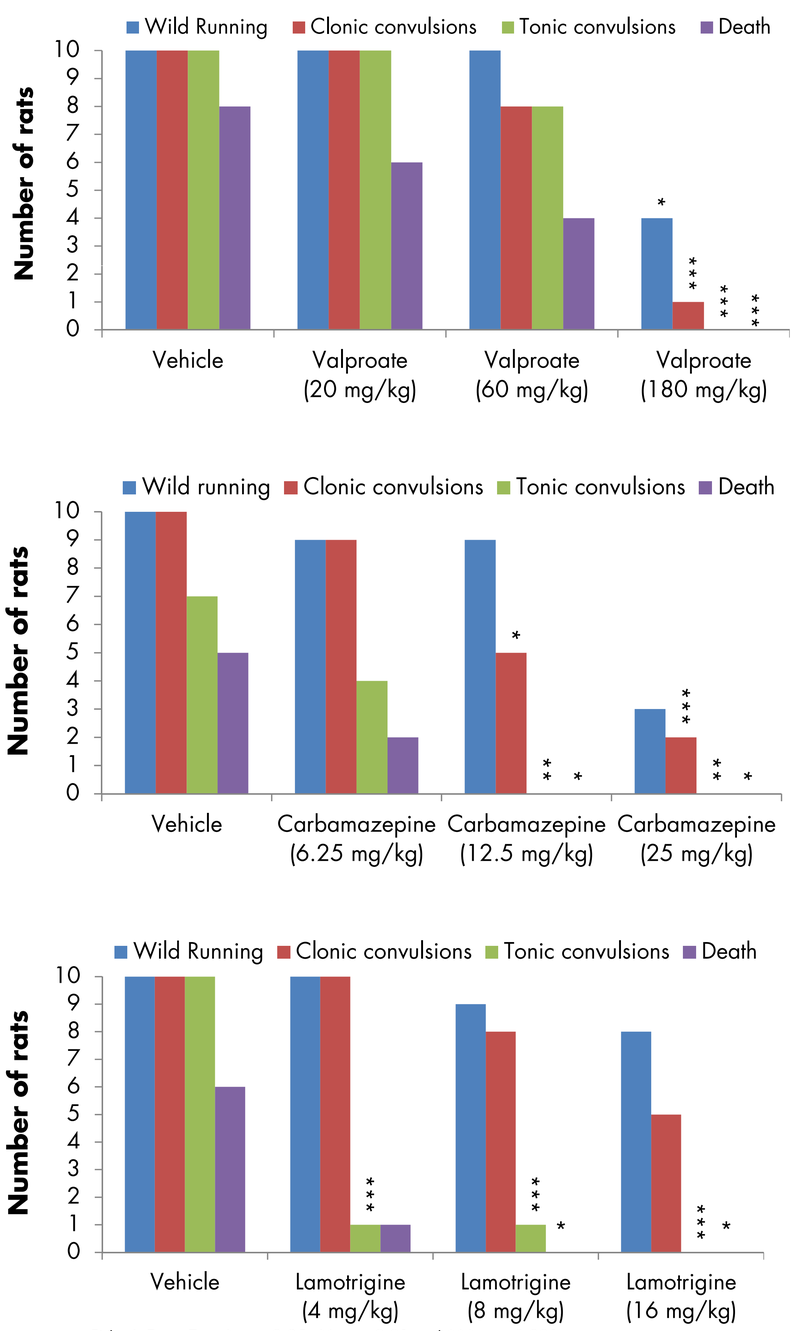
Three well-known antiepileptic drugs, carbamazepine, lamotrigine and valproate, were evaluated in different tests of epilepsy in the mouse and in the rat. These substances were compared in two models used to assess generalized tonic-clonic seizures, the audiogenic seizure test in the DBA/2 mouse and the maximal electroshock (MES) test in the rat as well as in the amygdala kindling test in the rat considered as a model of partial seizures with secondary generalization.

