Analgesic Effect of Olipiphate on Mouse Model of Chemical Stimulation of Peritoneum

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We studied the analgesic effect of olipiphate, a product of lignin, against writhing provoked by intraperitoneal injection of acetic acid. Paracetamol was used as the reference drug. Both agents dose-dependently decreased the number of motor reactions caused by the irritant. Olipiphate possessed analgesic activity and efficiency comparable with those of paracetamol, but produced a more long-lasting effect.

Key Words: *olipiphate; paracetamol; analgesic effect*

Olipiphate is a dark-brown multicomponent solution of unknown composition obtained from lignin after rigorous chemical and physical procedures. In experiments, olipiphate demonstrated low toxicity and pronounced antitumor activity not associated with its direct cytotoxic or cytostatic action [2]. The first-stage clinical trials showed olipiphate safety for chosen administration routes. At the same time it was hypothesized that the preparation exhibits also analgesic activity. Our aim was to test this hypothesis.

MATERIALS AND METHODS

The study was carried out on 280 DBA/2 male mice (body weight 20-25 g) kept 10 per cage under standard vivarium conditions at a 12-h day-night cycle, temperature 22±1°C, 60% humidity, and food and water *ab libitum*. The mice were adapted to vivarium conditions for at least 1 week.

Olipiphate was applied in a liquid form (solution containing 50 mg active substance per 1 ml). The reference drug was nonnarcotic analgetic paracetamol. Before the experiment, paracetamol was dissolved, while olipiphate was diluted with isotonic NaCl. The drugs were injected intramuscularly in a volume of 0.1 ml/10 g body weight. The maximum examined doses of the drugs (300 mg/kg paracetamol and 500 mg/kg olipiphate) were injected into each hind limb in a volume of 0.05 ml/10 g body weight. The control mice were injected with the same volume of isotonic NaCl.

The data were analyzed statistically using INSTAT and Pharmacological Calculation System software.

For chemical stimulation of the peritoneum (writhing test) 1% acetic acid was intraperitoneally injected in a volume of 0.1 ml per 10 g body weight [1]. The test mice were placed into individual boxes (4 per cage) and their behavior was recorded for 10 min. Specific nociceptive responses (writhing) were counted. The analgesic effect was evaluated by suppression of the writhing response.

The analgesic activity of test preparations was evaluated according to alternative and gradual criteria. The latter was calculated by the formula:

$$A=(P_C-P_E)/P_C\times100\%,$$

where P_C and P_E are the numbers of convulsions for 10 min after injection of acetic acid in the control and experimental groups, respectively. Regression analysis was used to calculate dose-dependence (gradual criterion), the mean effective dose (ED_{50}), and relative activity of the test drug.

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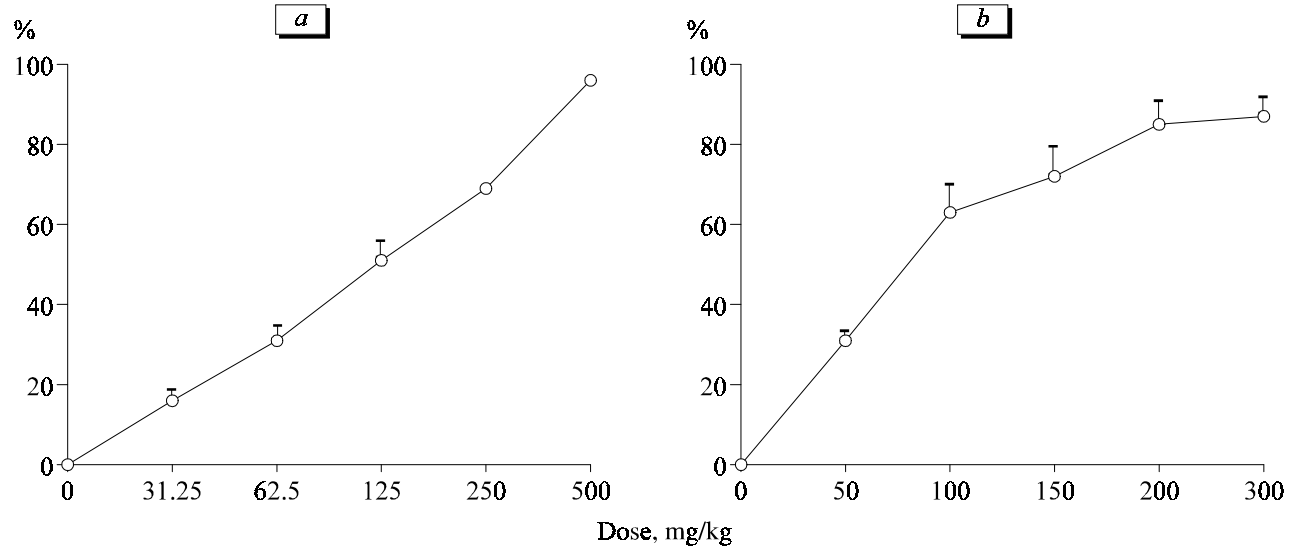

Fig. 1. Dose-dependent effect of olipiphate (*a*) and paracetamol (*b*) on mouse model of acetic acid-induced writhing. Ordinate: suppression of writhing response.

