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PHARMACOKINETICS AND DRUG DISPOSITION

Ethanol and production of the hepatotoxic metabolite of acetaminophen in healthy adults

Background: Recent case reports suggest that consumption of ethanol may increase the risk of liver injury induced by acetaminophen (INN, paracetamol). However, this possibility is at odds with previous clinical studies that showed that acute ethanol ingestion could protect against hepatotoxicity by inhibiting CYP-mediated acetaminophen oxidation. We tested the hypothesis that ethanol ingestion can increase susceptibility to acetaminophen toxicity if acetaminophen ingestion occurs shortly after ethanol is cleared from the body.
Methods: Ten healthy volunteers each received a 6-hour intravenous infusion of ethanol (to achieve a blood concentration of 100 mg/dL ethanol) or 5% dextrose in water, administered in random order. Acetaminophen (500 mg) was ingested 8 hours after the end of the infusion. Blood and urine were collected for assessment of formation of *N*-acetyl-*p*-benzoquinone imine (NAPQI), the hepatotoxic metabolite of acetaminophen.
Results: Mean NAPQI formation was enhanced by 22% (range, 2% to 38%; $P < .03$) when the acetaminophen dose was given after an ethanol infusion, compared with after 5% dextrose in water infusion. This mean increase was similar in magnitude to that predicted by a mathematical model describing the induction of CYP2E1, the main enzyme catalyzing NAPQI formation, by a mechanism of enzyme stabilization.
Conclusions: Consumption of up to one 750-mL bottle of wine, six 12-ounce cans of beer, or 9 ounces of 80-proof liquor over the course of a single evening modestly increases the fraction of an acetaminophen dose converted to its toxic metabolite, NAPQI, when acetaminophen is ingested soon after ethanol has been cleared from the body. This change in acetaminophen metabolism may present an incremental increase in the risk of acetaminophen hepatotoxicity. (Clin Pharmacol Ther 2000;67:591-9.)

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It is now generally accepted that after an overdose of acetaminophen (INN, paracetamol), persons with chronic alcoholism are at increased risk of acetaminophen-induced hepatotoxicity.[1-4] This susceptibility may in part relate to the observation that persons with chronic alcoholism have increased activity of CYP2E1,[5,6] the major liver enzyme that produces *N*-acetyl-*p*-benzoquinone imine (NAPQI) from acetaminophen.[7-10] NAPQI is a chemically reactive molecule that can interact with hepatocellular proteins and other molecules, triggering a cascade of intracellular changes that culminate in cell death.[11] After currently recommended doses of acetaminophen (up to 4 g daily), hepatic NAPQI formation should be of no clinical consequence because only 4% to 10% of the dose is cleared from the body by this pathway and because the metabolite is rapidly detoxified by conjugation with glutathione and excreted into the urine as several secondary thioether metabolites.[12] However, an increased level of CYP2E1 activity may result in the conversion of a greater proportion of the ingested dose to NAPQI, increasing susceptibility to acetaminophen-induced liver toxicity.

There has been little reason to suspect that moderate drinkers in good general health are at increased risk of acetaminophen toxicity. However, this is now a controversial issue. In a recent report of 69 patients in whom acetaminophen hepatotoxicity developed after taking acetaminophen,[3] nine individuals reported daily alcohol ingestion of less than or equal to 60 g (approximately 7 ounces of 80-proof liquor). Five of these also reported acetaminophen ingestion of 4 g or less daily.

There are currently no scientific data to support an association between ethanol and increased susceptibility to acetaminophen toxicity outside the population of persons with chronic alcoholism. Indeed, previous studies have shown that NAPQI formation from acetaminophen is actually reduced in healthy volunteers who were given ethanol.[13,14] This observation is consistent with animal studies that showed that ethanol exposure can protect against acetaminophen-induced liver toxicity.[15,16] However, in these studies acetaminophen was administrated when ethanol was still present in the body. Ethanol is both a substrate and an inhibitor of CYP2E1.[17] It is well-established that ethanol and other CYP2E1 substrates and inhibitors (ligands) induce the enzyme but that enhanced catalytic activity is only observed once the ligand is eliminated.[18-22] Therefore any increase in NAPQI formation caused by ethanol ingestion may only occur after ethanol is cleared from the body.

