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The Effect of Ibuprofen on Ethanol Concentration and Elimination Rate

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ABSTRACT: Pursuant to a recent driving under the influence (DUI) case, a medical study of six subjects was cited reporting that ibuprofen causes a decrease in the maximum rate of elimination of ethanol. Such a drug interaction is of significant forensic science interest and warrants further examination. This study investigates the effect of ibuprofen on ethanol elimination rate and ethanol concentration in nineteen volunteers. Volunteer subjects were randomly assigned to two groups administered either a placebo followed by ethanol or ibuprofen followed by ethanol. Subjects served as their own control. Blood ethanol concentrations were monitored every 30 to 60 min for up to 4 h with Intoximeter 3000 instruments. A blood sample was drawn at the final Intoximeter test and analyzed for ethanol and ibuprofen by gas chromatography and mass spectrometry, respectively. The mean elimination rate ($\pm$ SD) as calculated using Widmark's elimination factor was 0.018 $\pm$ 0.006 g/dL for ethanol and 0.017 $\pm$ 0.007 g/dL/h for ethanol with ibuprofen. Mean ethanol concentrations (g/dL $\pm$ SD) were: 0.095 $\pm$ 0.026 (ethanol) and 0.095 $\pm$ 0.033 (ethanol and ibuprofen) at 30 min; 0.077 $\pm$ 0.026 (ethanol) and 0.075 $\pm$ 0.031 (ethanol and ibuprofen) at 150 min; and 0.089 $\pm$ 0.025 (ethanol) and 0.087 $\pm$ 0.030 (ethanol and ibuprofen) overall. There was no statistically significant affect of ibuprofen on either the peak blood ethanol concentration or the ethanol elimination rate ($p \leq 0.001$). These results reveal no evidence of a significant ethanol-ibuprofen interaction.

KEYWORDS: toxicology, ibuprofen, alcohol, blood-alcohol concentrations

Ibuprofen is a nonsteroidal anti-inflammatory drug currently of widespread use and easy accessibility. There is potential for its concomitant use with alcohol, but little is known about ibuprofen and the presence or absence of a significant drug interaction with alcohol.

Several reports have been published concerning drug-alcohol interactions with the nonsteroidal anti-inflammatory agents. Some of these agents such as indomethacin have been reported to impair eye-hand coordination and divided attention when psychomotor skills were measured with a choice reaction test [*1*]. In the presence of alcohol, indo-

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methacin proved less harmful with alcohol than without. Impairment of test skills by phenylbutazone was increased in the presence of alcohol. In a recent study, a large dose of aspirin was reported to cause a small increased in the blood-alcohol concentration in nonfasting subjects [2].

Minocha et al. [3] investigated the effects of ibuprofen on the pharmacokinetics and pharmacodynamics of ethanol in six fasting subjects. They reported an increase in visual impairment during combined ibuprofen and ethanol dosing but a decreased impairment in the auditory-verbal memory performance. Furthermore, they reported a decrease in the maximum rate of elimination of ethanol. Such a drug interaction is of significant forensic science interest and warrants further examination. This study investigates the effect of ibuprofen on the ethanol elimination rate and blood-ethanol concentration in nineteen volunteers in a semi-fast state.

Materials and Method

Nineteen volunteer subjects were randomly assigned to two groups administered either a placebo followed by ethanol or ibuprofen followed by ethanol. Each subject served as his or her own control. The subjects consumed alcoholic beverages over 1 h after fasting approximately 5½ h on each of the two days. The total ethanol dose prescribed as a guideline to each subject was based on their body weight to approximate 0.1 g/dL [4]. The time intervals, number of ounces, and type of liquor were recorded and repeated on the second night. On one of the two days, subjects took the placebo or ibuprofen (400 mg) twice by mouth at 5.5 and 1.0 h before ethanol consumption.

Blood-ethanol concentrations were estimated every 30 to 60 min for up to 4 h using four Intoximeter 3000 instruments. Before and during the study, the Intoximeter's performance was verified with multiple standards. A blood sample from each subject was drawn at the final Intoximeter measurement and analyzed for alcohol with a Perkin-Elmer Sigma 2000 headspace gas chromatograph using the following conditions: nitrogen carrier flow rate of 20 mL/min, injector 150°C, column 100°C, and detection at 150°C. A Supelco column was used with an outer diameter (OD) of 0.31 mm, length of 1.3 m, and packed with 0.2% Carbowax 1500 on 60/80 Carbopak C. Blood-alcohol concentrations were calculated using peak area ratios of ethanol to internal standard (*n*-propanol) by the method of linear regression. Ibuprofen concentrations were determined from blood samples using an acidic drug extraction and a Hewlett-Packard 5890 gas chromatograph coupled to a 5970 mass spectrometer with the following conditions: helium carrier flow rate of 1.0 mL/min, injector 250°C, transfer line 280°C, column 120°C for 1.5 min, then programmed at 25°C/min to 280°C. An Ultra 2 column was used: 0.2 mm by 12 m, film thickness 0.35 μm, and 5% diphenyl/95% dimethypolyselocane. Mass spectrometer data was acquired using a scan range of 40 to 400 AMU and electron ionization. Quantitation was determined by extracted ion chromatography.

