Alcohol antagonism of hypercortisolism induced by naloxone

The reversal of acute alcohol intoxication by naloxone is controversial. Naloxone increases cortisol secretion but there are no reports of this effect during acute alcohol intoxication. This study examines the effect of 20 mg naloxone on alcohol-induced intoxication using a balanced placebo design to investigate the role of cortisol, participant expectancy of treatment, and possible pharmacokinetic interactions during intoxication. Our results show differences in the time course of subjective self-evaluation of drunkenness in the presence of naloxone. Also, changes are observed in naloxone pharmacokinetic parameters with the ingestion of alcohol, specifically a decrease in plasma clearance. Whereas the cortisol response induced by naloxone was greater in the subgroup of participants with positive expectancy, the presence of alcohol the naloxone effect on cortisol response was not observed. These observations may help explain the observed reversal of alcohol-induced coma by naloxone in a subgroup of patients. (Clin Pharmacol Ther 1988;43:599-604.)

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suggested that participant expectancy can affect the results.7,8

Naloxone is known to increase cortisol secretion,9,10 and it has been suggested that the beneficial response of naloxone in septic shock can be explained partially by the cortisol response.11 However, there are no data regarding possible changes in cortisol response to naloxone during acute alcohol intoxication. The clinical trial described in this article considers the role of cortisol in situations of acute alcohol intoxication and investigates participant expectancy and possible pharmacokinetic interactions of the drugs.

SUBJECTS, MATERIAL, AND METHODS

Forty-eight healthy male student volunteers aged 21 to 30 years were selected. Candidates with medical and psychiatric pathologic antecedents, specifically those who fulfilled criteria of drug dependence (but not abuse) according to the DSM-III (except tobacco smokers), were excluded. Only subjects who reported personal experience with high doses of alcohol (moderate intoxication a minimum of five times per year) were accepted in the study. The volunteers selected were submitted to physical examination and laboratory tests to exclude any abnormality before the experiment. Subjects were required to fast for at least 4 hours and abate from alcohol use for 48 hours before each experiment. This was confirmed for all subjects by chemical analysis of plasma samples taken before drug and placebo administration. All subjects included in the study were fully informed of the purposes of the investigation and gave their written consent, according to authorized protocol (Dirección General de Farmacia y Productos Sanitarios 82/460).

A balanced, placebo, double-blind clinical trial was designed in which 48 participants were randomly assigned to 12 subjects in each of the four treatment groups listed in Fig. 1. The experiments were performed in groups of two subjects (whose experimental conditions were random) and began at 4 PM. To induce positive or negative alcohol expectancy, each set of two subjects was given the results of a false lottery immediately before drug administration. This created the required expectancy independently of how drug administration was randomly selected and led 50% of participants to falsely believe that they would (or would not) consume alcohol.

Acute alcohol intoxication was induced by ingestion during a period of 15 minutes of an alcoholic drink based on vodka and tonic water containing a total dose of 1 gm/kg ethanol. To this mixture was added several drops of bitters and lemon juice to successfully mask the placebo drink, which was the same mixture minus the vodka. At time zero the ingestion of alcohol or placebo was begun simultaneously with the infusion of 20 mg naloxone or a placebo (in a volume of 250 ml saline solution). The infusion was terminated at 30 minutes.

Throughout the experiment subjective effects and vital signs were recorded and blood samples were taken for analytic measurements at predose and 30, 45, 60, 75, 90, 120, 180, and 240 minutes after administration of the drugs.

Blood alcohol concentrations were measured by GC using direct injection of whole blood12 and flame ionization detection, which permitted measurement of ethanol to levels of 2.71 mmol/L. Naloxone in plasma was measured by HPLC with electrochemical detection according to a slight modification of methods published previously.13,14 A mixture of acetonitrile:0.1 mol/L phosphate buffer (pH 4.5) containing 0.5 mmol/L EDTA (85:15) as a mobile phase and a octadecylsilane column (Spherisorb ODS-2, Phase Separations, Queensferry, U.K.) was used. Recovery of naloxone

| Oral Placebo/ | Oral Alcohol/ |
| IV Placebo   | IV Placebo   |
|             |             |
| Positive Expectancy |                         |
| 6 Subjects    | 6 Subjects    |
|             |             |
| Negative Expectancy |                        |
| 6 Subjects    | 6 Subjects    |

| Oral Placebo/ | Oral Alcohol/ |
| IV Naloxone   | IV Naloxone   |
|             |             |
| Positive Expectancy |                         |
| 6 Subjects    | 6 Subjects    |
|             |             |
| Negative Expectancy |                        |
| 6 Subjects    | 6 Subjects    |

