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Review Article

Indicators of Changes in Motor and Emotional Tests in A State of Ethanol Intoxication

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Abstract

Alcohol intoxication refers to a clinically dangerous condition caused by recent alcohol consumption, in which alcohol and its metabolites accumulate in the bloodstream faster than they can be metabolized by the liver. Alcohol has a range of effects on the central nervous system at different doses. Acute effects include Wernicke's encephalopathy, traumatic brain injury, memory loss, seizures, stroke, and hepatic encephalopathy. We observe an increase in the mobility of rats after the introduction of alcohol and its sharp decline after the introduction of grapefruit juice.

As for the number of short and long washings, as well as the "climbing" and "rering" stands, their number, after the introduction of alcohol, decreases somewhat, and after the introduction of grapefruit juice, also continues to decrease.

Keywords: motor and emotional tests; ethanol intoxication

Introduction

Alcohol intoxication refers to a clinically dangerous condition caused by recent alcohol consumption, in which alcohol and its metabolites accumulate in the bloodstream faster than they can be metabolized by the liver [9]. Alcohol has a range of effects on the central nervous system at different doses. Acute effects include Wernicke's encephalopathy, traumatic brain injury, memory loss, seizures, stroke, and hepatic encephalopathy [10]. When alcohol is consumed orally, ¼ of it is absorbed in the stomach and ¾ in the upper part of the small intestine. Through the mucous membrane of the stomach and intestines, most of the alcohol, or more precisely ethanol, enters directly into the blood, and then through the portal vein system into the liver. [3] In our body, 90-98% of the alcohol consumed is oxidized and processed; from 2 to 10% of it is excreted unchanged with exhaled air, with urine, feces, with saliva and through the skin with sweat. 90-98% of the alcohol consumed is metabolized in the liver. In small quantities, ethanol is broken down in other organs. [3] Alcohol oxidation occurs in three ways: with the participation of the enzyme alcohol dehydrogenase, with the help of catalase and with the help of cytochromes. [8] The oxidation reaction of ethanol with the participation of alcohol dehydrogenase occurs in the presence of the coenzyme nicotinamide acetyl dinucleotide (NAD) with the subsequent formation of acetic acid aldehyde. With the participation of the enzyme acetaldehyde dehydrogenase, acetaldehyde is converted into acetic acid.[11] The reaction can occur in both directions. Both enzymes work only in the presence of NAD, which converts them into an active oxidized form. [1] NAD itself is restored during the oxidation of these enzymes. Acetic acid burns during subsequent oxidation to carbon dioxide and water with the release of energy.[2] The first stage of alcohol oxidation to the formation of acetaldehyde is five times slower than the second stage of oxidation to the formation of final products. [7] If the first occurs mainly in the liver, then the second stage can proceed intensively in many tissues of the body: in the liver, kidneys, and brain. When small doses of alcohol are consumed, about 90% is oxidized by alcohol dehydrogenase in the liver and about 10% by catalase. This type of reaction occurs in cells that have cytochrome systems and depends on the concentration of alcohol in the tissues.[8] The third type of oxidation occurs with the participation of the microsomal ethanol-oxidizing system (MEOS).[6] The introduction of large doses of alcohol causes an excess of reduced forms of pyridine nucleotides NADH and NADPH and a deficiency of oxidized forms of NAD and NADP. This triggers the oxidation and reduction reactions of cytochromes of the p450 family during the first stage of xenobiotic detoxification in the liver.[5] Cytochrome P450 has many isoforms - isoenzymes, of which more than a thousand have already been isolated. They play an important role in the

