J. Pharm. Pharmacol. 1997, 49: 1045–1049
Received March 21, 1997
Accepted June 2, 1997

Assessment of the Antitussive Efficacy of Codeine in Cough Associated with Common Cold

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Abstract

Codeine is generally accepted as the standard antitussive against which new antitussive medications are compared. This presents a problem because the support for codeine's antitussive activity comes from studies on cough in animals, and chronic and induced cough models in man, whereas antitussives are almost exclusively used for the treatment of cough associated with acute upper respiratory tract infection (URTI). The aims of this study were twofold. Firstly, to study the antitussive efficacy of codeine in cough associated with URTI and, secondly, to validate a sound meter as tool for quantifying cough.

The efficacy of codeine was assessed in a double-blind, stratified, placebo-controlled, parallel-group, clinical trial using three different measures of cough: cough sound-pressure levels (CSPLs) measured on a sound meter; subjective scores of cough severity; and cough frequency recorded by means of a microphone connected to an ink-pen recorder. A group of 82 subjects (51 females and 31 males; mean age 23·5 years, range 18–46 years) with cough owing to acute URTI were included in the study. The study took place on two separate study days. On study day 1 cough measurements were made before and 90 min after treatment with a single dose of either 50 mg codeine or matched placebo in capsule form. The same three measures of cough were repeated 2–5 days later (study day 2). On study day 1 a highly significant ($P < 0.0001$) decrease in all three measures of cough was found after treatment with both placebo and codeine yet there was no significant difference between the treatment groups. A highly significant ($P < 0.0001$) decrease in the three measures of cough was also found between days 1 and 2.

The results demonstrate that codeine is no more effective than placebo in reducing cough associated with acute URTI, as measured by CSPLs, cough frequency or subjective symptom scores. This result might be explained on the basis of two central pathways for cough; a reflex pathway via the brain-stem which is sensitive to codeine and a voluntary pathway via the cortex which is unaffected by codeine. The results also demonstrate that the sound-level meter appears to be a potentially useful investigative tool for the assessment of cough and antitussive efficacy.

Antitussive medications are widely marketed for the relief of cough associated with common cold or acute upper respiratory tract infection (URTI) yet there is very little clinical evidence to demonstrate that these antitussives are effective in treating this form of cough. Most of the data regarding antitussive efficacy have been obtained either from patients with chronic cough associated with lung disease or from healthy volunteers in whom cough has been induced by exposure to a chemical irritant. There is at present no accepted model of cough for patients with URTI. This is probably because it is logistically much more difficult to recruit patients with this acute form of cough and the severity of cough varies greatly between patients and in the same patient over time as the infection resolves.

Codeine was one of the first antitussive medications to be studied extensively in animal models and then using human models of chronic cough and induced cough; much of this work has been reviewed (Eddy et al 1969). Although codeine can be shown to inhibit fictive cough in animal models it is debatable if this type of cough is similar to cough associated with URTI in man (Bolser 1991). Similarly, one can criticize the induced and chronic cough models in man as not being relevant to cough associated with URTI although there is some evidence to support the efficacy of codeine as an antitussive in both induced and chronic cough models (Bickerman & Barach 1954; Sevelius et al 1971; Matthys et al 1983; Cox et al 1984). Because of the studies demonstrating antitussive efficacy in these models, codeine is generally accepted as a standard or reference antitussive against which new antitussive medications can be compared. However, there are very few studies which have investigated the antitussive efficacy of codeine using cough associated with URTI.

We have developed a new method of cough assessment for patients with cough associated with URTI using a digital sound-level meter of the type widely used in industry to measure noise-exposure levels. The meter provides a measure of the average cough sound over a set period of time, which is called the cough sound-pressure level (CSPL). The measurement of CSPLs provides a single unit of cough which takes into account both the frequency and the intensity of cough.

The aims of this study were twofold: to study the antitussive efficacy of codeine in cough associated with URTI, and to validate the sound-level meter as tool for quantifying cough.

The efficacy of codeine was assessed in a double-blind, placebo-controlled, parallel-group clinical trial using three different measures of cough: CSPLs measured on the sound meter; subjective scores of cough severity; and cough frequency recorded by means of a microphone connected to an ink-pen recorder.

