THE EFFECT OF CODEINE PHOSPHATE ON THE ABSORPTION OF ETHYL ALCOHOL

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- 1 The effect of syrup, B.P. and codeine phosphate syrup, B.P.C. on blood alcohol levels was determined in six normal subjects.
- 2 Treatment with syrup alone had little or no influence on the concentration of ethanol in blood.
- 3 In contrast, pretreatment with codeine phosphate syrup significantly reduced alcohol absorption, as assessed by the maximum blood levels achieved or the area subtended by the blood concentration-time curve. It is suggested that the diminished absorption of ethanol is related to the pharmacological action of codeine on the stomach.
- 4 It was considered that the concentration of ethanol in linctuses or syrups containing codeine was unlikely to have any significant effect on the central nervous system.

Introduction

The consumption of excessive volumes of cough mixtures containing ethyl alcohol has obvious medico-legal implications. Thus, opiate squill linctus (Gee's linctus) contains 17-20% (v/v) of ethyl alcohol (British Pharmaceutical Codex, 1973), and was recently incriminated as a contributory factor in a drink and driving offence (Ratcliffe, personal communication; *Daily Express*, 1974). Little is known of the influence of other constituents in cough mixtures on the absorption or metabolism of ethyl alcohol. Some simple sugars (for instance, fructose, sorbitol and galactose) may delay the absorption of ethanol (Clark, Hughes & Letley, 1973), and it is possible that any linctus may act in a similar manner. Indeed, it has been suggested that codeine linctus may account for a positive blood alcohol test which would otherwise have been below the legal limit (Pearson, personal communication; *Birkenhead News*, 1972).

The aim of this study was to analyse the effect of codeine phosphate syrup, B.P.C. and syrup, B.P. (the vehicle in which codeine phosphate is dispensed) on blood alcohol levels in normal healthy individuals of similar age.

Methods

Eighteen experiments were performed on six student volunteers (mean body weight, 65.2 kg; range 54.3-86.0 kg), using a randomized block design analysed as a two-way analysis of variance

(Colquhoun, 1971). Alternative concurrent drug therapy was excluded, and the informed consent of each subject was obtained. No alcohol was consumed for at least 20 h before each experiment. After overnight fasting, each subject swallowed water (10 ml), codeine phosphate syrup, B.P.C. (10 ml), or syrup, B.P. (10 ml) at 30 min intervals for 2 hours. A sample of venous blood was then removed by means of an indwelling cannula. Immediately afterwards the subjects were given ethanol (0.4 g kg^{-1}) as vodka, which they were asked to drink over a 10 min period. Venous blood samples were removed at 20, 40, 60, 80, 100 and 120 min after ingestion of the alcohol.

Ethanol concentrations in blood were determined by gas chromatography (Curry, Walker & Simpson, 1966) using a Pye Gas Chromatograph (Series 104) with a flame ionization detector and a digital integrator (Autolab 6300). Blood samples (0.1 ml) were diluted 1 in 10 with a solution of *n*-propanol (0.006% w/v) and sodium citrate (0.2% w/v) in water. The concentration of ethanol in blood was calculated from a linear calibration graph relating ethanol concentration in blood to the relative areas subtended by the ethanol and *n*-propanol peaks.

Results

The effect of water, syrup, and codeine phosphate syrup on the concentration of alcohol in blood is

Figure 1 The effect of codeine phosphate syrup (○), syrup (■) and water (●) on the concentration of ethanol in blood. Each point represents the mean of six observations.

shown in Figure 1. After codeine phosphate, mean blood ethanol concentrations were reduced between 0 and 120 minutes. The differences between the mean blood levels after codeine and water were statistically significant at 80, 100 and 120 min (Table 1). Analysis of variance confirmed that differences between the blood alcohol levels produced by the three treatments were significant, as assessed by the maximum blood concentration ($F = 4.1$; d.f. = 2, 10; $P = 0.05$) or the area under the blood concentration-time curve between 0 and 120 min ($F = 4.7$; d.f. = 2, 10; $0.05 > P > 0.02$). The maximum blood level (mean $\pm$ s.d.) after codeine phosphate (29 ± 7 mg/100 ml) was

approximately 20% less than with water (35 ± 7 mg/100 ml) or syrup (37 ± 10 mg/100 ml).

