Estimation Fast-Reversible of Effects of Ethanol and Pharmacokinetic Forecast

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The alternative and graduated methods for estimation of fast-reversible effects of ethanol are compared. Estimation of the myorelaxing and anticonvulsive effects of ethanol by the alternative method can be used with some limitations for the effector analysis of ethanol pharmacokinetics. It is shown that the effector expectation of pharmacokinetic profile for ethanol based on the minimal effective doses of bicuculline inducing clonic convulsions and tonic extension is comparable to experimentally determined brain contents of ^{14}C-ethanol.

Key Words: *aliphatic alcohols; fast-reversible pharmacological effects; GABA-receptor complex*

The pharmacodynamic profile of neurotropic preparations, including aliphatic alcohols, is determined by their pharmacokinetics [5]. At the same time, pharmacodynamic parameters of ethanol and other ligands of the GABA—receptor complex (GABA—RC) can serve as the basis for the analysis of their pharmacokinetics [2]. The effector modeling of pharmacokinetics is possible after quantitative evaluation of fast-reversible effects, which change in parallel with the concentration of physiologically active compounds in the effector compartment [3].

In the present study we examined some fast-reversible effects of ethanol.

MATERIALS AND METHODS

Experiments were performed on outbred and C57Bl/6 male mice weighing 18-22 g. The myorelaxing effect was estimated in the rotating stick test [1]. Ethanol was administered intragastrally in doses 1-5 g/kg, and its myorelaxing effect was examined after 5 min-24 h of the experiment. Control mice were injected with corazol (66.7 mg/kg), picrotoxin (4 mg/kg), or bicuculline (4 mg/kg). All preparations were injected intraperitoneally. These doses caused no tonic extension or death. Ethanol was administered intragastrally in doses 1-3 g/kg, and the probability of clonic convulsion was assessed.

C57Bl/6 mice were given ethanol (1-3.5 g/kg intragastrally), and the minimal effective doses of bicuculline causing tonoclonic convulsions (D_{TCC}) and tonic extension (D_{TE}) were determined after 30 min of intravenous infusion of 0.01% bicuculline at a rate of 0.01 ml/sec. Group I mice received ^{14}C-ethanol (1.3 Ci/mol intragastrally, 1-3.5 g/kg), and the content of radioactive material in the brain was determined after 30 min. Group II mice were given ^{14}C-ethanol in a dose 2 g/kg, and the total brain radioactivity was measured after 5 min-6 h in a Rack-beta scintillation photometer [3]. The results were processed according to the algorithms described elsewhere [4].

The effector forecast for the brain content of ^{14}C-ethanol ($C_{itheor.}$) was based on the following equations:

$$ED_i = ED_c + aD_i, \quad (1)$$

$$C_{iexp.} = a'D_i, \quad (2)$$

$$C_{itheor.} = a'/a\ (ED_i - ED_c), \quad (3)$$

which describe linear dependence (1) between the administered dose of ethanol (D_i) and change in the intensity of anticonvulsive effect in experimental animals (ED_i) in comparison with the control (ED_c); linear dependence (2) between the concentration of ethanol (C_i) and its administered dose (D_i). The ex-

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pected brain content of ethanol ($C_{itheor.}$) was calculated from the D_{TCC} and D_{TE} values in experimental and control mice (3), where a is the coefficient.

RESULTS

Administration of ethanol in increasing doses results in rapid development of myorelaxation (Fig. 1). This effect was observed 5 min after administration of low doses of ethanol. The duration of the effect depends on the administered dose; however, at 5 g/kg (lethal dose) myorelaxation was observed for 21 h (Fig. 1, *a*). The dose—effect relationship in semilogarithmic coordinates is described by an S-shaped curve (Fig. 1, *b*). Previously, it was shown that brain content of ^{14}C-ethanol grows in a dose-dependent manner, reaching the maximum within 10-30 min, which coincides with the highest occurrence of the highest effect. Consequently, this effect can be referred to as fast-reversible. However, the correctness of this test for pharmacodynamic analysis of ethanol kinetics lowers because of qualitative (alternative) estimation of the effect and S-shaped dose—effect relationship.

