LOCAL ANESTHETIC PROPERTIES OF A TRIMECAINE POLYMER

Yu. D. Ignatov, Yu. N. Vasil'ev,
L. I. Shal'nova, E. L. Trofimova,
K. A. Makarov, and T. S. Mikhailova

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Research is currently in progress on modification of local anesthetics by mixing them with polymers, by copolymerization, and by incorporating them into the structure of water-soluble natural and synthetic polymers with the aid of different chemical bonds [2, 4, 8]. This increases the duration of the anesthetic effect and reduces their resorptive and local-irritant action [6, 7]. However, certain polymers of procaine, trimecaine, and amethocaine do not possess sufficiently prolonged action. The aim of this investigation was to study the local anesthetic activity of a new polymer of trimecaine and to compare it with that of trimecaine hydrochloride.

EXPERIMENTAL METHOD

Experiments were carried out on rabbits and rats. To investigate the local anesthetic activity of the preparations in terminal analgesia, the classical technique of Regniers was used on rabbits. As screening models of infiltration and conduction anesthesia the tail flick method [9] in rats was used with the thermal effect of a focused beam of light from a 100-W incandescent lamp. Polymers of trimecaine were used, and as the polymer matrix, the substance carboxyl, containing a water-soluble copolymer of vinyl alcohol, was chosen. To assess the local anesthetic activity of the preparations in infiltration anesthesia, the test substance was injected in a volume of 0.5 ml into the proximal third of the tail, and in conduction anesthesia uniform ring block of the tail with 1 ml of a solution of the preparation was used. Complete anesthesia was taken to be an increase in the latent period of the nociceptive reflex, determined every 15-30 min for 3-4 h (2 trials), by 100%, for a special series of experiments showed that subsequent exposure to heat, despite injury to the tail, was not accompanied by the onset of aversive reactions. For a more detailed analysis of the local anesthetic properties of the new preparations, methods of electrical stimulation of the pulp of the tooth and of a cutaneous nerve were used in chronic experiments on rabbits, whereby all components of the complex nociceptive response can be estimated [3]. Solutions of trimecaine and of its polymer were injected in a volume of 2 ml into the region of the nerve trunk. The time course of release of trimecaine from the polymer under model conditions was studied by the method of UV-spectroscopy. Statistical analysis was carried out by the usual methods.

EXPERIMENTAL RESULTS

The minimal local anesthetic effect of trimecaine hydrochloride in terminal anesthesia appeared after injection of 0.1% solution of the drug; the duration of complete anesthesia was 15 min (Fig. 1a). The longest duration of the local anesthetic effect was observed when 1-2% solutions were used; complete anesthesia in this case was present for 45-60 min respectively. The sample of the trimecaine polymer tested gave a prolonged anesthetic effect. On a model of terminal anesthesia the duration of action of trimecaine polymer was 15-20 min longer than that of trimecaine hydrochloride (Fig. 1a).

The initial local-anesthetic effect of trimecaine on a model of infiltration anesthesia lasted 15-30 min after injection of a 0.1% solution of the preparation (Fig. 1b). The anesthetic action of 1-2% solutions of trimecaine hydrochloride lasted 60-90 min. The trimecaine polymer had an action two to three times as long as that of

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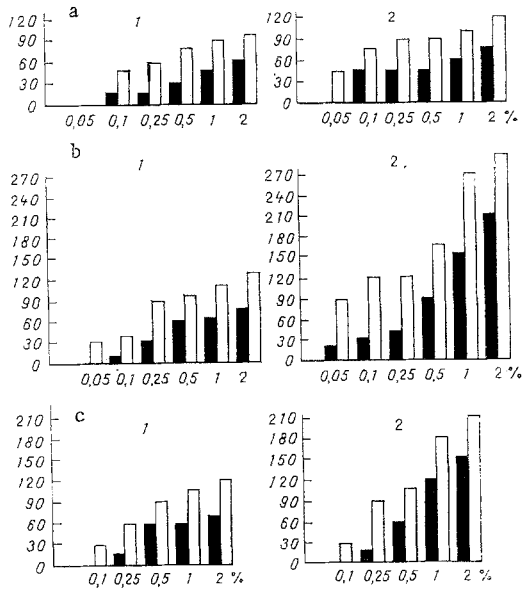

Fig. 1

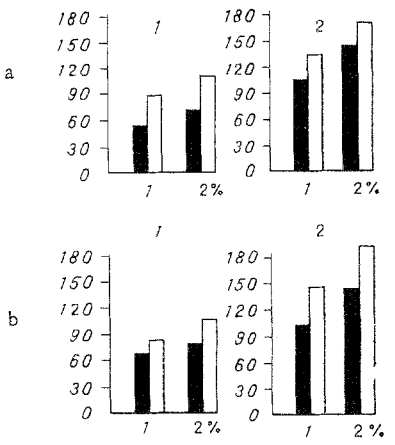

Fig. 2

Fig. 1. Effect of trimecaine hydrochloride (1) and of trimecaine polymer (2) on corneal reflex in rabbits (a) and latent period (tail flick method) during infiltration (b) and ring block of root (c) of tail in rats. Black columns show duration of complete anesthesia; white columns – recovery period. Ordinate, duration of anesthesia (in min). Abscissa, concentration of test solutions of preparations.

