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The effect of acute alcohol intoxication on gut wall integrity in healthy male volunteers; a randomized controlled trial

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ABSTRACT

The aim of the study is to determine the effect of acute alcohol consumption on enterocytes. Chronic alcohol consumption has been known to induce a decrease in gut wall integrity in actively drinking alcoholics and patients with alcohol-induced liver disease. Data on the extent of the damage induced by acute alcohol consumption in healthy human beings is scarce. Studies show that heavy incidental alcohol consumption is a growing problem in modern society. Data on this matter may provide insights into the consequences of this behavior for healthy individuals. In a randomized clinical trial in crossover design, 15 healthy volunteers consumed water one day and alcohol the other. One blood sample was collected pre-consumption, five every hour post-consumption, and one after 24 h. Intestinal fatty acid binding protein (I-FABP) was used as a marker for enterocyte damage. Liver fatty acid binding protein (L-FABP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT) were used as markers for hepatocyte damage. Lipopolysaccharide binding protein (LBP) and soluble CD14 (sCD14) were used as a measure of translocation. Interleukin-6 (IL-6) was used to assess the acute inflammatory response to endotoxemia. Alcohol consumption caused a significant increase in serum I- and L-FABP levels, compared to water consumption. Levels increased directly post-consumption and decreased to normal levels within 4 h. LBP, sCD14, and IL-6 levels were not significantly higher in the alcohol group. Moderate acute alcohol consumption immediately damages the enterocyte but does not seem to cause endotoxemia.

Introduction

Chronic alcohol consumption has been shown to lead to a decrease in gut wall integrity in actively drinking alcoholics and patients with alcohol-induced liver disease (Bjarnson, Peters, & Wise, 1984; Parlesak, Schäfer, Schütz, Bode, & Bode, 2000). Animal studies show that the mucosal damage caused by alcohol consumption increases the permeability of the gut to macromolecules (Beck & Dinda, 1981). This facilitates translocation of endotoxins from the gut lumen into the portal circulation. In response to the increased endotoxemia, the immune system is activated. These effects cause additional damage to various organs, mainly the liver and gut (Bode & Bode, 2003).

However, data on the acute effects of alcohol consumption on gut wall integrity in healthy non-alcoholics is scarce. Keshavarzian and colleagues (Keshavarzian, Fields, Vaeth, & Holmes, 1994) demonstrated that acute alcohol consumption did not lead to permeability of the small intestine. However, they did not address the extent of the damage induced by acute alcohol consumption in healthy volunteers.

Acute and heavy alcohol consumption is common in all layers of society and is a growing problem in modern society (Nephew, Williams, Stinson, Nguyen, & Dufour, 1999). Studies on the incidence of alcohol abuse in trauma patients admitted to the emergency department report rates of 24–47% (Cherpitel et al., 2005; Rivara et al., 1993). This poses a substantial economic burden. Data on the extent of gut damage induced by acute alcohol consumption may aid in campaigns to reduce alcohol abuse.

In trauma patients, a decrease in gut wall integrity has been associated with the presence of shock, and the subsequent developing inflammatory response (de Haan et al., 2009). Trauma patients are frequently alcohol-intoxicated upon admission to the

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emergency department. The gut damage induced by alcohol consumption may therefore contribute to a detrimental clinical course in trauma patients.

Studies reporting on the direct hepatotoxic effects of chronic alcohol abuse are numerous. Damage to the hepatocyte in chronic alcohol abuse eventually leads to fibrosis, failure of the liver, and death (Bataller & Brenner, 2005). More recent insights, however, show that it is not only direct damage to the hepatocyte from alcohol exposure that triggers this mechanism (Wynn & Ramalingam, 2012). Translocation of LPS, because of a decrease in gut wall integrity, leads to activation of the innate immune system. This in turn activates Kupffer and stellate cells in the liver, leading to damage and ultimately fibrosis (Wynn & Ramalingam, 2012).

Data on the extent of the damage induced by acute alcohol consumption may provide insights into the consequences of this behavior for healthy individuals. This may have future clinical implications for alcohol-intoxicated patients admitted to hospitals for various medical conditions.

Accurate markers to assess the extent of damage to the gut following acute alcohol intoxication were previously unavailable. Fatty acid binding proteins (FABPs) are intracytosolic proteins that are directly released into the systemic circulation upon rupturing of the cell. The intestinal and liver isoforms have proven to be accurate markers of even minute damage to the enterocyte and hepatocyte, respectively (Pelsers et al., 2003).

LBP and sCD14 are acute phase proteins that are widely used as indirect markers of translocation of LPS from the gut lumen to the systemic circulation. LBP binds LPS and forms a ternary complex on the cell surface with the LPS receptor molecule, CD14 (Schumann et al., 1990; Wurfel, Kunitake, Lichenstein, Kane, & Wright, 1994). The activation of endothelial cells by LPS is primarily achieved using sCD14 (Pugin et al., 1993).

This study is designed to investigate the immediate effects of moderate alcohol consumption on gut wall integrity and hepatocytes.