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The validity of the sound meter and CSPLs as a measure of cough was determined by comparing the changes in the three measures of cough induced by codeine and during the natural resolution of the cough over a period of 2–5 days.

Materials and Method

Study subjects

Subjects were recruited from the student and staff population of the University of Wales College of Cardiff and from the general population of Cardiff, in response to advertisements for volunteers with cough associated with common cold.

Subjects were examined by a clinician to determine their state of health and suitability for the study. All subjects included in the study fulfilled nine criteria: they were healthy as determined by their medical history, that is, apart from the presence of an acute cough as a result of URTI; they had a history of a common cold within three weeks before the date of enrolment in the study; they were aged between 18 and 60 years; there was no clinical evidence of lower respiratory tract disease; they had no history of asthma; they had no clinically significant disease of the cardiovascular, endocrine or neurological systems; they had not taken a product containing menthol within the hour before commencement of the study; they had not taken any medication (apart from the oral contraceptive pill) in the 24 h before the start of the study; they had a CSPL greater than 70 dBA.

Procedure

Cough measurements were made on two days and on each day subjects were seated in a comfortable chair, in a quiet room, throughout the duration of the study. Day 1 measurements took place before and 90 min after treatment with codeine or matched placebo. Subjects sat quietly and watched a video film during the treatment period. Day 2 measurements occurred 2–5 days after the initial visit.

Subjective scores

The subjective impression of cough symptom severity was scored on a 5-point rating scale, with scores ranging from 0 for no cough to a score of 4 for very severe cough.

Sound-meter measurements

CSPLs and cough frequency were recorded by means of a condenser microphone (frequency response 50 Hz-20 kHz; diameter 12·7 mm; sensitivity 50 mV Pa^{-1}) attached to the subject's throat with a neck band. The microphone was connected to a digital sound-level meter (GA111 data-logging sound-level meter, Castle Associates, Scarborough, UK). The sound-level meter (frequency response 16 Hz–20 kHz) was programmed to record the amount of sound produced by cough over a 10-min period. It was calibrated daily by means of a dual-level acoustic calibrator which supplied 94 dB and 104 dB at a frequency of 1 kHz. To ensure that only cough sounds were recorded, all subjects were given strict instructions before a cough recording not to make any sound apart from cough. To reinforce the importance of these instructions, a clearly labelled notice was placed in front of the subject throughout all recording periods.

On completion of the 10-min baseline recording period, the data from the sound-level meter were downloaded on to a computer. The computer was installed with dBdata interface software, supplied for the GA111 sound-level meter (Castle Associates). At this stage, any subject with a CSPL of less than 70 dBA was excluded from the study. A cut-off point of 70 dBA was used because previous unpublished results from our laboratory have demonstrated that subjects with a CSPL < 70 dBA actually cough very little, usually fewer than five coughs in a 10-min period.

Cough frequency

Cough frequency was recorded by a microphone placed on the floor in front of the subject. The sound signal from the microphone was displayed as an integrated sound trace on an ink-pen recorder with coughs represented as spikes of varying amplitude. Coughs were counted in accordance with a previously employed method (Hutchings et al 1993).

Medication

On day 1 subjects with a CSPL greater than 70 dBA were randomly allocated a single, oral dose either of 50 mg codeine phosphate in capsular form or of matched placebo. Treatments were stratified in two groups (70–81·9 dBA and > 82 dBA) according to the CSPL recorded during their initial 10-min baseline cough.

Statistical analysis

An independent sample *t*-test was used to determine if there was any significant difference between the two treatment groups at baseline and 90 min after treatment, for measures of CSPLs and cough frequency. The non-parametric Mann-Whitney *U*-test was employed to determine if there was any difference between the two treatment groups at baseline and post-treatment, for subjective scores.

The results are expressed as means (with standard deviations) and medians (with the interquartile range). Where appropriate, the 95% confidence intervals for the difference between means are also quoted. The paired sample *t*-test was employed to compare CSPLs and cough frequency on day 1 before and after treatment and also to compare cough measures on day 1 and day 2. The non-parametric Wilcoxon matched-pairs signed-rank sum test was used to compare subjective scores before and after treatment on day 1 and also to compare cough scores on day 1 and day 2.

