

## FELBAMATE, GABAPENTIN AND TOPIRAMATE AS ADJUVANT ANTIEPILEPTIC DRUGS IN EXPERIMENTAL MODELS OF EPILEPSY

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Newly diagnosed epileptic patients start their medication with monotherapy. Around 30% of epileptic patients require more than one antiepileptic drug. Results from experimental studies provide evidence that administration of two antiepileptic drugs may result in antagonistic, additive, or supra-additive (synergistic) anticonvulsant effects. If adverse effects of a synergistic combination also show supra-additive summation then the protective index may not change. In this context, drug combinations, possessing synergistic anticonvulsant effects and additive (or infra-additive) toxicity, are of clinical interest. Recent experimental data indicate that topiramate and gabapentin generally potentiate the protective activity of conventional antiepileptic drugs against maximal electroshock-induced convulsions in mice. The anticonvulsant action of carbamazepine, diphenylhydantoin, phenobarbital, and valproate was not modified in this test by felbamate at subprotective doses against threshold electroconvulsions. Interestingly, conventional antiepileptics (at subeffective doses) enhanced the protection offered by felbamate. It may indicate that beneficial effects of a drug combination may be observed at only some drug ratios.

**Key words:** antiepileptics, combined treatment, drug interactions, seizures, epilepsy

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Approximately, 60–70% of newly diagnosed epileptic patients may expect a therapeutic benefit with monotherapy [17]. This clearly indicates that significant number of patients with epilepsy require polytherapy with at least two antiepileptic drugs. Nowadays, in many cases at least one drug used for the combined treatment is a novel antiepileptic. Animal models of epilepsy may provide evidence on clinically relevant drug combinations. The anti-convulsant effect of a drug combination may be evaluated with the isobolographic method on the basis of equieffective doses of individual drugs administered alone or combined [22]. An alternative method examines the effect of one antiepileptic (at subprotective doses in a threshold convulsive test) upon the  $ED_{50}$  value of the second one against maximal seizures. Changes in the  $ED_{50}$  values are then compared with the method of Litchfield and Wilcoxon [13].

Shank et al. [18], using the isobolographic method, studied the interaction of the novel antiepileptic drug, topiramate, with conventional antiepileptic drugs, diphenylhydantoin, phenobarbital and carbamazepine against maximal electroshock-induced seizures in mice. Topiramate was co-administered with a conventional antiepileptic drug at fixed ratios (0.75/0.25, 0.50/0.50, and 0.25/0.75) of their respective  $ED_{50}$  values. The combination of topiramate with diphenylhydantoin was purely additive. A synergy was evident when topiramate was combined with carbamazepine or phenobarbital. Świąder et al. [21] co-injected topiramate (at subprotective doses of 2.5 and 5 mg/kg evaluated in the electroconvulsive threshold test in mice) with conventional antiepileptic drugs. This novel antiepileptic drug (at 5 mg/kg) reduced by 41% the  $ED_{50}$  of carbamazepine against maximal electroshock in mice. Phenobarbital and diphenylhydantoin  $ED_{50}$ s were decreased respectively by 30 and 28%. The weakest interaction was observed for the combination of topiramate (5 mg/kg) with valproate whose  $ED_{50}$  value was decreased by only 18%. Since the  $ED_{50}$  of topiramate against maximal electroshock in mice was 62.1 mg/kg [21], the subprotective doses of this antiepileptic are only a small fraction of its  $ED_{50}$ . Anyway, its interaction with valproate seems to be additive only. Although, topiramate potentiated the carbamazepine anticonvulsant activity [18, 21], the involvement of a pharmacokinetic mechanism is probable since this novel antiepileptic drug significantly elevated the free plasma concentration