To investigate this possibility, we administered ethanol intravenously to healthy volunteers for 6 hours, mimicking the consumption of a standard 750-mL bottle of wine, six 12-ounce cans of beer, or 9 ounces of 80-proof liquor. The production of NAPQI was determined just after ethanol was cleared from the body. The results we obtained were consistent with those predicted by a recently reported mathematical model for induction of CYP2E1 activity.[22]

MATERIAL AND METHODS

Human subjects. Subjects were studied in the General Clinical Research Center at the University of Michigan Medical Center (Ann Arbor, Mich) with Institutional Review Board approval and written informed consent. They were between 21 and 50 years old, were in good health (history and physical examination), were nonsmokers, were without biochemical evidence of renal or hepatic dysfunction, and were not pregnant. Abstainers or individuals who admitted to consuming alcohol on more than an occasional basis (once a week) were excluded. Subjects were identified through flyers posted around the University of Michigan campus and were paid for their participation.

Study design. Five men and five women were enrolled in an open-label, randomized crossover study with two treatment phases. In the first phase, 10% ethanol (wt/vol) in 5% dextrose in water (D_5W) was infused; in the second phase, only D_5W was infused. Subjects were instructed to refrain from drinking alcoholic beverages and from taking medications that contained acetaminophen for the duration of the study.

Ethanol or D_5W infusions were started at 6 PM. Subjects were instructed to fast between 12 noon and the beginning of the infusion, at which time they were fed. Subjects were randomly assigned to receive either ethanol or D_5W infusion in the first session and were crossed over to the alternate treatment at least 1 week later. Ethanol administration began with a bolus infusion of 7.5 mL/kg of 10% ethanol in D_5W over 30 minutes. A maintenance ethanol (10% in D_5W) infusion rate of 1.39 mL/kg/hour was started at the same time and continued for 6 hours.[23] Blood ethanol levels were obtained frequently and when found to be greater than 150 mg/dL the ethanol infusion was stopped for 30 minutes and then resumed at 75% of the previous rate. There were two instances in which this occurred (subjects 2 and 4). When D_5W was administered, it was given as a bolus and maintenance infusion at the same initial rates used for the ethanol infusion. Blood samples drawn at 0 and 6 hours confirmed the absence of ethanol in all subjects.

Acetaminophen (500-mg oral tablet) was administered 8 hours (8 AM) after the end of the ethanol or D_5W infusion. Blood was collected serially for 12 hours after

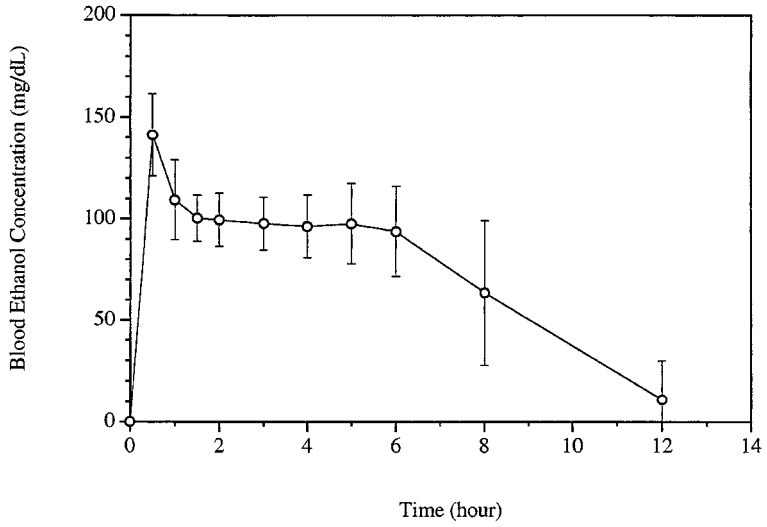

Fig 1. Ethanol concentration–time profiles after a 6-hour constant rate infusion. Each data point is the mean ± SD for 10 subjects.

acetaminophen ingestion. Plasma was separated and stored at –20°C until analysis. Urine was collected for 24 hours after acetaminophen ingestion and maintained at 4°C over 3 g L-ascorbic acid.[24] Total volume was recorded and an aliquot was stored at –80°C until analysis. Acetaminophen in plasma and urine and its metabolites in urine were assayed by HPLC.[19] Blood ethanol was quantified by an enzymatic assay (Vitros Chemistry Products, Rochester, NY).