Widmark's elimination factor (β) was calculated according to Wallgren and Barry [5]. The means and the standard deviation of the means were determined for the treatment groups. The significance of the effect of ibuprofen on ethanol concentrations and elimination rates were analyzed by student's *t*-test applied to paired comparisons [6].

Results

The correlation of the paired results ($n = 38$) between the blood-alcohol concentrations determined by the headspace gas chromatograph (x) and the blood-alcohol concentration estimated by the intoximeter (y) was $r = 0.98$ with $y = (1.014)x + 0.0029$. The standard error of estimate for the correlation was 0.0048 g/dL; the mean and the 95% confidence interval were $0.77 \pm <0.01$ g/dL. The blood-ethanol concentrations ranged from 0.023

to 0.142 g/dL. Ibuprofen levels ranged from 0.29 to 5.67 μg/mL with a mean and standard deviation of 2.98 μg/mL ± 1.38 (Table 1).

The effect of ibuprofen on the elimination rate of ethanol was compared using Widmark's elimination factor (Table 1). The mean elimination rate as calculated using Widmark's elimination factor [5] was 0.018 ± 0.006 g/dL/h for ethanol alone and 0.017 ± 0.007 g/dL/h for ethanol and ibuprofen. There was no statistical difference between the paired groups ($p \leq 0.001$).

A comparison between the effect of ibuprofen on ethanol concentrations at selected time intervals postconsumption is shown in Table 1. There was no statistical difference between any of the paired groups at the various time intervals ($p \leq 0.001$).

Discussion

Understanding the presence or absence of drug-alcohol interactions is of great significance to the forensic toxicologist or medical examiner in the interpretation of cases involving the operation of a vehicle or machinery requiring a high degree of mental judgment and motor coordination. A previous study by Minocha et al. [3] using six fasting subjects reported a statistically significant 10% decrease in the maximum rate of elimination (K_{max}) of ethanol by ibuprofen and attributed this decrease to an inhibition of alcohol dehydrogenase. If a significant inhibition of alcohol dehydrogenase by ibuprofen did occur, one would have also expected a significant increase in the blood-ethanol concentration, yet Minocha et al. reported no change in the ethanol concentration. Since Minocha et al.'s investigation was undertaken on a small sample population, and they modeled ethanol elimination using Michaelis-Menten kinetics, we undertook this investigation to determine if a therapeutic level of ibuprofen would have an effect on peak blood-ethanol concentration or elimination of ethanol or both as calculated by Widmark's elimination factor (β).

In this study, nineteen subjects followed common drinking behavior with multiple drinks and obtained peak blood-ethanol concentrations ranging around 0.10 g/dL. The concentrations of ibuprofen for the nineteen subjects fell within ibuprofen's therapeutic range based on dosage and half-life [7,8]. Alcohol metabolism proceeds at a rate that is independent of dose (zero order) at blood concentrations between 0.02 and 0.3 g/dL as described by Widmark's hypothesis [5,7]. The elimination kinetics have been described as first order or nonlinear (Michaelis-Menten) at concentrations either less than or greater than this range [9–11]. Since the range of ethanol concentrations during this study fell between 0.023 and 0.176 g/dL, the data would be best described by the zero order kinetic

TABLE 1—*Summary statistics of the effect of ibuprofen on ethanol elimination rate and concentration.*[a]

	Ibuprofen μg/mL	Blood-Alcohol Concentration (g/dL Estimated by Intoximeter)						Widmark, g/dL/h	
		1.5 hr		3.5 hr		Overall			
		E	E+I	E	E+I	E	E+I	E	E+I
Mean	2.98	0.095	0.095	0.077	0.075	0.089	0.087	0.018	0.017
Standard deviation	1.38	0.026	0.033	0.026	0.031	0.025	0.030	0.006	0.007
Maximum	5.67	0.162	0.176	0.142	0.140	0.162	0.176	0.030	0.026
Minimum	0.29	0.058	0.050	0.024	0.023	0.028	0.023	0.010	0.006

[a]E = ethanol alone; E+I = ibuprofen followed by ethanol. Degrees of freedom = 18. No statistically significant differences between the test and control groups were established ($p \leq 0.001$).

model of Widmark. There was no evidence that ibuprofen significantly affected either the peak blood concentration of ethanol or the ethanol elimination rate as determined by Widmark's elimination factor (Table 1). The lack of a significant effect on these parameters with such a number of observations makes it unlikely that different results could be obtained or the opposite conclusions could be reached. In summary, this study produced no evidence to verify a significant ethanol-ibuprofen interaction.

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