Inhibition of Prostaglandin Synthesis and Effects of Ethanol and Pentobarbital in Humans

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ABSTRACT

Results from animal research suggest that pretreatment with prostaglandin synthesis inhibitors (PGSIs) may inhibit physiological and behavioral effects of moderate ethanol ingestion. We examined the effects of ethanol and pentobarbital in humans with and without pretreatment with indomethacin, a potent PGI. Ten male subjects with histories of recreational use of ethanol and sedative/hypnotics participated in this inpatient study. The effects of indomethacin alone (0.66 mg/kg), indomethacin (0, 0.17, 0.33, 0.66 and 1.33 mg/kg) in combination with ethanol (0 and 1 g/kg) and indomethacin (0 and 0.66 mg/kg) in combination with pentobarbital (0, 1.33 and 4 mg/kg) were tested. On test days, subjects swallowed capsules containing indomethacin or placebo. One hour later, they swallowed capsules that contained pentobarbital or placebo and a large drink (500 ml) of tonic water that contained ethanol or placebo (tonic water with 2 ml of ethanol floated on top). Both ethanol and pentobarbital affected subjective ratings, performance measures and heart rate. However, indomethacin pretreatment had no influence on drug-induced changes to ethanol and pentobarbital. The results of this study illustrate the relationship between depressant drugs and human performance, but they do not support the hypothesis that inhibition of prostaglandin synthesis diminishes the effects of ethanol and pentobarbital in humans.

Alcohol consumption is widespread and results in significant mortality. In the United States, ethanol ingestion is implicated in traffic accidents and hospital admissions and is the primary cause of death for 100,000 citizens each year (McGinnis and Foege, 1993). The profound public health implications of ethanol consumption have spurred a variety of pharmacological approaches to diminish the effects of acute ethanol administration or to reduce the appeal of ethanol to the dependent patient. For example, the opiate antagonist naltrexone decreased craving for ethanol, ethanol-induced euphoria and ethanol consumption in dependent subjects (for a review, see O’Brien et al., 1996). Selective serotonin reuptake inhibitors, such as fluoxetine, appear to attenuate ethanol craving and self-administration in depressed and nondepressed heavy drinkers (Gorelick and Paredes, 1992; Naranjo et al., 1994) Ondansetron, a 5-hydroxytryptamine5 receptor antagonist, exaggerated the subjective effects of intoxication but did not influence the effects of ethanol on measures of performance (Swift et al., 1996). Some animal studies suggest that certain calcium channel blockers suppress ethanol intake (De Beun et al., 1996).

PGSIs have been shown to antagonize some of the effects of ethanol in animal studies. For example, indomethacin reduced excitatory (George and Collins, 1979; Ritz et al., 1981) and depressant (George et al., 1982) effects of ethanol in rodents. Gender and the genetic sensitivity of the animal strain to ethanol influenced the interaction between indomethacin and ethanol (George et al., 1983, 1986). Indomethacin also reduced responding for ethanol in a self-administration paradigm (George, 1989). Pretreatment with PGSIs (e.g., aspirin, indomethacin) inhibited the rate-depressant effects of ethanol in operant responding (George and Meisch, 1990). The BAL indicated that the effects were due to diminished sensitivity to ethanol and not the result of pharmacokinetic differences in ethanol metabolism. In a test of central nervous system depressant activity, there was a high correlation between the PGI potency and inhibition of the ethanol response (Elmer and George, 1991). Prostaglandins mediated the rate depressant and narcosis induced by ethanol (Elmer and George, 1996). Prostaglandin E1 and prostanooid precursor fatty acids modulated ethanol withdrawal behavior in mice, an effect that was inhibited by PGI administration (Segarich et al., 1985). Aspirin pretreatment reduced ethanol withdrawal severity in a mouse model of binge drink-

ABBREVIATIONS: PGSi, prostaglandin synthesis inhibitor; PAB, (Walter Reed) Performance Assessment Battery; DSST, digit symbol substitution; ARCI, Addiction Research Center Inventory; BAL, blood alcohol level; ANOVA, analysis of variance; hsd, honestly significant difference; MBG, morphine-benzodrine group (ARCI subscale); PCAG, pentobarbital-chlorpromazine-alcohol group (ARCI subscale); LSD, lysergic acid diethylamide (ARCI subscale); A, alcohol (ARCI subscale).
ing (Hale et al., 1992). Overall, these animal studies suggest that some of the effects of ethanol in the brain are due to an increase in prostaglandin synthesis or release and that PG-SIs diminish these effects.

