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# Antitussive Efficacy of Dextromethorphan in Cough Associated with Acute Upper Respiratory Tract Infection

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**Abstract**

Dextromethorphan is one of the most widely used antitussives for the treatment of cough associated with acute upper respiratory tract infection. However, there is very little data to support the efficacy of dextromethorphan in this disease state. This aim of this study was to obtain more information about the efficacy of a single dose of 30 mg dextromethorphan in the treatment of cough associated with acute upper respiratory tract infection.

The study was a double-blind, stratified, randomized and parallel group design. Both objective and subjective measurements of cough were recorded over 10-min recording periods in a quiet room before (baseline) and at 90, 135 and 180 min after treatment. Forty-three patients (30 females and 13 males), mean age 22·9 years (range 18–46 years), with acute dry or slightly productive cough and otherwise healthy were included in the study. Patients were randomized to placebo treatment (n = 22) and dextromethorphan treatment (n = 21). The results showed similar trends in both treatment groups with statistically significant reductions ($P < 0{\cdot}05$) in cough sound pressure level (CSPL), cough frequency (CF) and subjective scores for cough severity within treatment groups but little difference between the treatment groups during the study period. The only statistically significant difference between treatment groups was for the mean CSPL changes from baseline to 90 min ($P = 0{\cdot}019$). There was a significant positive correlation between CSPL and CF ($r = 0{\cdot}752$, $P = 0{\cdot}000$) for changes in cough measurements from baseline to 90 min after treatment and this indicates that CSPL may be a useful measure of cough severity.

This study provides very little if any support for clinically significant antitussive activity of a single 30 mg dose of dextromethorphan in patients with cough associated with acute upper respiratory tract infection.

Dextromethorphan is one of the most widely used antitussives and is a common ingredient in many over the counter (OTC) cough–cold medications. Since some of the first reports by Cass & Frederik (1953) and Cass et al (1954) on the effects of dextromethorphan on cough in patients with chronic respiratory disease, there have been many studies on the efficacy of dextro-
methorphan as an antitussive using chemically-induced cough in healthy volunteers and chronic cough models (Salem & Aviado 1970; Braga 1989). Much of the clinical trial work was reported between 1950 and 1965, and although many of those studies were not as well designed as modern trials, in general a number of positive findings support some antitussive activity for dextromethorphan in models using induced and chronic cough. More recent studies on induced and chronic cough also provide evidence of antitussive activity (Matthys et al 1983; Ruhle et al 1984; Fuller et al 1989; Grattan et al 1995). However, the induced and chronic cough models may not be relevant to the disease state of cough associated with acute upper respiratory tract infection and dextromethorphan is only marketed for the treatment of cough associated with acute upper respiratory tract infection. The antitussive efficacy of dextromethorphan is primarily based on induced and chronic cough models and some reports indicate that dextromethorphan may not be very

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effective in the treatment of cough associated with acute upper respiratory tract infection (Taylor et al 1993).

The aim of this study was to obtain more information about the efficacy of dextromethorphan in the treatment of cough associated with acute upper respiratory tract infection. It is important to be able to establish the efficacy of the medication in the disease state in which it is used to properly assess the risk–benefit profile of dextromethorphan.

## Materials and Methods

*Study design*

The study was a double-blind, stratified, randomized and parallel group design. Both objective and subjective measurements of cough were recorded in a quiet room before (baseline) and at 90, 135 and 180 min after treatment.

*Patients*

Patients, aged 18–60 years, with a history of the acute upper respiratory tract infection (common cold) in the 3 weeks prior to the study, with acute dry or slightly productive cough but otherwise healthy, were recruited from the student and staff population of Cardiff University and from the general population of Cardiff city. Patients were excluded from the study if: they had a history of asthma or lower respiratory tract infections, clinically significant cardiovascular, endocrinological, or neurological disease; they were taking monoamine oxidase inhibitors; they were lactating or pregnant; they had taken any medications deemed by the clinician to be contraindicated (e.g. antitussives, antihistamines). The study was approved by the Bro Taf Health Authority, Ethics Committee.