Anticonvulsive effect of ethanol can be examined upon alternative (Fig. 2) and graduated [2,3] (qualitative and quantitative estimation, respectively) assessment of effects of a convulsive agent. In the first case (Fig. 2, *a*) a decrease in the probability of convulsive

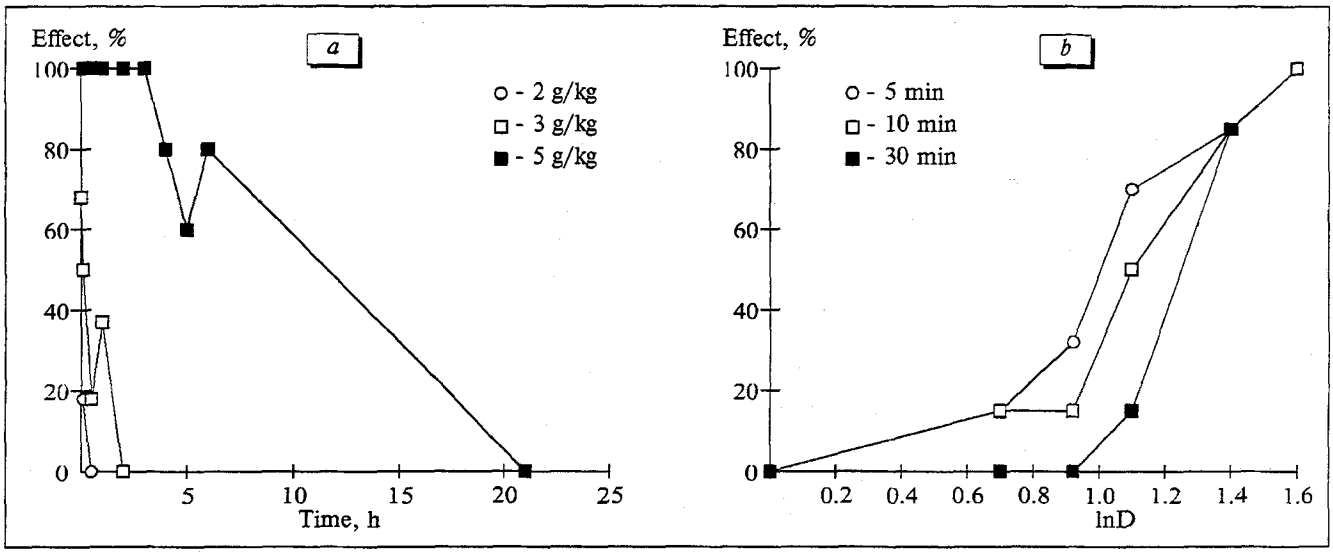

Fig. 1. Change in myorelaxing effect as a function of time (*a*) and ethanol dose (lnD, *b*).

