ORAL FRUCTOSE-INDUCED CHANGES IN BLOOD ETHANOL OXIDOKINETIC DATA AMONG HEALTHY NIGERIANS

I Onyesom¹ and Emmanuel O Anosike²

¹Department of Biochemistry, Delta State University, Abraka, Delta State; ²Department of Biochemistry, University of Port Harcourt, Choba, Port Harcourt, Nigeria

Abstract. Reports on the influence of fructose on blood alcohol clearance have not always been consistent. Notwithstanding, information concerning the Nigerian population is yet to be documented. In this present study, ten consenting adults in apparent sound health, and who did not have any traceable history of alcohol or drug abuse were selected. The subjects were non-smoking Nigerians with an average age of 23.3 years and body weight of 55 kg, and were matched in body frame size and weight. The volunteers were given 0.55g (20%) ethanol/kg body weight as single dose about 4 hours after their breakfast meal, and on another occasion, 0.25g fructose/kg body weight was used to sober the intoxicating effect produced by 0.55g (20%) ethanol/kg body weight. In each case, the blood alcohol level (BAL) was determined every 30 minutes using about 0.5 ml whole blood obtained by venipuncture. The mean peak BAL obtained for the male and female subjects (0.093% vs 0.096%) imply that the women were more intoxicated, though for a shorter time (314 minutes vs 280 minutes). This investigation also demonstrates that the group of women cleared blood alcohol faster (0.026%/hr) and oxidized blood alcohol more rapidly (115.8 mg/kg/hr) than the men, who respectively recorded mean values of 0.021%/hr and 102 mg/kg/hr. However, among the male and female volunteers, oral fructose intake significantly (p<0.05) increased the blood ethanol clearance rate by 66.7 and 92.3%, decreased intoxication time by 41.7 and 40%, reduced peak BAL by 18.3 and 0%, but enhanced blood ethanol oxidation rate by 71.2 and 66.7%, respectively. The oxidokinetic data obtained suggest that Nigerian women may be more susceptible to alcohol’s effects than Nigerian men, and oral fructose seems promising in the treatment of Nigerian alcoholics.

INTRODUCTION

It has been reported that in a fasting individual about 20 to 25% of a dose of alcohol consumed is absorbed from the stomach and about 75 to 80% from the small intestine, largely by simple diffusion (Cortot et al, 1986). However, when the stomach is full, as much as 70% of the ingested alcohol can be absorbed from the stomach (Eckardt et al, 1998).

Absorbed alcohol is rapidly carried throughout the body in the blood, and once absorption is complete, an equilibrium occurs such that blood at all points in the system contains approximately the same concentration of alcohol (Ellenhorn, 1997).

About 90 to 98% of ingested alcohol is eliminated from the body through oxidative metabolism, and the basic pathways involve the progressive oxidation of ethanol to ethanoic acid via ethanal (Peters and Preedy, 1998). The major site of this oxidation is the liver parenchyma cells, but other potential sites include the stomach (Baraona et al, 1991), vascular tissues, and the brain (Lieber, 1977).

A major pathway for alcohol oxidation involves hepatic alcohol dehydrogenase, ADH (EC 1.1.1.1), a dimeric zinc metalloenzyme (Bosron et al, 1983b) that catalyzes the conversion of ethanol to ethanal. In ADH-mediated oxidation of alcohol, hydrogen is transferred from the substrate (ethanol) to the cofactor, NAD⁺, converting it to its reduced form, NADH, and ethanal is produced. This leads to a marked shift in the redox potential of the cytosol and oxidation of the generated ethanal by aldehyde dehydrogenase, ALDH (EC...
1. 2.1.3) results in a similar effect in the mitochondria. These increases in both cytosolic and mitochondrial NADH/NAD⁺ ratios become the hallmark of the metabolic consequences of ethanol and ethanal, its metabolite (Lieber, 1977).

Hepatic ADH exhibits genetic polymorphism (Smith et al, 1992), and there are significant racial (Bosron et al, 1983a) and ethnic (Smith et al, 1992) variations in the activity of the enzyme. Again, it has been reported that gender (Pozzato et al, 1995) and ethnicity (Bosron et al, 1993; Eckardt et al, 1998) influence alcohol bioavailability and its attendant consequences, which include the problem of dependence and a multitude of other medical, behavioral, and social disorders (Lieber, 1995; O’Connor and Schottenfeld, 1998) that could culminate in the death of alcohol addicts (Odebunmi, 1994). Unfortunately, there are no accurate data to describe the frequency of such deaths in Nigeria, but speculations indicate a high percentage, with no apt approach to rehabilitate chronic drinkers.