Pearson's correlation coefficients were used to examine the association between changes in CSPLs and cough frequency from baseline measurements to those made during recovery. The 95% confidence interval for the correlation coefficient in each case was also quoted. Spearman rank-correlation coefficients were used to determine relationships between changes from baseline measurements to those made during recovery, in cough-symptom severity as measured subjectively by symptom scores and objectively by CSPLs and cough frequency.

The study was approved by the South Glamorgan Local Research Ethics Committee.

Results

A group of 82 subjects (51 females and 31 males; mean age 23·5 years, range 18–46 years) with cough owing to acute URTI were included in the study. Ninety-three subjects were recruited for the study and eleven were excluded; nine had a

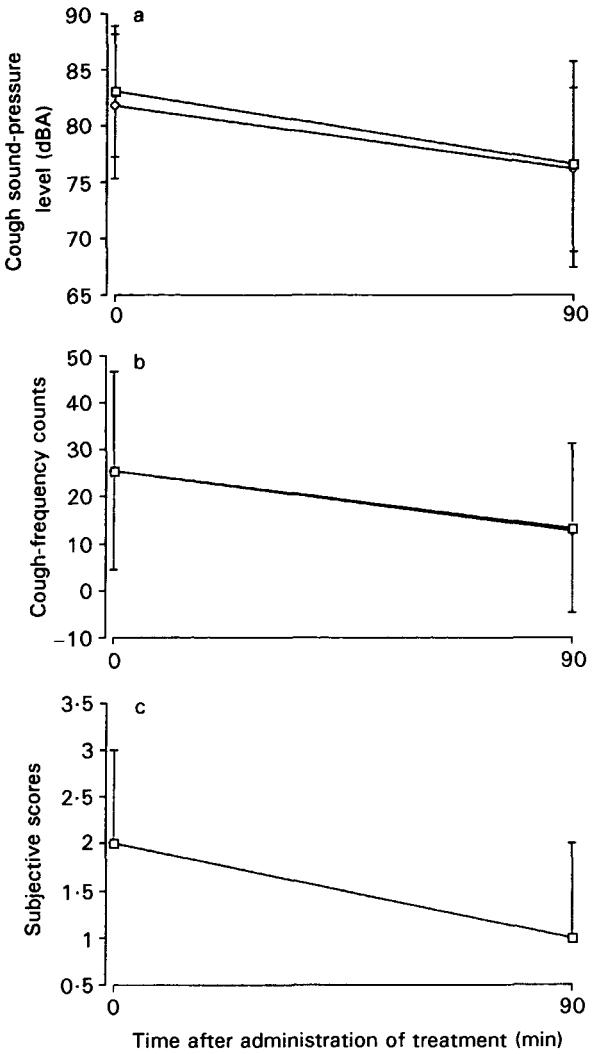

FIG. 1. Measures of cough before and after treatment with either codeine 50 mg (□) or placebo (◇). a. Cough sound-pressure levels, b. cough frequency, c. subjective scores.

CSPL of less than 70 dBA during the initial 10-min cough recording and two sneezed during this recording period. Forty-eight subjects were randomly allocated treatment with codeine and thirty-four subjects placebo. The codeine and placebo groups were well balanced at baseline, with no significant differences as regards CSPLs, cough frequency, subjective scores, subjects' age or the number of smokers in each group.

Out of the eighty-two subjects who participated in the treatment phase of the study on day 1, sixty-nine returned to the study centre for day 2 measurement of cough. Two subjects sneezed during the CSPL recording on day 2 and therefore these data were excluded from the analysis. No adverse events were reported in this study.