Fig. 1. Experimental groups according to drugs and expectancy. IV, intravenous.
Table I. Pharmacokinetic parameters of intravenous naloxone*

<table>
<thead>
<tr>
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<th>Placebo group</th>
<th>Alcohol group</th>
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<tbody>
<tr>
<td>$K_w$ (min$^{-1}$)</td>
<td>0.0430</td>
<td>0.0566</td>
</tr>
<tr>
<td>$K_{el}$ (min$^{-1}$)</td>
<td>0.0473</td>
<td>0.0128</td>
</tr>
<tr>
<td>$V_c$ (L)</td>
<td>57.3</td>
<td>22.7</td>
</tr>
<tr>
<td>CL (L · min$^{-1}$)</td>
<td>2.46</td>
<td>1.28</td>
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*The mean values for the plasma levels were analyzed by the CONSAM Program, Laboratory of Mathematical Biology, National Cancer Institute, National Institutes of Health, Bethesda, Md.

from plasma was 75% ± 4%. The assay sensitivity was 15.25 nmol/L and the coefficient of variation was 3.5% at 30.50 nmol/L. Cortisol was measured in duplicate with an RIA technique in the solid phase (Coat-A-Count Diagnostics Products Corp., Los Angeles, Calif.). Cross-reactivity was less than 0.1% and the assay was sensitive down to plasma levels of 27.86 nmol/L cortisol whereas mean interassay and intraassay variabilities were 11.0% and 5.0%, respectively.

Subjects completed a series of six visual analog scales (depressed-euphoric, active-passive, tired-alert, relaxed-tense, calm-anxious, and sober-drunk) to assess subjective effects simultaneously with the other tests. The visual analog scales were 100 mm long without anchor points. All comparisons were made by the Student t test, except in the case of visual analog scales where factor analysis was applied and data are presented as means ± SD.

RESULTS

Fig. 2. A shows the mean time course of drunkenness subjective self-evaluation for those subjects who received ethanol alone (solid line) and those who received both alcohol and naloxone (broken line). Each group contained 12 subjects, six with positive and six with negative alcohol expectancy. No differences were found between positive and negative expectancy for either drug treatment. Factor analysis of the visual analog scales revealed that subjects distinguished between the sensation of drunkenness and other sensations such as nervousness and alertness throughout the experiment. In an interview carried out at the end of the experiment, 23 of the 24 subjects to whom it was administered showed that the subjects could not distinguish the alcohol from the placebo.

Table I shows the pharmacokinetic data for naloxone. For alcohol, the experimental peak plasma drug concentration ($C_{max}$) was approximately 22 nmol/L and the time to reach peak concentration ($t_{max}$) was 75 minutes for both expectancy groups (Fig. 2, B). Comparison of maximum naloxone levels reached at the end of infusion ($C_{max}$) reveals significantly higher levels of naloxone in the alcohol/naloxone group ($p < 0.05$) (Fig. 2, C). The experimental mean values are 413 nmol/L for the placebo group and 980.0 nmol/L for the alcohol group. A comparison of the pharmacokinetic parameters of naloxone between both groups reveals that differences in the half-life ($t_{1/2}$) cannot be established. However, in the group that ingested alcohol the naloxone plasma clearance was about 50% lower than in the placebo group. No significant differences were found in alcohol pharmacokinetic parameters obtained in the absence or
presence of naloxone (Fig. 2, B). No pharmacokinetic differences were found based on subject expectancy.

