Chlorpromazine—a specific effect on breathlessness?

P. A. O'NEILL, P. B. MORTON & R. D. STARK
Clinical Pharmacology Unit, Imperial Chemical Industries PLC, Pharmaceuticals Division, Macclesfield, Cheshire, UK

1 Previous work has left unresolved questions on whether promethazine reduces the sensation of breathlessness. This study was designed to provide a definitive answer and to determine the contributions from promethazine's major pharmacological actions.
2 Twelve healthy subjects participated in a double-blind, within-subject comparison of promethazine and placebo each given acutely by mouth. Breathlessness was assessed with visual analogue scales during a progressive exercise test and was related to minute ventilation.
3 Promethazine had no significant effect on breathlessness nor on the relationship between breathlessness and ventilation.
4 The role of histamine-antagonism was investigated in a subgroup of the subjects by administration of mebhydrolin. No effect on breathlessness was detected. In contrast, the standard phenothiazine, chlorpromazine, caused a marked and statistically significant reduction in breathlessness without affecting ventilation and without causing detectable sedation.
5 This unexpected finding merits further study in patients and is discussed with reference to the role of chlorpromazine as a constituent of Brompton's Mixture.

Keywords chlorpromazine promethazine breathlessness exercise visual analogue scales

Introduction

In recent years, there has been interest in whether drugs can be used to ameliorate the sensation of breathlessness in patients with irreversible cardiorespiratory disease. Mitchell-Heggs et al. (1980) reported that diazepam reduced dyspnoea in patients with the 'pink puffer' syndrome but the larger study of Woodcock et al. (1981) failed to confirm this effect in similar patients. Any benefit of diazepam might be secondary to sedation and for this reason Stark et al. (1981), in their investigation in healthy subjects, included promethazine as a control treatment. Surprisingly, breathlessness during exercise was reduced but this effect did not achieve statistical significance. In Woodcock's study in patients (1981), promethazine caused a very small but highly significant reduction in breathlessness during exercise.

These findings with promethazine are not clear-cut and it is necessary to know whether this agent does or does not reduce breathlessness. Further, if the effect is real, it would be of some interest to determine which of promethazine's pharmacological properties is responsible. This might be due to antagonism of H1-receptors or to the broad effects on neuropsychiatric function of a phenothiazine.

In the study in normal subjects mentioned

Correspondence: Dr R. D. Stark, Clinical Pharmacology Unit, Imperial Chemical Industries PLC, Pharmaceutical Division, Alderley Park, Macclesfield. Cheshire, UK

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above (Stark et al., 1981) the separation of promethazine and placebo was quantitatively greater than in patients (Woodcock et al., 1981). The system in healthy subjects therefore seemed more appropriate for resolving the effects of promethazine but, of course, it was necessary to include an adequate number of subjects based on statistical advice. In the second part of the study, efforts were made to determine whether any effect on breathlessness was due to antagonism of histamine by testing mebhydrolin, a specific H1-receptor antagonist with minimal sedative properties and comparing it with the effects of chlorpromazine, the archetypical phenothiazine.

Methods

Subjects

Twelve subjects, shown by history and examination to be healthy, volunteered and gave consent to participate in the study which had been given approval by the Ethics Committee. Smoking and consumption of alcohol were prohibited for 2 and 10 h respectively before the exercise tests. For each subject, exercise was performed at the same time of day under similar environmental conditions. Familiarisation with the tests preceded participation. All subjects were 'naive', that is they were unconnected with the project and its immediate objectives.

Exercise test

The test was similar to that described in detail previously (Stark et al., 1981). In brief, sub-maximal exercise was undertaken on a treadmill to achieve a range of values of minute ventilation and breathlessness was assessed with visual analogue scales (VAS) at intervals of 1 min. The maximum point on the VAS was anchored on each day of study before any treatment was given by a standard period of strenuous exercise. Responses were described by the relationship of breathlessness to ventilation.