Day 1 results

Cough sound-pressure levels (CSPLs). The mean CSPL for the codeine and placebo groups before and 90 min after treatment are shown in Fig. 1a. In the codeine group, the mean CSPL was 83·07 dBA (s.d. 5·9) and this decreased significantly ($P <$ 0·0001) to 76·55 dBA (s.d. 9·2) 90 min after treatment. The mean CSPL at baseline in the placebo group was 81·76 dBA (s.d. 6·5) and this decreased to 76·10 dBA (s.d. 7·3) 90 min after treatment ($P < 0·0001$). There was no significant difference in mean CSPLs between the codeine and placebo groups before ($P = 0·3520$; 95% CI (−1·5, 4·1)) or 90 min after ($P = 0·8165$; 95% CI (−3·4, 4·3)) treatment.

Cough frequency. The mean cough-frequency for the codeine and placebo groups before and 90 min after treatment are shown in Fig. 1b. The mean cough-frequency for the codeine group was 25·58 (s.d. 21·1) and this decreased significantly ($P < 0·0001$) to 13·23 (s.d. 18·0) 90 min after treatment. The mean cough-frequency at baseline in the placebo group was 25·44 (s.d. 19·0) and this decreased to 12·71 (s.d. 14·1) 90 min after treatment ($P < 0·0001$). There was no significant difference in mean cough-frequency counts between the treatment groups before ($P = 0·9751$; 95% CI (−8·9, 9·2)) or 90 min after ($P = 0·8879$; 95% CI (−6·8, 7·9)) treatment.

Subjective scores. The median subjective scores for the codeine and placebo groups before and 90 min after treatment are shown in Fig. 1c. In the codeine group the median (interquartile range) subjective score was 2·0 (2·0, 3·0) and this decreased to 1·0 (1·0, 2·0) 90 min after treatment (tied P value $< 0·0001$). The median subjective score in the placebo group was 2·0 (2·0, 3·0) and this decreased to 1·0 (1·0, 2·0) 90 min after treatment ($P < 0·0001$). There was no significant difference between the mean subjective scores of the treatment groups before (tied P value $= 0·7593$) or 90 min after treatment (tied P value $= 0·8020$).

Day 2 results

CSPLs. The mean CSPLs on days 1 and 2 are shown in Fig. 2a. The mean CSPL on day 1 was 82·59 dBA (s.d. 5·9) and this decreased to 75·14 dBA (s.d. 9·0) on day 2 ($P < 0·0001$; 95% CI (5·4, 9·6)).

Cough frequency. The mean cough-frequency on days 1 and 2 are shown in Fig. 2b. The mean cough-frequency on day 1 was 25·57 (s.d. 19·5) and this decreased to 11·46 (s.d. 9·9) on day 2 ($P < 0·0001$; 95% CI (10·2, 18·0)).

Subjective scores. The median subjective scores on days 1 and 2 are shown in Fig. 2c. The median (interquartile range) subjective score at baseline was 2·0 (2·0, 3·0) and this decreased to 1·0 (1·0, 2·0) on day 2 (tied P value $< 0·0001$).

Correlations of the three different measures of cough symptom severity Significant correlations were found between the changes from day 1 to day 2 for: CSPLs and cough frequency ($r = 0·524$, $P < 0·0001$; 95% CI for the correlation coefficient (0·32 to 0·68)) and for CSPLs 0·41, tied P value $= 0·0008$); cough frequency 0·43, tied P value $= 0·0005$).

Discussion

The results of this study clearly demonstrate that codeine is no more effective than placebo in reducing cough associated with acute URTI, as measured by CSPLs, cough frequency or subjective symptom scores.

Critical evaluation of the study indicates that the results obtained cannot easily be attributed to flaws in the design or