Pharmacokinetic analyses. Total area under the acetaminophen plasma concentration–time curve (AUC) was calculated by WinNonlin (Scientific Consulting, Inc, Cary, NC). Plasma clearance (CL) of acetaminophen was calculated as Dose/AUC. The fraction of dose accounted for in urine as acetaminophen and the various metabolites was 94.1% (4.7%) and 91.9% (3.4%) for the D_5W and ethanol phases, respectively. The fraction metabolized (f_m) is the amount of each metabolite recovered in urine divided by the acetaminophen dose. Recovery of all thioether metabolites (derived from the conjugation of NAPQI with glutathione) was summed for the calculation of NAPQI f_m. Metabolite formation clearance (CL_f, the fraction of acetaminophen clearance accounted for by formation of the respective metabolite) was calculated as the product of f_m and CL. Pharmacokinetic computations and analyses of blood and urine were performed by investigators blinded to the treatment phases.

Biostatistics. For acetaminophen pharmacokinetic parameters, the percent difference between the D_5W and ethanol infusion phases of the study was calculated as the value of the ethanol phase minus the D_5W phase divided by the value of the D_5W phase. Results are reported as mean (SD). Statistical significance was determined with the Student two-tailed paired *t* test (SigmaStat, Jandel Scientific Inc, San Rafael, Calif), with $\alpha = .05$.

Model simulations. A kinetic model that relates the inhibition and induction of CYP2E1-dependent clearance to substrate concentration and the substrate Michaelis-Menten constant (K_m), and the concentration of the inhibitor-inducer and its enzyme dissociation constant (K_i) has been described and appears to successfully predict isoniazid induction of CYP2E1 in humans.[22] Based on experimental data,[19,21] the model includes two physical pools of CYP2E1, the first subject to both rapid ($k_{deg,fast}$) and slow degradation ($k_{deg,slow}$) and the second in which only the slow process operates. Synthesis of new enzyme is assumed to occur at a constant rate (R_{syn}) and adds to the first enzyme pool. Enzyme is transferred from pool 1 to pool 2 according to a first-order rate process (k_{trans}). Rat studies show that ligand stabilizes the enzyme from degradation by the rapid process without affecting the slower one.[25-27] The model treats CYP2E1 inhibition as competitive and provides for enzyme to accumulate as a consequence of its stabilization through occupation of the active site by ligand:

$$[f_u = 1/1 + (I/K_i)]$$

in which f_u is the fraction of the enzyme pool that is free of ligand and K_i is the equilibrium dissociation

Table I. Individual urinary recovery and formation clearance of NAPQI conjugates

	Ethanol (mg/dL)		*Total thioethers (% recovered dose)*			*Thioether formation clearance (L/h)*		
Subject No.	*6 h**	*12 h†*	*5% Dextrose in water*	*Ethanol*	*Change (%)*	*5% Dextrose in water*	*Ethanol*	*Change (%)*
1	140	52	6.45	7.34	13.8	1.78	1.62	–8.99
2	74	Below detectable limit	4.92	6.76	37.4	1.89	2.46	30.2
3	81	Below detectable limit	9.86	12.4	25.8	2.05	2.89	41.0
4	98	Below detectable limit	6.96	8.66	24.4	1.29	1.82	41.1
5	70	Below detectable limit	5.38	6.22	15.6	2.04	2.14	4.9
6	102	21	7.97	11.0	38.0	3.10	4.90	58.1
7	78	Below detectable limit	8.82	10.1	14.5	1.91	2.21	15.7
8	80	Below detectable limit	7.27	8.59	18.2	1.36	1.46	7.35
9	120	35	11.4	14.4	26.3	1.52	2.20	44.7
10	97	Below detectable limit	5.87	5.99	2.04	1.00	1.03	3.00
Mean	94		7.49	9.15‡	21.6	1.79	2.27‡	23.7
SD	22		2.05	2.80	11.2	0.58	1.06	22.2

*Blood ethanol concentration 6 hours after start of infusion.
†Blood ethanol concentration 6 hours after end of infusion.
‡$P < .03$, comparison of ethanol versus 5% dextrose in water phases by the Student two-tailed paired *t* test.

