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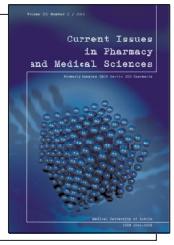

Influence of astemizole, an H_1 receptor antagonist, on the locomotors activity of carbamazepine and valproate in mice

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ABSTRACT

In the present study, we examined the influence of the second generation H_1 receptor antagonist, astemizole, co-administered with carbamazepine and valproate on the exploratory and spontaneous activities in mice. Locomotor activity was monitored electronically using a Digiscan system with relation to the ambulatory and rearing activities, as well as, total distance traveled by animals within two 15-min periods. Results indicated that astemizole given alone did not affect on the three variable of motor activity, i.e. horizontal activity, total distance or vertical activity in mice. However, this H_1 receptor antagonist significantly worsened horizontal and vertical activity of mice when was co-administered with valproate or carbamazepine in exploratory time. Moreover, it decreased total distance in combination with carbamazepine evaluated in spontaneous time. Our data clearly indicated that even newer generation of histamine receptor antagonists should be used with caution in patients suffering on epilepsy. It should be stressed that combined treatment of astemizole with carbamazepine or valproate may be clinically hazardous.

Keywords: exploratory locomotor activity, spontaneous locomotor activity, antiepileptic drugs, astemizole, adverse-effect profile

INTRODUCTION

The biogenic amine histamine has recently been suggested to be a neurotransmitters or neuromodulator in the mammalian brain [7, 14]. It was previously reported that histamine affects a variety of brain activity such as: arousal state, locomotor behavior, feeding behavior or regulation of pain [5, 14] but the role of central histamine and histamine receptors in convulsions are still uncertain. There are reports that H_1 receptor antagonists occasionally produce convulsions in healthy children [15] and in adult epileptic patients [1]. On the other hand, in experimental studies, Gerald and Richter [4] observed effects of histaminergic agents on the susceptibility to mice of seizure. Moreover, Tuomisto and Tacke [13] suggested that brain histamine may be important in inhibition of maximal electroshock seizure in rats. Also, Scherkl et al. [6] found that L-histidine, which elevated brain histamine levels as a precursor of histamine, increased the threshold for pentetrazole-induced seizure. Then, centrally acting H_1 receptor antagonists like diphenhydramine, antazoline or pyrilamine were shown to potentate electro- [3, 8, 9, 11] or chemoconvulsions [12].

The aim of this study were evaluated the effect of astemizole on locomotor activity of some conventional antiepileptic drugs. Carbamazepine and valproate were given at doses equal to their ED_{50}s against maximal electroshock in mice, whilst astemizole was administered at dose 2 mg/kg, which did affect the electroconvulsive threshold [10].

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MATERIALS AND METHODS

Animals

Adult male Swiss albino mice (weighing 22-26 g) were purchased from a licensed breeder (Dr. T. Gorzkowska, Warszawa, Poland). The animals were housed in colony cages with free access to food (chow pellets) and tap water. The experimental temperature was 23 2C and mice were on a natural light-dark cycle. After 7 days of adaptation to laboratory conditions, the animals were randomly assigned to experimental groups (consisting of 12 animals). Each mouse was used only once. All experimental procedures were approved by Local Ethics Committee of Lublin.

Drugs

The following drugs were used throughout the study: astemizole (Polfa Warszawa, Poland) and conventional antiepileptic drugs: valproate magnesium (Dipromal, Polfa Rzeszów, Poland) and carbamazepine (Amizepin, Polfa Warszawa, Poland). Valproate was dissolved in distilled water, while astemizole and carbamazepine were suspended in a 1% solution of Tween 80 (Sigma, St. Louis, MO, USA). All drugs were administered intraperitoneally (i.p.) in a volume of 0.1 ml/g body weight. The drugs were given 30 min prior to the test.

Locomotor activity

Apparatus. Locomotor activity was assessed with a Digiscan Animal Activity Monitor System (Omnitech Electronics, Columbus, OH, USA). Each monitor consisted of a 41 x 41 x 32 cm Plexiglas open field box with a grid of infrared beams mounted horizontally every 2.5 cm and vertically every 4.5 cm. Photocells located on the wall directly opposite each photo-beam were activated when the animal interrupted the beam. Each box was partitioned with acrylic cross into four (20 x 20 x 32 cm) quadrants. Mice were placed and tested in the opposite quadrant of each unit (i.e. two mice per box). The photocells of each activity box were connected to the Digiscan analyzer that transmitted the number of beam breaks (activity data) to a computer. During operation, the pattern of beam interruptions was electronically recorded and analyzed by IBM-PC compatible computer. The activity monitoring system checked for interruptions of each infrared beam at a frequency of 100 Hz. Interruption of any beam was recorded as an activity score. Simultaneous interruptions of two or more consecutive beams separated by at least 1 s were recorded as a movements score. All activity data were collected during two consecutive 15-min periods. Cumulative counts were compiled and downloaded every 15 min into the data collection software, which organized these counts into different motor indices.

