ANTICONVULSANT ACTIONS OF TRIMECAIN AND XILOCAIN

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In their resorptive action, local anesthetics of the xilidene series (of which the best known is xilocain) exert a characteristic influence on the central nervous system and have mainly an anticonvulsant action. Bernhard et al. [5-9] came to the conclusion that for effectiveness and safety xilocain was better than the other substances they investigated. The first clinical trial of xilocain for treatment of certain forms of epilepsy gave favorable results [8].

In the Soviet Union trimecain, another preparation of the xilidene series, has been proposed as a local anesthetic; its influence on the central nervous system has not been sufficiently studied. There are indications that it reduces the frequency of spontaneous cerebral electrical activity in the rabbit [1], and is able also to inhibit activation of the EEG by nociceptive stimulation [2]. No descriptions have been published of the anticonvulsant action of trimecain.

The object of the present work has been to establish the nature and "spectrum" of the anticonvulsant action of trimecain, to compare it with those of xilocain, and to determine the nature of certain other central influences which come under the heading of side effects.

EXPERIMENTAL METHODS

The "spectrum" of anticonvulsant action of trimecain and xilocain was determined by the standard methods: the determination of maximum electric shock (MES) and the corasole convulsions test. A criterion of the anticonvulsant effect of electric shock was the prevention of the tonic extensor component of the attack. In evaluating the results obtained with the corasole test we determined three separate indices: prevention of clonic spasm, elimination of tonic extension of the hindlimbs, and survival. The observations were made for one hour after the subcutaneous injection of 100 mg/kg corasole, given 5 min after injection of the preparations. The muscle-relaxant effect usually observed after injection of large amounts of these substances was estimated by the "rotating arm" method [12], where the effect measured was the failure of the animal to maintain itself on a horizontal bar 22 mm in diameter rotating at 5 rev/minute. The animals tested were white male mice weighing 20-25 g. For all the indices, the 50% effective dose (ED_{50}) was determined by Litchfield and Wilcoxon's method [14] 15 min after the substance had been injected. Xilocain and trimecain were injected intraperitoneally as aqueous solutions.

In white mice, both compounds revealed the power to prevent the development of the tonic phase of the convulsions in electric shock. This effect was marked even 15 min after the injection, and died away over the next 30 min. Figures for the absolute and relative activities of xilocain and trimecain in terms of their power to alter the nature of a convulsive attack induced by electrical shock are given in Table 1.

As can be seen from Table 1, trimecain is about half as active as xilocain.

The results obtained led us to test the substances by another method, the corasole convulsions test, which is also widely used on drugs to combat epilepsy.

The experiments with xilocain and trimecain whose results are given in Table 2 show the complete absence of any protective effect of these compounds against the clonic convulsions; nevertheless, the tonic extensor phase

of the attack and death which followed were prevented. In order that the substances could protect against death, both had to be given in considerably larger doses than were sufficient to eliminate tonic extension.

TABLE 1. Comparison of the Activities of Trimecain and Xilocain in Terms of Maximum Electric Shock (MES)

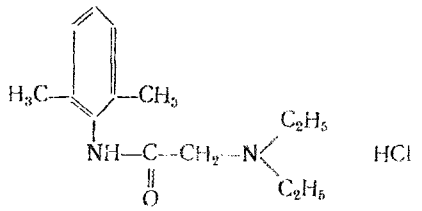
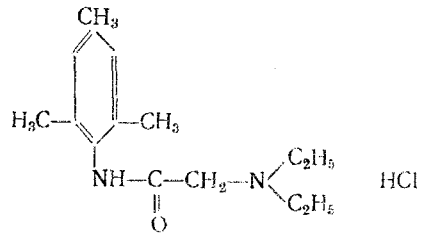
Substance, and its chemical structure	Molecular weight	ED_{50} (mg/kg of salt)	Relative activity
Xilocain 	270,5	21,6 (18,9—27,7)	
Trimecain 	284,5	46 (38—55,6)	0,47 (0,37—0,59)

TABLE 2. Comparison of the Activities of Trimecain and Xilocain in Terms of the Prevention of Convulsions Induced by Corasole

Substance	ED_{50} (mg/kg of salt)	Relative activity
Prevention of clonic spasm		
Xilocain	—	—
Trimecain	—	—
Prevention of tonic extensor phase of attack		
Xilocain	25.9 (24-27.9)	1 0.53
Trimecain	49 (42.6-56.4)	(0.45-0.62)
Prevention of death (for 1 h)		
Xilocain	39.3 (32.3-48)	1
Trimecain	76 (58.5-98.9)	0.52 (0.37-0.72)

When the doses were increased, there was a serious disturbance of the gait, an ataxia developed, movements were disorderly, and the animals fell on one side. The ataxia, which is interpreted as a side effect, was shown as an inability of the mice to remain on the rotating arm. This action developed very rapidly after the injection, and reached its maximum after 10 min. Usually it did not last for more than 1 h. The development of this effect is shown in Fig. 1, where for comparison the development of the muscular relaxant action of aminasine is also given. In these experiments the doses were calculated so that the maximum action of all three substances induced ataxia in 90-95% of the animals. The muscular relaxant action of aminasine developed gradually, reaching a peak at the end of the first hour after injection. For the xilidene products the effect reached a maximum after 10 min, then rapidly waned, and disappeared completely at the end of 1 h.