constant. The time course for enzyme accumulation in pools 1 and 2 after administration of an inhibitor-inducer (I) is described by the following:

$$\frac{dE_1}{dt} = E_{0,1}(k_{deg,fast} + k_{trans}) - \frac{E_1 \cdot I/K_i}{1 + I/K_i}(k_{deg,slow} + k_{trans}) - \frac{E_1}{1 + I/K_i}(k_{deg,fast} + k_{trans})$$

$$\frac{dE_2}{dt} = E_1 \cdot k_{trans} - E_2 \cdot k_{deg,slow}$$

Assuming that the basal clearance of a substrate in the absence of the inducer-inhibitor is described by the single-enzyme Michaelis-Menten equation, clearance of acetaminophen to NAPQI at time *t* in the presence of the competitive inducer-inhibitor can be described by the equation:

$$\frac{CL(t)}{CL_0} = \frac{E\,(1 + S/K_m)}{E_0\,(1 + I/K_i + S/K_m)}$$

Simulations of the effect of ethanol on NAPQI formation were conducted with use of the mean concentrations of ethanol and acetaminophen observed in this study and their respective K_i (16.5 mmol/L) and K_m (1 mmol/L) values for human CYP2E1. Because human CYP2E1 half-lives are not known, the simulation was performed with fast and slow degradation half-life values (7 and 37 hours, respectively) measured directly in rats.[26,27]

RESULTS

All subjects completed the study without a significant adverse event. After an initial overshoot after the bolus ethanol infusion, blood ethanol concentration was effectively maintained at ~100 mg/dL for the duration of the infusion (Fig 1). Six hours after the end of the ethanol infusion, blood ethanol concentration was below the limit of quantitation (10 mg/dL) in seven of 10 subjects but measurable in the other three (Table I). However, on the basis of the 6-hour concentration and observed rates of ethanol elimination, ethanol concentrations in these three subjects were projected to be <10 mg/dL at the time of acetaminophen administration 2 hours later.

Examples of the acetaminophen concentration–time profile for a subject in the study are shown in Fig 2. Administration of ethanol had no significant effect on acetaminophen clearance—25.3 (9.74) L/h versus 25.3 (9.72) L/h for the D_5W and ethanol phases, respectively. There were no major effects on the fractional formation clearances to the sulfate and glucuronide metabolites. Mean fractional clearances to the sulfate metabolite were 6.09 (1.95) L/h versus 5.93 (1.93) L/h for the D_5W and ethanol phases, respectively. The mean fractional clearances to the glucuronide metabolite were 15.1 (7.40) L/h versus 14.3 (6.52) L/h for the D_5W and ethanol phases, respectively. These pharmacokinetic results were expected with selective modification of a quantitatively minor route of elimination (ie, NAPQI formation).

The effect of ethanol on the formation of NAPQI is summarized in Table I. There was a significant 21.6% (11.2%) increase in the fraction of the dose eliminated as thioether metabolites and a 23.7% (22.2%) increase in the formation clearance of NAPQI. All 10 subjects

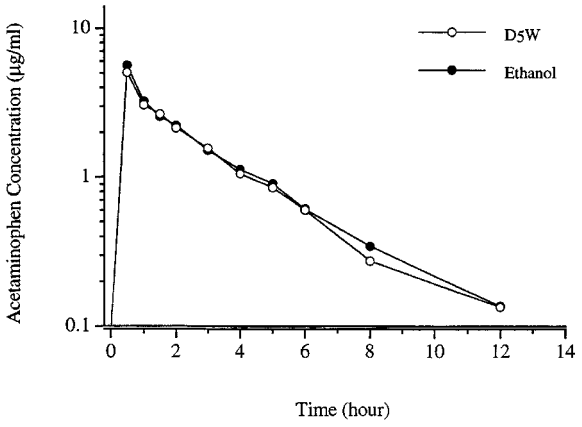

Fig 2. Acetaminophen concentration–time profiles from a representative subject. *Open symbols,* 5% dextrose in water (D_5W) infusion; *solid symbols,* ethanol infusion.

