EFFECTS OF CODEINE ON THE RESPIRATORY RESPONSES TO EXERCISE IN HEALTHY SUBJECTS

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1 In six healthy subjects, respiration and the sensation of breathlessness were assessed during submaximal exercise and the subsequent recovery. The overall responses were expressed by the relationship of breathlessness to minute volume.

2 Because of the high subjective component in the assessments, validation of the method in these particular subjects was an integral part of the study. The relationship of breathlessness to ventilation during identical periods of exercise was highly reproducible and sensitivity was demonstrated by an alteration in this relationship in the presence of an inspiratory resistance.

3 Codeine at a dose of 60 mg by mouth was compared with placebo, each treatment being given on two occasions. The study was conducted in a double-blind fashion with randomisation of the order of treatments.

4 Codeine at this dose allowed higher levels of carbon dioxide to be tolerated during breath-holding; oxygen uptakes at rest and during exercise were unaffected. Ventilation and breathlessness at the end of exercise were each slightly but significantly reduced by codeine but the relationship between breathlessness and ventilation was not changed. Codeine did not prevent detection of an inspiratory resistance.

Introduction

Considerable interest has been registered in the search for drugs which may reduce the sensation of breathlessness in patients with severe irreversible cardio-respiratory disease. The benefits of morphine in acute left ventricular failure are well established but the mechanisms of such effects are not understood. These could be related to haemodynamic changes, to general effects on the central nervous system or to more specific interactions with pathways which are responsible for the perception of dyspnoea. In a recent study (Timmis *et al.*, 1980) intravenous administration of morphine reduced dyspnoea in left ventricular failure but this was unaccompanied by improvement in left ventricular filling pressure or stroke index. Such findings suggest that a non-haemodynamic mechanism is more likely.

Because of risks of respiratory depression, opiates are not commonly used in the management of chronic respiratory disease. Recently, the milder effect of dihydrocodeine has been studied in a group of patients with the 'pink puffer' syndrome (Woodcock *et al.*, 1981). Dihydrocodeine increased exercise tolerance and reduced breathlessness score. In

addition, the oxygen uptake during exercise was reduced but the explanation for this was unclear. The possibility that dyspnoea may be affected by this group of drugs is worthy of further investigation, and this should include determination of the effects in healthy man as well as in various pathophysiological states.

Our laboratory has developed and validated methods for assessing breathlessness (Stark *et al.*, 1981; Stark *et al.*, 1982a). The sensitivity of the assessment was demonstrated in normal subjects using an inspiratory resistance and in asthmatic patients by treatment with salbutamol. We have proposed (Stark *et al.*, 1982a,b) that studies directed at measuring the effects of drugs on breathlessness should incorporate validation procedures directed not only at the methods *per se* but also at the way in which they are used by the subjects participating in the study.

The present study of codeine in healthy subjects has incorporated validation, examination of the relationship of breathlessness to ventilation since either or both might change, and measurements of oxygen uptake.

Methods

Subjects

Six subjects unconnected with the project or its aims volunteered to take part in the study and, after full explanation of the procedures, gave informed consent. None had evidence of disease from history or clinical examination and all had normal electrocardiographs.

Smoking, consumption of beverages containing caffeine and alcohol were withheld before the exercise tests and an interval of at least 5 days was maintained between tests. Environmental factors including room temperature and staffing were similar on the different days of the study. Subjects were familiarised with the procedures and measurements before entering the double-blind part of the study.

Exercise test

The test was similar to that described in detail previously (Stark *et al.*, 1981; Stark & Gambles, 1981). Submaximal exercise was undertaken by walking on an inclined treadmill at three speeds (2 min at 2 kph, 2 min at 4 kph and 2 min at 6 kph). Measurements were made during a control period, during 6 min of exercise and during a 5 min period of recovery with the subject wearing a tight-fitting face mask to permit collection of expired gases. Ventilation and tidal volume (BTPS), oxygen uptake and carbon dioxide production (STP), and respiratory and cardiac frequencies were measured continuously and the ECG was displayed on an oscilloscope. Data from the pneumotachograph, oxygen and carbon dioxide analysers and ECG were processed by a Minc 11 computer and presented at intervals of 1 min. Calibration preceded every study. Breathlessness was assessed with visual analogue scales (VAS) administered by a PET Commodore Computer at intervals of one minute during the test. The maximum point on the VAS ('very breathless') was set before administration of the treatment by a short period of strenuous exercise on the treadmill which increased heart rate to approximately 160 beats/min.