*Cough frequency (CF)*

CF was recorded using a microphone connected to a pen recorder (Lafayette Datagraph ink pen recorder) using the integrator channel of an EMG amplifier. The microphone was mounted on a stand and placed on the floor in front of the patient. The sensitivity of the pen recorder was adjusted so that maximum pen deflections were produced when a patient was coughing. The mean (mm) of the three largest deflections was calculated and any cough deflection which was greater than one third of this mean maximum deflection was counted as a cough (Hutchings et al 1993). CF was expressed as the number of coughs in a 10-min recording period.

*Cough sound pressure level (CSPL)*

A Sound Level Meter (GA111; Castle Group Limited, Scarborough, UK) was used to record CSPL as previously described (Freestone & Eccles 1997). The meter was calibrated at the beginning and at the end of study using a sound calibrator (GA602; Castle Group Limited, Scarborough, UK). Cough sounds were recorded using a microphone which was attached to the patient's throat. CSPL was measured as the average integrated sound pressure level (dB) over a 10-min recording period and represents a measure of both the frequency and intensity of cough. Patients were instructed both verbally and with a written notice, not to make any noise apart from coughing during the 10-min recording period. Patients were excluded from the study if their CSPL was $\leq 70$ dB. If a noise other than cough occurred within the 10-min recording period, the recording was started again and this procedure was repeated up to maximum delay of 15 min from the allocated time point.

*Subjective scores for cough (SS)*

A questionnaire was completed by each patient to determine the severity of their cough. Cough severity was scored on a scale from 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and each patient was asked to mark one of four boxes to best describe the cough at each time point.

*Medication*

A single dose of 30 mg dextromethorphan powder in a hard gelatin capsule or matched placebo containing lactose powder, was ingested by the patient with a small amount of water. The medication was made by a pharmacy with a licence to manufacture medications for use in clinical trials. The gelatin capsule had been previously shown in dissolution studies to completely dissolve after approximately 30 min. The treatments were stratified into low CSPL group (70–81·9 dB) and high CSPL group ($> 82$ dB) according to the baseline CSPL.

*Statistics*

The outcome measures for the study were defined as the differences between treatment groups for the changes in cough measurements from baseline to 90, 135 and 180 min, and the areas under the curve from baseline to 180 min. According to distribution, normality, parametric and non-parametric statistical tests were performed for comparisons within and across treatment groups. CSPL was expressed as mean with standard deviation. CF and subjective scores were expressed as medians with

interquartile range. SPSS 7·5 and Minitab 11 statistical packages were used to generate the statistics.

## Results

Sixty-four patients with dry or slightly productive cough associated with a history of acute upper respiratory tract infection were recruited for the study. Of these, 20 patients with CSPL < 70 dB were excluded. Forty four patients were randomized to receive medication. One patient who in the opinion of the investigator was inappropriately motivated was excluded. Forty-three patients (30 females and 13 males), mean age 22·9 years (range 18–46), completed the study. Patients were randomized to placebo treatment (n = 22) and dextromethorphan treatment (n = 21). No adverse events were reported in the study.

*Cough sound pressure level (CSPL)*

The treatment groups were well balanced at baseline for mean CSPL and the difference between the two groups was not significant ($P = 0{\cdot}72$, independent-samples *t*-test, 95% CI 4·7, 3·2).

The changes in CSPL from baseline to 180 min are shown in Figure 1. The results show that there was a similar trend in both treatment groups with a significant decline in CSPL during the study period. Mean CSPL at baseline in the placebo group was 80·99 (5·3) dB and this declined to 76·69 (8·1) dB at 180 min ($P = 0{\cdot}015$, paired-samples *t*-test, 95% CI 0·91, 7·68). Similarly, in the dextromethorphan group, the mean CSPL fell from 81·71 (7·5) dB at baseline to 73·65 (8·1) dB at 180 min ($P = 0{\cdot}0001$, paired-samples *t*-test, 95% CI 4·78, 11·33).