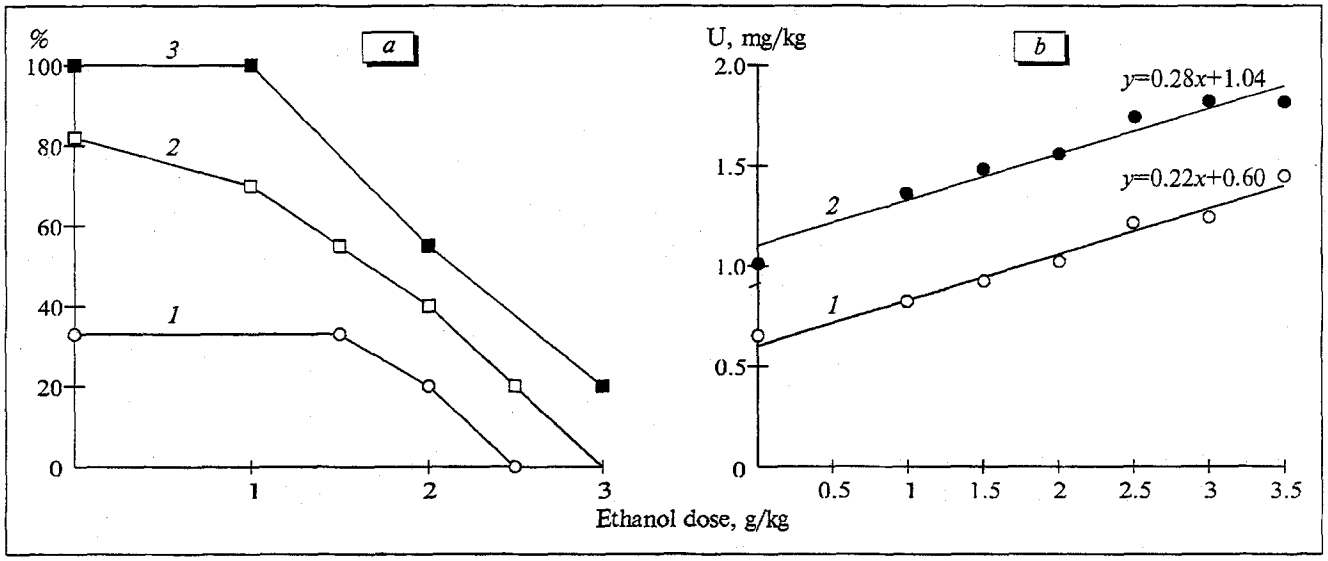

Fig. 2. Change in the intensity of myorelaxing effect expressed in alternative (% of the effect of clonic convulsions caused by intraperitoneal administration of picrotoxin, pentylenetetrazole (corazol), or bicuculline, *a*) and graduated form (change in the minimal effective doses of bicuculline, *b*) as a function of ethanol dose. *a*: *1*) picrotoxin, 4 mg/kg; *2*) pentylenetetrazole, 66.7 mg/kg; *3*) bicuculline, 4 mg/kg; *b*: doses inducing tonoclonic convulsions (*1*) and tonic extension (*2*).

