ENHANCED RATE OF ETHANOL ELIMINATION FROM BLOOD AFTER INTRAVENOUS ADMINISTRATION OF AMINO ACIDS COMPARED WITH EQUICALORIC GLUCOSE

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Abstract—Aims: To investigate the effect of an amino acid mixture given intravenously (i.v.) on the rate of ethanol elimination from blood compared with equicaloric glucose and Ringer’s acetate as control treatments. Methods: In a randomized cross-over study, six healthy men (mean age 23 years) fasted overnight before receiving either Ringer’s acetate, glucose or the amino acid mixture (Vamin 18 g N/l) by constant rate i.v. infusion over 4.5 h. Ethanol (0.4 g/kg) was given by an i.v. infusion lasting 60 min during the time each of the treatments was administered. At various times post-infusion, blood samples were taken for determination of ethanol by headspace gas chromatography. Blood glucose and heart rate were monitored at regular intervals. Concentration–time profiles of ethanol were plotted for each subject and the rate of ethanol disappearance from blood as well as other pharmacokinetic parameters were compared by repeated measures analysis of variance. Results: The rate of ethanol elimination from blood was increased significantly (P<0.001) after treatment with amino acids (mean ± SD, 0.174 ± 0.011 g/l/h) compared with equicaloric glucose (0.121 ± 0.016 g/l/h) or Ringer’s acetate (0.110 ± 0.013 g/l/h). Heart rate was also slightly higher during infusion of the amino acid mixture (P<0.05). Conclusions: When the rate of ethanol elimination from blood is relatively slow, such as after an overnight fast, it can be increased by ~60% after treatment with i.v. amino acids. The efficacy of amino acid treatment was not related to the supply of calories because glucose was no more effective than Ringer’s acetate. We suggest that amino acids might increase hepatic oxygen consumption, resulting in a more effective conversion of NADH to NAD⁺ in mitochondria. An important feature of the experimental design was ensuring hepatic availability of amino acids during much of the time that ethanol was being metabolized.

INTRODUCTION

Human metabolism of ethanol is tightly linked to hepatic oxygen consumption, energy requirements of the body and the individual’s basal metabolic rate (Wallgren, 1970). Marked species differences exist, and rats and mice can dispose of ethanol considerably faster than humans or dogs (Newman, 1941; Wallgren, 1970). Speeding up the rate of ethanol metabolism has not been easy to accomplish because hepatic enzyme activity, oxygen consumption and basal metabolism are important controlling factors (Wallgren, 1970; Lumeng et al., 1979; Crow and Hardman, 1989).

Under fasting conditions, when energy reserves are depleted, the rate of ethanol oxidation is relatively slow, as is the activity of liver alcohol dehydrogenase (ADH), the major enzyme involved in the metabolism of ethanol (Lumeng et al., 1979; Braggins and Crow, 1981). Administration of nutrients increases the elimination rate of ethanol compared with the fasting state, but whether carbohydrates are more effective than proteins or fat still remains an open question (Rogers et al. 1987; Jones et al. 1997a; Ramchandani et al., 2001).

We reported a faster disappearance of ethanol from the bloodstream after severe thermal injury and suggested the mechanism might involve a more effective reoxidation of NADH to NAD⁺, probably mediated by availability of certain amino acids and other substrate substrates (Jones et al., 1997b; Zdolsek et al., 1999). After a major burn trauma the victim enters a hypermetabolic state and the activity of the hepatic mitochondrial respiratory chain increases appreciably (Demling and Seigle, 2000). Among other things, this leads to enhanced catabolism of proteins, and gluconeogenesis also increases owing to a break-down of muscle with a preferential release of alanine and glutamine into the circulation (Brown et al., 1994; Herndon and Tompkins, 2004).

In this article we investigate whether availability of exogenous amino acids might also accelerate the elimination rate of ethanol from blood even in the absence of burn trauma or mental stress. In healthy men, an amino acid mixture was infused intravenously (i.v.), during which time the volunteers also received ethanol (0.4 g/kg) by constant rate i.v. infusion. The effectiveness of amino acids was compared with that of equicaloric glucose or Ringer’s acetate as control treatments.