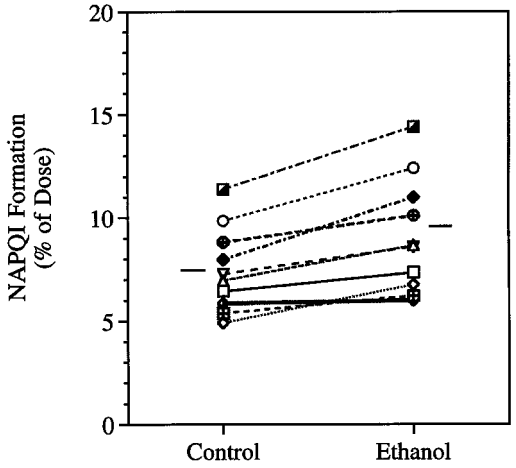

Fig 3. Induction of NAPQI formation by ethanol infusion. Each pair of data points represents the amount of NAPQI recovered in a 24-hour urine collection from a single subject. Acetaminophen was administered to 10 subjects 8 hours after the end of a 6-hour D_5W (control) and ethanol (100 mg/dL) infusion. The mean recovery for each treatment group is denoted by the *horizontal bar.*

showed an increase in the fraction of the acetaminophen dose metabolized to NAPQI (Fig 3). Nine of 10 subjects showed an increase in NAPQI formation clearance. Both parameter changes were significant by paired *t* test ($P < .03$).

Although CYP2E1 dominates NAPQI formation,[7-9] other P450 isoforms, CYP3A4 in particular, can catalyze the reaction in vitro.[8,9] To exclude induction of CYP3A4 by short-term exposure to ethanol[28] as a mechanism of enhanced NAPQI formation, a carbon dioxide breath test measure of hepatic CYP3A activity[29] was performed just before the start of each phase of the study. Results showed no difference in CYP3A4-dependent erythromycin metabolism between D_5W and ethanol phases [2.50% (1.02%) versus 2.47% (0.81%) of ^{14}C dose exhaled per hour], indicating the absence of CYP3A4 induction by short-term ethanol infusion.

A mathematical model was used to simulate changes in liver CYP2E1 content and catalytic activity produced by the plasma levels of ethanol we observed in our study (Fig 4). The simulation shows that the total amount of CYP2E1 in the liver increases during the period of ethanol exposure [$E(t)/E_0$] and then declines to baseline as ethanol is eliminated. Peak enzyme level occurs 4 hours after the end of a 6-hour ethanol infusion (100 mg/dL). However, because ethanol strongly inhibits the catalytic activity of the enzyme, it must be almost entirely removed from the body before inhibition is substantially reversed. The model predicts that peak capacity to produce NAPQI from acetaminophen [$CL(t)/CL_0$] does not occur until 6 to 7 hours after the end of the ethanol infusion and declines thereafter. As a result of the study design, ethanol and acetaminophen concentrations varied little among the subjects. Therefore the model could not account for differences in NAPQI formation clearance among individuals. However, as shown in Table II,[30] the predicted peak $CL(t)/CL_0$ (1.21) was very similar to the observed mean value (1.24).

DISCUSSION

We found that short-term ethanol exposure in healthy adults resulted in a statistically significant increase in the mean production of NAPQI from a single 500-mg acetaminophen dose. Investigators have previously reported that there was a 67% *decrease* in NAPQI urine recovery relative to control when acetaminophen was administered just after the start of an oral ethanol dosing scheme (0.6 g/kg ethanol loading dose, followed by 0.1–0.16 g/kg, hourly for 8 hours).[14] However, our data are not at odds with the published report. Because of the biphasic nature of the ethanol-acetaminophen interaction, the timing of acetaminophen ingestion is critical to demonstrating the inductive effect of ethanol (Fig 4). Ethanol inhibits the enzyme that dominates NAPQI production (CYP2E1) so that increased capacity to produce NAPQI is not evident until virtually all of the ethanol is cleared from the body. Our data indicate that in most individuals with a blood ethanol level at the legal limit of intoxication (100 mg/dL), a lapse of 8 hours from the time of last ingestion is sufficient for the transition from inhibited to enhanced NAPQI formation.

