Br. J. clin. Pharmac. (1982), **14**, 555–558

DOUBLE-BLIND COMPARISON OF THE RESPIRATORY AND SEDATIVE EFFECTS OF CODEINE PHOSPHATE AND (±)-GLAUCINE PHOSPHATE IN HUMAN VOLUNTEERS

J.B.S. REDPATH & B.J. PLEUVRY

Departments of Anaesthesia and Pharmacology, University of Manchester, Stopford Building, Oxford Road, Manchester M13 9PT

1 Two antitussive agents (±)-glaucine phosphate and codeine phosphate have been compared with placebo with respect to ventilation, ventilatory response to carbon dioxide, pulse, blood pressure, digit symbol substitution, sedation score and the Zahlen-Verbindung test performance in ten healthy volunteers (22–36 years). The study was double-blind and the two doses of each antitussive agent and the placebo were administered as a syrup.

2 Both codeine phosphate and (±)-glaucine phosphate displaced the ventilatory response to carbon dioxide to the right.

3 The effect of codeine phosphate on the ventilatory response to carbon dioxide was not dose dependent: 30 mg produced greater effects than the 60 mg dose.

4 Only the highest dose of (±)-glaucine phosphate (60 mg) caused respiratory depression and this was associated with sedation and decreased performance in the digit symbol substitution test.

5 Neither antitussive agent had significant effects upon pulse or blood pressure and codeine phosphate had no detectable sedative activity.

Introduction

(+)-Glaucine is an alkaloid which can be extracted from *Glaucium Flavum Crantz* (Papaveraceae) and it is used in eastern Europe as an antitussive agent (Chachaj *et al.*, 1972; Aleshinskaya, 1976), the compound can now be prepared synthetically and animal studies have shown that (+), (−) and (±)-glaucine hydrobromide have similar antitussive activity. Preliminary clinical and volunteer trials with (±)-glaucine hydrobromide indicated that the compound was equipotent with codeine as an antitussive and that it might have less respiratory depressant properties than codeine (Criscuolo, 1980; Arnold *et al.*, 1980; Dierckx *et al.*, 1981). However, formulation research has suggested that the phosphate salt of (±)-glaucine has more suitable stability and solubility characteristics than the hydrobromide salt.

The present study was designed to compare the respiratory effects of (±)-glaucine phosphate and codeine phosphate in volunteers with regard to both intensity and duration of effect. Initial trials with the phosphate, in man, have suggested that the drug may cause some sedation and thus some psychological tests were included to quantify this side effect.

Methods

The ten volunteers, four female, were between 23 and 36 years old (mean 26 years) and weighed between 50 and 73 kg (mean 64 kg). Volunteers were free from chronic respiratory, cardiovascular or psychiatric diseases and had not taken medication (with the exception of oral contraceptives) for 14 days preceding the trial.

On the day of the trial each volunteer was allowed a light breakfast at least 2 h before the commencement of the preliminary tests and the three smokers were asked to refrain from smoking for the whole trial day. The subjects were asked to refrain from alcohol for the 12 h preceding the trial. After administration of the drug the subjects were allowed to drink water at 2 h and to have a light lunch after 3.5 h. At least 7 days separated trials on the same volunteer.

Ventilation and ventilatory response to CO_2

A bell closed-circuit spirometer (Ealing) with the cylinder filled with air was used to measure minute volume, tidal volume and respiratory rate. Gases

0306–5251/82/100555–05 $01.00

were sampled at the mouth piece and measured continuously by an infra-red CO_2 analyser (Morgan) before being returned to the circuit. The CO_2 analyser was connected to a Rikadenki single channel pen recorder so that a continuous record can be obtained. End tidal Pco_2 was obtained from this trace.

The ventilatory response to CO_2 was assessed using a rebreathing method. The soda lime canister was removed from the spirometer circuit and the cylinder filled (to the 8 l mark) with 5% CO_2 in oxygen. The final spirometer concentration 4.85% CO_2 and the total volume of spirometer and tubing was 11.5l. Following a maximal expiration, the subject was connected to the spirometer and after an initial deep inspiration was allowed to breath quietly into the apparatus. Rebreathing took place for not more than 5 minutes.

After the first minute, minute volume was plotted against end tidal Pco_2 at 30 s intervals and the best straight line calculated by the method of least squares. The slope of each line and 20 l intercept was calculated. This method does not measure the ventilatory response to CO_2 at equilibrium conditions, thus comparisons of drug activity are made in the same individual.

Other measurements

Pulse and blood pressure was measured using an electronic sphygmomanometer (BE 237R). Readings were taken using the same arm on all occasions with the subject sitting quietly on a chair. Two readings, one minute apart, were taken at each time interval.

Sedation was measured using a visual analogue 100 mm scale marked at one end 'Wide awake' and at the other end 'Nearly asleep'. Cognitive function was tested using the digit symbol substitution test (Wechsler, 1944). The test involved substituting symbols for digits according to the code given in the box at the top of the page. The number of symbols correctly substituted in 90 s was counted.