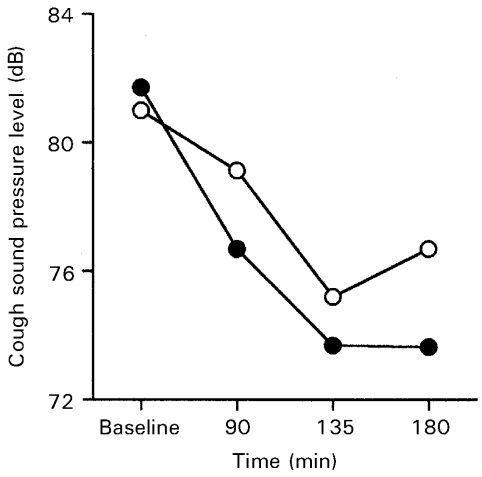


Figure 1. Mean cough sound pressure levels for placebo (○, n = 22) and dextromethorphan (●, n = 21) treatment groups.

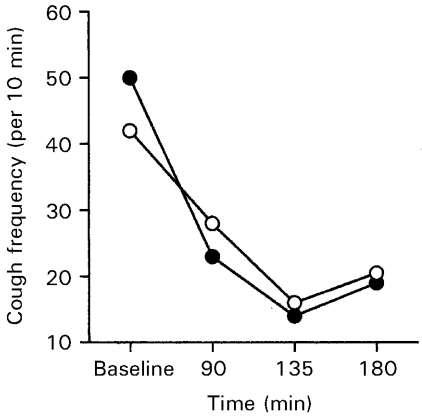


Figure 2. Median cough frequency for placebo (○, n = 22) and dextromethorphan (●, n = 21) treatment groups.

There was a significant difference ($P = 0{\cdot}019$) in mean CSPL changes from baseline to 90 min between the two treatment groups (placebo 1·86 (3·3); dextromethorphan 5·24 (5·6); 95% CI −0·6, −6·2). However, the difference in mean CSPL changes between the two groups was not significant from baseline to 135 min ($P = 0{\cdot}34$) and to 180 min ($P = 0{\cdot}10$). The difference between the two groups in terms of area under the curve from baseline to 180 min was not significant ($P = 0{\cdot}37$, independent-samples *t*-test, 95% CI 354·2, 922·7).

*Cough frequency (CF)*

The treatment groups were similar at baseline for median CF and the difference between the two groups was not significant ($P = 0{\cdot}58$, non-parametric Mann–Whitney U-test, 95% CI 28·0, 11·0).

The changes in CF from baseline to 180 min are shown in Figure 2. There was a similar trend in both treatment groups with a significant decline in CF during the study period. Median CF at baseline in the placebo group was 42·00 (22·75–64·00) and this declined to a median CF of 20·50 (10·75–24·25) at 180 min ($P = 0{\cdot}002$, non-parametric Wilcoxon test, 95% CI 8·5, 33·0). Similarly, in the dextromethorphan treatment group median CF decreased from 50·00 (21·50–77·50) at baseline to 19·00 (7·50–31·50) at 180 min ($P = 0{\cdot}000$, non-parametric Wilcoxon test, 95% CI 15·5, 39·5).

The difference in median CF changes between the two groups was not significant from baseline to 90 min ($P = 0{\cdot}28$), to 135 min ($P = 0{\cdot}36$) and to 180 min ($P = 0{\cdot}38$). The difference between the two groups in terms of area under the curve from baseline to 180 min was not significant ($P = 0{\cdot}80$, non-parametric Mann–Whitney U-test).

*Subjective scores for cough severity*

The treatment groups were similar at baseline for the median subjective scores and the difference between the two groups was not significant ($P = 0{\cdot}27$, non-parametric Mann–Whitney U-test, 95% CI 0·00, 1·0).