It is on this note that the treatment value of some supportive agents, which could either reduce drinking behavior or enhance blood alcohol clearance, are currently being investigated. In this study, the effect of fructose, a simple ketose, on blood alcohol clearance, is being investigated for possible therapeutic benefits among Nigerians.

MATERIALS AND METHODS

Subjects

Ten consenting adults in apparent good health were selected. Their average age and body weight were 23.3 years and 55 kg, respectively. They were non-smoking Nigerians with no traceable record of alcohol and/or drug abuse, and were matched in body frame and size. The subjects were selected from the Urhobo ethnic group that dwells in the Niger-Delta Region of Southern Nigeria.

Testing process

About 4 hours after breakfast, eaten around 0600 hours the volunteers were given a moderate dose of 0.55g (20%) ethanol/kg body weight via the oral route, on two different occasions separated by two weeks. They were instructed to consume the alcohol single dose within 10 minutes after diluting to 20% with orange squash. On both occasions, the experiments were conducted in a similar manner, with the exception of fructose use. During the first occasion, alcohol alone was consumed, but during the second, 0.25g fructose/kg body weight was administered orally after about 40 minutes of ingesting the alcohol.

Blood alcohol level (BAL) was determined every 30 minutes for 90 minutes using 0.5 ml whole blood obtained from the vein BAL was quantified using the Alcohol Dehydrogenase, ADH and NAD⁺ method (Busher and Redetzki, 1951).

Factors and conditions identified to alter alcohol absorption and elimination patterns were strictly excluded. The oral route was investigated, since intravenous infusion of fructose has been demonstrated to dangerously elevate plasma lactate and urate (Levy et al, 1977) and causes intense pain in the liver and its region if too much is given too rapidly (Brown et al, 1972).

The alcohol absorption and oxidation curves were fitted for each participant by plotting a graph of BAL(%) vs post-consumption time (hour). The mean alcohol oxidokinetic data were determined from the individual curves and presented in a table. The results were replicated after 3 months in order to minimize the limitations associated with the small sample population.

Statistical analysis

Two related mean values were compared and the level of statistical significant difference was established at 5% using the Student’s t-test.

RESULTS

The results of the study are presented in Table 1.

Subjective feelings of alcohol intoxication associated with alcohol drinking has been reported to occur during the ascending period (absorption phase) and this was observed to be about 47 minutes in the males, and about 36 minutes in the females.

The data recorded (Table 1), coupled with the above observations, show that females had higher peak blood alcohol levels (PBAL) and faster rates of absorption, distribution, and dis-
appearance of blood alcohol.

Administration of oral fructose however, produced some remarkable changes in the kinetics of alcohol absorption and elimination in both the male and female subjects. The male peak blood alcohol level (PBAL), which represents the degree of intoxication, was reduced from 0.093 to 0.076%, and the time taken to attain the PBAL dropped by 23.5%. In the female group, the PBAL and the time taken to reach such peak were not affected by oral fructose.

The total intoxication time, that is, the time taken to record zero BAL was reduced by 41.7% (5.4 to 3.15 hours) in the men and by 40% (4.75 to 2.85 hours) in the women. Blood ethanol clearance rate (β60), an index of blood ethanol metabolic rate, in both the male and female subjects was increased by 66.7 and 92.3%, respectively, in the presence of fructose. The increases in both genders were demonstrated to be statistically significant (p<0.05).

### DISCUSSION

The mean time taken for the male subjects to attain PBAL was 0.85 hour, as against 0.65 hour for the females (Table 1). Females thus have faster absorption and distribution rates, though not statistically significant (p>0.05). The PBAL for the male and female subjects were 0.093 and 0.096%, respectively. But among Caucasians, Jones and Jones (1976) obtained 0.063 and 0.072% for similar measurements. It follows that Nigerians become more intoxicated compared with Caucasians. However, both trends indicate that women were more intoxicated, as judged by the PBAL recorded. Notwithstanding, the intoxication time was shorter in the women (280 minutes) compared with the men (314 minutes).

From this investigation too, the blood ethanol clearance rate (β60), and blood ethanol elimination rate (BEER) for the group of men and women were found to be: 0.021%/hr vs 0.026%/hr, and 102 mg/kg/hr vs 115.8 mg/kg/hr. For Caucasian subjects, average values of 0.015%/hr vs 0.020%/hr, and 113.2 mg/kg/hr vs 128.7 mg/kg/hr have been reported (Jones and Jones, 1976; Jones and Neri, 1985). These data suggest that Nigerians clear blood alcohol more rapidly than Caucasians, but the oxidation of blood alcohol is faster among Caucasians. However, the group of women have faster β60 and BEER, irrespective of race. Since β60 follows the Michaelis-Menten kinetics (Ellenhorn, 1997) the higher the PBAL, the faster the rate of the initial descent, and this accounts for the gender difference in the total period of intoxication.

