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Ethanol concentrations in the human gastrointestinal tract after intake of alcoholic beverages

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ABSTRACT

Introduction: The goal of this study was to monitor gastric and duodenal ethanol concentrations arising from the consumption of commonly used alcoholic beverages.
Materials and methods: In a cross-over study, five fasting volunteers were asked to drink two standard consumptions of commercially available alcoholic beverages, including beer (Stella Artois®, 500 mL, 5.2% ethanol), wine (Blanc du Blanc®, 200 mL, 11% ethanol) and whisky (Gallantry Whisky®, 80 mL, 40% ethanol). The volunteers finished drinking beer within 10 min and wine or whisky within 5 min. Ethanol concentrations in gastric and duodenal fluids, aspirated as a function of time, were analyzed by headspace gas chromatography.
Results: In all three conditions, the average gastric profile shows a maximum ethanol concentration (C_{max}) at 7 min, while the mean duodenal profiles have a T_{max} at 20, 7 and 12 min for beer, wine and whisky, respectively. The median gastric ethanol C_{max} (min–max) for the beer, wine and whisky conditions amounts to 4.1% (3.1–4.1), 4.1% (2.6–7.3) and 11.4% (6.3–21.1), respectively. The mean duodenal profiles follow the same pattern as their corresponding gastric profiles, albeit with lower percentages of ethanol. Median duodenal ethanol C_{max} (min–max) for beer, wine and whisky are 1.97% (0.89–4.3), 2.39% (2.02–5.63) and 5.94% (3.55–17.71), respectively. Intraluminal ethanol concentrations appear to decline relatively rapidly in fasting conditions: both stomach and duodenum contained less than 0.05% of ethanol after 120 min.
Conclusions: This *in vivo* study is the first to present intraluminal ethanol concentrations in man after the intake of alcoholic beverages. Relatively low and fast declining gastric ethanol concentrations were observed, contrasting with the current Food and Drug Administration guidelines for the *in vitro* testing of formulations with respect to ethanol resistance. The presented gastric and duodenal ethanol concentrations and their variation may serve as reference data to design relevant models for predicting (i) ethanol resistance of drug formulations and (ii) ethanol effects on drug solubility and permeability.

1. Introduction

In clinical trials and bio-equivalence studies, drugs are typically administered orally with 240 mL of water (FDA, 2002) This does not necessarily reflect what happens in daily practice. Patients take their medication with soft drinks, hot drinks or even alcoholic beverages. The resulting intraluminal alterations in fluid volume, pH, temperature, osmolality and solubilizing capacity can influence the local behavior of the administered formulation and may cause significant variability in drug absorption and systemic exposure.

As the consumption of alcoholic beverages is widespread and socially accepted, patients may co-ingest their medication with ethanol. Many drugs interact with ethanol at a pharmacodynamic and/or pharmacokinetic level, potentially leading to serious adverse effects (Lennernäs, 2009). Ethanol is also known to disrupt the extended release mechanism of formulations resulting in dose dumping and possible safety concerns (Jedinger et al., 2014). In 2005, the US Food and Drug Administration (FDA) requested Perdue Pharma to suspend their pain treatment drug Palladone®, an extended-release capsule of the opioid analgesic hydromorphone, after the observation of severe ethanol-induced dose-dumping in healthy volunteers (FDA, 2005). Compared with water, ingestion of a single dose of Palladone® with 240 mL of an ethanol solution at 4, 20 and 40%, resulted in an increased mean C_{max} of hydromorphone by 1.06-, 1.89-, and 5.53-fold, respectively. One volunteer even had a 16-fold increase in C_{max} when the formulation was co-ingested with a 40% ethanol solution (Walden et al., 2007). This type of ethanol induced dose dumping poses serious safety concerns for

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drugs with a small therapeutic window or known pharmacodynamic interaction with ethanol. Ever since, the FDA established guidelines to test the robustness of certain drug formulations towards ethanol *in vitro*. These tests are required for all (generic) extended release formulations containing opioid drugs and are preferred for other modified-release formulations with risk of alcohol-induced dose dumping (FDA, 2013, 2015). Drug release from the dosage form should be tested during 2 h in a medium of 0.1 N HCl with concentrations of 0, 5, 20 and 40% ethanol in order to simulate the consumption of common alcoholic beverages like beer (5%), mixed drinks (20%) and liquor (40%) (FDA, 2014; Anand et al., 2011). The European Medicines Agency (EMA) recommends *in vitro* ethanol resistance testing for all modified-release products and other formulations with scientific grounds for an ethanol effect on release characteristics. The EMA does not provide authoritative methodological requirements in terms of minimum testing time or dissolution medium. The dissolution medium should contain ethanol at levels that are likely to be reached in the proximal gastrointestinal tract: concentrations of 5%, 10% and 20% ethanol are suggested (EMA, 2009). Based on literature, Lennernäs et al. concluded that the FDA test is physiologically relevant (Lennernäs, 2009). However, it is important to note that the relevance of the *in vitro* test imposed by the FDA has never been judged by *in vivo* studies.

