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Acetaminophen Fails to Inhibit Ethanol-Induced Subjective Effects in Human Volunteers

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PICKWORTH, W. B., S. A. KLEIN, F. R. GEORGE AND J. E. HENNINGFIELD. *Acetaminophen fails to inhibit ethanol-induced subjective effects in human volunteers.* PHARMACOL BIOCHEM BEHAV **41**(1) 189–194, 1992.—In animals, ethanol causes some of its CNS effects by releasing prostaglandins (PG); this is demonstrated by reports that prostaglandin synthetase inhibitors (PGSIs) diminish ethanol-induced effects. However, use of animals in these studies has precluded testing for subjective effects. We studied the interaction of ethanol and acetaminophen, a PGSI, in a double-blind crossover experiment. Six adult males were given no drug or acetaminophen (0, 325, 650, 1300 or 1950 mg) 75 min before ethanol (total dose = 0.625 g/kg; five divided doses). Physiologic, subjective and performance measures were collected. Compared to the no drug condition, ethanol significantly increased ratings of drug "liking," "drunk," "sluggish" and "drug strength" and decreased ratings of "sober." Ethanol increased heart rate and acetaminophen did not diminish or enhance this effect. The failure to antagonize ethanol-induced subjective and physiologic effects by acetaminophen in humans may be due to species differences or inadequate dosage of the PGSI. It is also possible that subjective and certain physiologic effects of ethanol in humans are not mediated by prostaglandin-dependent neural processes. Nevertheless, the finding that at greater than typical analgesic doses, acetaminophen failed to prevent subjective effects of ethanol is of clinical significance.

Acetaminophen Ethanol Prostaglandin inhibitors Paracetamol

ANIMAL studies have shown that prostaglandin synthetase inhibitors (PGSI's) antagonize some of the effects of ethanol. For example, indomethacin reduced the excitatory (13,31), depressant (14), hypothermic (13) and lethal effects (14) of ethanol in rodents. The interaction between ethanol and indomethacin appeared to be related to genetic sensitivity to ethanol, and sex (15,17). In a self-administration paradigm, indomethacin decreased responding for ethanol in a dose-related manner (12). Aspirin and indomethacin pretreatment inhibited the rate-depressant effects of ethanol in rats responding on a fixed ratio operant schedule (16). Further, blood ethanol levels obtained in these studies indicated that PGSI antagonism of ethanol was the result of diminished central nervous system sensitivity to alcohol and not due to an alteration in ethanol metabolism. In tests of CNS depressant activity, there appears to be a strong correlation between potency of PGSI and the degree of inhibition of the ethanol response (13). However, not all actions of ethanol are consistently affected. For example, indomethacin failed to inhibit ethanol-induced motor impairment in mice and rats and hypothermia in mice (18). Grupp et al. (19) reported that indomethacin inhibited ethanol-induced motor impairment in rats but attributed the effect to the renin-angiotensin system. Overall the results of the animal studies indicate that some of the effects of ethanol in the CNS are due to an increase in prostaglandin synthesis or release (11,12).

The interaction of PGSIs with ethanol in humans has not been systematically studied. Two PGSIs, aspirin (37) and indomethacin (1), block the flush induced by alcohol in some patients taking chlorpropamide. The palliative effects of aspirin on ethanol-induced hangover are well known; pretreatment with tolfenamic acid also reduces hangover (24). Minocha et al. (27) reported that visual memory was more impaired by combinations of ethanol and ibuprophen than after either drug alone, but ibuprophen treatment prevented ethanol-induced impairment of auditory-verbal memory. The purpose of the present study was to determine if pretreatment with various doses of acetaminophen, a widely used over-the-counter PGSI, changes the effects of ethanol on subjective, physiologic and performance tests in humans. Acetaminophen was tested because it inhibits brain prostaglandin synthetase (7) and causes less gastritis than other PGSIs. Ethanol was administered in divided doses over 2 h to simulate social drinking behavior.