Table 1

<table>
<thead>
<tr>
<th></th>
<th>Male (n=3)</th>
<th>Female (n=7)</th>
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<tbody>
<tr>
<td></td>
<td>(a)</td>
<td>(b)</td>
</tr>
<tr>
<td>Peak blood alcohol level (PBAL)%</td>
<td>0.093 ± 0.002</td>
<td>0.076 ± 0.002</td>
</tr>
<tr>
<td>Time to attain PBAL (hr)</td>
<td>0.85 ± 0.21</td>
<td>0.65 ± 0.17</td>
</tr>
<tr>
<td>Time to reach zero BAL (hr)</td>
<td>5.4 ± 0.5</td>
<td>3.15 ± 0.46</td>
</tr>
<tr>
<td>Blood alcohol clearance rate (β60)%/hr</td>
<td>0.021 ± 0.003</td>
<td>0.035 ± 0.004</td>
</tr>
<tr>
<td>Blood alcohol oxidation rate (mg/kg/hr)</td>
<td>102.0 ± 8.8</td>
<td>174.6 ± 16.7</td>
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</table>

Values are expressed as mean ± SD of 2n determination in the absence (a) and presence (b) of fructose. n=no. of subjects.
Again, the water content in females is influenced by changing hormones that regulate their menstrual cycle, and so, this cycle could affect the PBAL. It has been demonstrated that women in their pre-menstrual period, when given the same dose of alcohol and compared with women both at their menstrual (blood flow) or intermenstrual (ovulation) period, have significantly higher PBAL and become more intoxicated (Seitz et al., 1990).

Recently, it has been discovered that alcohol dehydrogenase (ADH) in the gastric mucosa contribute substantially to alcohol oxidation (first-pass metabolism). Studies of gastric ADH activity in women suggests a significant decrease in such activity in women compared with men, at least below the age of 50 years (Frezza et al., 1990; Seitz et al., 1993). This could explain the findings in women of higher PBAL and higher bioavailability, and this is compounded by women’s lower body weight and frame size, which reduce the total volume for alcohol distribution.

Thus, modulation of drinking pattern would be difficult for females, because a given dose of alcohol could produce different effects at different times probably due to body composition, body weight, reduced gastric ADH activity, and changing hormonal levels. These factors produce higher PBAL and more blood alcohol, which may account for the greater susceptibility of women to alcohol. Alcohol intake by Nigerian women especially should be sparing, if at all.

In this study, oral fructose administration produced interesting changes in the kinetics of alcohol oxidation. The decrease in the PBAL suggests that fructose reduced the degree of intoxication and enhanced the rate of alcohol absorption in men, but not in women. Fructose in the stomach delays gastric emptying, and this allows increased gastric ADH oxidation (first-pass metabolism) of alcohol (Eckardt et al., 1998). This reduces the amount of alcohol absorbed and decreases its bioavailability. First-pass metabolism may offer protection against alcohol’s deleterious effects in men, which is unlikely in women, due to a significant decrease in gastric ADH activity (Frezza et al., 1990) and thus, higher alcohol availability (Seitz et al., 1993).

This study demonstrated that oral fructose accelerated the clearance of alcohol from the blood in both genders, though faster in the females. This confirms the reports of other workers, who observed an increase of about 50% (Brown et al., 1972), 80% (Rogers et al., 1987) and 100% (Rawat, 1974). However, Mascord et al. (1991) observed a greater range of individual variations from a 13% decrease to a 300% increase in the ten subjects studied. The mechanism by which fructose accelerates alcohol metabolism is uncertain, but fascinating hypotheses have been proposed, and the most famous seems to be that, since the rate of alcohol oxidation by hepatic ADH is 30% dependent upon the rate of re-oxidation of NADH, the metabolism of fructose to sorbitol or to glycerol utilizes NADH and so, offers the means of re-oxidizing NADH. This facilitates further alcohol metabolism. Therefore, in the presence of alcohol, the metabolism of fructose in the liver is diverted from NADH- to NADH-requiring pathways, which in turn generates the NAD+ needed for alcohol oxidation. Available evidence (Tygstrup et al., 1965; Scholz and Nohl, 1976) has confirmed such diversion of fructose metabolism in the presence of ethanol.

Oral fructose appears to be a promising complement or adjunct in the management of alcohol-associated problems. Nonetheless, the safety of its long-term routine application as a supportive therapy deserves study before pronouncing its treatment value among Nigerians.

REFERENCES