However, interactions between PG-SIs and ethanol in human experiments have yielded mixed results. Aspirin (Strakosch et al., 1980) and indomethacin (Barnett et al., 1980) prevented the alcohol-induced flush in some patients taking chloropropamide. Minocha et al. (1986) reported that combinations of indomethacin and ethanol impaired visual memory more than either drug alone, but indomethacin prevented ethanol-induced impairment in auditory/verbal memory. In a systematic study of the interactions between ethanol and acetaminophen, Pickworth et al. (1991) reported that over a wide dose range, this PGSI did not inhibit physiological and subjective effects of moderate ethanol ingestion. That research was extended in the present study in which an intoxicating ethanol dose and a more potent PGSI, indomethacin, were tested in a larger group of volunteer subjects. In addition, doses of pentobarbital were added to the research design because ethanol and pentobarbital have similar pharmacological profiles in that their effects may be mediated through modulation of γ-aminobutyric acid activity at the chloride channel (for a review, see Tabakoff and Hoffman, 1996). Furthermore, there is cross-tolerance between barbiturates and ethanol, and the abstinence syndrome from ethanol can be diminished by administration of barbiturates (Jaffe, 1970). However, the role of prostaglandins in ethanol and pentobarbital tolerance and withdrawal has not been defined.

Methods

Subjects

Ten male subjects with histories of recreational use of ethanol and sedative/hypnotics within the past 2 years volunteered for this impatient study. The subjects’ average age was 33.7 years (range, 26–42 years) and weighed an average of 74.6 kg (range, 60–110 kg). None of the subjects were addicted to a drug other than nicotine, and they had never been diagnosed as an alcoholic or treated for alcoholism. Nine subjects reported current cigarette smoking (mean number cigarettes per day, 21.9). All of the subjects reported lifetime use of alcohol and either barbiturates or other tranquilizers. Mean current alcohol use was reported as being ~12 standard drinks per week. Subjects with histories of active hepatitis, pancreatic disease, cardiovascular disease, seizures, Parkinson’s disease, ulcers, or allergies to the study drugs were not eligible to participate. Each subject signed a consent form that had been approved by the local institutional review board and met U.S. Department of Health and Human Services guidelines for the protection of human research subjects. For the duration of the experiment, subjects resided on a clinical research unit. They ate a usual hospital diet, but they were not allowed to consume caffeine-containing foods. On the morning of the study days, they were asked to eat a light “cereal and toast” breakfast. Subjects who completed the protocol were paid an average of $600.

Study Design and Drug Administration

During their first 5 days on the research unit, subjects were familiarized with the cognitive and psychomotor tasks of the study. Training sessions were repeated several times to permit acquisition and stabilization on performance tests. This was a double-blind crossover study. Each subject was tested on 11 occasions; study days were separated by ≥48 hr. The treatment conditions are summarized in table 1. On test days, subjects swallowed capsules containing indomethacin (0.17, 0.33, 0.66 or 1.33 mg/kg) or placebo with a large glass of water (480 ml). One hour later, they swallowed capsules that contained pentobarbital (1.33 or 4 mg/kg) or placebo and a large drink (500 ml) of tonic water that contained ethanol (1 g/kg) or placebo (tonic water with 2 ml of ethanol floated on top) that was consumed in 15 min. The order of presentation of the drug conditions was randomized across subjects with the restriction that the low dose of pentobarbital always preceded the higher dose.