METHOD

Subjects

Six adult male volunteers recruited from the community by advertisements in the local newspaper participated in this study. All of the subjects were "social drinkers" in that they did not admit to a current addiction to alcohol and had never been

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treated for alcoholism. Each subject used ethanol in the week before their admission at a self-reported level of five drinks per day. All of the subjects had been drinking for more than 10 years; all started drinking during their teenage years. Their mean age was 34.6 years (range 27–40) and their mean weight was 83.7 kg (range 70–101). Four subjects were caucasian and two were African Americans. Each subject signed an informed consent document which was written in accordance with the Department of Health and Human Services guidelines for the protection of human subjects and was approved by the Institutional Review Board. For the duration of the experiment (approximately 3 weeks per subject), the subjects resided on a clinical research unit. They ate a usual hospital diet except that they were not allowed to consume caffeine-containing foods or beverages. Each subject received a thorough medical and psychological examination before their participation in the study. They resided on the research unit for approximately 7 days before they began the experimental protocol. Subjects were paid $15 per day; they earned additional money for their performance on the tasks of the study and for completing the study.

Study Design

During their first 3–4 days on the research ward, the subjects were familiarized with the requirements of the study. They were taught to answer the computer-displayed subjective questions and were trained on the hand-eye coordination test and two tasks from the Walter Reed Performance Assessment Battery (PAB) (38): a rapid arithmetic task and a logical reasoning task. Training sessions were repeated several times to permit acquisition and stabilization of performance on the performance tasks.

This was a double-blind cross-over study. Each subject was tested on six occasions; study days were separated by at least 48 hours. On the first study day, subjects were given no drugs. On subsequent study days, the subjects ate a light breakfast, and at 9:15 a.m. swallowed six capsules containing a total of 0, 325, 650, 1300 or 1950 mg of acetaminophen. The order of presentation of the acetaminophen dose was randomized across subjects. Beginning at 10:15 a.m., the subjects were given orange juice solutions (10:1 dilution with 95% ethanol) to drink every 30 min. The first solution contained no alcohol; the next five solutions contained 0.125 g/kg ethanol (in orange juice). Thus each subject consumed a total of 0.625 g/kg ethanol over a period of 120 min beginning at 10:45 a.m.

Measures

Physiologic, subjective and performance measurements were collected at: 9:00 (pre), 10:30, 11:00, 11:30 a.m., noon, 12:30, 1:00, 1:30, 2:00, 2:30, 3:00, 3:30, 4:00 p.m.

Physiologic effects. At each measurement time, diastolic and systolic blood pressure, heart rate, skin temperature, respiration rate and pupil diameter were recorded. Pupil diameter was measured using a Polaroid CU camera (26).

Subjective effects. At each measurement time, subjects assessed their current feeling state on a computer which presented ten visual analog scales which surveyed: "drug liking," "drug disliking," "drug strength," "sober," "drunk," "sleepy," "calm," "dizzy," "clumsy" and "sluggish." The 60 mm scale used the phrases "not at all" and "extremely" to define the scales' extremes.

Performance effects. At each measurement time, the subjects completed a hand-eye coordination test. The procedure involved pushing lighted buttons on a 71×71 cm^2 wall-mounted panel. At the start of the trial, one of the thirty-three buttons was illuminated. Pushing that button added one point to the counter and lighted another button at a random position. The score was the total number of points in the one-minute session. As an incentive for their performance, subjects were paid a penny per point.

The two tasks from the PAB have been described elsewhere (20, 36, 38). In the rapid arithmetic task, two digits were presented in sequence followed by a "+" or "−" sign. Subjects were to complete the indicated operation. If the answer was a two-digit number, the correct response was the second digit. If the answer was a negative number, 10 was added to the answer. Thus all correct answers were single-digit positive numbers. In the logical reasoning task, a statement describing the relationship between two letters (e.g., A precedes B) appeared on the video screen. Below the statement the same letters appeared in the order AB or BA. The subject was asked to determine if the statement accurately described the sequence of the letters. This task lasted 150 s or until 32 trials had been completed.

Data Analysis

The measures were analyzed using a two-way repeated measures analysis of variance (ANOVA). The main factors were time (13 levels) and drug-condition (six levels when the no drug condition was included, five levels when only study days with active drug were included in the analysis). When the analysis indicated significant main effects of time or drug condition or the interaction of time and drug conditions, post hoc dependent *t*-tests were used to identify the responsible components.

RESULTS

Blood levels of alcohol were not measured in all subjects. In those ($n = 2$) where the data were available, the expired alcohol concentration suggested blood levels peaked at 50 mg% after the fourth and fifth alcohol drinks.