A comparison of the activity of xilocain and trimecain by several tests has enabled us to form an idea of the "spectrum" of the two substances. Graphically, the "spectrum" can be expressed as the sum total of the effective 50% doses of each of the two substances to be compared. In Fig. 2 the height of the column represents the ED_{50} for each of the tests. All the ED_{50}s of xilocain lie, as can be seen, below the corresponding values for trimecain. It should be noted that the ED_{50} of trimecain as determined by the rotating bar test was smaller than that of the same substance as determined by the survival of mice after the injection of corasole. This principal difference between trimecain and xilocain appears still more clearly (Table 3) if the value of the ED_{50} of the substance for each of the tests is expressed as a percentage of the ED_{50} for the test on the rotating bar (side effect).

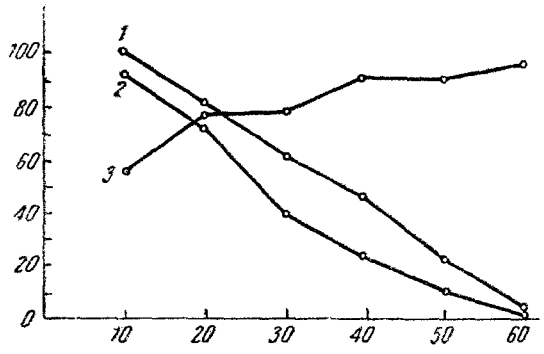


Fig. 1. Development of the muscular relaxant action of trimecain, xilocain, and aminasine. Ordinate – number of animals with signs of ataxia (percentage). Abscissa – time (in min). 1) Xilocain (60 mg/kg); 2) trimecain (80 mg/kg); 3) aminasine (4 mg/kg).

TABLE 3. Selectivity and Therapeutic Range of Action of Xilocain and Trimecain in Different Tests

Criterion of drug action	ED_{50} (anticonvulsive effect) × 100% / ED_{50} (ataxia)	
	xilocain	trimecain
Incapability on "rotating bar" (ataxia)	100	100
Survival after injection of corasole	85	129
Prevention of tonic phase of corasole convulsions	56	83
Elimination of tonic-extensor component in electric shock	47	78

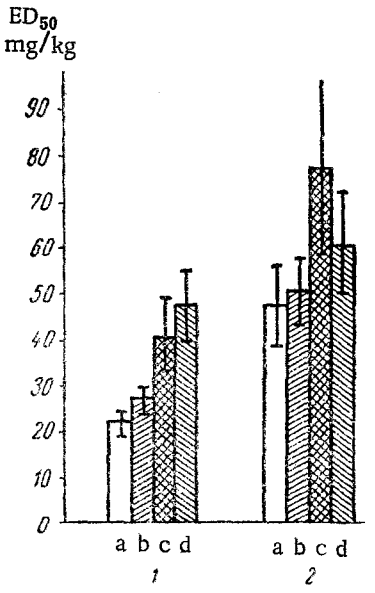


Fig. 2. Comparison of trimecain and xilocain showing identity of various features of their central action. Horizontally – activity of (1) xilocain and (2) trimecain in the elimination of the tonic extensor phase of convulsions induced (a) by electric shock, and (b) by the injection of corasole; (c) indicates the prevention of death in mice after the injection of corasole; (d) indicates the muscular relaxant effect.

The results of Table 3 indicate the smaller therapeutic range of trimecain in comparison with xilocain, and confirm the relative activities of the substances as stated above.

A comparison of the anticonvulsive activity of trimecain and xilocain leads us to conclude that there is a great resemblance between the two substances. The known property of xilocain to protect against the tonic component of convulsions in maximum electric shock is possessed also by trimecain, though to a far smaller extent. The relative activity of trimecain according to this test is 0.47 of that of xilocain.

Experiments with the corasole convulsion test, which showed that the preparations did not influence the course of the clonic component but did eliminate the tonic phase of the convulsions, confirm what Berry et al. [10] found when they made a comparative study of xilocain and another new anesthetic of the xilidene series – mepivacain. They

showed also that xilocain derivatives did not prevent convulsions induced by strychnine, and we therefore did not carry out this test in the present investigation. The incomplete antagonism with corasole and the absence of any antagonism with strychnine do not contradict the clinical finding of the effectiveness of xilocain derivatives in various forms of epilepsy [7, 8, 11]. It is known, for example, that the highly effective anticonvulsant substance, diphenine, does not protect against corasole convulsions, and the antagonism against strychnine is more characteristic of substances with myanesin-like action than it is of typical anti-epileptiform preparations [13].

Because of the complete resemblance of the spectra of the anticonvulsant action of the two drugs, trimecain can be used in cases where xilocain is applicable. If, however, we take into account that trimecain has approximately half the activity, and that its toxicity is 1.4 times less [3], it follows that xilocain is to be preferred in such cases. In its resorptive action, trimecain closely resembles xilocain: with both drugs the maximum effect occurs 10 min after injection; it then falls rapidly, and disappears completely after 1 h. This property apparently explains the rapid arrest of the convulsive attack and the unsuitability of these substances for prolonged prophylaxis [7, 8].

SUMMARY

Two local anesthetics – xilocain and trimecain (diethylamino-2,4,6-trimethylacetanilide hydrochloride) – employed clinically were tested on mice for their anticonvulsive actions, by applying the maximum electric shock seizure test (MES) and by the corasole induced convulsions test (metrasole test). Their side-effects (neurological toxicity) were studied by the "rotating bar" technique. Both drugs failed to prevent clonic convulsions after administration of 100 mg/kg corasole. Conversely, they abolished the hindlimb tonic extensor phase of the maximum electrical and corasole shock seizures. The ED_{50} was determined for both drugs, and their relative activity calculated by the Litchfield and Wilcoxon method (1949). Trimecain proved to be only half as potent as xilocain. It is suggested that both drugs have a common anticonvulsant action.

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