The time taken to assimilate information was assessed using the Zahlen-Verbindung Test (Oswald & Roth, 1978). Twenty-four numbers were arranged randomly in a circle and they have to be connected in ascending order. The time taken for completion of this task was recorded.

(±)-Glaucine phosphate 30 mg and 60 mg, codeine phosphate 30 mg and 60 mg and placebo were prepared in 10 ml of identical syrup vehicles. The drugs were assigned to the subjects on a double-blind cross-over design. The sequence of administration was arranged on the basis of two 5 × 5 Latin squares. All tests were carried out prior to drug administration and ventilatory measurements were repeated 0.5, 1.5, 2.5, 3.5, and 6 h after administration of the syrup. Pulse, blood pressure and psychological tests were performed 1, 2, 3, 4 and 6 h after the syrup had been taken.

Significance was assessed using Duncan's multiple range test.

Results are expressed as mean values ± s.e. mean.

Results

Two of the syrups tested caused significant displacement of the ventilatory response to carbon dioxide at 20 l min^{-1} (Table 1) and these were codeine phosphate 30 mg and (±)-glaucine phosphate 60 mg. There were no significant differences in slope change between treatments and there were no significant differences between respiratory parameters breathing air after the five treatments. Pulse and blood pressure were not affected by any of the treatments and neither was performance in the Zahlen-Verbindung Test. However, sedation scores were significantly increased by 60 mg glaucine at 60 min post drug (Table 2).

The lower dose of glaucine also tended to increase sedation but this did not reach statistical significance in the number of subjects tested. The sedative effect of 60 mg glaucine was coupled with a decreased performance at 60 min in the digit symbol substitution test ($P < 0.05$). Performance was reduced by 4.5 ±

Table 1 Effect of (±)-glaucine phosphate and codeine phosphate on the displacement (kPa) of the ventilatory response to carbon dioxide

Treatment	*Pre-drug*	*Change from pre-drug records at 20 l minute volume*				
		30 min	*90 min*	*150 min*	*210 min*	*360 min*
Glaucine 30 mg	6.27 ± 0.20	+0.23 ± 0.17	+0.22 ± 0.17	+0.10 ± 0.08	−0.03 ± 0.19	+0.06 ± 0.12
Codeine 30 mg	6.16 ± 0.22	+0.39 ± 0.18	+0.62 ± 0.23*	+0.55 ± 0.24*	+0.40 ± 0.24	+0.76 ± 0.29
Codeine 60 mg	6.51 ± 0.43	+0.19 ± 0.26	+0.21 ± 0.19	+0.29 ± 0.13	+0.04 ± 0.28	+0.18 ± 0.34
Glaucine 60 mg	6.39 ± 0.31	+0.53 ± 0.21	+0.80 ± 0.22*	+0.63 ± 0.20*	+0.40 ± 0.16	+0.54 ± 0.17
Placebo	6.70 ± 0.45	−0.17 ± 0.26	−0.20 ± 0.28	−0.08 ± 0.23	−0.21 ± 0.18	−0.01 ± 0.25
F value		1.44	3.09	2.55	1.58	1.81
Significance between treatments		NS	$P < 0.05$	$0.1 > P > 0.05$	NS	NS

*Significant change from placebo values ($P < 0.05$)

Table 2 Effect of (±)-glaucine phosphate and codeine phosphate on sedation score

Treatment	Pre-drug	< Change from pre-drug score (mm on 100 mm visual analogue scale) > 60 min	120 min	180 min	240 min	360 min
Glaucine 30 mg	12.9 ± 3.2	+13.7 ± 5.0	+15.7 ± 8.1	+4.9 ± 4.8	+2.9 ± 4.4	+5.7 ± 7.0
Codeine 30 mg	14.7 ± 5.7	+2.9 ± 3.4	+6.9 ± 8.5	−1.2 ± 4.4	−4.3 ± 2.1	+2.6 ± 3.4
Codeine 60 mg	18.4 ± 7.5	+1.7 ± 2.2	−4.2 ± 5.8	−5.8 ± 5.1	−9.9 ± 6.5	−8.9 ± 7.0
Glaucine 60 mg	17.1 ± 7.9	+20.0 ± 7.6*	+15.1 ± 9.0	+4.3 ± 8.3	−3.9 ± 7.1	−4.8 ± 9.3
Placebo	14.2 ± 3.8	+1.1 ± 2.9	+2.3 ± 4.4	−1.3 ± 2.9	−3.0 ± 2.2	+2.8 ± 4.7
F value		3.38	1.31	0.68	0.84	0.84
Significance between treatments		$P < 0.05$	NS	NS	NS	NS

*Significant change from placebo ($P < 0.05$)

2.0 symbols in 90 s by 60 mg glaucine whilst the same subjects given placebo increased their performance by 0.7 ± 1.1 symbols in 90 s.

Discussion

The study has shown that both (±)-glaucine phosphate and codeine phosphate are capable of displacing the ventilatory response to carbon dioxide to the right, suggestive of respiratory depression. Furthermore 30 mg codeine phosphate had greater depressant effects than 30 mg glaucine phosphate which was indistinguishable from placebo responses. However, codeine phosphate did not appear to produce a dose dependent effect as 60 mg produced less respiratory effects than 30 mg.