An important aspect of the study was to establish that the subjects used the VAS in a reliable and consistent way. Each volunteer received placebo on two occasions and the relationships of breathlessness score to ventilation were compared as a measure of reproducibility. In addition, comparison was made of this relationship in the presence and absence of a low value inspiratory resistance (0.7 cm H₂O) to determine the sensitivity of the assessment in these subjects. This comparison was performed in double-blind conditions and the sequence was randomised.

Breath-holding time after a maximum inspiration was measured with a stop watch and the peak CO₂

concentration in the expirate was measured at breaking point and expressed as a P_{CO_2} . Peak expiratory flow rate (PEFR) was recorded on a Wright peak flow meter before and 90 min after administration of the treatments.

Treatment and design

The study was a double-blind within-subject comparison of codeine and placebo with the order of treatments randomised. Subjects received each treatment on two different occasions in order to increase the sensitivity of the comparison. Two exercise tests were performed 90 min and approximately 130 min after treatment, one in the presence and the other in the absence of the inspiratory resistance with the order randomised. Codeine phosphate tablets (30 mg, BP) were administered at a dose of 60 mg.

Statistical analysis

The data analysed were complete apart from P_{CO_2} values after breath-holding. Four measurements were technically unsatisfactory and were excluded from analysis; no bias was expected from these exclusions.

A simple method was sought for summarising the information contained in the plots of breathlessness score vs ventilation. The following system was adopted.

Each volunteer generated 8 graphs. The last point representing the final minute of exercise on each graph was examined and, from the one with the lowest ventilation, a line perpendicular to the ventilation axis was drawn to cut the other 7 graphs. This defined 8 breathlessness values, corresponding to the interpolated points and the original point all relating to a single value of ventilation. In addition, the penultimate point on each graph was examined and the procedure repeated. Thus, two values were chosen to represent each graph. These, and the mean of the two, were analysed in a similar manner to other variables.

All responses to treatment were analysed by the technique of analysis of variance in accordance with the factorial design. The effects of interest, chiefly the differences between placebo and codeine means, were tested by means of *F*-tests. Crude means are shown in Table 1. Adjusted means were also calculated as part of the analysis of variance procedure but, as these differed minimally from the more understandable crude means, they have not been presented. The fitted models included terms to allow for differences between volunteers, differences between days of testing, and the effect of inspiratory resistance (when relevant). The differences between volunteers were generally highly significant statistically, as expected in a 'within-volunteer' study, but there was no

Table 1 Effects of placebo and codeine on heart rate and oxygen uptake at rest and during exercise and on PEFR and breath-holding.

Mean values for the two tests are shown. (* $P < 0.04$)

	Placebo	Codeine
PEFR (l/min)		
before treatment	575.0	575.4
after treatment	576.7	579.2
Heart rate (beats/min)		
rest	81.4	78.3
2 min exercise	98.4	94.3
4 min exercise	115.7	113.3
6 min exercise	136.9	135.6
Oxygen uptake (ml/min)		
rest	383.3	385.5
2 min exercise	1020.8	1003.3
4 min exercise	1628.6	1630.5
6 min exercise	2223.0	2156.2
Breath-holding		
duration (s)	73.0	80.2
P_{CO_2} (kPa)	5.64	6.06*

evidence of trends related to the day of testing. Attempts to find statistically significant interactions between volunteers and treatments, days and treatments, and inspiratory resistance and treatment (where relevant) were all unsuccessful.

Results

Subjects

The mean age of the subjects was 32.3 years (range 26–41 years) and mean body weight was 77.4 kg (range 69.3–87.5 kg). Baseline values for PEFR, heart rate and oxygen uptake for placebo and codeine were similar (Table 1).

Validation of method

During exercise, the increase in ventilation was accompanied by an increase in the level of breathlessness indicated on the VAS and during recovery both values decreased (Figure 1). The relationships between breathlessness and ventilation for the six subjects were very similar for the two placebo tests. Thus, a high level of within-subject reproducibility was apparent although considerable between-subject variation occurred (see Statistical methods).