The dose of ethanol (1 g/kg) and doses of pentobarbital (1.33 and 4 mg/kg) were selected because they reliably produced impairment on performance tests used in previous studies (Pickworth et al., 1997; Pickworth et al., in press). Dose-response relationships on the interaction of PG-SIs and ethanol in animal studies indicate that many PG-SIs, including indomethacin, have an inverted U shape (Elmer and George, 1991). This indicates that only a limited range of doses are effective. For that reason, the dose of indomethacin in the present study was extended from 0.17 to 1.33 mg/kg. The usual therapeutic range of single doses of indomethacin is 0.35 to 0.7 mg/kg.

Dependent Measures

Physiological, subjective and performance measures were collected before the first capsules (9:00 A.M.); 1 hr after the capsules, but before the drink and the second capsules (10:30 A.M.), and 30, 60, 90, 120 and 240 min after the drink and the second capsules.

Physiological measures. At each measurement time, BAL, diastolic and systolic blood pressures, heart rate, respiratory rate and oral and skin temperatures were recorded.

Subjective measures. At each of the time points, subjective effects of the drugs were assessed by means of computer-delivered questions from a shortened form of the ARCI (Haertzen, 1966; Jasinski, 1977). The questions formed the following subscales: MBG, which measures euphoria; PCAG, which measures apathetic sedation; and LSD, which measures drug-induced dysphoria. Six computer-delivered visual-analog scales rated subjective responses to “like drug,” “good effects,” “bad effects,” “drug strength,” “tired” and “drunk.” The 100-mm scale used the phrases “not at all” and “extremely” to define the scale’s extremes. Subjects placed a cursor along the line to rate their level of endorsement using computer keystrokes.

Performance measures. Subjects completed several tests of cognitive and psychomotor performance. Two tests (serial arithmetic and six-letter search) from the PAB (Snyder et al., 1989; Thorne et al., 1985) were used. In the serial arithmetic task, two digits appeared sequentially on the computer screen for 250 msec, with each followed by a plus or minus sign. The subject mentally performed the indicated operation. If the answer was a two-digit number (e.g., 15),
the correct response was the unit digit (e.g., 5). If the answer was a negative number (e.g., −2), 10 was added to the answer, and the resulting single positive digit was entered (e.g., 8). In the six-letter search task, subjects answered with a single keystroke (“Y” or “N”) if each of the six letters displayed at the top of the computer screen were contained in the random string of 24 letters concomitantly displayed below.

In the computer-delivered DSST, a digit appeared on the computer screen, and the subject reproduced the geometric pattern associated with the digit using three keystrokes on the numeric keypad (Heishman et al., 1988). The dependent measures in the DSST and PAB tasks were the number of correct responses, percent correct and response time. An incentive of $0.01 for each correct response was given on these tasks.

In the circular lights task (Heishman et al., 1990), subjects rapidly pushed lighted buttons on a wall-mounted panel that consisted of 33 button lights. As the one illuminated button was pushed, another lighted. The dependent measure was the number of illuminated buttons pushed during the 1-min task. Subjects were given $0.01 for each correct button press as an incentive.

In the 1-min rotary pursuit task, subjects attempted to keep a wand with a photoelectric cell directly above a rotating (30 rpm) lighted target. The dependent measures were the time on target and the number of times the tracking was lost. An incentive of $0.01 was paid for each second on target.

In a hand steadiness test, subjects inserted a stylus (diameter, 1 mm) into a series of eight holes with diameters ranging from 15 to 2 mm and held the stylus without touching the side for 15 sec per hole. The dependent measures were the number of seconds without touching a side and the total number of times the subject touched a side. For each second without a side touch, the subjects were awarded $0.01.

Subjects completed a series of four card-sorting tasks of increasing difficulty (Berry et al., 1965) that are sensitive to the effects of ethanol and pentobarbital [Pickworth et al., 1997]. A well-shuffled deck of 32 playing cards was sorted into two (color), four (suit) and eight piles (suit and type, face or number). As a motor control, cards were placed one at a time into two piles without regard to color or suit. The dependent measures for the card tasks were time to sort, number of mistakes and dropped cards.

