Pharmacological Reports 67 (2015) 921–927

Contents lists available at ScienceDirect

Pharmacological Reports

journal homepage: www.elsevier.com/locate/pharep

Original research article

Influence of tobacco smoke exposure on pharmacokinetics of ethyl alcohol in alcohol preferring and non-preferring rats

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ARTICLE INFO

Article history:
Received 2 April 2014
Received in revised form 14 February 2015
Accepted 17 February 2015
Available online 28 February 2015

Keywords:
Tobacco smoke
Ethanol
Pharmacokinetic interactions
Animals
Alcohol preferring rats

ABSTRACT

Background: A vast majority of people who abuse alcohol are also defined as "heavy smokers". Tobacco smokes induces CYP1A1, CYP1A2, CYP2A6 isoenzymes, but on the other hand, ethanol activates CYP2E1, which can be important during combined, chronic use of both of them. The aim of the study was to evaluate the influence of tobacco smoke xenobiotics on ethanol pharmacokinetics and the level of its metabolites in alcohol preferring and non-preferring rats.
Methods: Ethanol, acetaldehyde, methanol, *n*-propanol and *n*-butanol were determined in whole blood by means of gas chromatography. Cotinine in serum was determined by LC–MS/MS. A non-compartmental analysis (cotinine, acetaldehyde) and Widmark equation (ethanol) were used for pharmacokinetic parameters calculation.
Results: Ethanol levels were lower in animals exposed to tobacco smoke compared to rats receiving this xenobiotic, without a prior exposure to tobacco smoke. Lower values of the studied pharmacokinetic parameters were observed in the alcohol preferring males compared to the non-alcohol preferring rats. Both *n*-propanol and *n*-butanol had higher values of the pharmacokinetic parameters analyzed in the animals exposed to tobacco smoke and ethanol compared to those, which ethanol was administered only once.
Conclusions: An increase in maximum concentration and the area under concentration–time curve for ethanol after its administration to rats preferring alcohol and exposed to tobacco smoke are accompanied by a decrease in the volume of distribution. The changes in the volume of distribution may be caused by an increase in the first-pass effect, in the intestinal tract and/or in the liver. The acetaldehyde elimination rate constant was significantly higher in alcohol-preferring animals.

Introduction

The interaction of tobacco smoking and ethanol drinking has for a long time been an object of interest for scientists and clinicians. Smoking is very common among ethanol addicted people and reaches 85%, moreover, the number of cigarettes smoked is higher in this group compared to social or non drinkers [1–7]. This is a significant public health problem because of the increased risk of head and neck cancers [8–11]. Coexistence of ethanol and nicotine addiction has been well known for a long time. The interaction mechanisms of these two xenobiotics are not fully known as yet [12].

Another very important point is the effect of both tobacco smoke and ethanol on enzymes metabolizing xenobiotics. Smoking increases the metabolism rate of various xenobiotics by activation of CYP1A1 and CYP1A2 isoenzymes and decreases the nicotine

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http://dx.doi.org/10.1016/j.pharep.2015.02.007
1734-1140/

metabolization rate as a result of isoenzyme CYP2A6 inhibition [13,14].

The other P450 cytochrome isoenzyme, CYP2E1, is responsible for metabolizing other organic compounds, such as carbon tetrachloride, halothane, diethyl ether, benzene, styrene, acetone, and vinyl chloride as well as tobacco specific nitrosoamines [8,15]. Both ethanol and nicotine induce CYP2E1 activity, which results in faster ethanol elimination in smoking people [8,15]. Many carcinogenic substances require metabolic bioactivation by CYP2E1 isoenzyme, this process is also induced in alcohol-addicted people and the coexistence of these two risk factors makes it more dangerous [13]. Another component of tobacco smoke – carbon monoxide inhibits cytochrome P450 izoenzyme [16].

The influence of tobacco smoke and ethanol on biotransformation processes of xenobiotics is significant and can affect pharmacotherapy. The drug metabolism rate changes most often if the patient starts or gives up smoking or alcohol drinking during the therapy, and can result in a decrease or increase in blood drug levels [17].

The aim of the study was to assess the effect of tobacco smoke components on the pharmacokinetics of ethanol and on the level of its main metabolite – acetaldehyde, and other coexisting compounds – acetone, methanol, *n*-propanol and *n*-butanol in alcohol preferring and non-preferring rats.

Materials and methods

Animals

Two hundred male (141 ± 13 g body mass weight) Wistar rats housed at the Department of Toxicology, Poznan University of Medical Sciences were bred in polycarbonate cages containing sterile sawdust. The number of animals necessary for the next step of experiment was subsequently selected from this group. Animals that were not classified for the experiment were euthanized. The animals were fed with standard laboratory diets. Labofeed B Plant Feed and water were available in unlimited quantities. The animals were housed in 12/12 h light/dark cycle, at a temperature of 20–22 °C and 50–60% relative humidity was maintained throughout the experiment. The rats were acclimatized for 14 days before the experiment.