The need for validation of a test which relies on subjective assessments has been stressed previously (Stark et al., 1983). In preliminary tests reproducibility was determined by comparing the responses to identical exercise tests and sensitivity was measured by comparing these with a similar test when the subject breathed against a low value inspiratory resistance during exercise.

Only subjects who showed responses which were reproducible and sensitive to change proceeded to the drug comparison.

Other tests

Peak expiratory flow rate (PEFR) was measured with a Wrights Peak Flow Meter before and after treatment and after exercise.

Breath-holding time was measured in duplicate from total lung capacity after maintenance of hyperoxia for 3 min. The time was measured with a stop watch and the peak level of CO2 in the expired gas was measured at breaking point.

Sedation after treatment was assessed immediately before the exercise test using the scales of Bond & Lader (1974). Total scores for each treatment were derived and related to the score after placebo.

Drug treatment

The study was conducted under double-blind conditions and the order of treatments was randomised. Promethazine was given as 25 mg tablets (Phenergan, May and Baker). Within-subject comparison of promethazine and placebo was based on 12 subjects.

Six of these subjects selected on the basis of availability proceeded to the second part of the study in which chlorpromazine 25 mg tablets (Largactil, May and Baker), mebhydrolin 50 mg tablets (Fabahistin, Bayer) and placebo were compared.

Measurements started 75 min after administration of the treatment.

Analysis

Differences between the relationships of breathlessness to ventilation were tested according to the method first described by Stark et al. (1983). The two parts of the study were analysed separately.

In the promethazine section two graphs were produced for each volunteer relating breathlessness to ventilation. The last point representing the final minute of exercise was examined and from the one with the lower ventilation a line perpendicular to the ventilation axis was drawn to cut the other graph. This defined two values of breathlessness corresponding to the interpolated point 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 of breathlessness at standardised ventilations 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. Differences
between treatments were tested by means of $F$ tests. The fitted models included terms to allow for differences between volunteers and between days of testing. The differences between subjects were generally highly significant as expected in a within-subject study but there was no evidence of trends related to the day of testing.

The differences between the levels of sedation after the active treatment with that after placebo were tested by means of Wilcoxon's signed rank test.

The remaining statistical analyses were performed with Student's $t$-test.

**Results**

**General**

Twelve subjects took part in the study. Their mean age was 30 years (range 23–39 years), mean height 1.79 m (range 1.66–1.84 m) and mean weight 74.8 kg (range 62.5–95.0 kg). There were 10 non-smokers and two cigarette smokers (10 and 15 per day) in the group.

All subjects showed a high level of reproducibility of the relationship between breathlessness and ventilation during each of the exercise periods (Figure 1). The ratio of breathlessness to ventilation in the presence of the inspiratory resistance was significantly higher for each of the subjects compared to their results in the absence of the resistance (Figure 1).

![Figure 1 Promethazine study, reproducibility and sensitivity, $n = 12$. The mean relationships of breathlessness (VAS) to ventilation ($\dot{V}$) for the 12 subjects in the presence (R^1, ▲) or absence (R^3, ○, ●) of the small inspiratory resistance (0.7 cm water).](image)

**Promethazine**

Subjects were sedated with promethazine ($P < 0.05$). There were no significant differences in PEFR after promethazine and after placebo. Breath-holding time was unchanged after promethazine (mean 125 ± 41 s) compared with placebo (mean 129 ± 42 s).

There was no significant difference between treatments in the relationships of breathlessness to ventilation during exercise. The mean relationships are shown in Figure 2. At the standardised level of ventilation (see analysis) the mean breathlessness score after placebo was 51.4% and after promethazine 50.2%. Six subjects recorded higher and five recorded lower scores for breathlessness after promethazine with one unchanged.

**Chlorpromazine and mebhydrolin**

The level of sedation after either agent was not significantly different to that after administration of placebo. PEFR also showed no significant changes. Breath-holding time was not changed after chlorpromazine (mean 121 ± 41 s) or mebhydrolin (mean 122 ± 40 s) compared to placebo (mean 129 ± 39 s).