of carbamazepine by 47% [21]. The free plasma levels of the remaining antiepileptics were not altered by topiramate [21]. As already mentioned, the interaction of topiramate with valproate was likely of an additive nature. However, the combined treatment of both drugs resulted in no adverse activity (impairment of motor coordination or long-term memory). Valproate alone at its  $ED_{50}$  of 248 mg/kg against maximal electroshock was much worse in this respect, disturbing both motor performance and long-term memory [21]. In the pentetrazol seizures in mice, the best protection was encountered in case of topiramate combined with clobazam or phenobarbital. Limited and/or variable protection was obtained for its combinations with valproate, primidone and ethosuximide [19]. Another novel antiepileptic drug, felbamate, at subeffective doses against maximal electroshock in mice, failed to affect the protective activity of carbamazepine, diphenylhydantoin, phenobarbital, or valproate [5]. Using an identical experimental procedure, Gordon et al. [11] showed that all conventional antiepileptic drugs at their noneffective doses reduced the  $ED_{50}$  value of felbamate (42.9 mg/kg) against maximal electroshock in mice: carbamazepine (4 mg/kg) by 70%, diphenylhydantoin (6 mg/kg) by 60%, phenobarbital (4 mg/kg) by 45%, and valproate (150 mg/kg) by 69%. The protective index of felbamate, defined as its  $TD_{50}/ED_{50}$ , was significantly elevated after combinations with standard antiepileptic drugs. The pharmacokinetic mechanism was unlikely to participate in the observed interaction [11]. This is indicative of the significance of dose ratios of antiepileptic drugs for an interaction to occur. The third novel antiepileptic drug, gabapentin, at a subprotective dose of 25 mg/kg, decreased the  $ED_{50}$  values of carbamazepine (by 28%), diphenylhydantoin (by 52%), phenobarbital (by 58%) and valproate (by 28%) against maximal electroshock in mice. Considering that there was a bell-shaped response for gabapentin alone against maximal electroshock (the maximal protection was 50% for the dose of 300 mg/kg), especially combinations with diphenylhydantoin and phenobarbital seem to be supra-additive. The free plasma levels of the conventional antiepileptic drugs were not affected by gabapentin, so a possibility of the pharmacokinetic interaction may be rejected [7]. The isobolographic analysis provided an additional evidence – it turned out that the combinations of gabapentin with these antiepileptic drugs were synergistic in

all cases [unpublished data]. The synergistic ratios of conventional antiepileptic/gabapentin were: starting from 1/3 (for carbamazepine), from 1/1 (for diphenylhydantoin), from 1/5 (for phenobarbital) and from 20/1 to 3/1 for valproate. Combinations of novel antiepileptics (felbamate, gabapentin, topiramate) and conventional ones are listed in Table 1. Gabapentin was also combined with conventional antiepileptic drugs in a model of reflex epilepsy – sound-induced seizures in DBA/2 mice [10]. At a non-protective dose of 2.5 mg/kg, gabapentin increased the protective efficacy of carbamazepine, diazepam, diphenylhydantoin, phenobarbital and valproate. In case of diazepam, phenobarbital and valproate, the potentiation of their anticonvulsant effect was the most expressed. The therapeutic indexes of the antiepileptic drugs alone were worse than those of combined treatments. The pharmacokinetic mechanism may be excluded because gabapentin did not significantly affect the plasma concentration of antiepileptic drugs.

Table 1. Interactions of conventional and novel antiepileptic drugs in the maximal electroshock-induced convulsions in mice

Conventional antiepileptic drug	Novel antiepileptics		
	Felbamate	Gabapentin	Topiramate
Carbamazepine	0	+	++
Diphenylhydantoin	0	++	+
Phenobarbital	0	++	++
Valproate	0	+	+

Novel antiepileptics were administered at non-protective doses in the threshold electroconvulsive test. The protective activity of conventional antiepileptics was expressed in the form of their ED<sub>50</sub> values against maximal electroshock. 0 – no interaction (insignificant changes of ED<sub>50</sub> values for conventional antiepileptic drugs); + – positive interaction (up to 40% reduction of ED<sub>50</sub> values); ++ – very potent interaction (more than 40% reduction of ED<sub>50</sub> values). Data are from references [5, 7, 18, 21]

### Concluding remarks

Animal studies are aimed to provide a good experimental basis for the add-on treatment of epilepsy. They indicate which combinations of antiepileptic drugs may be expected to exert a significant protection in clinical conditions. A very detailed review, comparing the experimental and clinical data, has been recently published [9]. A correlation exists between results of experimental studies and clinical observations. A good example is D-CPP-