The alternative approach was based on the count of mice with specific pharmacological effect. The number of convulsions equal to M-2σ (the mean minus two standard deviations for the control group) was used as the criterion of analgesia. The analgesic effects of test preparations were compared by calculating ED_{50} using the methods of Litchfield and Wilcoxon.

The regression curve for olipiphate was used to determine the mean duration of 50% analgesia in the experimental group. The method of Litchfield and Wilcoxon for alternative criterion of pharmacological effect was used to estimate the mean time, during which analgesia persisted in 50% experimental mice.

Paracetamol was injected 15 min and olipiphate 15, 60, 120, 180, 240, 300, 360, and 420 min prior to acetic acid.

RESULTS

The test preparations produced maximum analgesic effect 15 min postinjection (Fig. 1). By gradual criterion, the ratio of ED_{50} values for olipiphate and paracetamol was 1.641 (1.17-2.44), while by the alterna-

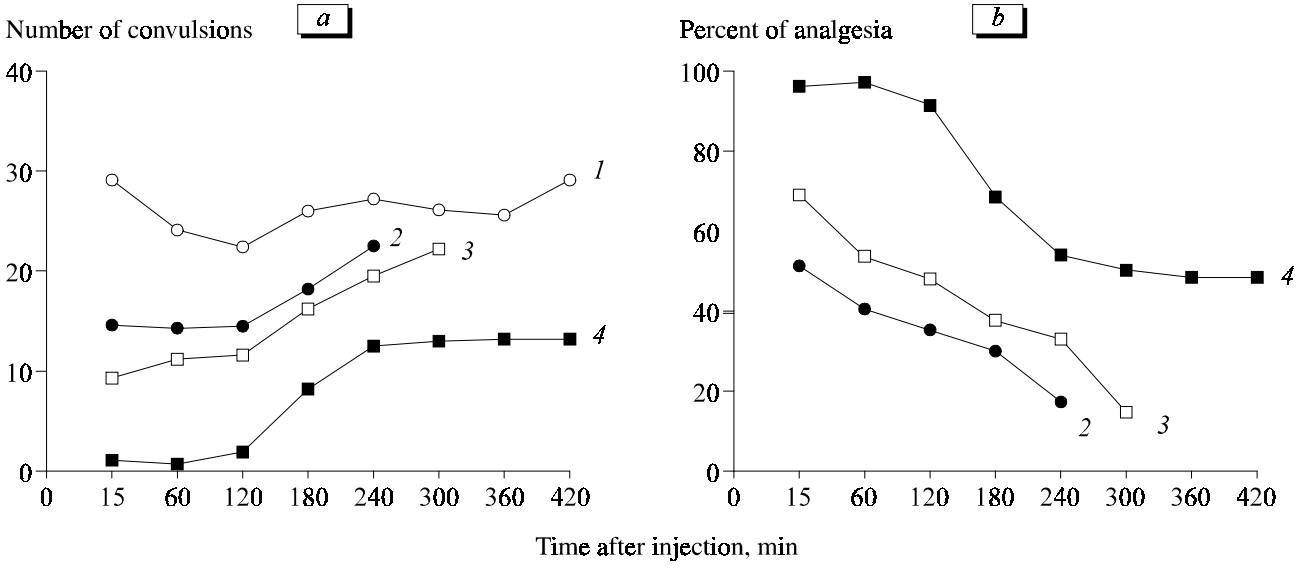

Fig. 2. Dynamics of analgesic effect of olipiphate on mouse model of acetic acid-induced writhing. Olipiphate was injected in doses 125 (*2*), 250 (*3*), and 500 mg/kg (*4*). *a*) mean number of convulsions, *b*) percent of analgesia. *Differences with control (*1*, physiological saline) are significant according to Student's *t* test.

tive criterion this ratio was 1.61 (0.86-3.0). The dose-effect curves for both preparations were parallel with insignificant difference between ED_{50}.

The analgesic effect of olipiphate attained the maximum 15 min postinjection. For example, the percents of analgesia for olipiphate doses of 31.5 and 62.5 mg/kg at this term were 15.9±2.1 and 31.1±3.6, respectively (differences from the control are significant). Higher doses of the preparations produced a more pronounced and long-lasting effect (Fig. 2). The mean duration of significant 50% analgesia was 74.9 (54.0-104.0) and 279.7 (150.3-520.5) min for 250 and 500 mg/kg olipiphate, respectively. The mean times during which significant analgesia retained in 50% animals were 224.4 (181.5-272.6) and 279.7 (150.3-520.5) min for 250 and 500 mg/kg, respectively.

Therefore, the pronounced analgesic effect of olipiphate was demonstrated on the mouse model of acetic acid-induced writhing. In this model, activity and efficiency of olipiphate were comparable with those of non-narcotic analgetic paracetamol. Olipiphate possesses low toxicity, good tolerance, and produces a long-term analgesic effect, and therefore can be useful as a perspective analgesic drug.

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