oxidation of numerous endogenous and exogenous compounds, including ethanol. The cytochrome P450-dependent microsomal ethanol-oxidizing system plays an insignificant role in the metabolism of small amounts of ethanol, but is significantly induced by its excess and acquires significant significance with its abuse.[9] Enormous importance in this system is given to the 6 main isoforms directly responsible for the metabolism of ethanol in the body. Among them: CYP2E1, CYP1A2, CYP3A4, CYP2C (exists in 4 variations, 3 of which are involved in the elimination of ethanol: CYP2C9, CYP2C8, CYP2C19). Let's consider the actions of each of them. [13] Cytochrome P450 2E1 (CYP2E1) is a key enzyme in the microsomal pathway of ethanol oxidation. CYP2E1 is unevenly distributed in the liver acini. Enzyme expression, both constitutively and after induction, such as with ethanol, is restricted to the centrilobular region of the liver, specifically the three to four hepatocyte layers most proximal to the central vein. After induction, CYP2E1 concentrations in these layers are approximately 0.1 mM. CYP2E1 has a higher Km for ethanol oxidation (8-10 mM) in hepatocytes compared to alcohol dehydrogenase (0.5-2.0 mM), and therefore metabolizes approximately 10-20% of ethanol at low blood alcohol concentrations (10 mM); with an increase in its level (40-70 mM) or after CYP2E1 induction, the proportion of ethanol metabolized by CYP2E1 can increase to 60%. Also, in a number of experiments to identify the effect on ethanol excretion, it was found that the average value of CYP2E1-dependent ethanol oxidation is twice as high as the total activity of CYP1A2 and CYP3A4, which indicates the primary role of CYP2E1 in ethanol metabolism in human liver microsomes.[7]. Cytochrome P450 1A2 (CYP1A2) is the next most important enzyme in microsomal ethanol oxidation. The participation of CYP1A2 in ethanol oxidation in the liver has been confirmed experimentally in rats, and subsequently in humans. It has been established that the CYP1A2 gene is constitutively expressed in the liver. The Km value for CYP1A2 in ethanol oxidation is 62.6 mM, which is significantly higher than that of CYP2E1, indicating its lower affinity for ethanol compared to the CYP2E1 isoform. However, the Vmax value of purified CYP1A2 (39.9 nmol/min) is higher than that of CYP2E1, indicating more efficient operation of CYP1A2 at high ethanol concentrations. [7,11]. Cytochrome P450 3A4 (CYP3A4) is the most abundant CYP enzyme in the liver, involved in the metabolism of endogenous compounds and xenobiotics, including ethanol. CYP3A4 accounts for approximately 30% of the total cytochrome P450 pool, while CYP2C9 accounts for ~20%, CYP1A2 for ~15%, and CYP2E1 for ~10%. CYP3A4 (in addition to CYP2E1 and CYP1A2) makes a significant contribution to the metabolism of ethanol to acetaldehyde. [7,12] Cytochrome P450 2C (CYP2C) is the most common in the liver after CYP3A4. Using recombinant human CYP and selective inhibitors on human liver microsomes, the participation of its isoforms in ethanol oxidation was proven. The human CYP2C subfamily includes four isoforms ranked in descending order of their relative abundance in liver tissue: CYP2C9 (50%), CYP2C8 (26%), CYP2C19 (16%), CYP2C18 (8%). The CYP2C18 isoform does not participate in ethanol metabolism. [7,12]. Despite the pleasant taste and color of grapefruit juice, it still has negative effects on the liver, especially on the same cytochrome P450 isoforms that were discussed earlier. These effects are caused by the chemicals contained in the juice, which are quite abundant both in the pulp and in the peel. Furanocoumarins (molecules based on one five-membered ring with oxygen - furan, and coumarin - two linked six-membered rings, one of which includes one oxygen atom, and the other is attached by a double bond) in citrus fruits suppress the action of the cytochrome P450 3A4 enzyme, irreversibly binding to it. Restoring the enzyme activity by 50% requires at least a day, and by 100% - at least 3 days. They can also prevent the cell from assembling new molecules of this protein according to the "instructions" translated into RNA form. Grapefruit juice reduces the level of cytochrome P450 3A4 by 47% in four hours, which enhances the effect of a number of drugs taken in the next 24 hours. It is important to note that under the influence of furanocoumarins, the amount of 3A4 decreases primarily in the enterocytes of the upper third of the duodenum. However, with excessive juice consumption (more than 500 ml per day), the amount of 3A4 decreases in the liver as well. [12]. Naringin, which gives grapefruit a bitter taste, has a similar effect, also on cytochrome 1A2, although it works weaker alone than in a mixture with other substances in citrus juice. Particular attention should also be paid to the group of flavonoids, the amount of which is especially high in the peel and outer layers of the fruit pulp. [14] Flavonoids that have a blocking effect mainly on CYP2C9, CYP2C19 and CYP2C8 include naringenin and dihydroxybergamottin. Naringin, naringenin and dihydroxybergamottin have a blocking effect exclusively on the liver isoforms of the enzyme. However, all of these substances (including furanocoumarin) act on the principle of complementarity, binding to specific sites of the corresponding isoform of the enzyme.[15]