In the presence of the inspiratory resistance, maximal ventilation achieved was slightly depressed ($P = 0.02$) but a significantly greater sensation of breathlessness in relation to ventilation occurred at the higher levels of ventilation ($P < 0.04$; Figure 2).

Figure 1 Codeine study: Reproducibility Relationship between breathlessness and ventilation during exercise and recovery. Mean values are shown for the two tests after placebo ($n = 6$).

In view of this demonstration of sensitivity, the results from all subjects have been pooled and analysed together.

Effects of codeine

The codeine was well tolerated although two subjects on codeine and one on placebo reported mild central effects ('strange', 'relaxed'). Codeine had no significant

Figure 2 Effects of inspiratory resistance ($n = 6$) Relationship of breathlessness to ventilation during exercise in the presence (●) and absence (○) of an inspiratory resistance. Left panel shows responses after placebo (test of sensitivity) and right panel shows responses after codeine (effect on load detection). This figure shows only the results from the second treatment with placebo and codeine. The statistical analysis was based on all treatments.

ant effect on PEFR (Table 1). The values for oxygen uptake at rest and during exercise were not significantly different from the values after placebo (Table 1).

The mean ventilations at rest were similar for codeine (11.2 l/min; range 9.3–12.8 l/min) and for placebo (10.9 l/min; range 9.1–12.7 l/min). During the final minute of exercise, ventilation was slightly lower on codeine (mean 46.0 l/min; range 30.9–59.9 l/min) than on placebo (mean 48.7 l/min; range 35.8–67.7 l/min) and the combined results showed statistical significance ($P < 0.05$).

After codeine, the lower ventilation at the end of exercise was associated with a lower score for breathlessness ($P < 0.05$). However, the relationship between breathlessness and ventilation was almost identical for placebo and for codeine and no statistically significant differences were demonstrated (Figure 3).

An alternative approach to examining the data involved selecting the subject who showed greatest reproducibility and sensitivity in the tests of validation. He, too, showed no change in relationship after codeine.

After codeine, the subjects were still able to detect the inspiratory resistance (Figure 2).

Breath-holding time was prolonged after codeine in five of the six subjects but this was not statistically significant although the P_{CO_2} in the expired gas breaking point was significantly higher ($P < 0.04$; Table 1).

Discussion

As in previous studies in normal subjects and in patients, the responses have been summarised by the relationship between breathlessness score and ventilation. Adequate reproducibility and sensitivity were demonstrated although the latter was less quantitative than reported previously (Stark *et al.*, 1981). For statistical purposes it is necessary to extract numerical data from these curves and we have described a new method for achieving this. Essentially, treatments were assessed by comparing breathlessness scores at fixed levels of ventilation. This approach has the advantage of taking ventilation into account but focusing on the level of breathlessness occurring particularly at the higher ventilations occurring towards the end of exercise. An effective treatment would be expected to display its clearest effect on these measures.

For the reasons outlined in the Introduction, the opioid group of drugs and their effects on breathlessness are worthy of investigation. As a starting point, we have studied codeine at a dose in clinical usage. It is necessary, however, to place the dosage of codeine into perspective. Mild respiratory effects including the increase in CO_2 tolerated during breath-holding

Figure 3 Effects of codeine on breathlessness. Relationship between breathlessness and ventilation during exercise and recovery. Mean values (two tests) are shown for placebo (●) and codeine (○) ($n = 6$).

and the reduction in ventilation during exercise were detected. The mean decrease in ventilation at the end of exercise was 2.7 l/min which was quantitatively similar to the effect of morphine at a dose of 0.2 mg/kg given intramuscularly (Santiago *et al.*, 1979). After parenteral administration, 60 mg codeine is approximately equivalent to 5 mg morphine or 30 mg dihydrocodeine; the relationship after oral administration is likely to change because of the favourable absorption characteristics of codeine (Goodman & Gilman, 1980). It seems reasonable to conclude, therefore, that the dose of codeine used in this study was within the range that induces respiratory effects.

The present study has shown no evidence that codeine altered the relationship of breathlessness to ventilation. When breathlessness alone was examined, it showed a significant decrease probably as a consequence of a decrease in ventilation. In other words, codeine induced a retreat down the line of relationship between breathlessness and ventilation and not a departure from this line. Detection of the inspiratory resistance provided an alternative test for respiratory sensations but codeine did not abolish this.