MATERIAL & METHODS

- **Treatments:**
  - Valproate was administered i.p. 30 minutes before the test. Carbamazepine and Lamotrigine were administered p.o. 60 or 120 minutes before the test.
- **Maximal Electroconvulsive Shock (MES) in the rat:**
  - Rats were administered MES (50 mA, rectangular current: 0.6 ms pulse width, 1.5 s duration, 200 Hz) via earclip electrodes connected to a constant current shock generator (Ugo Basile: Type 7801). The number of tonic convulsions was recorded.
- **Audiogenic Seizure Test:**
  - Mice (DBA/2, 3-4 weeks old) were placed in a Plexiglas jar mounted with an electric bell (110-120 dB). Upon activating the bell, the number of wild runnings, clonic and tonic seizures and deaths were measured. The bell was activated until death was observed or for a maximum of 60 seconds.
- **Amygdala Kindling Test:**
  - Rats were implanted with 2 depth electrodes into the amygdala. Following recovery, rats were stimulated twice daily. Rats showing behaviorally at least 4 consecutive stage 5 seizures were included in the drug study phase. A control stimulation was applied approximately 24 hours prior to administration, serving as a baseline measurement. The following day, stimulation was applied at different time points. For each stimulation, the behavior was observed and the seizure severity scored on a 6 point scale (0: no response, 1: mouth and facial movements, 2: head nodding, 3: forelimb clonus, 4: rearing and 5: rearing and falling).

RESULTS

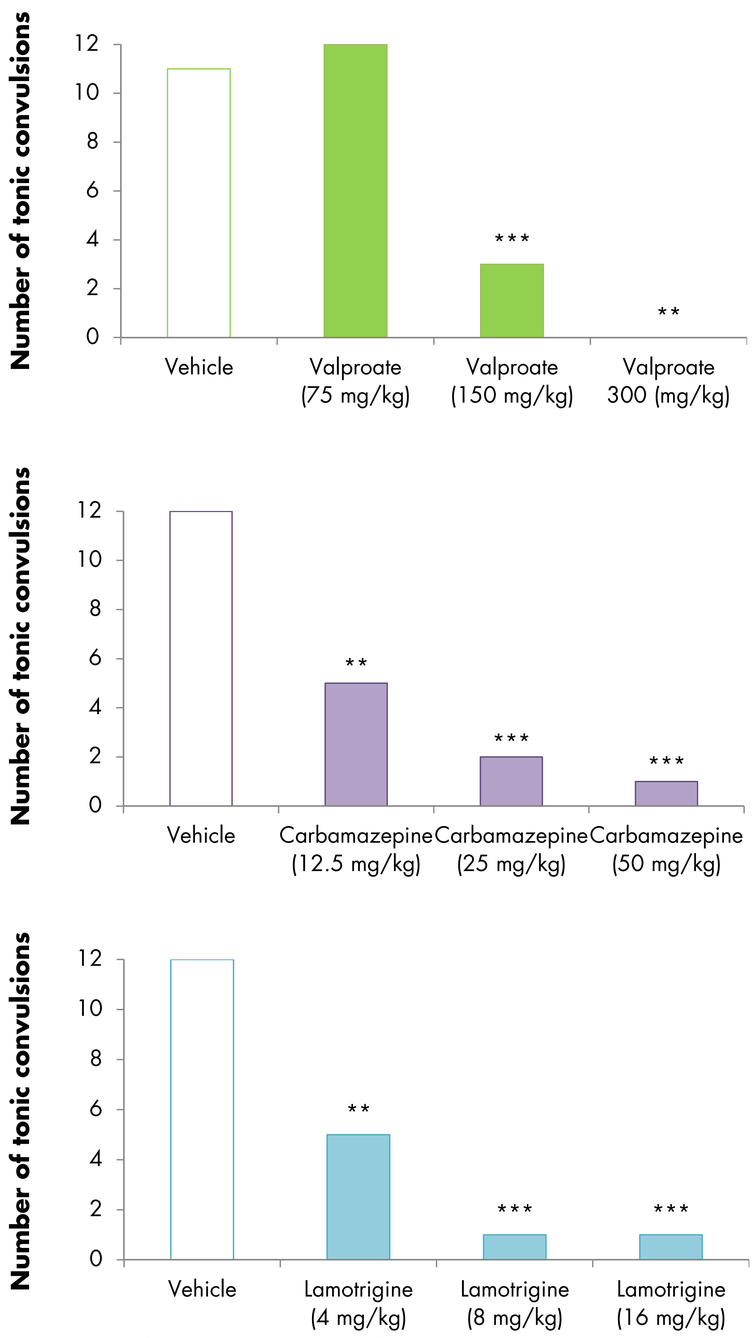
Audiogenic Seizure Test in the mouse



Fisher's Exact Test: *, $p < 0.05$, **, $p < 0.01$ and ***: $p < 0.001$.