Discussion

It was concluded from these studies that large doses of codeine *per se* are unlikely to produce positive blood alcohol tests that might otherwise have been below the legal limit (*Birkenhead News*, 1972). On the contrary, codeine phosphate significantly reduced ethanol absorption, as assessed by the maximum blood level achieved or the area subtended by the blood concentration-time curve. It is possible that diminished alcohol absorption is related to the pharmacological effects of the drug on the stomach. In general, both morphine and codeine decrease gastric motility, augment pyloric muscle tone, and delay gastric emptying (Jaffe, 1970); in these conditions, ethanol absorption may be relatively slow and incomplete. In addition, drugs that diminish gastric motility by other pharmacological mechanisms (for instance, propantheline bromide) may reduce or retard the absorption of both alcohol (Finch, Kendall & Mitchard, 1974) and other drugs (Nimmo, Heading, Tothill & Prescott, 1973). Unrelated compounds with anticholinergic actions may produce similar effects on drug absorption (Consolo, Morselli, Zaccala & Garattini, 1970; Rivera-Calimlim, Castaneda & Lasagna, 1973). Although analogous effects were observed with codeine, a relatively large dose of the phosphate (200 mg) was used in this study; when taken as directed, codeine phosphate linctus (or syrup) is unlikely to affect the absorption of alcohol or other drugs.

Large doses of simple sugars delay the absorption of ethanol (Clark *et al.*, 1973). In the present experiments, pretreatment with syrup and water was associated with almost identical blood alcohol concentration-time curves and peak blood levels. Clearly, the amount of sucrose administered as syrup (26.7 g during 2 h) produced little or no discernable effect on ethanol absorption.

Even before administration of alcohol, all six subjects experienced some central side-effects of codeine, for example, headache and dizziness, euphoria, and disorientation; none considered themselves capable of driving safely. In preparations containing codeine phosphate, the minimum concentration of the drug is usually 3 mg/ml, and the maximum concentration of ethanol (as chloroform spirit) is 0.02 ml/ml. Thus, the dose of codeine used in the present experiments would be administered with 1.33 ml alcohol, and the subsequent effect on blood ethanol levels would be almost undetectable. These considerations suggest

Table 1 Statistical analysis of the differences between blood alcohol levels after the three treatments. Values for *t* were obtained by the paired Student's *t*-test

Time (min)	Values for <i>t</i> between		
	water and syrup	water and codeine	syrup and codeine
20	1.78	0.41	2.29
40	0.50	0.74	1.52
60	0.35	1.49	1.75
80	1.30	5.70*	3.53*
100	5.40	11.00*	2.20
120	0.57	2.60*	0.64

* Statistically significant at $P = 0.05$

that the concentration of ethanol in linctuses or syrups containing codeine is unlikely to have any significant effect on the central nervous system. Nevertheless, excessive doses of codeine phosphate, when taken with alcohol, may well have additive effects on the brain. Patients who are

prescribed cough mixtures should be warned of this possibility.

The technical assistance of Miss S. Newby is gratefully acknowledged. Reprint requests should be addressed to T.N.C.

References

- 'BIRKENHEAD NEWS' (1972). 28 July, p. 13.
- BRITISH PHARMACEUTICAL CODEX (1973). p. 725. London: The Pharmaceutical Press.
- CLARK, E.R., HUGHES, I.E. & LETLEY, E. (1973). The effect of oral administration of various sugars on blood ethanol concentrations in man. *J. Pharm. Pharmac.*, **25**, 319-323.
- COLQUHOUN, D. (1971). *Lectures on Biostatistics*, p. 195. Oxford: The Clarendon Press.
- CONSOLO, S., MORSELLI, P.L., ZACCALA, M. & GARATTINI, S. (1970). Delayed absorption of phenylbutazone caused by desmethylinipramine in humans. *Eur. J. Pharmac.*, **10**, 239-242.
- CURRY, A.S., WALKER, G.W. & SIMPSON, G.S. (1966). Determination of ethanol in blood by gas chromatography. *Analyst*, **91**, 742-743.
- 'DAILY EXPRESS' (1974). 9 March, p. 13.
- FINCH, J.E., KENDALL, M.J. & MITCHARD, M. (1974). An assessment of gastric emptying by breathalyser. *Br. J. clin. Pharmac.*, **1**, 233-236.
- JAFFE, J.H. (1970). Narcotic Analgesics. In *The Pharmacological Basis of Therapeutics*, 4th Ed., ed. Goodman, L.S. & Gilman, A. p. 245. London: Collier-Macmillan.
- NIMMO, J., HEADING, R.C., TOTHILL, P. & PRESCOTT, L.F. (1973). Pharmacological modification of gastric emptying: Effects of propantheline and metoclopramide on paracetamol absorption. *Br. med. J.*, **1**, 587-589.
- RIVERA-CALIMLIM, L., CASTANEDA, L. & LASAGNA, L. (1973). Effects of mode of management on plasma chlorpromazine in psychiatric patients. *Clin. Pharmac. Ther.*, **14**, 978-986.

(Received September 11, 1974)