MATERIALS AND METHODS

Subjects

Six healthy male students with mean age 23 years (range 22–24), body weight 86 kg (range 70–100) and height 183 cm (range 175–194) were paid a fee to participate in the experiments. None of the volunteers was a smoker and they were not using any medication at the time of the study. They were informed verbally and in writing about the purposes and possible risks of the study. The protocol for the study was approved by the Ethics Committee at the Faculty of Health Sciences at the University Hospital, Linköping, Sweden.

Procedure

The subjects participated in a controlled randomized study, each receiving one of three treatments separated by an interval of ~7 days. For the randomization procedure, we prepared three envelopes—one set for each subject—with details of the different treatments. A person not involved with the study was asked to shuffle the envelopes and then to mark them 1, 2 or 3 corresponding to the order of treatments.

After an overnight fast, the volunteers came to the hospital at ~8 a.m. and were taken to a research ward (23–25 °C) where venous catheters (Venflon®, Becton Dickinson, Helsingborg,
Sweden, inner diameter 1.7 mm) were inserted into each forearm. Heart rate was monitored by a pulse oximeter and arterial pressure was measured sphygmomanometrically at the start and before each blood sample was taken. Oxygen saturation and arterial pressure were in the normal range throughout the experimental period and did not change appreciably over time (data not given).

In each experimental session, one of three different fluids was infused before and during the time ethanol was administered by i.v. infusion. Randomization was ensured by means of sealed opaque envelopes. One fluid was Ringer’s acetate (Ringer-Acetate Braun®, B. Braun Medical, Bromma, Sweden), given at a rate of 222 ml/h, and this contained (mmol/l) Na⁺ (130), K⁺ (4), Ca²⁺ (2), Mg²⁺ (1), acetate⁻ (30), Cl⁻ (110). The glucose solution was 100 mg/ml (Glucos B Braun®, 400 kcal/l), and was infused at a rate of 222 ml/h. A commercially available amino acids mixture (Vamin 18 g N/l®, Fresenius Kabi, Uppsala, Sweden) was infused at a rate of 195 ml/h. This solution, which provides 460 kcal/l, is used clinically for parenteral nutrition to enhance protein synthesis. The amino acids and glucose were infused in equi- aloric amounts (400 kcal). Ethanol was given as a 10% (w/v) solution in 50 g/l isotonic glucose (Apopetksbolaget, Sweden).

Each experiment started with the administration of either Ringer’s acetate, glucose or the amino acid mixture at a constant rate over 270 min. Beginning 30 min later ethanol (0.4 g/kg) was administered i.v. over 60 min. Venous blood samples were drawn from the opposite arm at −30, 60, 90, 105, 120, 135, 150, 180, 200, 220 and 240 min timed from the start of the infusion of the ethanol. Glucose was analysed in whole blood at the bedside with a HemoCue® (C14) glucometer. Blood specimens for determination of ethanol were taken into Vacutainer® (heparin-fluoride, Becton Dickinson, Stockholm, Sweden) and were stored at 4°C until they were analysed 3–8 days later.

Determination of blood ethanol concentration

Blood ethanol concentration was determined in duplicate by headspace gas chromatography, as described in more detail elsewhere (Jones and Schuberth, 1989). In brief, two laboratory technicians, each working independently with different sets of equipment, took aliquots of whole blood (100 μl) and diluted these 1 + 10 with an internal standard (n-propanol). The ratio of the response of ethanol-to-propanol with a flame ionization detector was used for quantitative analysis, which is a standard procedure in forensic toxicology. Known strength aqueous ethanol standards (0.20, 0.50, and 1.00 g/l) were run before each series of blood samples and also every 10th sample throughout the analytical run. The people responsible for blood ethanol analysis were unaware of the various treatments given.