**Data Analysis**

Because the purpose of the present study was to examine the effects of indomethacin on either ethanol or pentobarbital, the data from the two drugs were examined separately. Table 1 summarizes the drug conditions used in each of the two ANOVAs. On the measure of “drug liking,” data provided by one subject were eliminated from the analysis due to the subject’s misunderstanding of the question.

To examine the interactions between indomethacin and ethanol, data from all dependent measures, except card sorting, were subjected to two-way repeated measures ANOVA (Winer et al., 1991). The two factors of each ANOVA were drug condition (seven levels: conditions 1–7 from table 1) and time (seven levels: each of the seven time points described in Dependent Measures). Where there were significant drug condition × time interactions (P < .05), post hoc comparisons were made using Tukey’s hsd test. To assess the sensitivity of each measure to pentobarbital, comparisons were made between the placebo-placebo condition (condition 1) and the two conditions in which placebo was followed by active pentobarbital (1.33 or 4 mg/kg; conditions 8 and 10 from table 1, respectively). For measures that were found to be sensitive to pentobarbital’s effects, comparisons were made between each active pentobarbital dose with and without indomethacin pretreatment (i.e., comparisons were made between conditions 8 vs. 9 and 10 vs. 11).

Data from the card-sorting tasks were analyzed using two three-way repeated measures ANOVAs. The three factors of the ANOVAs were condition (six or seven levels for pentobarbital and ethanol, respectively), time (seven levels) and task difficulty (four levels: two-, four- and eight-pile sort and motor control). Post hoc comparisons were made using Tukey’s hsd test as described above.

For all measures, to assess the effects of indomethacin (0.66 mg/kg) alone across the entire session, comparisons were made between the placebo-placebo condition (condition 1) and the indomethacin-placebo condition (condition 7) at each time point. Also, to assess differences between indomethacin doses alone, comparisons were made on the data collected from a single time point (1 hr after the first capsule) between placebo (condition 2) and all active indomethacin doses (0.17, 0.33, 0.66 and 1.33 mg/kg; conditions 3–6, respectively).

**Results**

Table 2 shows the results of the two-way repeated measures ANOVAs for both ethanol and pentobarbital. The table illustrates the drug condition × time interaction F values, their significance level and whether the measure was sensitive to either ethanol or pentobarbital as described in Data Analysis. Post hoc analyses on measures in which there was a significant drug condition × time interaction on the ANOVA for either ethanol or pentobarbital showed that indomethacin alone had no effect on any subjective, physiological or performance measures [i.e., there were no significant differences between the placebo-placebo condition (condition 1) and the indomethacin-placebo condition (condition 7) at any time point during the session]. Furthermore, subjective, physiological or performance measures were not significantly altered 1 hr after administration of any dose of indomethacin (conditions 3–6) compared with placebo (condition 2).

**Ethanol.** Drug condition time interaction effects were noted on a variety of subjective (fig. 1), physiological (fig. 2) and performance (figs. 3 and 4) measures. Significant drug condition × time interactions were shown on visual-analog scale measures of “drug strength,” “drunk,” “liking,” “good effects,” “bad effects” and “tired.” On each of these visual-analog scale measures, significant differences were found between the placebo-placebo combination (condition 1) and the placebo-ethanol combination (condition 2), demonstrating that these measures were sensitive to ethanol’s effects. On each measure, significant score elevations in condition 2 over condition 1 levels were shown as soon as the 30-min postdrinking time point and lasted throughout the session, with the exceptions of “bad effects,” which became elevated at the 90-min time point, and “tired,” which was only significantly increased at the 240-min time point. Significant drug condition × time interactions were also shown on the PCAG scales of the ARCI. Scores on the PCAG scale were significantly elevated after ethanol (condition 2) over scores after...
placebo (condition 1). Post hoc analyses showed no differences between the placebo-ethanol combination (condition 2) and the conditions in which the four active doses of indomethacin were combined with ethanol (conditions 3–6). Significant drug condition × time interactions were also shown on the LSD scale of the ARCI. However, scores on the LSD scale were not sensitive to the effects of ethanol (i.e., no difference between conditions 1 and 2).