Subjective Effects

As illustrated in Fig. 1, ethanol caused reliable and significant changes on scales that estimate ethanol-induced subjective effects. Overall the data suggest that acetaminophen pretreatment did not influence the subjective effects caused by the ethanol. As shown in Fig. 1, ethanol significantly increased ratings of "drug strength" [time: $F(5,12) = 5.87$, $p<0.01$; condition by time: $F(5,60) = 2.36$, $p<0.01$], "drug liking" [condition: $F(5) = 6.23$, $p<0.01$; time: $F(12) = 5.19$, $p<0.01$; condition by time: $F(5,60) = 2.11$, $p<0.01$], and "drunk" [time: $F(12) = 2.06$, $p<0.05$]. Ethanol also significantly decreased ratings of "sober" [time: $F(5,12) = 4.03$, $p<0.01$; condition by time: $F(5,60) = 1.61$, $p<0.01$]. When the no drug condition was not considered in the analyses, there were no significant condition, or condition by time interactions. This finding indicates that ethanol had the same subjective effects regardless of the pretreatment. As illustrated in Fig. 1D, ratings of "sluggish" increased across the experimental conditions, $F(5,12) = 2.48$, $p<0.01$. However, not all subjective questions were significantly influenced by the ethanol and acetaminophen administration. For example, on scales rated for: "calm," "sleepy," "clumsy," "dislike drug," and "dizzy," no significant effects occurred.

Performance Effects

Generally, ethanol did not significantly affect the performance measures of this study. Acetaminophen pretreatment did not change the performance that followed ethanol administration. For example, performance on the circle of lights task was not