Similar trends were found in both treatment groups with a significant decline in subjective scores during the study period. Median subjective scores at baseline in the placebo group was 2·00 (2·00–3·00) and this declined to a median of 1·50 (1·00–2·00) at 180 min ($P = 0{\cdot}001$, non-parametric Wilcoxon test, 95% CI 0·5, 1·0). Similarly, in the dextromethorphan treatment group, median subjective scores decreased from 2·00 (1·50–2·00) at baseline to 1·00 (1·00–1·50) at 180 min ($P = 0{\cdot}002$, non-parametric Wilcoxon test, 95% CI 0·5, 1·0).

The difference in median subjective scores changes between the two groups was not significant from the baseline to 90 min ($P = 0{\cdot}95$), to 135 min ($P = 0{\cdot}12$) and to 180 min ($P = 0{\cdot}93$). The difference between the two groups in terms of area from baseline to 180 min was not significant ($P = 0{\cdot}082$, non-parametric Mann–Whitney U-test)

*Correlation between cough measurements*

Changes in cough measurements from baseline to 90 min after treatment were plotted to determine the extent of any correlation between the different measures of cough.

There was a significant positive association between CSPL and CF ($r = 0{\cdot}752$, $P = 0{\cdot}000$). The association between the two parameters is shown in Figure 3. The correlation was suspected to be influenced by the two outliers (CF changes 109 and 150) (Figure 3). However, a significant correlation between the two parameters ($r = 0{\cdot}714$, $P = 0{\cdot}000$) was still found when the two outliers were excluded from analysis. Positive correlation between the CSPL and subjective scores ($r = 0{\cdot}375$, $P = 0{\cdot}013$), and between CF and subjective scores ($r = 0{\cdot}380$, $P = 0{\cdot}012$) were also found.

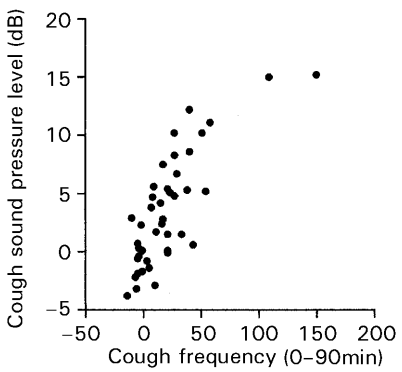


Figure 3. Correlation between changes in cough sound pressure levels and changes in cough frequency between baseline and 90 min ($n = 43$, $r = 0{\cdot}752$, $P = 0{\cdot}000$).

## Discussion

Our results do not provide much support for the antitussive efficacy of a single dose of dextromethorphan in the treatment of cough associated with acute upper respiratory tract infection. The only positive finding in support of dextromethorphan was a significant difference between treatment groups for the change in CSPL between baseline to 90 min. However, no statistical difference between treatment groups was found for any other CSPL time point, or any time points for the measurement of CF or subjective scores. In general the changes in cough associated with treatment were similar in both the placebo and dextromethorphan treatment groups. Taking all the results for objective and subjective measures into account, in this study dextromethorphan treatment did not demonstrate clinically significant antitussive activity compared with placebo treatment. It is difficult to define what would be generally accepted as clinically significant antitussive activity but one would expect at least 20% superiority of dextromethorphan over placebo in both an objective and a subjective measure of cough. This study demonstrated this level of superiority for changes in CSPL between baseline and 90 min but this was not supported by any other positive findings in comparisons between treatment groups for CSPL, CF and subjective scores of cough severity.

The failure to demonstrate clinically significant antitussive activity for dextromethorphan in this study may be related to several factors such as the dose of dextromethorphan, the patient population used, and the study design and power. The standard dosing regimen for dextromethorphan in many OTC cough medicines is 7·5 mg dextromethorphan four times daily. Some cough medications use a dose of 15 mg four times daily and very few use the higher dose of 30 mg. Therefore the 30 mg dose of dextromethorphan used in this study is the highest dose used in OTC cough medicines.

