ORIGINAL ARTICLES

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, in 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.)

Jordi Camí, MD, Rafael de la Torre, PhD, Lluís Garcia-Sevilla, MD,
Balbina Ugena, RN, Hernando Knobel, MD, and Jordi Segura, PhD *Barcelona, Spain*

The first case of reversal of an alcoholic coma by naloxone was described in 1978.[1] However, many recent experimental and clinical studies have reported contradictory results, hence it is difficult to recommend the systematic use of naloxone in acute alcohol intoxication.[2] In patients with acute alcohol intoxication the reversal of coma by naloxone usually occurs only in a subpopulation not yet fully characterized.[3-5] Although naloxone has been shown to reverse some of the effects of alcohol under laboratory conditions,[6] it has been

599

Oral Placebo/
IV Placebo

Oral Alcohol/
IV Placebo

┌────────Positive Expectancy────────┐
6 Subjects   6 Subjects

6 Subjects   6 Subjects
└────────Negative Expectancy────────┘

Oral Placebo/
IV Naloxone

Oral Alcohol/
IV Naloxone

┌────────Positive Expectancy────────┐
6 Subjects   6 Subjects

6 Subjects   6 Subjects
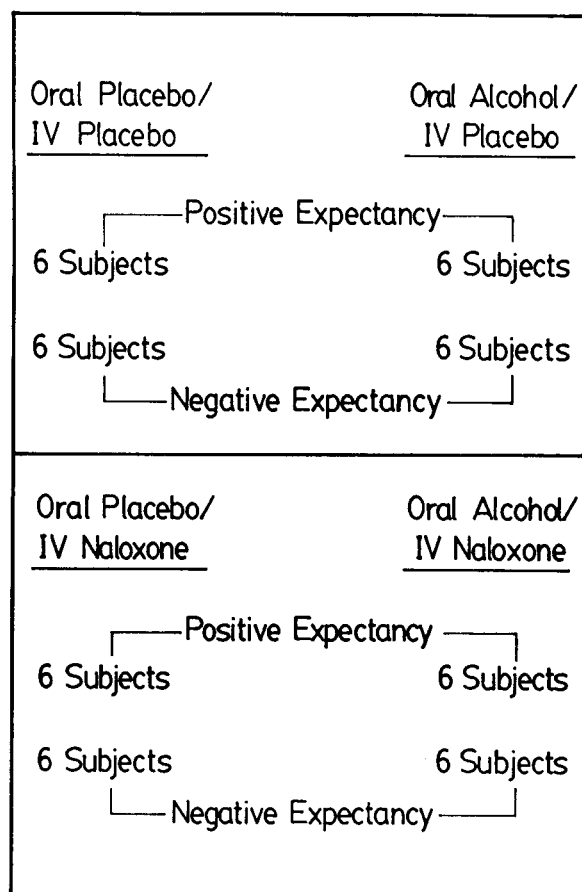└────────Negative Expectancy────────┘

Fig. 1. Experimental groups according to drugs and expectancy. *IV*, intravenous.

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 intox-

ication 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 abstain 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 blood[12] 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

Table I. Pharmacokinetic parameters of intravenous naloxone*

	Placebo group	Alcohol group
K_{e1} (min^{-1})	0.0430	0.0566
K_{12} (min^{-1})	0.0473	0.0313
K_{21} (min^{-1})	0.225	0.0128
V_C (L)	57.3	22.7
CL (L · min^{-1})	2.46	1.28

*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 mmol/L and the time to reach peak concentration (t_{max}) was 75 minutes for both expectancy groups (Fig. 2, B). Comparison of
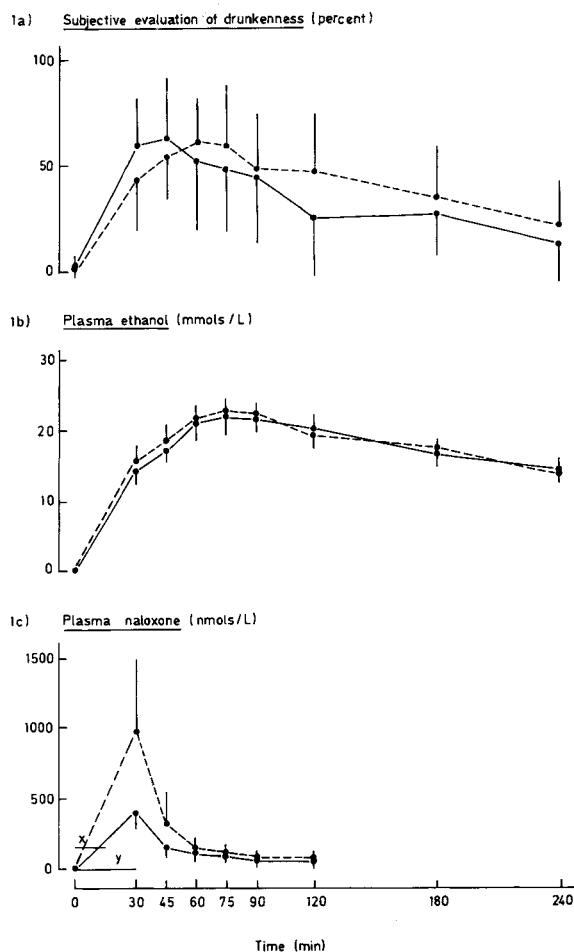