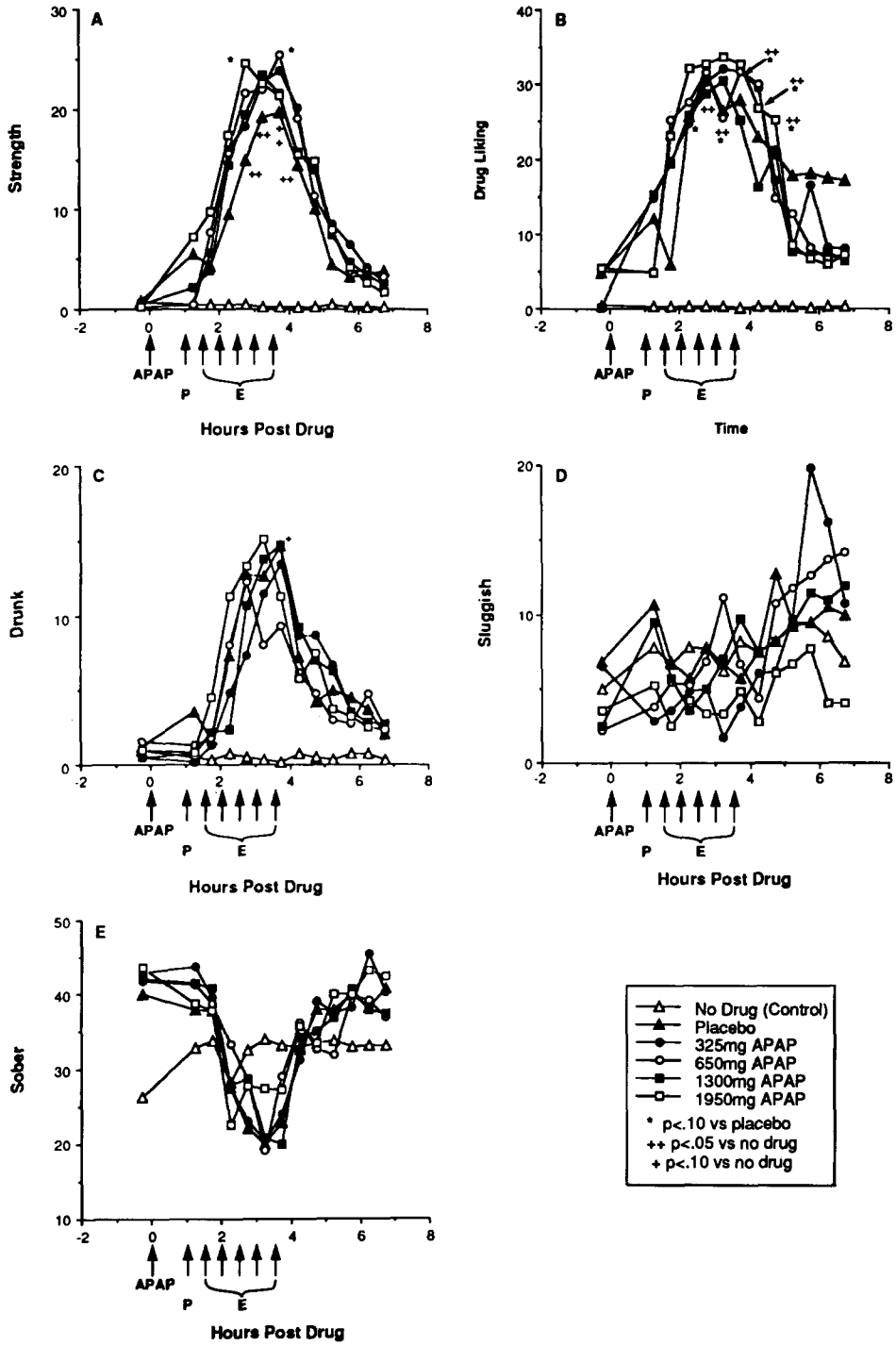

FIG. 1. Ethanol administration (0.125 g/kg) at each time E (total dose = 0.625 g/kg) caused increases in estimates of drug strength (A), drug liking (B), drunk (C), and sluggish (D) and decreases in sober (E). Acetaminophen (APAP) pretreatment in doses between 325 and 1950 mg did not change ethanol-induced subjective effects.

changed by ethanol. There was a significant, $F(3,12) = 2.71$, $p<0.05$, improvement in performance over time, but the score did not vary as a function of drug condition and condition by time interaction was not significant. Similar findings occurred in the computer-delivered logical reasoning and rapid arithmetic tasks where ethanol did not significantly change the number of correct responses, percent of responses correct or the response time. Acetaminophen pretreatment neither increased nor decreased the performance observed after ethanol. In the rapid arithmetic and logical reasoning tasks, there were time-related

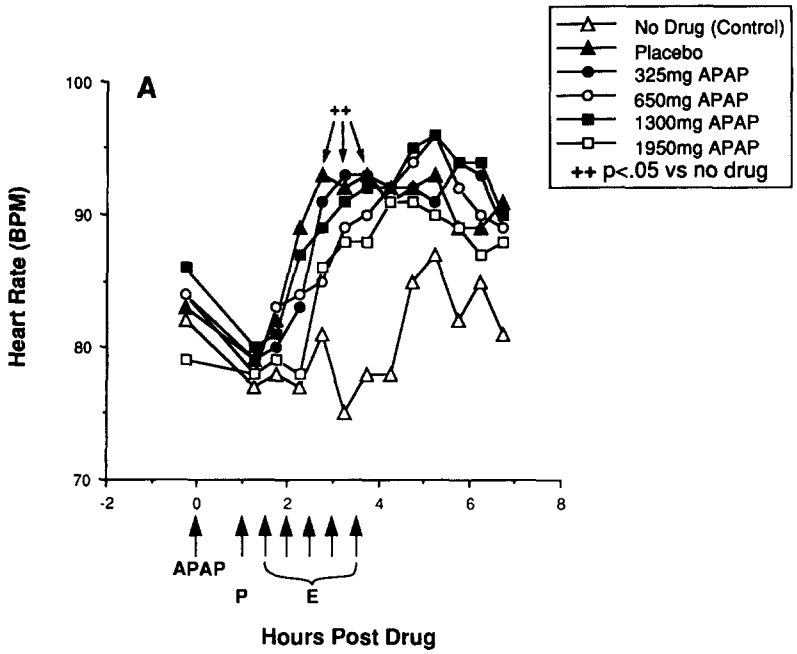

FIG. 2. Ethanol administration (0.125 g/kg) at each time E (total dose = 0.625 g/kg) caused a slight increase in heart rate. Acetaminophen (APAP) pretreatment did not change ethanol-induced tachycardia.

effects that indicated performance improved over the course of the experimental day. For example, the response time in the rapid arithmetic task averaged 897 ms before the drugs and decreased to 800 ms at the last recording period (mean collapsed across all drug conditions) $F(12) = 2.14$, $p < 0.02$. These results seem to suggest a practice effect on the performance measures of the study.