Besides the impairment of formulation behavior, high concentrations of ethanol in the stomach and duodenum may also act as a co-solvent and increase the solubilizing capacity for lipophilic compounds, resulting in more effective drug absorption. Fagerberg et al. measured the solubilities of 9 lipophilic compounds in fasted state simulated gastric fluid (FaSSGF) with 20% ethanol (Fagerberg et al., 2015). A large ethanol-induced increase in solubility was observed for the neutral compounds and for two out of three weak acids. The solubility of ionized weak bases was unaffected. The same group also investigated the apparent solubility of 22 poorly soluble compounds in Fasted State Simulated Intestinal Fluid (FaSSIF) in the presence of 0, 5 and 20% ethanol. The effects of 5% ethanol were negligible. 13 out of 22 compounds displayed a more than 3-fold increased solubility in FaSSIF with 20% ethanol, although this effect may be temporarily due to ethanol dilution and absorption in the intestine (Fagerberg et al., 2012; Lennernäs, 2009). A large increase in solubility may also affect the release mechanism of a drug from its dosage form; diffusion-mediated release will become more important than erosion-mediated release (Roberts et al., 2007).

Ethanol can also enhance drug absorption directly through modulation of the intestinal permeability by causing mucosal injury, disruption of membrane integrity and even mucosal leakage (Draper et al., 1983; Tarnawski et al., 1985; Lavo, 1992). Volpe et al. found that ethanol concentrations up to 5% significantly increased the permeability of oxycodone, oxymorphone and atenolol across Caco-2 cell monolayers (Volpe et al., 2008).

The demand for tools to evaluate ethanol impact on formulation performance and drug absorption on the one hand and the ignorance of relevant *in vivo* ethanol concentrations on the other hand, proves the need for further fundamental research in humans. In existing studies on the gastrointestinal fate of ethanol, artificial solutions are instilled directly into the stomach through a gastric tube (Johnoson et al., 1991; Levitt et al., 1997; Klockhoff et al., 2002; Franke et al., 2004; Halsted et al., 1973), which may affect the disposition of intraluminal ethanol in a non-relevant manner. The present study therefore aims to assess intraluminal ethanol concentrations in the stomach and duodenum of healthy volunteers after the consumption of common alcoholic beverages.

2. Materials and methods

2.1. Chemicals

Ethanol absolute AnalaR NORMAPUR was purchased from VWR Chemicals (Heverlee, Belgium). Na_2CO_3 was purchased from Merck (Darmstadt, Germany). Water was purified by using a Maxima system (Elga Ltd., High Wycombe Bucks, UK).

2.2. Alcoholic beverages

Gallantry Whisky and Blanc du Blanc Wine were purchased from Aldi market (Leuven, Belgium); Stella Artois Beer was purchased from Carrefour market (Leuven, Belgium). The characteristics of the administered beverages are reported in Table 1. pH and osmolality were measured using a Hamilton SlimTrode pH electrode (Bonaduz, Switzerland) and an Advanced Instruments osmometer model 3250 (Norwood, MA, USA), respectively.

2.3. In vivo study

Five healthy volunteers (3 females, 2 males) were enrolled in a cross-over study. Studies were performed at the University Hospitals Leuven and were approved by the Committee of Medical Ethics (ML10920). Candidate volunteers with gastrointestinal diseases, hepatitis B or C or HIV were excluded. All volunteers gave written informed consent prior to participation. After 12 h of fasting, two double-lumen catheters (Salem Sump Tube 14 Ch, external diameter 4.7 mm; Covidien, Dublin, Ireland) were introduced trough nose or mouth, and positioned into the stomach and the duodenum, respectively. Positioning was checked by fluoroscopy. In a cross-over design, volunteers were asked to drink two standard consumptions of beer, wine or whisky. One standard consumption was defined as 250 mL beer, 100 mL wine and 40 mL whisky. Volunteers finished drinking beer within 10 min and wine or whisky within 5 min. Subsequently, gastric and duodenal fluids were collected for 3 h. Sample preparation was performed on site immediately after aspiration.

2.4. Assessment of intraluminal ethanol concentration and osmolality

Immediately after aspiration, gastric and duodenal aspirates were centrifuged (20,817 g, 5 min, room temperature). Preliminary tests demonstrated that centrifugation did not affect the measured ethanol level. The supernatant of gastric aspirates was diluted in 0.4 mM Na_2CO_3 (1:50 for the wine and whisky conditions, 1:25 for the beer condition). The supernatant of duodenal aspirates was diluted in purified water (same dilution strength as gastric aspirates). Samples were sealed with PTFE/Sil-caps in 20 mL crimp top vials (Perkin Elmer, Zaventem, Belgium) and analyzed by a HP6890 gas chromatography system (Wilmington, DE, USA) equipped with a Perkin Elmer (Waltham, MA, USA) Turbomatrix 40 HS autosampler (balanced pressure system). Headspace parameters were as follows: oven at 80 °C, needle at 120 °C, transfer line at 140 °C and injector at 160 °C. Carrier pressure was set at 129.9 kPa. The withdrawal time was set at 0.4 s, injection time at 0.04 s and pressurization time at 1 min. Split ratio of injection was 1/5. Separations were carried out on a ZB-624 column (30 m × 0.53 mm, 3 μm film thickness) from Phenomenex (Utrecht, The Netherlands) with a flow of 4 mL/min helium 5.6. Detection was performed with a flame ionization detector at 220 °C, air: 450 mL/min, H_2: 40 mL/min, and make-up flow N_2: 45 mL/min. Separations were carried out using the following temperature program: holding for 7 min at

Table 1
Characteristics of administered beverages.

Beverage	Volume administered (mL)	Alcohol content (% ethanol)	pH	Caloric value (kcal)[a]	Osmolality (mOsm/kg)
Beer	500	5.2	4.09	960	2170
Wine	200	11.0	3.21	682	1085
Whisky	80	40.0	4.19	812	7208

[a] According to the Dutch nutrition databank (RIVM, 2013).