There is considerable controversy in the literature as to whether 60 mg codeine orally causes significant changes in the ventilatory response to carbon dioxide (Eddy *et al.*, 1970). Indeed in our laboratory we have demonstrated that 60 mg codeine phosphate in capsule form caused greater respiratory depression in female subjects than in male subjects (Pleuvry & Maddison, 1980). Harris (1965) found that 30 mg codeine orally had more effect upon the respiratory response to low oxygen than 60 mg and it was suggested that this might be due to the excitatory effects of high doses of codeine. In the present study subjects given 60 mg codeine phosphate tended to sedation scores lower than subjects given the other four treatments (Table 2) although this was not statistically significant. Bellville *et al.* (1958) commented on the extreme variability of the time necessary to reach maximum displacement of the CO_2 response curve in subjects given 63.9 mg codeine sulphate in a capsule. This may be related to variation in the absorption of the drug by the oral route. Adler *et al.* (1955) showed that high doses of codeine were less well absorbed than low doses.

There is evidence that a proportion of the constipative effect of opioid drugs is due to a local effect on transport processes in the intestinal mucosa (McKay *et al.*, 1981). Thus it is possible that high doses of codeine in the gut, in an easily absorbable form, might initially cause a high local concentration in the intestinal mucosa preventing or at least slowing its own further absorption. The late peak of displacement of the CO_2 response curve would support the suggestion of delayed absorption of the drug at the 60 mg dose.

Further work is necessary to determine whether any of these hypotheses have any relevance to the findings in this study concerning the lack of dose dependency for codeine.

It has been observed that drowsiness also causes a displacement of the ventilatory response to CO_2 (Eddy *et al.*, 1970) and thus the sedation caused by (±)-glaucine phosphate could contribute to its apparent respiratory depressant effects. However, our results indicate that the duration of respiratory depression with 60 mg glaucine exceeds the duration of measurable sedation.

The authors are grateful to Lepetit (Milan), especially Dr. D. Criscuolo, for financial assistance with the trial and advice on the statistical analysis.

References

ADLER, T.K., FUJIMOTO, J.M., LEONG WAY, E. & BAKER, E.M. (1955). The metabolic fate of codeine in man. *J. Pharmac. exp. Ther.*, **114**, 251–262.

ALESHINSKAYA, E.E. (1976). Glaucine, a new antitussive preparation. *Chim. Farm. Zu.*, **10**, 144–147.

ARNOLD, J., De SIMONE, A. & BRIGHT, T. (1980). Effects

of DL-283, a novel antitussive, on respiratory sensitivity to carbon dioxide challenge in healthy adult males. Paper presented at the *World Conference on Clinical Pharmacology and Therapeutics*, London, Abstract 0720.

BELLVILLE, J.W., WALLENSTEIN, S.L., WALD, G.H., DOWLING, M.D. & HOUDE, R.W. (1958). Effect of noscapine and codeine on the respiratory response to carbon dioxide. *Anesthesiology*, **19**, 545–551.

CHACHAJ, W., MALOLEPSZY, J., JANKOWSKA, R. & KRAUS-FILARSKA, M. (1972). Clinical investigation of Tussiglaucine. *Pol. Tyg. Lek.*, **27**, 2071–2073.

CRISCUOLO, D. (1980). Objective evaluation of cough: an analysis of two different methods. Paper presented at the *World Conference on Clinical Pharmacology and Therapeutics*, London, Abstract 0341.

DIERCKX, P., LEBLANC, G., DECOSTER, A. & CRISCUOLO, D. (1981). Double blind study of glaucine in chronic cough. *Int. J. clin. Pharmac. Ther. Tox.*, **19**, 396–399.

EDDY, N.B., FRIEBEL, H., HAHN, K-J. & HALBACH, H. (1970). *Codeine and its alternatives for pain and cough relief.* Genève: World Health Organization.

HARRIS, E.A. (1965). The effects of noscapine and codeine on the ventilatory response to excess carbon dioxide and lack of oxygen. *Br. J. Pharmac.*, **24**, 532–537.

McKAY, J.S., LINAKER, B.D. & TURNBERG, L.A. (1981). Influence of opiates on ion transport across rabbit ileal mucosa. *Gastroenterology*, **80**, 279–284.

OSWALD, W.D. & ROTH, E. (1978). *Der Zahlen-Verbindung Test.* Gottingen: Verlag fur Psychologie.

PLEUVRY, B.J. & MADDISON, S.E. (1980). A sex difference in the effects of oral codeine and promethazine on the ventilatory response to carbon dioxide in human volunteers. *Br. J. clin. Pharmac.*, **9**, 159–164.

WECHSLER, D. (1944). *The measurement of adult intelligence*, 3rd Edn. p. 185. Baltimore: Williams and Wilkins.

(Received March 23, 1982, accepted June 7, 1982)