Blood alcohol parameters

Concentration–time profiles of ethanol were plotted for each subject, and these were evaluated by response feature analysis, a modified form of the classic Widmark method, which assumes zero-order elimination kinetics in the post-absorptive phase (Jones, 2003). During the post-infusion period, the slope of the rectilinear elimination phase was determined by linear regression analysis. The areas under concentration–time curves were determined by the linear trap-ezoidal method, and the apparent volume of distribution of ethanol was calculated by dividing the dose (g/kg) by the y-intercept of the regression line (C₀). The x-intercept of the regression line gives the extrapolated time to reach zero blood alcohol concentration (min₀) and is an estimate of the rate of alcohol elimination from the whole body.

Statistics

Repeated measures one-way analysis of variance (ANOVA) was used to compare the effects of the three treatments on selected blood alcohol parameters (Crowder and Hand, 1993) and the Tukey test was used to make post hoc comparisons. A P-value <0.05 was considered statistically significant. The precision (SD) of blood alcohol analysis was determined from differences (d) between the duplicate determinations [SD = (Σd²/2N)½] and this was also expressed as a coefficient of variation (SD/mean × 100). The SD was 0.0069 g/l, which corresponds to a coefficient of variation of 2.1%, indicating high analytical precision.

RESULTS

Figure 1 shows the average blood alcohol curves for the three test treatments; a steeper slope of the rectilinear elimination phase was strikingly obvious after giving the amino acids. The rate of ethanol elimination from blood was increased by ~60% compared with the Ringer’s acetate treatment (P<0.001). Other blood ethanol parameters, reflecting disposition and elimination kinetics of ethanol for individual subjects, are shown in Table 1 for each of the three treatments. Glucose was no more effective than Ringer’s acetate in accelerating the elimination rate of ethanol from blood (P>0.05). The extrapolated time to reach zero BAC (min₀) was shorter after amino acids and the area under the concentration–time

Fig. 1. Mean concentration–time profiles of ethanol in blood after a dose of 0.4 g/kg body weight given i.v. during the time an amino acid mixture, glucose or Ringer’s acetate was also infused i.v. Mean values ± SD are plotted (n = 6).
curve was also smaller ($P < 0.001$). No differences in pharmacokinetic parameters were found when comparing the glucose and Ringer’s acetate treatments ($P > 0.05$) despite the extra calories from carbohydrates.

Figure 2 shows time-to-time changes in heart rate and blood glucose concentration during the study. At the outset, there were no group-related differences between these measures. However, at 60 min (end of ethanol infusion) blood glucose concentration was significantly higher ($P < 0.05$) after infusion of glucose compared with the other two treatments.

To compare the three treatments, the blood glucose and heart rate were averaged between 90 and 240 min and means and variances were compared. The mean heart rate was increased significantly ($P < 0.05$) after amino acids compared with the other two treatments. As expected, blood glucose was significantly ($P < 0.01$) higher after infusion of the glucose solution.

**DISCUSSION**

The idea to embark on the present study arose from our earlier observation that the rate of ethanol elimination from blood was considerably faster in patients suffering from burn trauma (Jones et al., 1997b; Zdolsek et al., 1999). A serious burn injury leads to changes in body composition, with disruption of metabolic processes, including an exaggerated stress response and hypermetabolic and catabolic states (Dolecek, 1989; Herndon and Tompkins, 2004). A state of stress caused by immobilization increased the rate of blood ethanol elimination in rats and this was attributed to an enhanced activity of hepatic ADH or increased gluconeogenesis (Badawy, 1998; Mezey, 1998).

None of the subjects showed overt signs of stress during administration of amino acids, and blood glucose levels remained unchanged. Furthermore, the administration of Vamin 18 g N/l/C210 during surgery to counteract hypothermia also failed to increase sympathoadrenal activity (Sellén and Lindahl, 1998). We consider that stress per se seems a less plausible explanation for the enhanced rate of ethanol elimination and the faster heart rate after administration of the amino acid mixture. The effect of amino acids on ethanol elimination rate more probably resembles the situation after a major burn trauma, with increased hepatic oxygen consumption, gluconeogenesis and hypermetabolism.