Fig. 2. A, Time course of subjective self-evaluation of drunkenness in the alcohol *(solid line)* and alcohol-naloxone *(broken line)* groups. B, Time course of blood alcohol concentrations in the absence *(solid line)* or presence *(broken line)* of naloxone. C, Time course of plasma naloxone concentrations in the absence *(solid line)* or presence *(broken line)* of alcohol. x, time period for oral ingestion; y, time period for intravenous infusion. All data (n = 12) are expressed as mean ± SD.

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
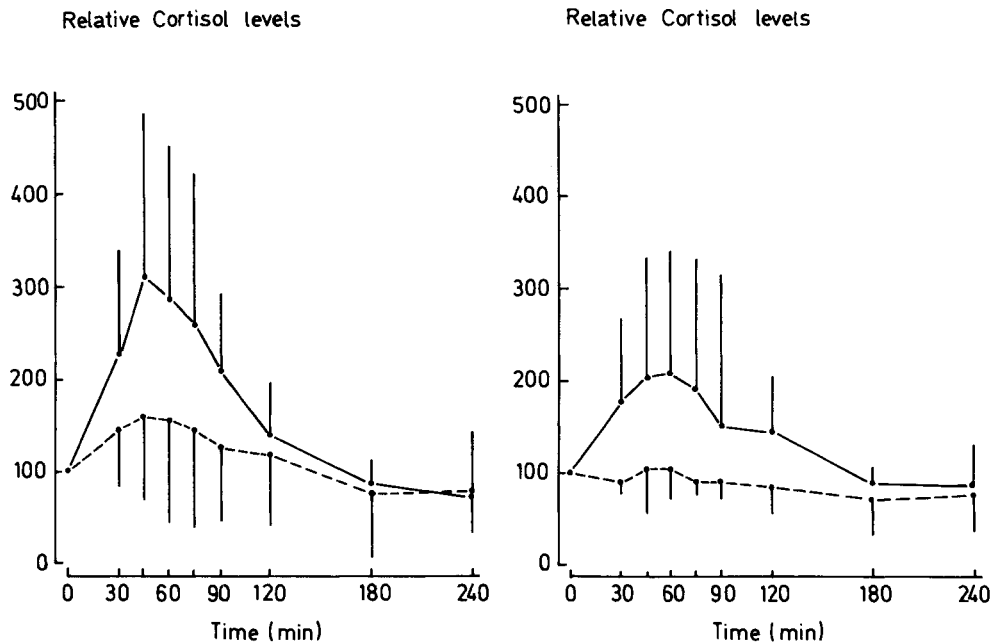
Relative Cortisol levels   Relative Cortisol levels

Fig. 3. Time course of relative cortisol plasma concentrations with positive *(left)* or negative *(right)* expectancy in the naloxone *(solid line)* or alcohol-naloxone *(broken line)* groups. All data (n = 6) are expressed as mean ± SD. The initial cortisol value of each individual was taken as 100%.

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.[15] These data confirm that subjective self-evaluation of alcohol effects is more intense when blood alcohol concentrations are rising.[16] 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.[17,18] 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.[19] Naloxone liposolubility, and consequently its antagonistic activity, is reduced dramatically in an acid environment[20] and it is possible that high doses of alcohol could induce acidosis.

As described by other authors,[9,10] 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.[21] 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.[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 β-endorphin and induces the adrenal release of cortisol.[23] It has been postulated that in septic shock naloxone might be beneficial because of cortisol response or its antagonistic action on the β-endorphin.[24,25] On the other hand, acute administration of alcohol in humans increases the levels of endogenous opioids in plasma and cerebrospinal fluid.[26] According to the dose of naloxone administered, the release of β-endorphin and cortisol occurs in different proportions.[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.[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 β-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 β-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,[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.