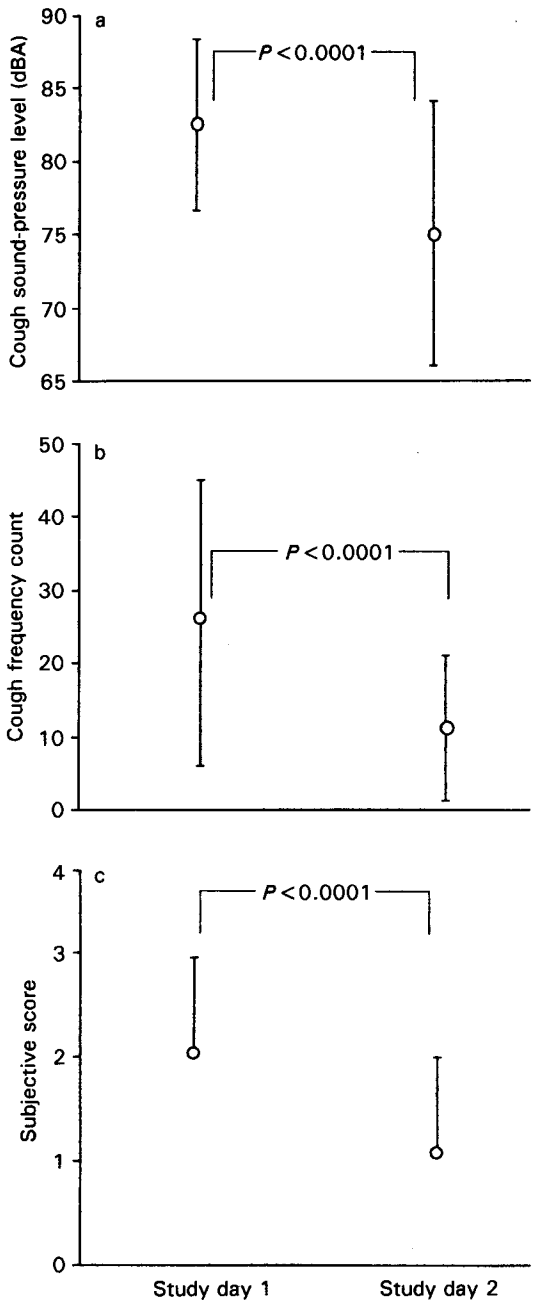

FIG. 2. Baseline measures of cough on study day 1 and 2–5 days later (study day 2). a. Cough sound-pressure levels, b. cough frequency, c. subjective scores.

conduct of the study. Both treatment groups were well balanced at baseline and the measurement of cough 90 min after treatment is a reasonable time-point at which to establish the antitussive efficacy of codeine. Codeine is rapidly absorbed after oral administration; peak plasma concentrations occur approximately 1 h after ingestion and the plasma half-life is approximately 3·5 h (Dollery 1991). The dose of 50 mg codeine was also considerably greater than the recommended OTC single adult dose of 15-30 mg (Nathan 1995).

Because all subjects underwent a period of rest throughout the study, a natural decrease in cough severity might have been expected. However, previous unpublished results from our laboratory have demonstrated that measurements of CSPLs and cough frequency are consistent over a period of 90 min. It is therefore likely that the decrease in cough severity observed was the result of a double-placebo effect in both treatment groups.

The failure to demonstrate any significant difference between codeine and placebo cannot be explained by the study being under-powered. A prospective power calculation demonstrated that to achieve a 90% chance of detecting a clinically significant change in CSPLs (20% change-7·26 dBA) at the 5% level, a total of 36 subjects would be required. A retrospective power calculation showed that the numbers of subjects included in the study (n = 82) gave a 90% chance of detecting a significant change (approximately 10·5%) in CSPLs of 3·78 dBA at the 5% significance level. Therefore, the present study was sufficiently powered to enable detection of a significant change in CSPLs between treatment groups and this is supported by the highly significant changes in cough shown in both treatment groups on both days of the study.

The results from the study indicate that the methods employed to measure cough and to evaluate the efficacy of codeine cannot account for the lack of effect of codeine in treating cough, because a reduction in cough severity from baseline to the return visit was successfully quantified with all three methods of assessment. These results demonstrate the sensitivity of each method in the detection of the natural decrease in cough severity over time during recovery from an acute URTI infection. The results demonstrate that the measurement of cough severity by CSPLs is comparable with the two well-established measures of cough frequency and subjective scores. The measurement of CSPLs by means of the digital sound-level meter in addition to taking into account both cough frequency and intensity also has a number of other advantages: the sound meter is portable, robust and easy to use; it can be readily standardized from one laboratory to another; and data analysis is easy because data are stored in a digital form.