Physiological Effects

In general, ethanol produced changes in certain physiologic measures, but these effects were not altered by pretreatment with acetaminophen. For example, ethanol caused a significant increase in heart rate [time: $F(5,12) = 17.7$, $p < 0.001$] but the increase was not altered by the acetaminophen pretreatment (Fig. 2). Skin temperature significantly increased across time, $F(5,12) = 2.70$, $p < 0.01$, but there were no differences between conditions or the time by condition interaction. Pupil diameter significantly decreased across time regardless of the treatment condition, time: $F(5,12) = 1.99$, $p < 0.05$; the time by condition interaction was not significant. Ethanol caused no significant effects on diastolic or systolic blood pressure. The effects on respiration were complex. Respiratory rate increased over time after pretreatment with 650 or 1950 mg of acetaminophen, but decreased over time after the 325 mg pretreatment. There were no significant effects of conditions or time, but there was a significant condition by time interaction, $F(5,48) = 1.68$, $p < 0.01$.

DISCUSSION

This study was inspired by results from animal studies indicating that pretreatment with PGSIs attenuate ethanol-induced toxicity and changes in behavior and physiologic function. We determined whether pretreatment with acetaminophen, a widely used PGSI, could affect the subjective, physiologic and performance effects of ethanol in humans. Given the mixed results of earlier studies with humans (25,27), we chose a moderate ethanol dose which could have provided information on additive or reducing interactions between ethanol and acetaminophen. Acetaminophen did not diminish or enhance ethanol-induced subjective or physiological effects. In this study, ethanol caused no significant changes in performance. From our data we can not predict the interaction of acetaminophen and ethanol on performance measures.

Results of in vitro and in vivo animal experiments suggest that ethanol causes some of its effects through interactions with prostaglandin dependent processes. Ethanol and other alcohols increase plasma membrane fluidity (2,33) which causes, among other effects, an increase in the activity of phospholipase A2 (22,23). Activation of phospholipase A2 increases the release of arachidonic acid from membrane phospholipid storage and leads to the increase in arachidonic acid metabolites called eicosanoids (21,40). One group of eicosanoids, the prostaglandins, are synthesized from arachidonic acid in a reaction catalyzed by the prostaglandin synthetase enzyme complex. Thus events that increase the availability of arachidonic acid, such as the administration of ethanol, increase plasma membrane fluidity and increase the production of prostaglandins (3). A growing body of evidence suggests that drugs that inhibit the synthesis of prostaglandins antagonize a wide range of the effects produced by ethanol (12). This antagonism was observed in human (25) and animal (13) studies where a variety of PGSIs decreased the CNS sensitivity to the depressant effect of several alcohols including ethanol.

In the present study we pretreated subjects with a wide range of doses of acetaminophen, a popular over-the-counter analgesic that is known to inhibit brain prostaglandin synthetase (7). The pretreatment dose was varied between 325 and 1950 mg, a dose range that bracketed the usual therapeutic dose of 650 mg. Dose ranging in the experiment seemed appropriate in light of experiments showing many PGSIs, including acetaminophen, have an

inverted U-shaped dose-response curve (5) indicating that a limited range of doses are effective. Compared to other PGSIs, acetaminophen weakly inhibited brain cyclooxygenase (7) but acetaminophen is relatively more effective on brain prostaglandin synthesis than on its peripheral synthesis (6, 8, 9, 41). These considerations further justified the extension of the dose range in our study to three times the usual therapeutic dose. In spite of the wide dosage range, none of the doses of acetaminophen altered the physiologic and subjective effects of ethanol. Subjects reported similar degrees of "drug-liking," "drunk," "sober" and "drug strength" regardless of the pretreatment dose of acetaminophen. Likewise, ethanol-induced tachycardia was not affected by the acetaminophen pretreatment.

Performance Effects

The dose of ethanol used in this study (0.625 g/kg, over 120 min) caused no significant effects on performance measures. These results are similar to those of Linnoila et al. (25) who administered a 0.5 g/kg dose and found it caused no significant effects on two coordination tests and a divided attention task. However, others have found that ethanol at blood alcohol concentration (BAC) levels close to the 50 mg% recorded in our subjects caused significant performance effects. Gengo et al. (10) reported the threshold BAC for detection of changes in performance depended on the task. For example, a BAC of 60 mg% was the calculated threshold for the digit symbol substitution test, whereas 40 mg% was the calculated threshold for a simulated driving task and a choice response task. Others have reported that BAC levels of 50 mg% are near threshold for the detection of performance impairment (4). The rate of administration of ethanol in the present study was evidently responsible for the lack of performance effects. In most studies, the ethanol is administered over 15–30 min. In an attempt to prevent nausea, which may have occurred in the high-dose acetaminophen pretreatment condition, we administered ethanol over 120 min. The longer administration interval may have prevented in our study the performance decrements which occurred after ethanol in other studies.