-ene (a competitive high-affinity antagonist of N-methyl-D-aspartate receptors) and its distinct adverse potential in rodents and epileptic patients [20, 25]. Also, psychotomimetic activity of dizocilpine (an uncompetitive antagonist of N-methyl-D-aspartate receptors) encountered in epileptic patients [16] was also present in amygdala-kindled rats [14]. Novel antiepileptic drugs are presently generally used in the form of add-on therapy [15]. It is quite obvious that the rational polytherapy with only new antiepileptics will be continuously growing. This is certainly a challenge for pharmacologists to characterize interactions between novel antiepileptics. So far, such evidence is only fragmentary.

Very intensive studies are being carried out with the use of glutamate receptor antagonists as potential adjuvant antiepileptic drugs [23]. It can be anticipated so far that especially antagonists of non-N-methyl-D-aspartate receptors and metabotropic glutamate receptor ligands bear a significant clinical potential [1–3, 4, 6, 8, 12]. Interestingly, N-methyl-D-aspartate diminished the anticonvulsant activity of some conventional antiepileptic drugs against electroconvulsions in mice [24] but, as already mentioned, high-affinity N-methyl-D-aspartate receptor antagonist produced considerable untoward effects in rodents [14]. Possibly, low-affinity N-methyl-D-aspartate receptor antagonists would be helpful as adjuvant antiepileptic drugs [3, 6].

### REFERENCES

1. Borowicz K.K., Kleinrok Z., Czuczwar S.J.: The AMPA/kainate receptor antagonist, LY 300164, increases the anticonvulsant effects of diazepam. *Naunyn-Schmied. Arch. Pharmacol.*, 2000, 361, 629–635.
2. Borowicz K.K., Kleinrok Z., Czuczwar S.J.: Influence of D(-)CPP and (±)CPP upon the protective action of conventional antiepileptic drugs against electroconvulsions in mice. *Pol. J. Pharmacol.*, 2000, 52, 431–439.
3. Borowicz K.K., Kleinrok Z., Czuczwar S.J.: Glutamate antagonists differentially affect the protective activity of conventional antiepileptics against amygdala-kindled seizures in rats. *Eur. Neuropsychopharmacol.*, 2001, in press.
4. Borowicz K.K., Łuszczki J., Szadkowski M., Kleinrok Z., Czuczwar S.J.: Influence of LY 300164, an antagonist of AMPA/kainate receptors, on the anticonvulsant activity of clonazepam. *Eur. J. Pharmacol.*, 1999, 380, 67–72.
5. Borowicz K.K., Stasiuk G., Teter J., Kleinrok Z., Gąsior M., Czuczwar S.J.: Low propensity of conven-