Fig. 2. Duration of anesthetic effect of trimecaine hydrochloride (1) and trimecaine polymer (2) during stimulation of dental pulp (A) and cutaneous nerve (B) in rabbits during free behavior. Legend as to Fig. 1.

trimecaine itself, depending on the concentration of the solution (Fig. 1b). Complete anesthesia during the action of the preparation in a 1-2% concentration was observed for 120-150 min.

The trimecaine polymer had a longer action than trimecaine hydrochloride in the case of conduction anesthesia also. Whereas trimecaine hydrochloride induced complete anesthesia for 60-90 min, the polymer compound in the same concentrations had a local anesthetic action which lasted 120-150 min.

Electrical stimulation of the dental pulp and cutaneous nerve of gradually increasing intensity in freely behaving rabbits enabled the sequence of appearance of individual components of the complex nociceptive response to be studied. Trimecaine hydrochloride, in the form of 1-2% solutions caused complete suppression of all components of the complex nociceptive response for 60-90 min, and during the next 30 min complete recovery of the initial response to pain was observed. The trimecaine polymer had an effect which lasted 1.5-2 times longer than its low-molecular-weight analog (Fig. 2). The mechanism of action of polymer compounds of local anesthetics has not been studied in detail, but when prolongation of their effect is explained it must be recalled that a local anesthetic, bound to a polymer, can block several sites on the nerve fiber membrane simultaneously and can be fixed in a definite position on account of dispersion or electrostatic forces of interaction with tissue biopolymers. This contributes to potentiation of the pharmacological effect of the polymer and prolongs the duration of its action. Prolongation of the effect of local anesthetics on a polymer matrix can also be explained by an increase in the duration of contact of the preparation with nerve fibers on account of increased viscosity of the polymer solutions used.

These views are confirmed to some degree by our data on the dynamics of trimecaine release from its polymer preparation under model conditions. The results are evidence of slow removal of the anesthetic from the carrier polymer and its migration from the zone of action of the polymer. Even after 6 h less than half of the initial quantity of the drug has been released from the polymer preparation. This situation is probably determined by gradual removal of the anesthetic and its slow release from the structure of the polymer compound.

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SELF-STIMULATION CHARACTERISTICS AND ENDOGENOUS ETHANOL IN RATS OF BOTH SEXES

L. M. Andronova, R. V. Kudryavtsev, M. A. Konstantinopol'skii, and A. V. Stanishevskaya

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Recent investigations have demonstrated the great importance of functional changes in the hypothalamic positive reinforcement system in the pathogenesis of alcoholic intoxication [3, 5, 7, 15]. However, the importance of sex differences in this matter has been neglected. Meanwhile the development of the metabolic concept of the genesis of alcoholism [2, 6] has led to widening of our ideas on the role of endogenous ethanol in the etiology of alcohol dependence in animals of both sexes.

The aim of this investigation was to study sensitivity of the positive reinforcement system in the lateral hypothalamus of rats of both sexes and the effect of prolonged self-stimulation of this system on the endogenous ethanol level in these animals.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats (11 females and 11 males). To obtain the self-stimulation reaction electrodes were implanted in accordance with coordinates from the atlas [11] at the level of the lateral hypothalamus. The animals were anesthetized with hexobarbital (150 mg/kg, intraperitoneally) for the operation. The rats were taught a self-stimulation reaction 5-7 days after the operation in a chamber with a pedal until a stable threshold and a stable frequency of self-stimulation had been reached for a period of 6 min, using currents of different strengths. Pressing the pedal was accompanied by stimulation of the brain with square pulses (Alvar stimulator, duration 0.1 msec, frequency 100 Hz, duration of volley 0.25 sec). The strength of the pulsed current was monitored on the scale of an S1-10 oscilloscope and with a M-195 microammeter. The sessions of self-stimulation lasted 30 min daily. Every week mean values of the threshold current were calculated for animals of each sex. Self-stimulation was studied in six females in two stages of the es-

TABLE 1. Self-Stimulation Parameters in Females Depending on Stage of Estrous Cycle

Stage of cycle	Threshold current strength, μA	Frequency of self-stimulations	
		threshold current	maximal current (350-400 μA)
Diestrus	205 (172—236)	176 (148—204)	406 (377—439)
Estrus	191 (158—224)	277 (254—300)	426 (388—464)

Laboratory of Pharmacology of Narcotics and Laboratory of Psychopharmacology, V. P. Serbskii All-Union Research Institute of General and Forensic Psychiatry, Moscow. Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 97, No. 6, pp. 688-690, June, 1984. Original article submitted July 12, 1983.

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