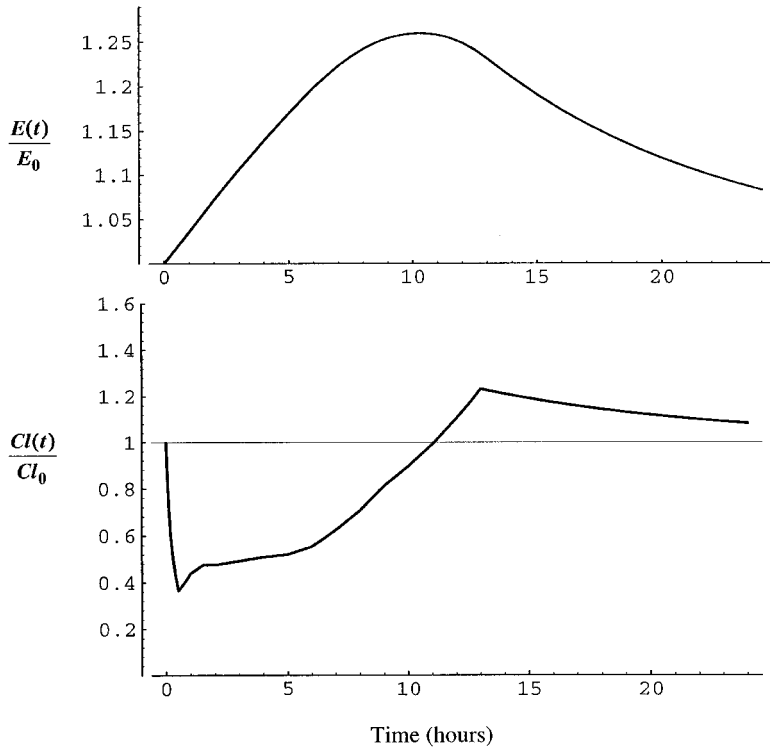

Fig 4. Simulated time course of NAPQI formation clearance and CYP2E1 enzyme ratios during and after a 6-hour infusion that maintained a 100-mg/dL blood ethanol concentration. The enzyme ratio **(upper panel)** is the CYP2E1 level predicted at any time during or after the ethanol infusion [E(t)] divided by the basal value predicted with D_5W infusion [E_0]. The formation clearance ratio **(lower panel)** is the clearance measured at any time during or after the ethanol infusion [CL(t)] divided by the value obtained with D_5W infusion [CL_0]. The simulated curve is based on 7-hour and 37-hour fast and slow CYP2E1 degradation half-lives.

Table II. Model simulated effect of ethanol concentration and duration of exposure on NAPQI formation

	Continuous									*Intermittent§*		
	6 h			*48 h*			*200 h*			*200 h*		
	T_{max}*	*Max* $CL(t)/CL_0$†	T_{enh}‡	T_{max}	*Max* $CL(t)/CL_0$	T_{enh}	T_{max}	*Max* $CL(t)/CL_0$	T_{enh}	T_{max}	*Max* $CL(t)/CL_0$	T_{enh}
100 mg/dL ethanol (experimental)		1.24										
100 mg/dL ethanol (simulated)	6	1.21	0	6	1.54	3	6	1.64	6	6	1.26	0
200 mg/dL ethanol (simulated)	10	1.34	0	10	1.78	8	10	1.95	13	10	1.48	0
300 mg/dL ethanol (simulated)	15	1.44	0	15	1.92	11	15	2.14	16	15	1.72	8

*Time (in hours) from end of continuous infusion to time of maximum clearance ration.

†Maximum clearance ratio (the maximum NAPQI formation clearance measured at any time during or after the ethanol infusion, [CL(t)], divided by the value obtained with 5% dextrose in water infusion, [CL_0]) at T_{max}.

‡Time period (in hours) over which the clearance ratio is >1.5 (ie, NAPQI formation clearance enhanced by 50%).

§Simulated ethanol infusion for 6 hours, every 24 hours, over a period of 8 or more days. The elimination of ethanol was calculated with use of literature parameters for V_{max} and K_m.[30]

For a 70-kg person, the total ethanol dose infused during our protocol (1.58 mL/kg) corresponds roughly to that in a standard 750-mL bottle of wine, six 12-ounce cans of beer, or 9 ounces of 80-proof liquor. Our data suggest that on the morning after such exposure, ingestion of two extra-strength acetaminophen tablets (1.0 g) would generate, on average, an amount of NAPQI expected from a 1.24-g dose. Any additional acetaminophen taken later would be subjected to declining induction. According to established criteria,[31] an adult without identifiable risk factors (ie, fasting, ethanol, or liver disease) must consume at least 7.5 g acetaminophen as a single dose to be at risk for liver injury. Our data therefore suggest that the maximum daily recommended dose of acetaminophen (4 g/day) can be safely consumed by healthy adults after ingestion of the amount of ethanol administered in our study.