- tional antiepileptic drugs for interaction with felbamate against maximal electroshock-induced seizures in mice. *J. Neural Transm.*, 2000, 107, 733–743.
6. Czuczwar S.J.: Perspectives for the use of excitatory amino acid ionotropic receptor antagonists as antiepileptic drugs. *Pol. J. Pharmacol.*, 2000, 52, 67–70.
  7. Czuczwar S.J., Kamiński R., Kleinrok Z., Kozicka M., Żółkowska D.: Influence of gabapentin on the anticonvulsive activity of conventional antiepileptic drugs in mice. *Epilepsia*, 1999, 40, Suppl. 2, 125.
  8. Czuczwar S.J., Świąder M., Kuźniar H., Gašior M., Kleinrok Z.: LY 300164, a novel antagonist of AMPA/kainate receptors, potentiates the anticonvulsive activity of antiepileptic drugs. *Eur. J. Pharmacol.*, 1998, 359, 103–109.
  9. Deckers C.L., Czuczwar S.J., Hekster Y.A., Keyser A., Kubova H., Meinardi H., Patsalos P.N., Renier W.O., Van Rijn C.M.: Selection of antiepileptic drug polytherapy based on mechanisms of action; the evidence reviewed. *Epilepsia*, 2000, 41, 1364–1374.
  10. De Sarro G.B., Spagnolo C., Gareri P., Gallelli L., De Sarro A.: Gabapentin potentiates the antiseizure activity of certain anticonvulsants in DBA/2 mice. *Eur. J. Pharmacol.*, 1998, 349, 179–185.
  11. Gordon R., Gels M., Wichmann J., Diamantis W., Sofia R.D.: Interaction of felbamate with several other antiepileptic drugs against seizures induced by maximal electroshock in mice. *Epilepsia*, 1993, 34, 367–371.
  12. Kłodzińska A., Bijak M., Chojnacka-Wójcik E., Kroczyńska B., Świąder M., Czuczwar S.J., Pilc A.: Roles of group II metabotropic glutamate receptors in modulation of seizure activity. *Naunyn-Schmied. Arch. Pharmacol.*, 2000, 361, 283–288.
  13. Litchfield J.T., Wilcoxon F.: A simplified method of evaluating dose-effect experiments. *J. Pharmacol. Exp. Ther.*, 1949, 96, 99–113.
  14. Löscher W., Hönack D.: Anticonvulsant and behavioral effects of two novel competitive N-methyl-D-aspartic acid receptor antagonists, CGP 37849 and CGP 39551, in the kindling model of epilepsy. Comparison with MK-801 and carbamazepine. *J. Pharmacol. Exp. Ther.*, 1991, 256, 432–440.
  15. Majkowski J.: Interactions between new and old generations of antiepileptic drugs. *Epileptologia*, 1994, 2, Suppl. 1, 33–42.
  16. Porter R.J.: New antiepileptic agents: strategies for drug development. *Lancet*, 1990, 336, 423–424.
  17. Sander J.W.A.S.: Some aspects of prognosis in the epilepsies: a review. *Epilepsia*, 1993, 34, 1007–1016.
  18. Shank P.R., Gardocki J.F., Vaught J.L. Davis C.B., Schupsky J.J., Raffa R.B., Dodgson S.J., Nortey S.O., Maryanoff B.E.: Topiramate: preclinical evaluation of a structurally novel anticonvulsant. *Epilepsia*, 1994, 35, 450–460.
  19. Sills G.J., Butler E., Forrest C., Thompson G.G., Brodie M.: Combination studies with the novel anticonvulsant topiramate in the pentylenetetrazol seizure model. *Epilepsia*, 1999, 40, Suppl. 2, 128.
  20. Sveinbjornsdottir S., Sander J.W.A.S., Upton D., Thompson P.J., Patsalos P.N., Hirt D., Emre M., Lowe D., Duncan J.S.: The excitatory amino acid antagonist D-CPP-ene (SDZ EAA-494) in patients with epilepsy. *Epilepsy Res.*, 1993, 16, 165–174.
  21. Świąder M., Kotowski J., Gašior M., Kleinrok Z., Czuczwar S.J.: Interaction of topiramate with conventional antiepileptic drugs in mice. *Eur. J. Pharmacol.*, 2000, 399, 35–41.
  22. Tallarida R.J.: Statistical analysis of drug combinations for synergism. *Pain*, 1992, 49, 93–97.
  23. Urbańska E.M., Czuczwar S.J., Kleinrok Z., Turski W.A.: Excitatory amino acids in epilepsy (invited review). *Restor. Neurol. Neurosci.* 1998, 13, 25–39.
  24. Urbańska E.M., Tomczyk T., Haberek G., Pilip S., Matyska J., Turski W.A., Kleinrok Z., Czuczwar S.J.: NMDA- but not kainate-mediated events reduce efficacy of some antiepileptic drugs against generalized tonic-clonic seizures in mice. *Epilepsia*, 1999, 40, 1507–1511.
  25. Żarnowski T., Kleinrok Z., Turski W.A., Czuczwar S.J.: The competitive NMDA antagonist, D-CPP-ene, potentiates the anticonvulsant activity of conventional antiepileptics against maximal electroshock-induced seizures in mice. *Neuropharmacology* 1994, 33, 619–624.

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