In their study of the effects of dihydrocodeine (60 mg; 1 mg/kg) in patients with the 'pink puffer' syndrome, Woodcock *et al.* (1981) found an increase in exercise tolerance and a decrease in breathlessness score of 20%. Although their results were not expressed in terms of the relationship between breathlessness and ventilation, the reduction in breathlessness score was greater than would be

expected from the decrease in ventilation of 1 l/min. This suggests that dihydrocodeine achieved a tilt of the relationship towards the ventilation axis. More recent work suggests that 'blue bloaters' experience less respiratory depression than 'pink puffers' after dihydrocodeine (Woodcock *et al.*, 1982). Our data on codeine in healthy subjects would be more consistent with the findings in 'blue bloaters' although differences in relative doses might be relevant.

An interesting aspect of the work concerns the effects of opioids on oxygen uptake. Santiago *et al.* (1979) reported that morphine decreased oxygen uptake during exercise and although the mechanism was not known, they discussed various possibilities including changes in muscle kinetics, heat production or patterns of metabolism. More recently, dihydrocodeine reduced oxygen uptake by about 9% during rest and exercise (Woodcock *et al.*, 1981). Our find-

ings with codeine in healthy subjects revealed no such effect.

Evidence is accumulating on the possible role of endorphins in chronic respiratory disease. Santiago *et al.* (1981) showed that a group of patients with chronic obstructive disease of the airways failed to increase respiratory effort in response to an inspiratory resistance. Treatment with naloxone restored the response to normal.

Without doubt, there is considerable scope for further work on the effects of endorphins and opioids on respiratory control and sensations.

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References

- GILMAN, A., GOODMAN, LOUIS S. & GILMAN, A. (1980). *The pharmacological basis of therapeutics*, sixth edition. New York: Macmillan Publishing Co. Inc.
- SANTIAGO, T.V., JOHNSON, J., RILEY, D.J. & EDELMAN, N.H. (1979). Effects of morphine on ventilatory response to exercise. *J. appl. Physiol.*, **47**, 112–118.
- SANTIAGO, T.V., REMOLINA, C., SCOLES, V. & EDELMAN, N.H. (1981). Endorphins and the control of breathing. *New Engl. J. Med.*, **304**, 1190–1195.
- STARK, R.D. & GAMBLES, S.A. (1981). Effects of salbutamol, ipratropium bromide and disodium cromoglycate on breathlessness induced by exercise in normal subjects. *Br. J. clin. Pharmacol.*, **12**, 497–501.
- STARK, R.D., GAMBLES, S.A. & CHATTERJEE, S.S. (1982a). An exercise test to assess clinical dyspnoea: estimation of reproducibility and sensitivity. *Br. J. dis. Chest*, **76**, 269–278.
- STARK, R.D., GAMBLES, S.A. & CHATTERJEE, S.S. (1982b). Is the assessment of dyspnoea by visual analogue scales sensitive enough to detect drug effects? *Clin. Sci.*, **62**, 13P.
- STARK, R.D., GAMBLES, S.A. & LEWIS, J.A. (1981). Methods to assess breathlessness in healthy subjects: a critical evaluation and application to analyse the acute effects of diazepam and promethazine on breathlessness induced by exercise or by exposure to raised levels of carbon dioxide. *Clin. Sci.*, **61**, 429–439.
- TIMMIS, A.D., ROTHMAN, M.T., HENDERSON, M.A., GEAL, P.W. & CHAMBERLAIN, D.A. (1980). Haemodynamic effects of intravenous morphine in patients with acute myocardial infarction complicated by severe left ventricular failure. *Br. med. J.*, **2**, 980–982.
- WOODCOCK, A.A., GROSS, E.R., GELLERT, A., SHAH, S., JOHNSON, M. & GEDDES, D.M. (1981). Effects of dihydrocodeine, alcohol, and caffeine on breathlessness and exercise tolerance in patients with chronic obstructive lung disease and normal blood gases. *New Engl. J. Med.*, **305**, 1611–1616.
- WOODCOCK, A.A., JOHNSON, M. & GEDDES, D.M. (1982). Opiate sensitivity in airways obstruction. *Am. Rev. resp. Dis.*, **125**, Suppl. 241.

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