Ethanol is, of course, consumed in higher amounts, often on a daily basis. Higher ethanol exposures were not studied for ethical reasons. However, given the agreement between model-based simulation, our experimental data (Table II), as well as published data,[14] and previous success with modeling the isoniazid-acetaminophen interaction in humans,[22] we simulated other scenarios of combined ethanol and acetaminophen use. As seen in Table II, the simulated peak increases in NAPQI formation were generally modest. For example, the model suggests that nightly ("intermittent") ingestion of the amount of ethanol administered in our study would produce only a minimal increase in NAPQI production (1.26) over that observed after single intake (1.21). Even an individual who has a blood ethanol level of 300 mg/dL for 200 hours (corresponding to steady consumption of greater than 50 bottles of wine over 8 days) would experience on average only a 2.1-fold enhancement of NAPQI formation. This increase in NAPQI formation would be the equivalent of doubling the acetaminophen dose actually consumed.

These simulations should be interpreted cautiously at present for several reasons. First, the magnitude and timing of the interaction that we observed were slightly underpredicted by the model simulation. Although the predicted peak increase in $CL(t)/CL_0$ produced after our 6-hour ethanol infusion is close to what was actually observed (Table II), the model predicted the peak would occur 6 to 7 hours after discontinuation of the ethanol infusion, whereas the acetaminophen dose was not given until 8 hours after the infusion was stopped. In addition, the production of NAPQI occurs over several hours and not just at the peak acetaminophen concentration. Further contributing inductive and inhibitory effects of the ethanol metabolite acetaldehyde were not taken into account in the simulations.

The simulations and estimates of NAPQI formation (Table II) also assume that CYP2E1 induction by ethanol occurs only through enzyme stabilization. At blood ethanol levels >250 mg/dL, in some species de novo synthesis of CYP2E1 protein increases through messenger ribonucleic acid (mRNA) stabilization,[32-34] increased translation efficiency, or both.[35] In addition, an increase in CYP2E1 mRNA in liver biopsy specimens from persons with chronic alcoholism has been reported.[36,37] Any induction of CYP2E1 by acetaldehyde or increased de novo synthesis would have a multiplying effect on the enhanced NAPQI formation estimates in Table II. However, the maximal twofold increase in NAPQI formation predicted from our model agrees well with the twofold elevation in mean chlorzoxazone 6-hydroxylation activity (a selective in vivo probe of CYP2E1 activity) reported in persons with severe chronic alcoholism when that activity was measured at least 12 hours after the last ingestion of alcohol.[5]

In addition to its effects on CYP2E1, ethanol may deplete hepatic glutathione[38] and possibly reduce glutathione transport into mitochondria (a critical hepatocellular glutathione pool),[39] enhancing cell sensitivity to the damaging effects of NAPQI. Other concomitant factors not directly related to ethanol may also enhance susceptibility to acetaminophen hepatotoxicity. Prolonged fasting and long-term treatment with acetaminophen, which could deplete hepatic glutathione, 3′-phosphoadenosine-5′-phosphosulfate, and uridine 5′-diphosphate glucuronic acid,[40] and obesity, which could increase CYP2E1 activity[41] and cause nonalcoholic steatohepatitis,[42] may exacerbate the hepatocellular response to acetaminophen attributable to CYP2E1 induction by ethanol alone. When concomitant risk factors are coupled with circumstances in which patients could have a significant increase in NAPQI production, then the dose of acetaminophen may have to be reduced. This view does not mean that acetaminophen should never be taken by the repeated consumer of large amounts of ethanol. Alternative analgesics (eg, nonsteroidal anti-inflammatory drugs) carry their own risks, some of which (gastritis and hemorrhage) can be exacerbated by alcohol abuse.[43]

We conclude that ethanol can increase susceptibility to acetaminophen-induced liver toxicity in healthy adults. The magnitude of the increase in risk is a function of the amount of ethanol consumed, the duration of ethanol ingestion, and the relative timing of acetaminophen and ethanol ingestions. When ethanol is in the body, it protects the liver from toxicity by diminishing the production of NAPQI. However, shortly after the elimination of ethanol from the body, susceptibility to toxicity may be enhanced.

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