Significant drug condition × time interactions were shown on physiological measures of heart rate, skin temperature and BAL. Post hoc analyses showed that both heart rate and BAL were significantly increased in the active drink condition (condition 2) above placebo drink levels (condition 1). In the condition in which ethanol administration was preceded by placebo, peak BALs were reached within 30 min after drinking; mean BAL at this time was 115 mg%. No significant differences were found between the placebo-ethanol combination (condition 2) and the four conditions in which the four active doses of indomethacin were combined with ethanol (conditions 3–6) on either heart rate or BAL measures.

Significant drug condition × time interactions were shown on performance measures, including circular lights, rotary pursuit (number of times off target and amount of time spent on target), serial math task and DSST. No significant effects of ethanol were found on the hand-steadiness task. Post hoc analyses showed that in general, performance was impaired in the placebo-ethanol condition (condition 2) compared with the placebo-placebo condition (condition 1). As on subjective and physiological measures, no significant differences were found between the placebo-ethanol combination (condition 2) and the four conditions in which the four active doses of indomethacin were combined with ethanol (conditions 3–6).

| TABLE 2 | Results of two ANOVAs showing drug condition × time interactions and direction of pentobarbital and ethanol effects |
|-------------|---------------------------------|-------------------|
| Measure                                      | Ethanol F(36, 324) | Pentobarbital F(30, 270) |
| **Subjective**                                |                    |                   |
| Visual-analog scales                          |                    |                   |
| Strength                                      | 6.3*               | 8.1*              |
| Drunk                                         | 6.2*               | 2.4*              |
| Drug liking                                   | 3.7*               | 5.7*              |
| Good effects                                  | 7.6*               | 7.3*              |
| Bad effects                                   | 1.9b               | N.S.              |
| Tired                                         | 1.5a               | 2.4*              |
| **Physiological**                             |                    |                   |
| Systolic blood pressure                       | N.S.               | N.S.              |
| Diastolic blood pressure                      | N.S.               | N.S.              |
| Heart rate                                    | 4.6*               | 2.1*              |
| Respiration rate                              | N.S.               | N.S.              |
| Oral temperature                              | N.S.               | N.S.              |
| Skin temperature                              | 1.9g               | N.S.              |
| BAL                                           | 40.0*              | N.S.              |
| **Performance**                               |                    |                   |
| Circular lights                               | 4.8*               | 5.3*              |
| Rotary pursuit                                |                    |                   |
| Number times off                              | 1.6*               | N.S.              |
| Time on target                                | 4.7*               | 8.5*              |
| Six-letter search                             |                    |                   |
| Attempts                                      | N.S.               | 1.6*              |
| Correct                                       | N.S.               | 2.0*              |
| % Correct                                     | N.S.               | 1.6*              |
| Response time                                 | N.S.               | 2.3*              |
| Serial math                                   |                    |                   |
| Attempts                                      | 2.0*               | 1.8*              |
| Correct                                       | 1.9*               | 2.3*              |
| % Correct                                     | N.S.               | 2.2*              |
| Response time                                 | 2.1c               | 1.9*              |
| DSST                                          |                    |                   |
| Attempts                                      | 1.9c               | 5.1c              |
| Correct                                       | 1.9c               | 5.0c              |
| % Correct                                     | N.S.               | 2.1c              |
| Response time                                 | 1.6c               | 3.3c              |

Numbers indicate the interaction F value and significance level (*P < .05; **P < .01; ***P < .001) from ANOVAs that measured the effects of ethanol (conditions 1–7, table 1) and pentobarbital (conditions 1 and 7–11). Arrows indicate the direction of a significant change from baseline due to ethanol (1 g/kg) or pentobarbital (4 mg/kg) (Tukey’s hsd).
and the four conditions in which an active dose of indomethacin preceded ethanol (conditions 3–6). On the card-sorting task, the three-way ANOVA yielded a condition × time × task interaction that neared significance [F(108, 972) = 1.76, P = .063]. In general, times to sort cards were longer on the more difficult tasks (i.e., sorting into eight piles) after active ethanol dosing than after placebo dosing. Indomethacin pretreatment did not affect ethanol-induced card sorting performance impairment.

