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CORRELATION BETWEEN EXPERIMENTAL AND CLINICAL EFFECTIVENESS OF BENZODIAZEPINES AND THEIR AFFINITY FOR BENZODIAZEPINE RECEPTORS

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KEY WORDS: benzodiazepines; tranquilizers; prognosis; receptors.

Recently during the study of the mechanism of action of the benzodiazepines great attention has been paid to analysis of their highly specific binding with certain regions of synaptic membranes in the human and animal brain [10, 13]. With respect to certain manifestations of the action of benzodiazepines, correlation has been found between the inhibition constants and activity of these drugs experimentally [7, 9, 12]. Meanwhile, the role of binding with the receptor for realization of the tranquilizing effect of benzodiazepines when used clinically has not been adequately studied. In addition, there are no clear criteria with which to assess the experimental action of benzodiazepines [1, 14], so that their clinical effects cannot be confidently predicted.

The object of this investigation was to discover correlation between effectiveness of the benzodiazepines, according to the most representative methods of experimental study, their integral clinical effect, and their affinity for benzodiazepine receptors.

EXPERIMENTAL METHOD

To assess tranquilizers in experiments on animals, the following tests were used: conditioned defensive and food reflexes, a conflict-inducing situation, external inhibition, aggressive reactions, spontaneous motor activity, antagonism tests with metrazol and thiosemicarbazide, and potentiation of hexobarbital sleep. The methods were all described previously [2].

The comparative clinical study of the compounds was carried out by a standardized method of clinical assay of psychotropic drugs [3]. The clinical material for the investigation consisted of 360 observations on patients with various neurotic and neurosis-like states. Groups of patients receiving the various tranquilizers were standardized by diagnosis and syndrome, the severity of individual symptoms, the duration of the syndrome, and also by sex, age, and numerical composition [5].

Specific binding of benzodiazepines with the receptor was determined by the usual method [10]. Affinity for the receptor was assessed by the value of IC_{50} (the concentration of the substance in which, in a state of equilibrium, the ligand occupies half of the maximal possible number of binding sites).

Correlation was determined by calculating Spearman's coefficient of correlation [4].

EXPERIMENTAL RESULTS

The experiments showed that all tranquilizers studied, namely, phenazepam (P), lorazepam (L), nitrazepam (N), diazepam (D), oxazepam (O), and chlorodiazepoxide (C) possess high pharmacologic affinity, by all tests used (Table 1). Clinical study of the psychotropic effects of the benzodiazepines enabled the degree of therapeutic activity of the various substances in relation to particular neurotic symptoms to be established and the integral, global tranquil-

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TABLE 1. Rank Correlation of Clinical Effectiveness, Experimental Pharmacologic Activity, and Affinity for Benzodiazepine Receptor

Values compared	Order of rank						Spearman's rank correlation coefficient
	F	L	N	D	O	C	
Clinical study							
Global tranquilizing effect	1	2	3	4	5	6	—
Experimenal study							
Conflict-inducing situation	1	2	3	4	5	6	1±0
External inhibition	2	1	4	3	5	6	0,89±0,086
Antiaggressive action	1	2	5	3	4	6	0,83±0,13
Conditioned food reflex in Skinner's box	4	2	1	3	5	6	0,6±0,26
Conditioned defensive reflex	1	5	2	4	3	6	0,6±0,26
Inhibition of motor activity	2	1	3	4	5	6	0,89±0,086
Antagonism with metrazol	2	1	3	4	5	6	0,9±0,041
Antagonism with thiosemicarbazide	1	2	3	4	5	6	1±0
Potentiation of hexobarbital	1	2	3	4	5	6	0,9±0,041
Affinity for receptor							
Ranks	1	2	3	4	5	6	1±0
Affinity IC_{50}, pM	2	57	34	35*	80*	1072*	—

*According to data in [13].

izing action, an integral parameter reflecting the general therapeutic effectiveness of a given preparation, to be distinguished. The benzodiazepines are shown in Table 1 in order of clinical effectiveness.

Comparison of the effectiveness of the tranquilizers experimentally and clinically showed strongest correlation when their clinical activity was compared with their effectiveness in the conflicting situation test and antagonism with thiosemicarbazide. The coefficient of correlation also was fairly high when clinical effectiveness was compared with the results of the external inhibition test and antagonism with metrazol. Meanwhile, in the conditioned defensive and food reflex tests correlation between the experimental and clinical data was completely absent (Table 1). This is evidence that the conditioned reflex tests which several workers have used [6, 8, 11] for the experimental assessment of benzodiazepines are unsuitable for predicting clinical tranquilizing effects. It was thus shown to be possible to predict the integral tranquilizing effect of benzodiazepines under clinical conditions on the basis of only a limited number of experimental tests: in the first stage of screening by antagonism with thiosemicarbazide or metrazol, and in the second stage by the conflict-inducing situation test.

The study of correlation between the integral clinical tranquilizing effect of the benzodiazepines and their experimental activity according to the most appropriate test (conflict-inducing situation) and affinity for benzodiazepine receptors showed a high degree of correlation between these parameters. The results suggest that the power of the integral tranquilizing effect is to a certain extent due to the degree of affinity of the substances for the benzodiazepine receptor.

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CORRELATION BETWEEN ANESTHETIC AND ANTIARRHYTHMIC ACTIVITY OF α-AZACYCLOALKANECARBOXYLIC ACIDS AND THEIR EFFECT ON PERMEABILITY OF BILAYER PHOSPHOLIPID MEMBRANES

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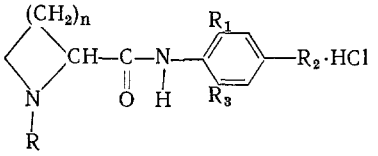
KEY WORDS: physicochemical properties; surface activity; artificial bilayer phospholipid membrane; anesthetic activity; antiarrhythmic activity.

In the search for new anesthetics, a number of aromatic amides of N-substituted α-azacycloalkanecarboxylic acids (AACACA) with the general formula



were synthesized at the Institute of Pharmacology, Academy of Medical Sciences of the USSR.

Meanwhile, the importance of physicochemical properties in the action of neurotropic drugs has been demonstrated [2, 4]. Correlation has been found between the anesthetic effect of compounds of various derivatives of the AACACA and their surface and interphase activity on different partition boundaries.

It was decided to study the effect of the most strongly surface-active substances on electrical conductance of bilayer phospholipid membranes, and the investigation described below was carried out for this purpose.

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