References

1. Sørensen SC, Mattison K. Naloxone as an antagonist in severe alcohol intoxication. Lancet 1978;ii:688-9.

2. Anonymous. Naloxone for ethanol intoxication? Lancet 1983;ii:145-6.

3. Jefferys DB, Flanagan RJ, Volans GN. Reversal of ethanol-induced coma with naloxone. Lancet 1980;i:308-9.

4. Cholewa L, Pach J, Macheta A. Effects of naloxone on ethanol-induced coma. Hum Toxicol 1983;2:217-9.

5. Jefferys DB, Volans GN. An investigation of the role of the specific opioid antagonist naloxone in clinical toxicology. Hum Toxicol 1983;2:227-31.

6. Jeffcoate WJ, Herbert M, Cullen MH, Hastings AG, Walder CP. Prevention of the effects of alcohol intoxication by naloxone. Lancet 1979;ii:1157-9.

7. Mattila MJ, Nuotto E, Seppälä T. Naloxone is not an effective antagonist of ethanol. Lancet 1981;i:775-6.

8. Ewing JA, McCarty D. Are the endorphins involved in mediating the mood effects of ethanol? Alcoholism (NY) 1983;7:271-5.

9. Volavka J, Cho D, Mallya A, Bauman J. Naloxone increases ACTH and cortisol levels in man. N Engl J Med 1979;300:1056-7.

10. Jeffcoate WJ, Platts P, Ridout M, Hastings AG, MacDonald I, Selby C. Endocrine effects of ethanol infusion in normal subjects: modification by naloxone. Pharmacol Biochem Behav 1980;13(suppl):145-8.

11. Peters WP, Friedman PA, Johnson MW, Mitch WE. Pressor effect of naloxone in septic shock. Lancet 1981;1:529-32.

12. Mann BR, Manno SE. Determination of alcohol by a direct injection technique. J Anal Toxicol 1978;2:257-61.

13. Asali LA, Nation RL, Brown K. Determination of naloxone in blood by high-performance liquid chromatography. J Chromatogr 1983;278:329-35.

14. Wilson TD. High-performance liquid chromatographic amperiometric determination of naloxone hydrochloride injection. J Chromatogr 1984;298:131-9.

15. Perez-Reyes M, Di Giuseppi S, Davis KH, Schindler VH, Cook CE. Comparison of effects of marihuana cigarettes of three different potencies. Clin Pharmacol Ther 1982;31:617-24.

16. Jone BM, Vega A. Cognitive performance measured on the ascending and descending limb of the blood alcohol curve. Psychopharmacology (Berlin) 1972;23:99-114.

17. Fishman J, Roffwarg H, Hellman L. Disposition of naloxone-7,8-^{3}H in normal and narcotic-dependent men. J Pharmacol Exp Ther 1973;187:575-80.

18. Ngai SH, Berkowitz BA, Yang JC, Hempstead J, Spector S. Pharmacokinetics of naloxone in rats and in man: basis for its potency and short duration of action. Anesthesiology 1976;44:398-401.

19. Kaufman JJ, Koski WS, Benson DW, Semo NM. Narcotic and narcotic antagonist pka's and partition coefficients and their significance in clinical practice. Drug Alcohol Depend 1976;1:103-14.

20. Kaufman JJ. Acidosis lowers in-vivo potency of narcotics

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

21. Naber D, Pickar D, Davis GC, et al. Naloxone effects on β-endorphin, cortisol, prolactin, growth hormone, HVA and MHPG in plasma of normal volunteers. Psychopharmacology (Berlin) 1981;74:125-8.

22. Carpenter WT, Groen PH. Cortisol's effects on human mental functioning. J Clin Psychopharmacol 1982;2:91-101.

23. Guillemin R, Vargo T, Rossier J, et al. β-Endorphin and adrenocorticotropin are secreted concomitantly by pituitary gland. Science 1977;197:1367-9.

24. Faden AI, Holaday JW. Experimental endotoxin shock: the pathophysiologic function of endorphins and treatment with opiate antagonists. J Infect Dis 1980;142:229-38.

25. Anonymous. Naloxone for septic shock. Lancet 1981; i:538-9.

26. Naber D, Soble MG, Pickar D. Ethanol increases opioid activity in plasma of normal volunteers. Pharmacopsychiatry 1981;14:160-1.

27. Cobb CF, Van Thiel DH. Mechanism of ethanol-induced adrenal stimulation. Alcoholism (NY) 1982;6:202-10.

28. Välimäki MJ, Härkönen M, Peter Eriksson CS, Ylikaari RH. Sex hormones and adrenocortical steroids in men acutely intoxicated with ethanol. Alcohol 1984;1:89-93.

29. Cohen G, Collins M. Alkaloids from catecholamines in adrenal tissue: possible role in alcoholism. Science 1970;167:1749-51.

30. Tampier L, Alpers HS, David VE. Influence of catecholamine-derived alkaloids and β-adrenergic blocking agents on stereospecific binding of ³H-naloxone. Res Commun Chem Pathol Pharmacol 1977;17:731-4.