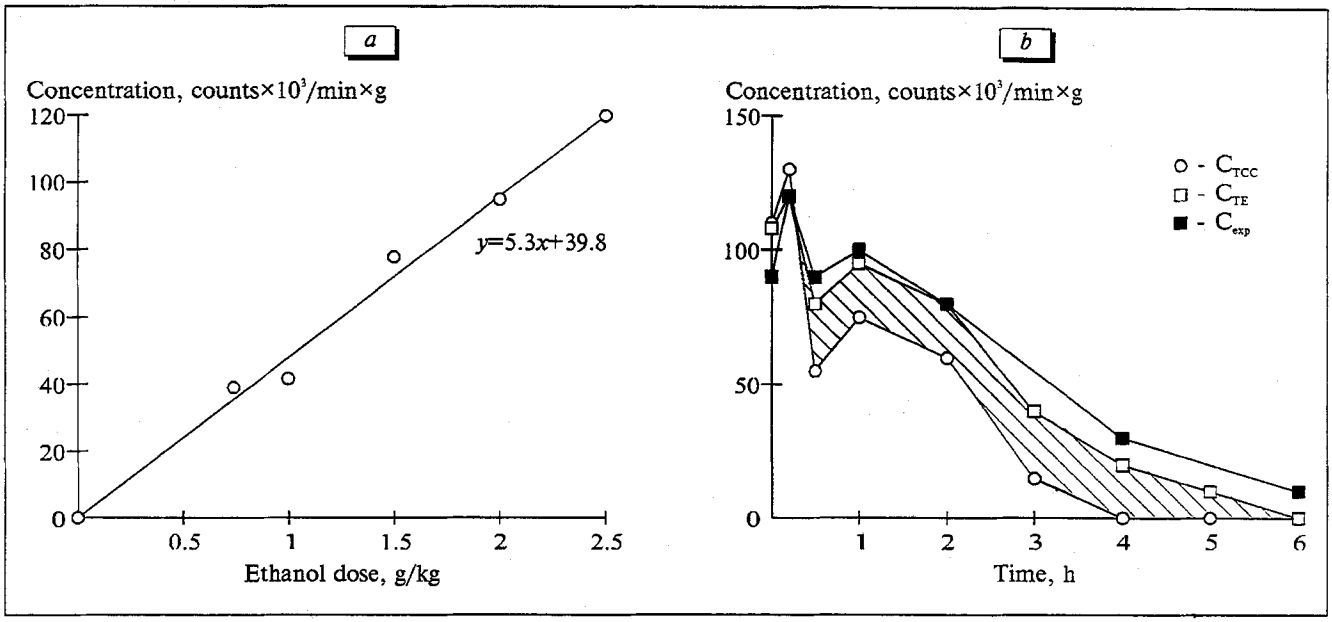

Fig. 3. Changes in brain content ^{14}C-ethanol as a function of ethanol dose (*a*) and time (*b*). C_{exp}) concentration of ^{14}C-ethanol in experiment; C_{TCC} and C_{TE}) predicted concentrations with the use of the anticonvulsive effect values (see text). Shaded sector is the divergence of the forecast.

effect caused by a GABA—RC agonist is recorded. A similar approach has been employed for screening tranquilizers [1,2]. The advantage of this method is a parallelism of the dose—effect curves for ethanol, irrespective of the convulsive agent (Fig. 2, *a*). By determining the probability of the development of a convulsive attack at various periods after administration of ethanol it is possible to examine its pharmacodynamics. However, the correlation of anticonvulsive effect of ethanol with the time between its administration and administration of a convulsive agent contains a systematic deviation determined by the dynamics of convulsive activity (±30 min) of the GABA—RC agonist, which also reduces the correctness of this method.

Quantitative evaluation of anticonvulsive effect of ethanol based on the determination of minimal effective doses of intravenously infused reverse agonists is much more advantageous [3,6]. This method allows determination of unequivocal relationship between the time of experiment (±1 min) and the effect intensity. Administration of ethanol to C57Bl/6 mice in varied dose causes a linear increase in the minimal effective dose of bicuculline which induces clonic convulsions and tonic extension (Fig. 2, *b*). A similar relationship was observed for brain content of ^{14}C-ethanol (Fig. 3, *a*). The parameters of linear regression describing the dose-dependence of anticonvulsive effect (Figs. 2 and 3) were used for the effector forecast of ^{14}C-ethanol content in the brain (Fig. 3, *b*).

The effector forecasts of brain contents of ^{14}C-ethanol based on the D_{TCC} and D_{TE} values are comparable to each other and to the brain content of ^{14}C-ethanol within the 5 min-6 h period. The discrepancies between the effector forecasts (shaded sector in Fig. 3, *b*) are admissible and comparable to the results of pharmacokinetic analysis. Consequently, on the basis of this approach it can be stated that the ethanol-induced changes in convulsive effects of bicuculline are fast-reversible and are unequivocally determined by ethanol content in the brain.

Previously, we showed that substantiation of a given effector model for 1,4-benzodiazepine and its metabolites based on mathematical description of the dose—concentration—effect relationship upon intravenous infusion of corazol offers a correct prediction of brain 1,4-benzodiazepine concentration in experimental animals [2].

Thus, our results and the approaches to their interpretation show the advantages and expand the use of quantitative evaluation of the fast-reversible effects of exogenous GABA—RC ligands, including aliphatic alcohols, in the effector modeling of their pharmacokinetics.

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