Six rats were injected intraperitoneally with ethyl alcohol solution at a dose of 0.5 mg/kg. After 15 minutes, the "open field" test was used to study motor disorders and changes in the emotional state of rats with alcohol intoxication. After this test, 2 ml of freshly squeezed grapefruit juice was injected through a gastric tube and the "open field" test was repeated. "Open field" test. The test is carried out on a flat surface, divided into 36 squares, fenced along the perimeter. In the "open field" they determine the time of the animal's exit from the center of the site, where it is placed at the beginning, activity in the horizontal and vertical planes of space, grooming (washing). In the "open field" it is possible to observe violations of motor activity by registering discoordination, the disappearance of voluntary movements or their limitation. The motor activity of animals in the horizontal plane includes running in different directions, walking in a circle. In this case, the participation of all the rat's limbs in the movement is assessed. One crossed square is taken as a unit of movement during visual registration of activity. Grooming can be short - in the form of quick circular movements of the front paws around the nose and whiskers, and long - washing the eyes, the area behind the ears, the entire head, paws, sides, back, anogenital area, tail. The motor activity of rats in the vertical plane is represented by two types of stances: climbing (ascending) - the animal's hind legs remain on the floor surface, and the front ones rest against the wall of the "open field", and rearing (from "rear" - "to stand on end") - the front limbs remain suspended. The obtained data were subjected to statistical processing and entered into the table:

Groups	Test «open field»				
	Distance traveled (cm) in 5 min	Muscle strength (dough holding time, min)	Number of washes	Number of racks «climbing»	Number of racks «rering»
Control	340 (300;380)	282,5 (265;290)	2(2;3)	7(6;8)	5,5(5;6)
Alcohol	135* (100;160)	175* (170;180)	1(0;1)*	2(0;3)*	2(2;3)*
Alcohol and grapefruit juice	35(25;45)*#	60(0;120)*#	1(0;2)	1(0;2)*	0(0;1)*#
A day after the introduction of alcohol	285*# (275;300)	250# (220;270)	1(1;2)	5(5;6)*#	4(3;4)*
One day after the introduction of alcohol and grapefruit juice	225*# (195;250)	192* (170;200)	1(0;1)*	3(2;4)*	2(1;3)*

* - $p<0.05$ compared to the "control" group

- $p<0.05$ compared to the "alcohol" group

Indicators of changes in motor and emotional tests in a state of ethanol intoxication at a dose of 1 g/kg and in ethanol intoxication at the same doses with the introduction of 2 ml of grapefruit juice into the stomach.

Thus, we observe an increase in the mobility of rats after the introduction of alcohol and its sharp decline after the introduction of grapefruit juice.

As for the number of short and long washings, as well as the "climbing" and "rering" stands, their number, after the introduction of alcohol, decreases somewhat, and after the introduction of grapefruit juice, also continues to decrease.

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