

INFLUENCE OF CHRONIC TREATMENT WITH H₁ RECEPTOR ANTAGONISTS ON THE ANTICONVULSANT ACTIVITY OF ANTIEPILEPTIC DRUGS

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Influence of chronic treatment with H₁ receptor antagonists on the anti-convulsant activity of antiepileptic drugs. M. ŚWIĄDER, K. CHWALCZUK, M. WIELOSZ, S.J. CZUCZWAR. Pol. J. Pharmacol., 2001, 53, 93–96.

The aim of this study was to evaluate the effects of chronic astemizole and ketotifen administration on the anticonvulsant activity of antiepileptic drugs against maximal electroshock-induced convulsions in mice. Adverse effects were evaluated in the chimney test (motor performance) and passive avoidance task (long-term memory). Brain and plasma levels of antiepileptics were measured by immunofluorescence. Astemizole (2 mg/kg) and ketotifen (8 mg/kg) significantly diminished the electroconvulsive threshold, being without effect upon this parameter at lower doses. Astemizole significantly reduced the anticonvulsant action of phenobarbital and diphenylhydantoin, but it did not affect that of carbamazepine and valproate. Moreover, ketotifen (at the subprotective dose of 4 mg/kg) remained without effect upon the protective activity of valproate, diphenylhydantoin or phenobarbital, but significantly diminished the anticonvulsant effect of carbamazepine. Histamine receptor antagonists combined with antiepileptic drugs, did not alter their brain and free plasma levels. Also, they did not influence adverse potential of carbamazepine, diphenylhydantoin and valproate while that of phenobarbital was significantly enhanced. Valproate, phenobarbital and diphenylhydantoin alone at their ED₅₀s against maximal electroshock or combined with the histamine receptor antagonists disturbed long-term memory. The results of this study indicate that H₁ receptor antagonists, should be used with caution in epileptic patients.

Key words: *astemizole, ketotifen, maximal electroshock, antiepileptic drugs*

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Various neurotransmitters and their receptors have been implicated in the initiation and termination of seizures in animals [7]. A specific role for endogenous histamine and histamine H₁ receptors in seizure mechanisms is emerging. Evidence that histamine in the brain is involved in the termination of seizures and plays a role of an endogenous anticonvulsant has been obtained in various animal models of epilepsy [16, 21] and is supported by the fact that seizures are sometimes induced in childhood epilepsy by treatment with an antihistamine drug [11].

Elevation of brain histamine concentrations with histamine N-methyltransferase inhibitor metoprine blocked maximal hindlimb extension following electroshock [16] and reduced audiogenic seizures in genetically epilepsy-prone rats [8]. L-histidine and metoprine increased pentetrazol-induced seizure thresholds in mice [1, 10] and decreased the duration of clonic convulsions, but not that of tonic convulsions, following electroshock [21]. Pyrilamine, ketotifen and D-chlorpheniramine increased the duration of tonic, clonic and convulsive coma phase following electroconvulsions in 21- and 30-day-old mice, but not in 42-day-old animals, while peripherally acting H₁ receptor antagonists had no influence on these parameters [20].

The clinical toxicity and proconvulsant activity of the first generation H₁ receptor antagonists were recognized and reviewed soon after their introduction [18]. Diphenhydramine has been documented to induce an activating effect on the cortical EEG of patients with epilepsy [4, 12]. Ketotifen given for the treatment of allergic rhinitis, caused an increase in seizure frequency in a child with secondary generalized epilepsy [20]. Moreover, EEG monitoring confirmed an increase in a number of epileptic discharges following D-chlorpheniramine challenge in this child while the substitution of terfenadine maintained adequate seizure control [20].

Brain toxicity following overdose of the H₁ antagonists included toxic psychoses with hallucinations resembling schizophrenia and other psychiatric emergencies [2, 9]. H₁ receptor antagonist-induced psychiatric toxicity may be secondary to seizures following overdose, which is consistent with clinical observation of postictal-psychosis [3, 5] and schizophrenia [15] in epilepsy.

The objective of the present study was to examine the influence of chronic treatment with histamine receptor antagonists on the anticonvulsant ef-

ficacy of conventional antiepileptics against maximal electroshock-induced seizures in mice. The following antiepileptic drugs were used: valproate magnesium (Polfa, Rzeszów, Poland), carbamazepine (Sigma, St. Louis, MO, USA), diphenylhydantoin (RBI, Natick, MA, USA) and phenobarbital sodium (Polfa, Kraków, Poland). In addition, the effects of antiepileptic drugs alone or in combination with histamine H₁ receptor antagonists were studied on long-term memory (tested in passive avoidance task) and motor performance (evaluated in the chimney test). The influence of astemizole (Polfa, Warszawa, Poland) or ketotifen (Sigma, St. Louis, MO, USA) on the brain and free plasma levels of the antiepileptic drugs was also evaluated by immunofluorescence. Animals were injected with histamine receptor antagonists once daily for a period of one week. On the 7th day, mice were given an antiepileptic + histamine receptor antagonists prior to the tests.