- Valproate (180 mg/kg), Carbamazepine (12.5-25 mg/kg) and Lamotrigine (4-16 mg/kg) suppressed tonic convulsions and protected from death. Clonic convulsions were also decreased.

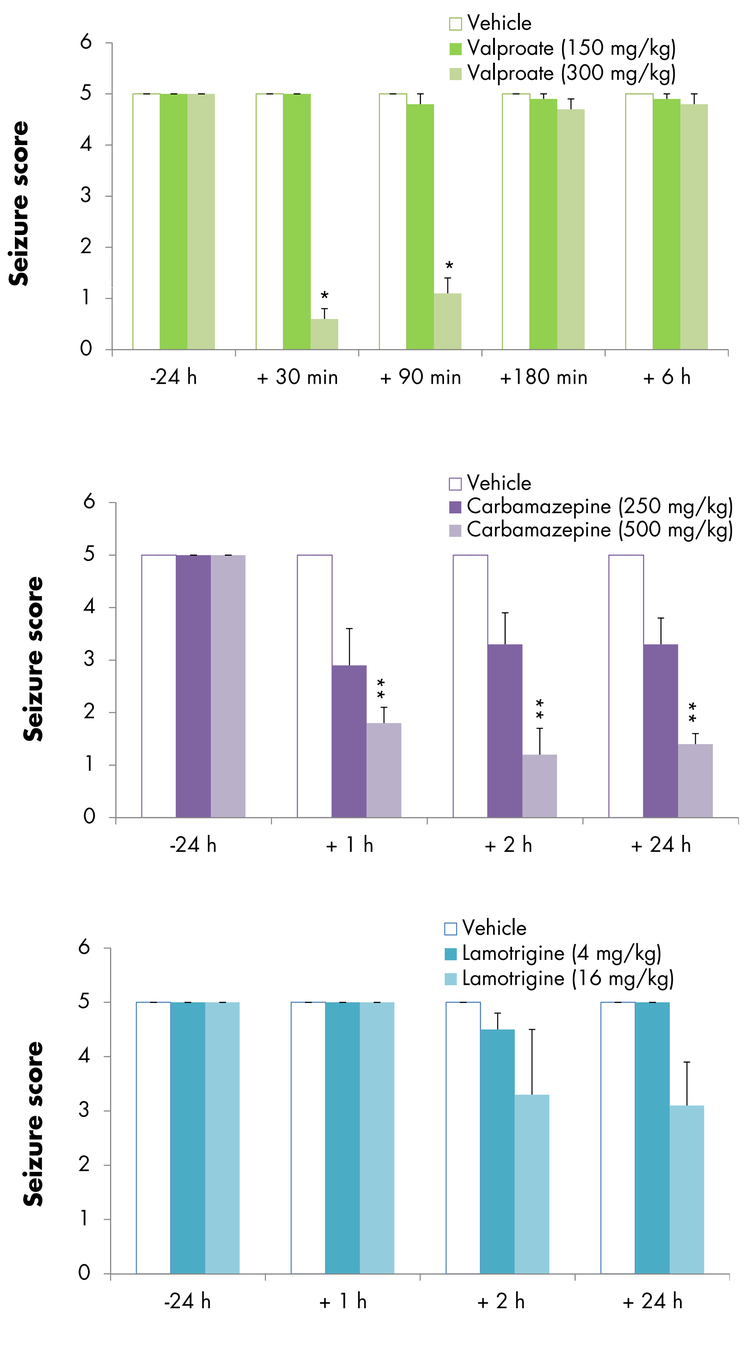
MES Test in the rat



Fisher's Exact Test: **, $p < 0.01$ and ***: $p < 0.001$.

- Valproate (150-300 mg/kg), Carbamazepine (12.5-50 mg/kg) and Lamotrigine (4-16 mg/kg) dose-dependently decreased tonic convulsions.

Amygdala Kindling Test in the rat



Wilcoxon Test: *, $p < 0.05$ and **: $p < 0.01$.

- Valproate (300 mg/kg) decreased the seizure score at 30 and 90 minutes. Similar effects were observed with Carbamazepine (500 mg/kg) at 1, 2 and 24 hours. No significant effects were observed with Lamotrigine at 4 or 16 mg/kg.

CONCLUSION

The results show that the active doses of carbamazepine, lamotrigine and valproate vary depending on the epilepsy model. Partial seizures with secondary generalization are antagonized after administration of these substances at higher dose strengths as compared with generalized seizures, confirming the importance of testing the same compound across several tests to assess anti-convulsant efficacy.

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