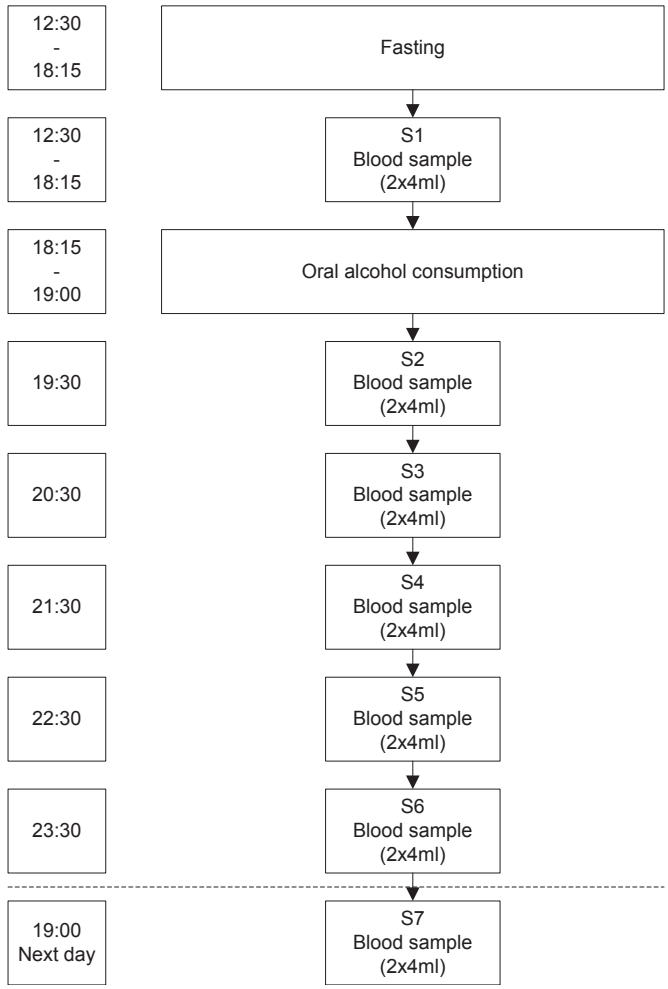

Fig. 1. Study design.

Materials and methods

A randomized, single-blinded, crossover study was conducted. The trial was approved by the Institutional Review Board of the University Medical Centre Groningen (UMCG) (NCT02126072). Included were healthy adult males between the ages of 18–60 years, after written informed consent. Volunteers were recruited by means of poster presentations in our hospital. No rewards were given to participating volunteers to insure their voluntary motivation. To avoid differences in response to alcohol between males and females, only males were included (Gubala & Zuba, 2003). Volunteers with a medical history of alcohol abuse, bowel disease, or any form of medication use were excluded. To identify a history or present form of alcohol abuse, the Michigan Alcoholism Screening Test (MAST) was used, excluding volunteers with a score $\geq$4 (Selzer, 1971). Volunteers fasted for 6 h before sampling to obtain a reproducible alcohol uptake. To avoid dehydration or hypoglycemia, volunteers were allowed to drink tea, water, or clear fruit juices until 2 h before sampling.

After withdrawal of a baseline sample (S_1), volunteers were randomized to drink either 1 g/kg body weight of alcohol in wine (Pinot noir, 12%), or water in identical volumes. 1 g/kg was chosen to obtain a blood alcohol level of 0.1%. Randomization was performed by randomly drawing an envelope. All investigators were blinded for the randomization. The beverages were consumed within 45 min. Thirty min after the entire beverage was consumed, a second blood sample (S_2) was collected, as shown in Fig. 1. The next 4 samples were taken in 1-h intervals (S_3, S_4, S_5, and S_6, respectively). The last sample was taken 24 h after consumption. This design was repeated 1 week later in the same population, switching the alcohol and water consumption per volunteer. The study was conducted at the department of surgery of the UMCG under strict supervision of medical staff.

Samples were obtained in two 4-mL EDTA tubes. One tube was stored at 4 °C and used for blood alcohol concentration (BAC) measurements the next day in whole blood. The other was centrifuged; plasma was withdrawn, and stored in 1.5-mL polypropylene tubes at −80 °C for batch analysis of the markers.

I-FABP was used as a marker for enterocyte damage in the small intestine (de Haan et al., 2009; Relja et al., 2010). L-FABP, AST, ALT, and GGT were used as markers for hepatocyte and cholangiocyte damage (Pelsers et al., 2003). LBP and sCD14 were used as translocation markers (Wurfel et al., 1994). IL-6 was used to assess the acute inflammatory response to endotoxemia (Nijsten et al., 1987).

Enzyme-linked immunosorbent assays (ELISA) were performed by a blinded analyst: I-FABP (R&D Systems, Minneapolis, MN, USA); L-FABP (Hycult Biotech, Uden, NL); LBP (Hycult Biotech, Uden, NL); sCD14 (R&D Systems, Abingdon, UK) and IL-6 (eBioscience, San Diego, CA, USA). AST, ALT, and GGT levels were obtained by the clinical hospital laboratory (Roche Modular P, Mannheim, DE). The blood alcohol concentration (BAC) was obtained using gas liquid chromatography (7890A GC Agilent, Santa Clara, CA, USA). All blood samples were analyzed in duplicate. The