**Pentobarbital.** The effects of pentobarbital on subjective measures were similar to those seen after ethanol (fig. 1). Significant drug condition × time interactions were shown on all visual-analog scale scores except “tired.” In each case, post hoc analyses showed that scores were significantly higher in the placebo-pentobarbital 4 mg/kg condition (condition 10) than in the placebo-placebo condition (condition 1). Shorter pentobarbital combined with placebo (conditions 8 and 10) decreased heart rate below placebo-placebo levels (condition 1). The active dose of indomethacin combined with pentobarbital 4 mg (condition 11) tended to decrease heart rate (maximum decrease, 6.2 bpm) more than the placebo-pentobarbital 4 mg/kg combination (condition 10) (maximum decrease, 2.6 bpm); however, these differences were not statistically significant.

Drug condition × time interactions were shown on all performance tasks measured with the exception of the hand steadiness task (fig. 3). For each measure, performance was slowed and accuracy was decreased in the placebo-pentobarbital 4 mg/kg condition (condition 10) below levels seen in the placebo-placebo condition (condition 1). In general, however, indomethacin had little or no effect on pentobarbital-induced performance decrements. As illustrated in fig. 4, a significant drug condition × time × task interaction effect was shown on the card-sorting task [F(90, 810) = 1.76, P < .001]. The 4 mg/kg dose of pentobarbital (condition 10) significantly increased sort times in the two-, four- and eight-pile sorts with mean increases of up to 8.5, 17.4 and 20.2 sec in these three tasks, respectively, over placebo times (condition 1). No significant effects of pentobarbital were seen on the motor control task. As on other performance tasks, indomethacin had

**Fig. 3.** Mean performance scores before and after administration of test drugs. △, ○ and □. Pretreatment (~60 min) with placebo capsules. ▲, ● and ■. Pretreatment with 0.66 mg/kg indomethacin. This pretreatment was followed by administration (0 min) of either placebo (△, ●), 1 g/kg ethanol (○, ●) or 4 mg/kg pentobarbital (□, ■).

**Fig. 4.** Mean time to sort cards into piles before and after administration of test drugs. △, ○ and □. Pretreatment (~60 min) with placebo capsules. ▲, ● and ■. Pretreatment with 0.66 mg/kg indomethacin. This pretreatment was followed by administration (0 min) of either placebo (△, ●), 1 g/kg ethanol (○, ●) or 4 mg/kg pentobarbital (□, ■). Subjects sorted cards into two, four or eight piles according to color, suit and denomination as described in Methods. Cards were sorted into two piles without regard to color as a motor control.
no significant effect on pentobarbital-induced card-sorting performance impairment.

Discussion

A major objective of this study was to determine whether inhibition of prostaglandin synthesis would alter the subjective, physiological and performance effects of ethanol and pentobarbital. In a previous clinical study, acetylsalicylic acid pretreatment did not reduce the subjective or cardiovascular effects of ethanol (Pickworth et al., 1991). The design of the present study offered several improvements. First, indomethacin, a more potent PGSI than acetylsalicylic acid, was used over a wide range of doses. Ethanol was administered at a higher dose (1 g/kg) over 15 min to maximize the intoxication and performance impairment. A more comprehensive battery of cognitive and psychomotor tests was used to determine the effects of the experimental drugs over a wide range of cognitive and motor functions. The interaction between indomethacin and pentobarbital was added to the design because there is evidence to indicate that both ethanol and pentobarbital exert their pharmacological effects through modulation of γ-aminobutyric acid activity at the chloride channel (Tabakoff and Hoffman, 1996). Finally, the power of the present study was increased by raising the sample size from six to 10. Despite these experimental changes, there was no evidence indicating that indomethacin pretreatment altered the effects of ethanol or pentobarbital.

