Influence of the antagonist of the glycine site of NMDA receptors, MRZ 2/576, on the anticonvulsant activity of conventional antiepileptic drugs in mice

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Abstract:
The purpose of this study was to evaluate the influence of the glycine site antagonist of the NMDA receptor, MRZ 2/576 (8-chloro-4-hydroxy-1-oxo-1,2-dihydropyridazino-[4,5-b]quinolin-5-oxide choline salt), on the anticonvulsant activity of carbamazepine, oxcarbazepine, diphenylhydantoin, phenobarbital and valproate against maximal electroshock (MES)-induced seizures and ethosuximide, valproate and clonazepam against pentetrazole (PTZ)-induced seizures in mice. MRZ 2/576 applied intraperitoneally 5 min before electroconvulsions, at the dose of 10 and 15 mg/kg, significantly raised the convulsive threshold (from 6.9 to 8.8 and 10.8 mA respectively). At lower doses, it did not affect the threshold. MRZ 2/576 applied at the dose of 5, 10 and 20 mg/kg did not influence the clonic phase of PTZ-induced seizures, but protected the animals against the tonic phase. The anticonvulsant effect of a given antiepileptic drug was expressed as its ED50 value (in mg/kg), which represents the dose of the drug required to protect 50% of animals against MES or PTZ seizures. MRZ 2/576 co-administered at a subprotective dose (5 mg/kg) with carbamazepine, oxcarbazepine, diphenylhydantoin, phenobarbital or valproate, significantly reduced their ED50 values in MES test. Also, at the dose of 2.5 mg/kg it enhanced the protective activity of carbamazepine and valproate. At the lowest tested dose (1.25 mg/kg), it still potentiated the anticonvulsant activity of valproate. However, MRZ 2/576 (5 mg/kg) applied with valproate, ethosuximide or clonazepam did not influence their protective effects in the PTZ test. The combinations of MRZ 2/576 with almost every studied antiepileptic drug (providing a 50% protection against maximal electroshock or PTZ-induced seizures) did not produce motor impairment in the chimney test nor long-term memory deficit measured in the passive avoidance task. Only valproate alone or combined with MRZ 2/576 impaired both of these measures. It may be concluded that MRZ 2/576 enhanced the anticonvulsive activity of antiepileptic drugs against MES without accompanying potentiation of adverse effects. However, there was no positive interaction in the PTZ test. Finally, pharmacokinetic interactions do not seem responsible for the obtained results because MRZ 2/576 (5 mg/kg) did not alter the free plasma levels of the antiepileptics tested in the present study.

Key words:
MRZ 2/576, glycine site antagonists, NMDA receptor, seizures, antiepileptic drugs, mice