Brundin and Wahren (1994a) observed higher energy expenditure, as evidenced by increased pulmonary oxygen uptake and splanchnic oxygen consumption, when Vamin 18 g N/l/C210 was given i.v. to healthy subjects. The splanchnic organs were thought to explain 50% of the amino acid-induced thermogenesis, and body temperature increased by 0.15–0.3°C after this treatment (Sellén et al., 1996). We consider that stress per se seems a less plausible explanation for the enhanced rate of ethanol elimination and the faster heart rate after administration of the amino acid mixture. The effect of amino acids on ethanol elimination rate more probably resembles the situation after a major burn trauma, with increased hepatic oxygen consumption, gluconeogenesis and hypermetabolism.

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**Table 1. Blood alcohol parameters for individual subjects after treatment with amino acids, glucose or Ringer’s acetate by i.v. infusion before and during the administration of ethanol (0.40 g/kg) also i.v.**

<table>
<thead>
<tr>
<th>Treatment/subject</th>
<th>$C_0$ g/l$^a$</th>
<th>$k_b$ g/l/h$^b$</th>
<th>min$_0$ min$^c$</th>
<th>$V_d$ l/kg$^d$</th>
<th>AUC g/l × h$^e$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Amino acids</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.604</td>
<td>0.187</td>
<td>193</td>
<td>0.662</td>
<td>44.7</td>
</tr>
<tr>
<td>2</td>
<td>0.693</td>
<td>0.187</td>
<td>222</td>
<td>0.577</td>
<td>61.1</td>
</tr>
<tr>
<td>3</td>
<td>0.684</td>
<td>0.169</td>
<td>243</td>
<td>0.584</td>
<td>66.9</td>
</tr>
<tr>
<td>4</td>
<td>0.726</td>
<td>0.174</td>
<td>250</td>
<td>0.551</td>
<td>74.4</td>
</tr>
<tr>
<td>5</td>
<td>0.614</td>
<td>0.165</td>
<td>222</td>
<td>0.651</td>
<td>54.0</td>
</tr>
<tr>
<td>6</td>
<td>0.641</td>
<td>0.161</td>
<td>238</td>
<td>0.624</td>
<td>65.0</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>0.660 ± 0.048</strong></td>
<td><strong>0.174 ± 0.011</strong>*</td>
<td><strong>228 ± 20</strong>*</td>
<td><strong>0.608 ± 0.044</strong></td>
<td><strong>61.0 ± 10.4</strong>*</td>
</tr>
<tr>
<td><strong>Glucose</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.590</td>
<td>0.124</td>
<td>285</td>
<td>0.677</td>
<td>77.5</td>
</tr>
<tr>
<td>2</td>
<td>0.690</td>
<td>0.148</td>
<td>279</td>
<td>0.579</td>
<td>81.8</td>
</tr>
<tr>
<td>3</td>
<td>0.635</td>
<td>0.104</td>
<td>366</td>
<td>0.629</td>
<td>92.3</td>
</tr>
<tr>
<td>4</td>
<td>0.796</td>
<td>0.129</td>
<td>369</td>
<td>0.503</td>
<td>104.4</td>
</tr>
<tr>
<td>5</td>
<td>0.620</td>
<td>0.103</td>
<td>361</td>
<td>0.645</td>
<td>86.8</td>
</tr>
<tr>
<td>6</td>
<td>0.604</td>
<td>0.119</td>
<td>304</td>
<td>0.661</td>
<td>79.6</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>0.656 ± 0.077</strong></td>
<td><strong>0.121 ± 0.017</strong></td>
<td><strong>327 ± 42</strong></td>
<td><strong>0.616 ± 0.065</strong></td>
<td><strong>87.0 ± 10.0</strong></td>
</tr>
<tr>
<td><strong>Ringer’s acetate</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>0.589</td>
<td>0.104</td>
<td>339</td>
<td>0.679</td>
<td>81.1</td>
</tr>
<tr>
<td>2</td>
<td>0.606</td>
<td>0.121</td>
<td>299</td>
<td>0.660</td>
<td>72.4</td>
</tr>
<tr>
<td>3</td>
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<td>0.093</td>
<td>345</td>
<td>0.750</td>
<td>72.1</td>
</tr>
<tr>
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<td>0.103</td>
<td>399</td>
<td>0.582</td>
<td>99.0</td>
</tr>
<tr>
<td>5</td>
<td>0.609</td>
<td>0.112</td>
<td>326</td>
<td>0.656</td>
<td>82.3</td>
</tr>
<tr>
<td>6</td>
<td>0.656</td>
<td>0.129</td>
<td>303</td>
<td>0.609</td>
<td>73.0</td>
</tr>
<tr>
<td><strong>Mean ± SD</strong></td>
<td><strong>0.613 ± 0.054</strong></td>
<td><strong>0.110 ± 0.013</strong></td>
<td><strong>335 ± 36</strong></td>
<td><strong>0.656 ± 0.058</strong></td>
<td><strong>79.9 ± 10.3</strong></td>
</tr>
</tbody>
</table>