Although the association observed between the changes from baseline to the return visit measurements of CSPLs and cough frequency was found to be significant, the correlation was not high. This result was expected because measurement of CSPL takes into account both the frequency and the intensity of cough and therefore a strong association between the different measures of cough was not expected.

Codeine was employed in this study because it is believed to be the most effective antitussive for acute cough and is regarded as the reference drug to which the effects of other antitussive agents are compared (Braga 1989; Sause 1994). However, the evidence for the antitussive effect of codeine has been obtained from studies on artificially induced or chronic cough (Bickerman & Barach 1954; Sevelius et al 1971; Matthys et al 1983; Cox et al 1984) and studies on cough associated with acute URTI have failed to demonstrate antitussive activity (Eccles et al 1992; Taylor et al 1993). A review article (Irwin et al 1993) suggests that the evaluation of codeine on different types of cough could account for discrepancies in the antitussive profile of the drug and that the essential mechanism of cough or the importance of the central component in the cough reflex is not the same in induced cough, chronic cough or cough caused by upper respiratory

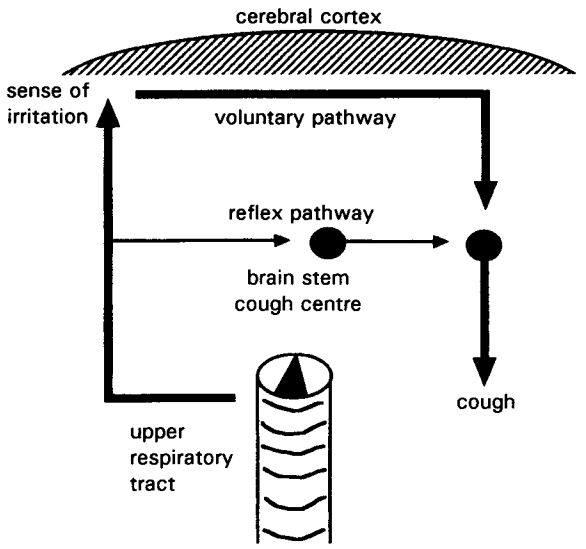

FIG. 3. A model illustrating two pathways involved in the control of cough. Cough associated with upper respiratory tract infection might be related to a sensation of throat irritation and be mainly controlled by a voluntary pathway which relays via the cerebral cortex and is not inhibited by codeine. Cough associated with animal experiments and induced and chronic cough in man might be mainly reflex in nature and this brain-stem pathway might be susceptible to inhibition by treatment with codeine. (Adapted from Eccles (1997).)

tract infection. This raises the question of whether the central mechanism in acute cough is in some way 'different' from chronic cough or artificially induced cough, because codeine is believed to act as an antitussive by depressing the 'cough centre' (Braga 1989; Nathan 1995), but appears to be largely ineffective in the treatment of acute cough.

A possible explanation of the difference in antitussive efficacy when different models of cough are used is that there might be two separate pathways involved in the control of cough, a reflex pathway and a voluntary pathway. A model illustrating the relationships of these two pathways is illustrated in Fig. 3. The model proposes that cough associated with URTI is mainly elicited by the voluntary pathway which passes via the cerebral cortex, with a sensation of airway irritation eliciting cough under voluntary control. Previous studies from this centre have shown that cough can be elicited voluntarily and that cough associated with URTI can be voluntarily suppressed (Hutchings et al 1993). The cough elicited in animal models and in studies on chronic and induced cough in man might be more reflex in nature with much less voluntary control. If codeine were to act mainly on the brain-stem reflex pathway of cough with little effect on the voluntary pathway, this would explain why cough associated with URTI in man is unaffected by treatment with codeine.

In conclusion, the results from this study indicate that codeine is no more effective than placebo for treating cough associated with acute URTI. This result might be explained on the basis of two central pathways for cough, a reflex pathway via the brain-stem which is sensitive to codeine and a voluntary pathway via the cortex which is unaffected by codeine. The results also demonstrate that the sound-level meter appears to be a potentially useful investigative tool for the assessment of cough and antitussive efficacy.

Acknowledgement

We would like to thank Dr M. Jawad for taking clinical responsibility for the conduct of the study.

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