During the administration of alcohol or placebo, basal cortisol figures varied within ±25% of mean values. The administration of a single dose of 20 mg naloxone stimulated cortisol secretion to plasma levels up to 200% above control values and the maximum cortisol levels were reached at 45 minutes. By contrast, in the presence of alcohol this naloxone effect on cortisol response was not found during the 4 hours that the experiment lasted. Fig. 3 shows the time course of cortisol response to naloxone separately for the experimental conditions of positive and negative expectancy. The group with positive expectancy shows that naloxone clearly induced higher plasma levels of cortisol, with a statistically significant difference at 45 minutes ($p < 0.05$).

**DISCUSSION**

There was no coincidence between the $C_{max}$ of participant-assessed intoxication and the peak of blood alcohol concentrations. This is a phenomenon observed previously with not only alcohol but also other psychoactive drugs. These data confirm that subjective self-evaluation of alcohol effects is more intense when blood alcohol concentrations are rising. In subjects who falsely believed they had ingested alcohol but had received only naloxone, the increase in cortisol secretion could have contributed to the deception and the estimation of the $C_{max}$ of intoxication at 45 minutes.

Despite the high dose used, the curve for plasma levels of naloxone is compatible with pharmacokinetic data from earlier studies that used far lower doses. Notable differences in the plasma clearance between the alcohol-naloxone and placebo-naloxone groups stand out. This could possibly be explained by changes in the volume of distribution ($V_{area}$), which could be the result of physicochemical properties of naloxone in the presence of a high-dose ingestion of alcohol. Naloxone liposolubility, and consequently its antagonistic activity, is reduced dramatically in an acid environment and it is possible that high doses of alcohol could induce acidosis.

As described by other authors, naloxone increases cortisol secretion. Alteration of the naloxone plasma clearance in the presence of alcohol could explain the differences found in the dose-dependent activity of naloxone and cortisol secretion. Our data suggest that there may be similarities in the mechanisms involved during stress or expectancy because we have found the cortisol response induced by naloxone to be greater in the subgroup of participants with positive expectancy.
It is possible that some behavioral component of expectancy is related to cortisol control in the same way that cortisol is involved in situations of stress.\textsuperscript{22}

The influence of a possible release of endogenous opioids cannot be ruled out, be it concomitant with the secretion of cortisol, as a response to the inhibition of opioid receptors, or because of both simultaneously. Pituitary release of ACTH occurs concomitantly with that of \textbeta-endorphin and induces the adrenal release of cortisol.\textsuperscript{23} It has been postulated that in septic shock naloxone might be beneficial because of cortisol response or its antagonistic action on the \textbeta-endorphin.\textsuperscript{24,25}

On the other hand, acute administration of alcohol in humans increases the levels of endogenous opioids in plasma and cerebrospinal fluid.\textsuperscript{26} According to the dose of naloxone administered, the release of \textbeta-endorphin and cortisol occurs in different proportions.\textsuperscript{21}

With regard to the effects of alcohol on the secretion of cortisol, research up to the present differs according to the conditions of the study.\textsuperscript{27,28} It might be suggested that in certain circumstances, or in subjects with a given susceptibility, naloxone reverses the effects of alcohol, by either inducing the release of cortisol, inhibiting the secondary effects of the \textbeta-endorphin, or doing both simultaneously. The first possibility should probably be ruled out because this study indicates that alcohol antagonizes the effects of cortisol secretion induced by naloxone. With the information currently available, we cannot reject possible inhibitory effects of \textbeta-endorphin and thus cannot say whether the alcohol inhibitory effect of the cortisol response to naloxone is produced at the hypothalamic, hypophyseal or adrenal level. The appearance of tetrahydroisoquinolines,\textsuperscript{29,30} which would compete with the opioid receptors where naloxone acts, could explain the inhibitory mechanism. However, the speed with which the interaction occurs must also lead one to consider other mechanisms.

The questions of whether this interaction occurs in actual clinical cases of acute alcohol intoxication and what role is played by endogenous opioids need further research. Variability of the different elements involved in the interactions studied and the difficult extrapolation into actual clinical settings may explain the conflicting results hitherto obtained regarding the role of naloxone in antagonizing acute alcohol intoxication.

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References
and narcotic antagonists and can even abolish narcotic antagonist activity. Lancet 1982;i:559-60.