EFFECT OF METRONIDAZOLE ON THE ACTION AND BIOLOGICAL TRANSFORMATION OF ETHYL ALCOHOL

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Metronidazole prevents the development of a habituation reaction to alcohol in rats, abolishes such a reaction if already developed, promotes the accumulation of acetaldehyde in the blood of these animals, and prolongs and deepens sleep induced by alcohol in mice.

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Metronidazole (trichopol, orvagil, flagil; 1- β-hydroxyethyl-2-methylnitroimidazole) is used for the treatment of trichomoniasis [4]. In recent years the compound has begun to be used for the treatment of alcoholism [2, 3, 9]. Treatment is carried out in the same way as with teturam (antabuse). The mechanism of the antialcoholic action of metronidazole has not been established. The compound in vitro inhibits xanthine oxidase and alcohol dehydrogenase from human liver, enzymes concerned in the oxidation of alcohol [5, 6].

The object of the present investigation was to study the effect of metronidazole on the sedative effect of ethyl alcohol, on the development of habituation of rats to alcohol, and on the conversion of this narcotic in the animal body.

EXPERIMENTAL METHOD

The effect of metronidazole on the sedative effect of alcohol was studied in experiments on 40 mice weighing 20-24 g. The Polish preparation trichopol was studied. LD_{50} of this compound when administered

TABLE 1. Duration of Sleep (M±σ) in Mice Produced by Ethyl Alcohol and Combined Action of Alcohol with Metronidazole (8 experiments in each group)

Compound	Dose (in g/kg)	Duration of sleep (in min)	P
Alcohol Metronidazole + alcohol	4,0 0,01 4,0	17,8±10,4 24,0±12,7	>0,05
Metronidazole + alcohol	0,05 4,0	71,0±25,1	<0,05
Metronidazole + alcohol	0,1 4,0	174,7±50,5	<0,05
Metronidazole + alcohol	0,5 4,0	386,1±74,3	<0,05

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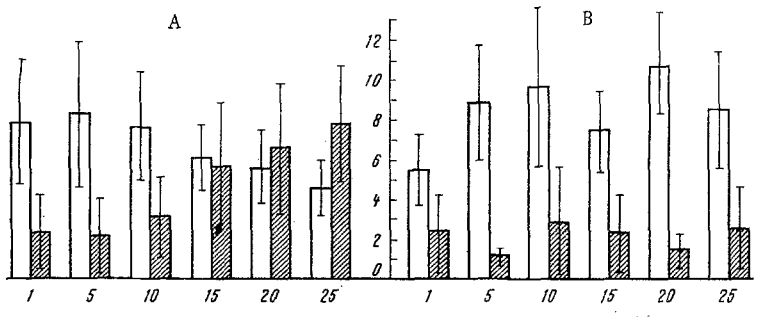

Fig. 1. Daily consumption of water and 5% ethyl alcohol by control (A) and experimental (B) rats (in mg/100 g body weight). Abscissa, days of experiment; ordinate, volume of liquid (in ml). Unshaded columns represent water, shaded columns alcohol.

by the gastric route into mice is 2.73 g/kg, and for rats 7 g/kg [1]. Metronidazole was given by gastric tube as a suspension in starch mucilage in a single dose not producing visible changes in mice (Table 1). Control animals received starch mucilage only. Both groups of mice received a subcutaneous injection of alcohol 1 h later in a dose of 4 g/kg body weight (dilution 1 : 1). The sedative effect was estimated from the time spent by the mice lying on their side.

Two series of experiments were carried out on 46 rats of both sexes weighing 120-180 g. In series I the effect of the compound was studied on development of habituation of the rats to alcohol. For this purpose the animals were kept in individual cages with free access to water, 5% alcohol, and food. The experimental rats (8) received metronidazole by gastric tube as a suspension of 0.2 LC_{50}/kg body weight once daily for 25 consecutive days, while the control rate (38) received starch mucilage only. The action of the compound was judged from the quantity of water and alcohol consumed during 24 h by each individual rat.

Rats of series II (18) were divided into three groups. The animals of groups 1 (control 1) and 2 (control 2) received a single dose of starch mucilage by the gastric route, while the rats of group 3 (experimental) received metronidazole in a dose of 0.2 LD_{50}/kg body weight. The rats of group 1 received a single subcutaneous injection of water 1 h later, while the animals of groups 2 and 3 received a subcutaneous injection of alcohol (dilution 1 : 1) in a dose of 5 g/kg. The animals were decapitated 30 min after the beginning of injection of alcohol and water, and the acetaldehyde concentration in the blood was determined by a colorimetric method [8]. The action of metronidazole on biological transformation of alcohol was estimated from the quantity of acetaldehyde in the blood of the control and experimental animals.

EXPERIMENTAL RESULTS

Metronidazole had a marked effect on the action and biological conversion of ethyl alcohol. The preparation studied prolonged the period of sleep in mice produced by alcohol (Table 1), promoted the development of quiet and deep sleep, and abolished the stage of excitation in the animals which as a rule precedes the sedative effect.

In the control animals the habituation reaction to the narcotic developed gradually, during the 20 days from the beginning of administration of alcohol solution (Fig. 1). By the 25th day of observation, all the rats showed well-marked habituation. At this time the animals consumed less water and more alcohol than at the beginning of the experiment. The daily consumption of the narcotic was three or more times greater than on the first day of observation (Fig. 1). These results are in complete agreement with data in the literature [3, 7]. No habituation reaction to the narcotic could be produced in the experimental rats, for metronidazole prevented its development. Unlike the controls, the experimental rats preferred water throughout the course of the experiment, and consumed much more of it than at the beginning of the experiment. The volume of alcohol which they consumed varied within the same limits as the initial data.

Experiments on the 38 control rats described above showed that metronidazole, if given by the gastric route daily for several consecutive days in doses of 0.5 or 0.2 LD_{50}/kg body weight, temporarily suppressed the developed habituation reaction in the animals to alcohol. From 10 to 15 days after the end of administration of metronidazole the rats again began to consume more alcohol than water.

TABLE 2. Concentration (in mg%) of Acetaldehyde in 100 ml Blood of Control and Experimental Rats (6 experiments in each group)

Animals	Acetaldehyde concentration (in mg%)
Control 1	27.0 (19.0-35.2)
Control 2	156.2 (125.4-187.0)
Experimental	278.0 (233.6-322.4)

The acetaldehyde concentration in the body increases following administration of alcohol and in the presence of inhibition of activity of enzymes catalyzing the conversion of acetaldehyde into acetyl-CoA.

In the present experiments the blood acetaldehyde concentration of the intact rats coincided with its concentration described in the literature [8], while in rats receiving alcohol (control 2) it was 5.7 times higher than in the intact animals (control 1; Table 2). A statistically significant increase in the acetaldehyde concentration was also observed in the blood of the experimental animals receiving metronidazole and alcohol. Its concentration in experimental rats was increased by 1.7 times compared with animals receiving starch mucilage and alcohol (control 2).

These results suggest that metronidazole inhibits biological conversion of alcohol in the same way as teturam. Metronidazole, by blocking xanthene oxidase activity [5, 6] and, evidently, activity of other enzymes oxidizing alcohol, delays the conversion of acetaldehyde into acetyl-CoA, as a result of which large quantities of acetaldehyde accumulate in the body. The acetaldehyde thus formed causes the development of symptoms of an alcohol-metronidazole reaction. This is confirmed also by clinical observations. The alcohol-metronidazole reaction is manifested by the same symptoms as the alcohol-antabuse reaction [2, 3, 9].

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