$^a$Theoretical expected concentration at time of starting the infusion ($C_0$).
$^b$Rate of ethanol disappearance from blood in the pseudolinear phase of the concentration–time curve.
$^c$Extrapolated time to reach zero blood alcohol concentration (min$_0$).
$^d$Volume of distribution ($V_d$) given by dose/$C_0$.
$^e$Area under the concentration–time curve (AUC).

***$P<0.001$ compared with glucose and Ringer’s acetate treatments according to ANOVA.
The metabolism of ethanol to acetaldehyde is mainly catalysed by hepatic Class I isozymes of ADH, with concomitant reduction of NAD⁺ to NADH. According to established concepts, the rate of reoxidation of NADH to NAD⁺ rather than the activity of ADH is the rate-limiting step in hepatic oxidation of ethanol (Crow and Hardman, 1989). Hydrogen derived from the oxidation of ethanol enters the mitochondrial space, most probably as malate, over a shuttle mechanism and is subsequently oxidized in the mitochondrial respiratory chain (Thurman and McKenna, 1975).

Carbohydrates, such as fructose or glucose, have received considerable attention as agents that might accelerate the clearance rate of ethanol from blood (Crow et al., 1981; Mascord et al., 1988; Berman et al. 2003). The mechanism of the fructose effect was thought to involve a swifter reoxidation of reduced coenzyme NADH back to NAD⁺ (Crow et al., 1981) but other biochemical explanations have also been proposed (Plapp, 1975). Furthermore, the experimental design, including the dose, route and timing of administration of fructose relative to alcohol, is important for the results of this treatment (Crownover et al., 1986). Moreover, large doses of fructose are likely to cause abdominal pains and nausea (Brown et al., 1972; Dundee, 1972) and there is also an increased risk of metabolic acidosis after concomitant intake of ethanol (Tygstrup et al., 1965).

This study has demonstrated that a mixture of amino acids given i.v. increases the elimination rate of ethanol from blood by ~60% compared with equicaloric glucose used as a control treatment. This finding was unequivocal and did not depend on the caloric content of the amino acids because glucose was no more effective than Ringer’s acetate, which lacks calories. The small amount of additional glucose from the ethanol solution was the same in each arm of the study so we do not consider this a confounding factor. The total fluid volume was about the same and the additional glucose from the ethanol infusion furnishes ~56 kcal energy for a 70 kg subject. Fluid substitution per se, by isotonic saline, did not change the elimination rate of ethanol from blood (Li et al., 1999).

A simple and effective method to increase the rate of ethanol elimination from blood might have clinical applications in emergency medicine to accelerate detoxification. Administration of fructose for this purpose, as mentioned above, seems contraindicated. The present study supports taking a closer look at using i.v. amino acids (e.g. Vamin 18 g N/l®,) to accelerate the metabolism of ethanol in grossly intoxicated patients. This treatment would also help to counteract hypothermia in drunken people exposed to the cold, such as alcoholics found outdoors in the winter.

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REFERENCES