Dextromethorphan is well absorbed from the gastrointestinal tract and is subject to first-pass metabolism in the liver where the parent compound is converted to an active metabolite, dextrorphan (Silvasti et al 1987). There is considerable inter-individual variation in the metabolism of dextromethorphan but since fast metabolizers generate more dextrorphan relative to dextromethorphan the difference between individuals does not appear to

influence the antitussive efficacy or safety of the medication (Bem & Peck 1992). It could be argued that the efficacy of dextromethorphan should have been measured after multiple doses rather than a single dose, but patients taking an OTC medication would expect some relief of cough after a single dose and the dosing instructions on OTC cough medicines do not indicate that multiple doses of the medication are required for the medication to be effective in controlling cough.

The patient population used in this study were selected on the basis that they had a dry or slightly productive cough associated with a history of an acute upper respiratory tract infection in the three weeks prior to the study. Patients with only mild cough symptoms (CSPL < 70 dB) were excluded from the study. In general the population used in this study consisted of patients that would be likely to respond to an OTC antitussive medication.

The study was of a placebo-controlled double-blind design so that a direct comparison could be made between the antitussive effects of placebo medication and dextromethorphan. Without the placebo control, the effects of dextromethorphan found in this study would appear deceptively efficacious with large and significant reductions in all cough measurements. The very large reduction in cough over time in the placebo group makes it very difficult to demonstrate any additional benefit of dextromethorphan. In a previous study on the effects of codeine on cough associated with upper respiratory tract infection, a similar large reduction in cough over time was seen in both placebo- and codeine-treated groups of patients (Freestone & Eccles 1997). In the codeine study it was proposed that the large reduction in cough in both treatment groups was associated with rest as patients were sat in a chair for the 90 min recording period. In the present study, cough was only measured for 10-min periods and the patients were moved between the waiting room and laboratory for each cough measurement. It was expected that the relatively short periods of cough measurement together with the change in rooms and the short walk between rooms would help overcome any rest effect. Despite these precautions there was still a very large reduction in cough in the placebo treatment group and this may indicate that this is a true placebo effect rather than the result of rest.

A retrospective power calculation on this study using the differences in CSPL between baseline to 90 min indicates that between 15 and 43 patients per group are required to give 80% power to the study at the 5% level of statistical significance. With a treatment group size of 21, this study could be considered underpowered. However, it is unlikely that a larger study would provide any more support for the antitussive efficacy of dextromethorphan as the trends in this study were the same for CF, CSPL and subjective scores of cough, with very little separation between placebo and dextromethorphan treatment groups. The results of our study are comparable with those of three studies conducted in India using quite different methods to measure cough (Parvez et al 1996). The Indian studies compared the effects of a single 30 mg dose of dextromethorphan with placebo in 343 patients with cough associated with upper respiratory tract infection. All studies show a marked reduction in cough parameters in both placebo and dextromethorphan treatment groups similar to our study. However, comparisons between treatment groups showed that one study provided no evidence of dextromethorphan superiority over placebo, and the other two studies only showed superior efficacy of dextromethorphan at a few time points.

The placebo effect of cough medications in man may be explained by the fact that cough is under voluntary control and can be readily suppressed. Studies on both chemically-induced cough and cough associated with acute upper respiratory tract infection have shown that when patients are asked to suppress cough they can almost completely abolish cough (Hutchings et al 1993a, b). In a double-blind trial the belief by the patient that a medication may have an effect on cough may provide such a large placebo effect that it is extremely difficult to demonstrate any additional pharmacological antitussive action of a medication. Studies between groups receiving no treatment versus placebo treatment could help to determine the extent of any placebo effect.

The significant positive association between CSPL and CF indicates that CSPL provides a relevant measure of cough severity. Since CSPL is a measure of both cough frequency and cough severity one would not expect a much greater level of correlation with CF. The advantage of using CSPL as a measure of cough is that a standard cough sound level meter may be used for measurements whereas there is no standard method of measuring cough frequency. In conclusion this study provides very little if any support for the antitussive activity of a single 30 mg dose of dextromethorphan in patients with cough associated with acute upper respiratory tract infection.

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