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The effectiveness and therapeutic index of chronic valproate in the mouse maximal electroshock seizure test

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A vast majority of studies evaluating interactions between antiepileptic and nonantiepileptic drugs are based on their single administration, whereas epileptic patients require chronic pharmacotherapy. The aim of this study was to evaluate the effect of repeated administration of valproate on its anticonvulsant action, neurological adverse effects, therapeutic index, as well as plasma and brain concentrations. The anticonvulsant effect was estimated in the maximal electroshock test in mice. The antiepileptic was applied in four protocols: once a day for one week (1x1), twice a day for one week (1x2), once a day for two weeks (2x1), and twice a day for two weeks (2x2). Single administration of valproate served as a control.

The ED_{50} (50% effective dose) of valproate given in the 2x2 protocol was significantly lower than the control value. No significant differences were found in three remaining administration protocols. Serum and brain concentrations of valproate were not altered during chronic treatment with this drug. Moreover, no significant deficit in memory was observed after repeated valproate administration in the passive-avoidance task. In contrast, TD_{50}s (50% toxic doses) evaluated for chronic valproate in the chimney were significantly lower than the control. Therapeutic indices (TIs) of this drug calculated in chronic protocols (1x1, 1x2, 2x1, and 2x2) were respectively 1.48, 1.39, 1.38 and 1.89. Summing up, repeated administration can change both effectiveness and toxicity of valproate. This effect does not seem to be dependent on pharmacokinetic events. To increase reliability of results obtained in animal models, antiepileptic drugs should be administered chronically.

Biography

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 = 191.273). At present she is the director of Unit of Experimental Neuropathophysiology, Medical University of Lublin, Poland.

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