Indomethacin is a potent inhibitor of brain PG synthesis. At 30 min after oral administration, doses as low as 1 mg/kg (IC50 < 1 μM/kg) completely inhibited the ex vivo production of prostaglandin E2 in mouse brain (Ferrari et al., 1990). Of the six PGIS tested (indomethacin, zomepirac, naproxen, ibuprofen, acetylsalicylic acid and aspirin), indomethacin was the most potent in the inhibition of prostaglandin E2 synthesis and analgesia. These results and those of Elmer and George (1991), in which indomethacin was the most potent in a series of PGISs in the inhibition of the ethanol responses in rodents, led to the selection of indomethacin for the present study. Indomethacin pretreatment did not significantly change the BAL profiles attained after the administration of ethanol. These results are similar to those obtained in rats by George and Meisch (1990), in which PGISs, including indomethacin, did not affect the pharmacokinetics of ethanol. Roine et al. (1990) reported that pretreatment with aspirin (1 g) increased BAL of subsequently administered ethanol (0.3 g/kg) by 30% and increased performance impairment. The authors attributed the increase in BAL to aspirin-induced inhibition of gastric alcohol dehydrogenase. The results of this study do not indicate that indomethacin significantly affects ethanol metabolism; however, the larger doses of ethanol used in this study may account for the differences between BALs obtained in this study and those obtained by Roine et al. (1990).

As in other studies (Pickworth et al., 1997; Pickworth et al., in press), ethanol decreased speed and accuracy on the computer-delivered PAB and DSST tests and on the circular lights score. However, ethanol in divided doses that totaled 0.625 g/kg over 2 hr did not cause significant changes in performance (Pickworth et al., 1991). Gengo et al. (1990) reported that the threshold for effects of ethanol on performance depended on the task: ~40 mg% for a driving simulator and ~60 mg% for the DSST. Others have reported that levels of ~50 mg% are near threshold for the detection of performance impairment (de Wit et al., 1987).

A series of card-sorting tasks (Berry et al., 1965) was among the performance measures of the present study. In a previous study (Pickworth et al., 1997), pentobarbital and ethanol impaired card-sorting speed. The advantage of this series of tasks is that they impose increasing levels of cognitive load, but the motor component of the performance stays relatively constant. In the present study, neither pentobarbital nor ethanol diminished card-sorting rate in the motor control task (no cognitive component) and in the easy two-pile sort task. However, as the task difficulty increased in the four- and eight-pile sorting tasks, both drugs significantly slowed the response. These data illustrate an intuitive but seldom demonstrated point; as task complexity increases, the effects of drugs become more apparent. The high dose of pentobarbital in the present study (4 mg/kg) did not cause significant impairment on the motor control task; however, in another study (Pickworth et al., 1997), a higher dose (5.7 mg/kg) did cause impairment in the motor control sorting task. Taken together, these indicate that pentobarbital affected the cognitive component of the task at doses lower than those needed to influence the motor component.

In summary, the results of the present study and those of a previous study (Pickworth et al., 1991) do not support the hypothesis that prostaglandin-dependent processes mediate the subjective or performance effects of ethanol or pentobarbital in humans. Although there are several reports that PGISs modify the effects of ethanol in rodents (for a review, see George, 1989), pretreatment with indomethacin, a potent PGSI over a wide dose range, failed to alter subjective, physiological or performance effects of ethanol and pentobarbital. From a practical standpoint, the results of the present study indicate that indomethacin (and other PGISs) does not prevent subjective and performance effects of ethanol. This suggests that PGISs are ineffective as treatments for acute alcohol or pentobarbital intoxication.

Although the present study did not yield significant interactions between indomethacin and ethanol and pentobarbital, there are limitations in the experimental design that might influence the overall interpretation. The interaction between indomethacin and ethanol was tested using a single dose of ethanol; the interaction between pentobarbital and indomethacin was tested using a single dose of indomethacin. It is possible that an extension of the dose range may have yielded significant interactions. The battery of performance tests used in the present study may not have captured the interaction between indomethacin and ethanol and pentobarbital. For example, some studies in animals that have demonstrated an interaction (George, 1989; George and Meisch, 1990) have used measures of operant behavior and self-administration. Furthermore, there was no direct measure of prostaglandin synthesis inhibition or prostaglandin levels in the present study.
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