Three types of activity were assessed: two variables of horizontal activity, such as total distance (cm) traveled and number of horizontal movements (number of separate horizontal movements executed by an animal with a minimum stop time of 1 s to separate movements), and vertical activity, recorded as the total number of photobeams interrupted on the elevated sensors.

Procedures. The day before the test, animals were to habituated to testing procedures and their particular activity chamber, and began immediately after i.p. injections of the water vehicle. The day after, mice were evaluated in the same condition. Prior to the test, the animals were deprived of all food for 24 h. Antiepileptic drugs were given at doses equal to their ED_{50} values against maximal electroshock-induced seizures. Mice were given drugs at times scheduled for the electroconvulsive test, according to Świąder et al. [10]. Each mouse immediately after injections was placed into designated activity chamber. Measurement was made two times in a 15 min period. First times was found as an exploratory activity, while second one was defined as a spontaneous activity of mice.

Treatment protocol

The animals were injected with a single dose of H_1 receptor antagonist and one of the antiepileptics at the time prior to the tests characterized above. Conventional antiepileptic drugs were tested at the time of their peak-anticonvulsant activity according to our previously published studies, whilst the astemizole-time of maximum activity was determined experimentally [10].

Statistics

The results from the locomotors activity were statistically verified by Kruskal-Wallis (non-parametric ANOVA test) followed by Dunn's test.

RESULTS

Effects of astemizole treatment alone or co-administered with antiepileptic drugs on locomotor activity of mice in exploratory time.

Astemizole given alone (at the dose of 2 mg/kg) did not affect on the three variable of motor activity, i.e. horizontal activity, total distance or vertical activity in mice. However, this H_1 receptor antagonist significantly decreased vertical activity of mice when was co-administered with carbamazepine or valproate. Moreover, it was noted that astemizole (2 mg/kg) significantly impaired of horizontal and vertical activity of animals receiving valproate (240 mg/kg) versus control group. On the other hand, increased of total distance have been shown in groups treated with valproate (at the doses of 240 and 252 mg/kg) or carbamazepine (10.4 mg/kg). In animals which received carbamazepine (10.4 mg/kg) alone has been observed intensification of total distance and vertical activity (Tabl. 1).

Table 1. Influence of astemizole (1-day treatment) on exploratory locomotors activity in mice

Drugs [mg/kg]	Horizontal activity		Vertical activity
	Movement	Total distance	Movement
Vehicle	1545±109	646±93	224±25
Astemizole [2]	1397±158	1435±131	341±22
CBZ [10.4]	1992±265	1026±67*	351±27*
CBZ [8.6]	1990±267	862±184	395±82
CBZ [8.6] + Astemizole [2]	1153±122	597±93	106±22*;#
VPA [252]	1832±181	1518±173*	213±33
VPA [240]	1863±178	1621±274*	256±34
VPA [240] + Astemizole [2]	969±179*;#	780±140#	81±26*;#

*p<0.05 vs. vehicle

#p<0.05 vs. to the respective dose of antiepileptic drug given alone

Carbamazepine (CBZ) and valproate (VPA) were given i.p. 30 min before testing. Astemizole in single dose was given i.p. 30 min before testing. Presented values are the means SD of 12 determinations. The results were statistically verified by the Kruskal-Wallis test followed by Dunn's test.

Effects of astemizole alone or administered with antiepileptic drugs on locomotor activity of mice in spontaneous time.

Astemizole (2 mg/kg) combined treatment with carbamazepine (8,6 mg/kg) significantly impaired movement and total horizontal distance of mice when compared to vehicle treated group. Additionally, decreased of total horizontal activity it was find versus animals receiving carbamazepine alone. Also, changed of horizontal activity (measured in movement or total distance) have been shown in group treated with valproate alone (at the doses of 240 or 252 mg/kg). In this context it seems very interesting the fact that combination of astemizole with valproate (240 mg/kg) significantly decreased horizontal activity movement in comparison to saline treated group. In contrast, locomotor activity of the remaining AEDs combined with astemizole or given alone are similarly to that of control groups (Tabl. 2).

Table 2. Influence of astemizole (1-day treatment) on spontaneous locomotors activity in mice

Drugs [mg/kg]	Horizontal activity		Vertical activity
	Movement	Total distance	Movement
Vehicle	1046±141	305±73	152±58
Astemizole [2]	630±192	207±67	128±18
CBZ [10,4]	1161±118	349±50	133±15
CBZ [8,6]	1108±282	464±126	2771±22
CBZ [8,6] + Astemizole [2]	321142*	108±75*,#	85±21
VPA [252]	1023±67	829±83**	119±19
VPA [240]	621±122*	478±89	71±21
VPA [240] + Astemizole [2]	263±79**	236±50	39±10

*p<0.05; **p<0.01 vs. vehicle
#p<0.05 vs. to the respective dose of antiepileptic drug given alone
Carbamazepine (CBZ) and valproate (VPA) were given i.p. 30 min before testing. Astemizole in single dose was given i.p. 30 min before testing. Presented values are the means SD of 12 determinations. The results were statistically verified by the Kruskal-Wallis test followed by Dunn's test.