The experiments were carried out on male Swiss mice weighing 20–25 g, housed under standard laboratory conditions. Electroconvulsions were produced with the use of ear-clip electrodes (altering current of 0.2 s duration, tonic hindlimb extension taken as the endpoint). Diphenylhydantoin, carbamazepine, astemizole and ketotifen were suspended in 1% solution of Tween 80, while valproate and phenobarbital were dissolved in sterile saline. All drugs were administered intraperitoneally in a volume of 10 ml/kg. Astemizole, carbamazepine and valproate were given 30 min prior to the test, ketotifen, phenobarbital – 60 min and diphenylhydantoin – 120 min before the test.

Astemizole (at a dose of 2 mg/kg) and ketotifen (at a dose of 8 mg/kg) reduced the electroconvulsive threshold. Both, histamine blockers were ineffective at lower doses.

Astemizole (7-day treatment) at 2 mg/kg produced a significant decrease in the protective potency of phenobarbital and diphenylhydantoin. This was reflected by an increase in their ED₅₀ values. ED₅₀ values of the remaining antiepileptics were not significantly changed by this antiallergic drug. At lower doses, astemizole did not influence the efficacy of any antiepileptic drug (Tab. 1).

Similarly, ketotifen (chronic treatment) at 4 mg/kg (the dose which did not influence the electroconvulsive threshold) produced a significant reduction in the anticonvulsant activity of carbamazepine. The protective activity of phenobarbital,

diphenylhydantoin and valproate was not significantly affected following ketotifen treatment (Tab. 1).

Table 1. Effect of astemizole and ketotifen upon the anticonvulsant efficacy of conventional antiepileptics against maximal electroshock-induced seizures in mice

Antiepileptic drugs	Astemizole		Ketotifen 4 mg/kg
	1 mg/kg	2 mg/kg	
Carbamazepine	–	–	
Diphenylhydantoin	–		–
Valproate	–	–	–
Phenobarbital	–		–

– decrease in the protective potency of antiepileptic drugs;
– – no effect on the anticonvulsant action of antiepileptic drugs

Astemizole impaired motor coordination when combined with phenobarbital, and did not influence the performance of mice when administered in combinations with the remaining antiepileptics. Ketotifen injected jointly with antiepileptic drugs did not produce any motor impairment.

Phenobarbital, valproate and diphenylhydantoin when given at doses equal to their ED₅₀s (antiepileptics + astemizole) against maximal electroshock-induced seizures, in combinations with astemizole, impaired long-term memory. Similarly, valproate (at doses providing a 50% protection against maximal electroshock-induced convulsions) when combined with ketotifen, disturbed memory. Ketotifen, astemizole and the combined treatment of astemizole and ketotifen with the remaining antiepileptics, applied at doses equal to their ED₅₀ values against maximal electroshock-induced seizures, did not affect the performance of mice in the memory test. Histamine receptor antagonists (after chronic treatment) did not significantly affect the free plasma and brain levels of antiepileptics.

The results indicate that the histamine receptor antagonists diminished the anticonvulsant activity of antiepileptics against maximal electroshock-induced seizures in mice. Ketotifen, a centrally acting histamine antagonist, increased the ED₅₀ value of carbamazepine only, which is in agreement with the study of Świąder et al. [14] who studied an interaction of antazoline with conventional antiepileptic drugs. On the other hand, astemizole, poorly penetrating blood-brain barrier, reduced the anti-

convulsant activity of phenobarbital and diphenylhydantoin.

Centrally acting histamine H₁ receptor antagonists accelerated the development of amygdala kindling in rats [22]. It suggests that central histamine plays an inhibitory role in the development of brief seizure-induced epileptogenesis in the brain. Generally, histamine H₁ receptor antagonists were reported to possess non-histaminergic properties, which affected other neuronal systems such as cholinergic, noradrenergic and serotonergic systems [6, 17]. However, Shishido et al. [13] showed that the doses of pyrilamine and ketotifen used in their study had no influence on other monoaminergic or cholinergic neuronal systems. Histamine receptor antagonists did not affect the brain and free plasma levels of carbamazepine, phenobarbital and diphenylhydantoin. Thus, a pharmacokinetic interaction does not seem probable.

Combined treatment with astemizole and phenobarbital resulted in an impairment of motor performance, as measured in the chimney test. Ketotifen did not produce any side effects in this test. Most combinations, however, produced considerable long-term memory impairment when compared with vehicle-treated controls.

In conclusion, our study demonstrates that second generation of antihistamine drugs does not necessarily seem to be safer than the first one in terms of interaction with antiepileptic drugs. Especially, the astemizole-induced impairment of protective action of diphenylhydantoin and phenobarbital is unexpected because of the poor penetration of this antiallergic drug into the brain. This indicates that either peripheral effects of astemizole are of importance in this regard or it enters the brain in concentrations enough to affect the anticonvulsant activity of some antiepileptics.

Acknowledgment. This study was supported by the grant No. P05A044-18 from the State Committee for Scientific Research, Warszawa, Poland.

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Received: January 23, 2001.