Animal experiment

Alcohol preference of rats to ethanol was performed for 9 weeks according to the previously established protocol [18–24] with authors' modifications. One month old rats, 200 males, were used in the first stage of the experiment. The necessary number of alcohol preferring rats was subsequently selected from this group after 9 weeks (361 ± 10 g body mass weight). The schedule of experiment is present in Fig. 1.

The measurements of total liquid and ethanol drinking, were helpful in dividing the animals into two groups of alcohol preferring and non-preferring individuals.

The animals were qualified as alcohol preferring when ethanol was less then 10–35% of total amount of consumed water and ethanol (calculated by a mean dose of ethanol/kg/day was 10.5 g) [23–26]. Animals were qualified as non-alcohol preferring when ethanol constituted less than 10% of total amount of drank water and ethanol.

Alcohol preferring (A) and non-alcohol preferring (NA) rats were randomized and divided into six groups of 21 animals each. The next steps of the experiment are presented in Fig. 1. The rats were exposed to tobacco smoke generated from a Polish brand of

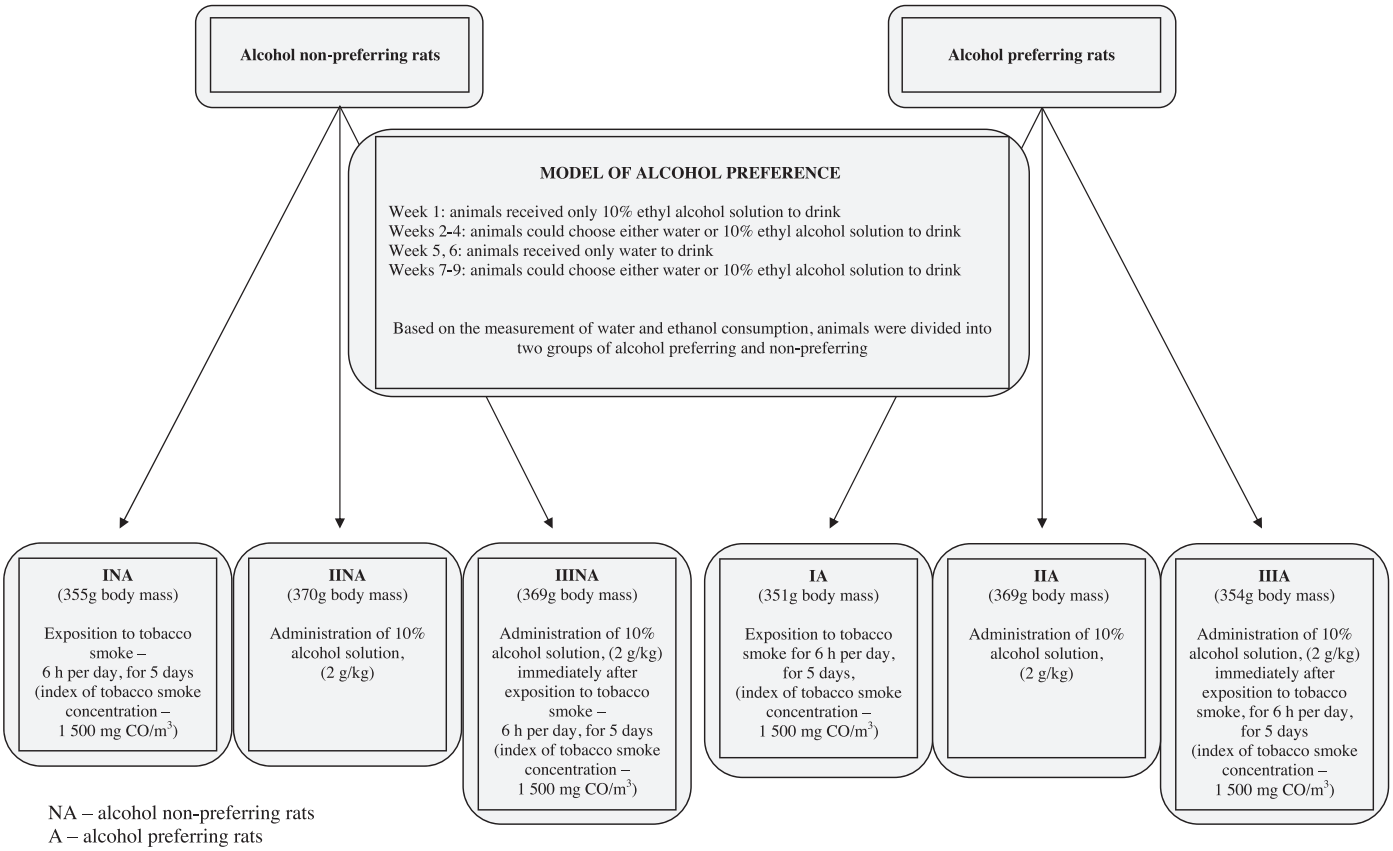

Fig. 1. The schedule of the experiment.