Mebhydrolin did not alter the relationship of breathlessness to ventilation during exercise. In contrast, chlorpromazine significantly reduced breathlessness at the highest levels of ventilation achieved during exercise in all of the subjects ($P = 0.001$). The mean reduction in breathlessness at the standardised ventilation was 19.3%. There was no significant change in the maximum ventilation achieved after chlorpromazine (50.5

![Figure 2 The mean relationships of breathlessness (VAS) to ventilation ($\dot{V}$) for the 12 subjects after promethazine (●) and after placebo (○).](image)
± 8.3 l/min chlorpromazine; 48.1 ± 3.1 l/min placebo).

The mean relationships of breathlessness to ventilation after each treatment are shown in Figure 3.

Discussion

The results from this study have to be discussed in the context of three main observations. Firstly, promethazine did not alter the sensation of breathlessness during exercise. The second finding was that chlorpromazine, in a small acute dose, reduced breathlessness by almost one third of the maximum achieved during exercise after placebo. This was observed at the highest workloads in all of the subjects and it is the biggest reduction in breathlessness documented with VAS as a measuring device. Finally, breath-holding time was not changed by chlorpromazine.

All subjects showed reproducibility in their use of the VAS and could employ them to indicate changes in the intensity of the sensation. As has been stressed previously, this validation is an important part of studies examining the effects of drugs on breathlessness and has usually been an integral part of the experimental design (Stark et al., 1983; O'Neill et al., 1984). In the present study, it has been shown that the validation can be performed at a single session.

We believe that the lack of effect of promethazine in normal subjects is genuine. In the earlier study on patients (Woodcock et al., 1981) promethazine was given chronically at a daily dose of 125 mg and several of the patients experienced drowsiness. Breathlessness and ventilation during exercise were measured separately and the relationship between them was not analysed. In addition to these differences, dissimilar mechanisms may operate in health and disease which could account for the contrasting effects of promethazine.

The large effect of chlorpromazine on breathlessness was not reflected by alterations in the ability to breath-hold. In a monograph on dyspnoea Stark & Guz (1984) indicated that respiratory sensations such as breath-holding and breathlessness have complex and probably different mechanisms. Thus in the search for drugs to affect dyspnoea, study of other respiratory sensations may be unhelpful.

There is no simple explanation for chlorpromazine’s beneficial influence on breathlessness. There was no apparent sedation compared with placebo but subtle effects may have gone undetected. On the basis of experimental work in cats (Bradley et al., 1966), Laros & Bergstein (1982) have suggested that chlorpromazine might specifically reduce breathlessness by lowering the sensory input to the mesencephalon. Killam & Killam (1958) argued that chlorpromazine increased the selective inhibition by the reticular formation of the afferent sensory information.

In clinical practice, chlorpromazine has been widely used in patients dying from malignant disease and has been one of the variable constituents of Brompton’s cocktail (Twycross & Lock, 1983). However, these authors suggested that, at least for analgesia, its use should be limited to those patients with a marked anxiety component. Others indicated that chlorpromazine may be an important adjunct to narcotics in the relief of breathlessness in patients where again anxiety was a major feature (Saunders & Barnes, 1983).

The present study has shown that chlorpromazine reduced breathlessness during exercise in normal subjects whilst leaving the drive to breathe unaltered. This is a therapeutic profile which has been identified as being attractive and contrasts with that of the narcotic analgesics (Stark & O’Neill, 1983). Although it is not possible to extrapolate directly to patients, chlorpromazine could offer a pharmacological intervention for the relief of breathlessness in dying patients. The importance of this area was underlined by Hinton (1963) in a study of patients dying in hospital who found that only 18% of those with breathlessness obtained adequate relief from this distressing symptom.

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Chlorpromazine and breathlessness

References


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