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Pharmacodynamic and pharmacokinetic interactions between classic antiepileptics and selected antiarrhythmic drugs

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Antiarrhythmic and antiepileptic drugs are often used in combination in epileptic patients with cardiac arrhythmias. Interactions between the two groups of medications are very probable since epilepsy and arrhythmias were proved to have common molecular background. It is widely known that antiarrhythmics may present anticonvulsant action, while some antiepileptics are useful in the treatment of dysrhythmias.

The main aim of this study was to evaluate pharmacodynamic and pharmacokinetic interactions between classic antiepileptic drugs and two selected antiarrhythmics, presenting different mechanisms of action, in maximal electroshock-induced seizures in mice, the basic screening model of epilepsy. Propafenone belongs to the class Ic, and mexiletine to the class Ib of antiarrhythmics. Both drugs block fast sodium channels. However, propafenone strongly inhibits conductivity, moderately prolongs the effective refractory period, and, additionally, acts also as beta-adrenergic and calcium channel blocker. In contrast, mexiletine has a little effect on conductivity and markedly increases the effective refractory period.

Obtained result showed that propafenone (2,5-50 mg/kg) enhanced the anticonvulsant action of carbamazepine, despite decreasing its brain concentration. This may suggest particularly strong pharmacodynamic interaction between the two medications. Effects of valproate, phenobarbital and phenytoin were potentiated by propafenone applied at doses 30-50 mg/kg. Only the interaction between propafenone and valproate seems to have, at least partially, pharmacokinetic nature, since the antiarrhythmic drug significantly enhanced the brain concentration of valproate.

On the other hand, mexiletine presented significant anticonvulsant action with ED50 (50% effective dose) value of 11.9 mg/kg. Isobolographic analysis of obtained results revealed synergistic interaction between mexiletine and valproate. However, mexiletine interacted additively with carbamazepine, phenobarbital and phenytoin. All revealed interactions seemed to be pharmacodynamic. Moreover, the synergistic interaction between mexiletine and valproate occurred in spite of lowering the brain concentration of valproate by this antiarrhythmic drug.

In conclusion, both antiarrhythmics tend to potentiate the anticonvulsant action of classic antiepileptic drugs in the mouse model of tonic-clonic convulsions. This, as well as lack of significant neurotoxic effects induced by combinations of tested drugs, may suggest that propafenone and mexiletine can be safely used in the treatment of epileptic patients with arrhythmias.

Kinga K. Borowicz has completed her Ph.D. at the age of 25 years from Medical University of Lublin and received the title of full professor of medicine at the age of 35 years. Her specialties are pharmacology, pathophysiology and internal diseases. She has published 195 papers in reputed journals (IF = 201.273). At present she is the director of Unit of Experimental Neuropathophysiology, Medical University of Lublin, Poland.

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