DISCUSSIONS

In our previously published data we indicated that astemizole reduced the threshold for electroconvulsions and at the lowest effective dose of 2 mg/kg, decreased the anticonvulsant activity of phenobarbital and diphenylhydantoin, but not that of valproate and carbamazepine and produce neurotoxic effects in the chimney test in mice [10]. It is noteworthy that astemizole diminished the anticonvulsant properties of conventional AEDs only following 7-day treatment, being without effect upon the ED_{50} values of the AEDs when given acutely. Furthermore, astemizole did not affect the free plasma and brain concentrations of conventional AEDs (12), so the possibility of pharmacokinetic events may be excluded.

On the other hand, astemizole at 2 mg/kg, given acutely, considerably enhanced a convulsant action of aminophylline, which was reflected by a decrease in aminophylline CD_{50} value. Moreover, astemizole (2 mg/kg) significantly shortened the latency to the onset of aminophylline-induced convulsions. Also, astemizole increased the number of animals with tonic seizures and enhanced mortality in comparison to the aminophylline alone-treated animals [12].

Moreover, astemizole prolongs a cardiac QT interval that may progress to a rare but fatal cardiac ventricular tachycardia known as "torsades de pointes" [2].

The presented data have been shown that astemizole may enhance disturbance of horizontal movements as well as total distance in animals receiving antiepileptics at its ED50 values studied – for combination of valproate - on exploratory locomotor activity. Furthermore, co-administration of valproate with H_1 receptor antagonist aggravates impaired of vertical activity. It is noteworthy, that carbamazepine given simultaneously with astemizole exert toxic effect in mice when is compared to group receiving AED alone (at the same dose). This affect has been clearly shown on spontaneous locomotor activity time for value of total distance.

It should be emphasized that astemizole and other second generation of H_1 receptor antagonists penetrates the blood-brain barrier very poorly and are largely devoid of significant sedative effects especially sedation. This is why, the second generation of H_1 receptor antagonists are very often prescribing by pediatric doctor in a broad spectrum of allergic problems.

However, as was mentioned above even small doses of astemizole seem to exacerbate the adverse effect of valproate and – to a lesser extent – carbamazepine.

In such cases newer generation of histamine receptor antagonists should be used with caution in patients suffering on epilepsy. It should be stressed that combined treatment of astemizole with carbamazepine or valproate may be clinically hazardous.

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REFERENCES

1. Churhull J.A., Gammon G.D.: The effect of antihistaminic drugs on convulsive seizures. *J. Am. Med. Assoc.*, 141, 18, 1949.
2. Estes K.S., González M.A.: Pharmacokinetic aspects of second-generation H1 antihistamines: a reply to Philpot. *Int. J. Clin. Pharmacol. Ther.*, 37, 310, 1999.
3. Fairbairn S., Sturman G.: The influence of central histaminergic modification on the susceptibility of mice to chemically-induced seizures [abstract]. *Br. J. Pharmacol.*, 1989, 97, supl. 317.
4. Gerald M.C., Richter N.A.: Studies on the effects of histaminergic agents on seizure susceptibility in mice. *Psychopharmacologia* 46, 277, 1976.
5. Onodera K., Watanabe T.: *Possible roles of brain histamine H3 receptors and the pharmacology of its ligands.* Nihon Shinkei Seishin Yakurigaku Zasshi 15, 87, 1995.
6. Scherkl R., Hashem A., Frey H.: Histamine in brain – its role in regulation of seizure susceptibility. *Epilepsy Res.*, 10, 111, 1991.
7. Schwartz J.C. et al.: Histaminergic transmission in the mammalian brain. *Physiol Rev.*, 71, 1, 1991.
8. Świąder M. et al.: Influence of antazoline on the anticonvulsant activity of conventional antiepileptic drugs against maximal electroshock-induced seizures in mice. *Pol. J. Pharmacol.*, 51, 104, 1999.
9. Świąder M. et al.: Influence of chronic treatment with H1 receptor antagonists on the anticonvulsant activity of antiepileptic drugs. *Pol. J. Pharmacol.*, 53, 93, 2001.
10. Świąder M. et al.: Interaction of astemizole, an H1 receptor antagonist, with conventional antiepileptic drugs in mice. Pharmacol. *Biochem. Behav.*, 76, 169, 2003.
11. Świąder M. et al.: Influence of antazoline and ketotifen on the anticonvulsant activity of conventional antiepileptics against maximal electroshock in mice. *Eur. Neuropsychopharmacol.*, 14, 307, 2004.c
12. Świąder M.J. et al.: Effect of histamine receptor antagonists on aminophylline-induced seizures and lethality in mice. *Pharmacol. Rep.*, 57, 531, 2005.
13. Tuomisto L., Tacke U.: Is histamine an anticonvulsive inhibitor transmitter. Neuropharmacology, 25, 955, 1986.
14. Wada H. et al.: Is the histaminergic neurons system a regulatory center for whole-brain activity? *Trends Neurosci.*, 14, 415, 1991.
15. Wyngarden J.B., Seevers M.H.: The toxic effects of antihistaminic drugs. *J. Am. Med. Assoc.*, 145, 277, 1951.