Subjective Effects

In the present study, ethanol caused significant and time-dependent effects on subjective measures of intoxication and drug liking. However, acetaminophen pretreatment failed to influence the magnitude of these effects. These findings suggest that PGSI inhibitors are unable to change ethanol-induced subjective effects. Our results differ from those of Truitt (39) who reported that aspirin pretreatment diminished some subjective effects of ethanol intoxication in sensitive individuals. Subjects in the present study had extensive histories of alcohol use and reported typical subjective effects at doses that did not cause performance impairment.

Physiologic Effects

We found that ethanol increased heart rate and that acetaminophen pretreatment did not change this response. Others have reported that ethanol increases heart rate (30). The small increase is thought to be caused by diminished cardiac venous return which is the result of a vasodilator effect of ethanol. Newlin et al. (28) proposed that cardiac acceleration is caused by a decrease in vagal tone. Whatever the mechanism, it appears from our study that the heart rate increase is not mediated by prostaglandin-dependent processes.

The ethanol-induced increase in skin temperature we observed has been reported by others and is thought to be due to peripheral vasodilation and increased cutaneous blood flow. Prostaglandin synthesis inhibitors are known to decrease body temperature that is elevated by fever, but generally do not affect normal temperature or temperature that is elevated by exercise or high ambient temperature.

Pupil diameter decreased over the course of each experimental day regardless of the drug treatment. These results seem to agree with those of a study recently completed in our laboratory in which dynamic pupillary measures were recorded in drug-free subjects between 6 a.m. and 9 p.m. (29). In that study as in the present one, we found the pupillary diameter decreased over the day.

Moderate amounts of ethanol may increase or decrease respiration (30). We found that ethanol increased respiration rate compared to the no drug condition. When subjects were pretreated with acetaminophen, the ethanol-induced increase in respiration was diminished. These results suggest that the acetaminophen pretreatment decreased this ethanol response. The results are similar to those of animal experiments in which pretreatment with PGSIs decreased respiratory depression and lethality after a high dose of ethanol (13). In other studies, ethanol suppressed ovine fetal breathing movements; the effect was directly correlated with prostaglandin release and was antagonized by indomethacin, a PGSI (34,35).

The results from animal studies suggest that PGSIs inhibit some of the effects of ethanol. The present study provides no evidence that such results occur in humans. In other clinical studies, PGSIs have been only weakly effective in antagonizing the effects of ethanol (25,27). Evidently, the subjective effects of ethanol are not dependent on prostaglandin-mediated neural processes. However, the dose of ethanol used in this study was small and divided, and partial antagonism effects of PGSIs, such as those usually seen in animal studies, may occur if higher single doses of ethanol were used. Further studies are warranted to fully investigate whether ethanol-induced performance decrements are sensitive to prostaglandin synthesis inhibitors. Roine et al. (32) reported that 1 g of aspirin increased blood ethanol levels by 30% and enhanced the performance decrements and subjective effects of ethanol. In that study, subjects drank 0.3 g/kg of ethanol over 10 min, a more rapid ingestion of ethanol than in our study. Roine et al. (32) attributed the increase in blood ethanol to aspirin-induced inhibition of gastric alcohol dehydrogenase. It is possible that some of the effects may have been due to inhibition of prostaglandin synthesis.

In summary, pretreatment over a wide dose range with acetaminophen, a popular over-the-counter PGSI, did not inhibit or enhance the subjective effects of moderate ethanol doses. These results are theoretically important and clinically relevant. In animal studies, PGSI's decreased ethanol-induced effects. In our small sample study, the failure of acetaminophen to prevent ethanol-induced subjective effects tentatively suggests that the subjective experiences of modest intermittant doses of ethanol are not dependent on prostaglandin-mediated mechanisms. Another study is being conducted to determine if a more potent PGSI, indomethacin, can prevent the subjective and physiologic effects of larger doses of ethanol. From a practical standpoint, the results of the present study indicate that acetaminophen does not prevent the subjective effects of moderate doses of ethanol.

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