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An electromyographic method of objectively assessing cough intensity and use of the method to assess effects of codeine on the dose-response curve to citric acid

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1 The integrated surface abdominal electromyogram (EMG) has been used as a simple measurement of cough intensity which correlates well with the volume, air flow and noise produced in different coughs.
2 Using the integrated abdominal EMG as a measure of cough intensity, dose response curves to inhaled citric acid can be drawn which are highly reproducible.
3 We have studied the effects of codeine (60 mg) on these curves, and have demonstrated a reduction in cough intensity.
4 It is suggested that this method of testing the effects of an antitussive on such a dose-response curve may be a useful one.

Keywords cough intensity electromyogram citric acid dose-response curves

Introduction

The objective assessment of cough can be of importance when investigating mechanisms of disease in patients, or the value of new therapeutic agents in patients or volunteers. In patients spontaneous cough can be counted over long periods (Loudon & Romans, 1967). Alternatively cough may be induced by such agents as citric acid and again counted (Bickerman & Barach, 1954). The threshold for such cough production can be measured by administering increasing concentrations of citric acid (Empey *et al.*, 1979). Attempts can be made to quantify the cough intensity by measuring noise (Gravenstein *et al.*, 1954) or air flow rates (Bickerman *et al.*, 1957). Unfortunately none of these measures of cough intensity has proved entirely satisfactory in the assessment of antitussive agents.

Bigland & Lippold (1954) demonstrated in man that the electrical activity measured by integrating the action potentials during muscle contraction was proportional to the force generated. Further, such integrated recordings of the electromyogram (EMG) were as well or better recorded by surface as by needle electrodes. This principle was applied in an attempt to develop a new objective method to assess the intensity of cough by recording the integrated abdominal EMG (reflecting activity of the abdominal muscles used in coughing) and constructing dose-response curves to inhaled citric acid.

The method has been further tested by demonstrating a shift of such dose-response curves by the known antitussive agent codeine.

Methods

Electromyography

The electromyograms were recorded using pregelled silver/silver chloride electrodes placed on the right hand side of the abdominal surface lateral to the rectus muscles. This was designed

to record from the oblique muslces, especially the external oblique, that are the driving force of the cough response. The skin surface was thoroughly cleaned and lightly abraided to ensure good electrical contact with resistances below 3 k ohms.

The EMG was amplified using an SE Lab EEG amplifier with a frequency response of 2–10,000 Hz. It was then processed through a high pass filter of 45 Hz and then rectified. The rectified EMG was passed through a time averaging filter with a time constant of 60 ms. This produced a smoother envelope of the rectified EMG called a time averaged EMG. The rectified EMG was also passed through an integrating circuit to give an integrated sum of the total electrical activity during each contraction. Thus raw EMG, time averaged EMG and the integrated EMG were recorded (Figure 1).

Cough flow and volume

Subjects coughed through a pneumotachograph which was calibrated to give airflow readings. To obtain the measurement for cough volume, the flow was integrated electronically. Ten subjects produced 50 voluntary coughs each of varying intensity through the pneumotachograph while EMG was recorded.

The peak of the time averaged EMG and the value of the integrated EMG were correlated with the peak of the cough flow and the volume of each cough.

Noise

The noise of individual coughs was recorded using a Bruel and Kjaer sound level meter type 2206 at one meter distance from the subject's mouth. Ten subjects produced 30 coughs while abdominal EMG recordings were performed. The integrated EMG during coughing was correlated with the peak decibel level of each cough.

Subjects

The subjects were fit males aged 20–35 years. They were all non-smokers and had normal

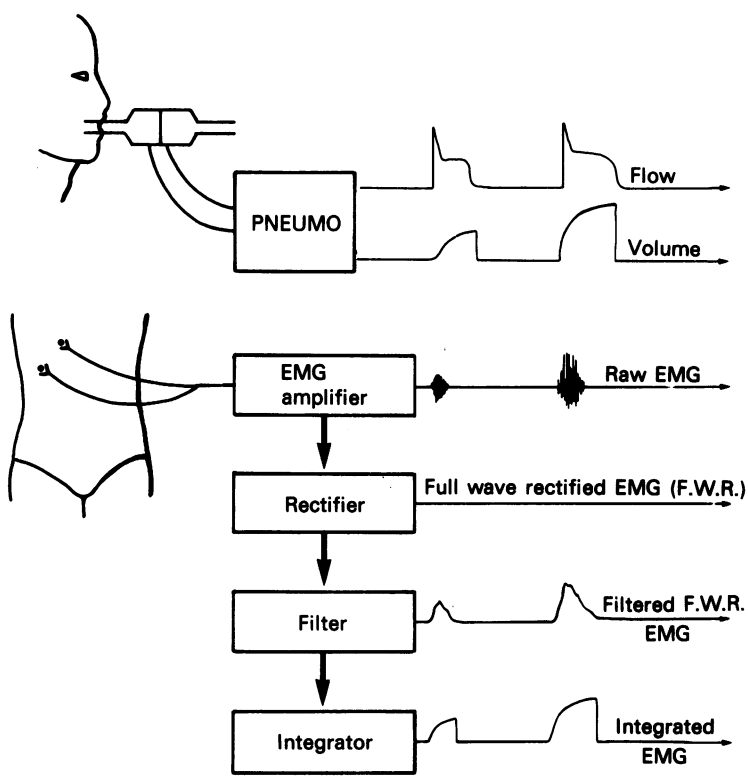

Figure 1 Diagrammatic representation of method of recording measurements of EMG and cough airflow with sample traces. The full wave rectified EMG trace is not shown.

spirometric measurements (vital capacity and FEV_1). They had performed similar inhalation challenge over the previous 3 months so that slow vital capacity inspirations were possible. All the studies were approved by the Hospital Ethical Committee.

To construct the dose-response curves subjects were seated in a comfortable chair, wtih EMG electrodes in place as described above. They inhaled citric acid from a Hudson nebuliser via a mouthpiece. For each concentration of citric acid three vital capacity inspirations were taken each over 5 s, separated by 15 s. Dose-response curves were constructed using a log dose scale of citric acid concentrations from 0.3% to 20% against the total integrated EMG produced during coughing for the relevant citric acid concentration.

Design of studies

Study No. 1. (Citric acid dose-response curves) Ten subjects were used to construct dose-response curves to citric acid and to assess the correlation between the mean integrated EMG and the concentration of citric acid inhaled as a challenge. Each subject inhaled increasing doses of citric acid between 0.3%–20%. The concentration of citric acid was doubled every 3 min and the challenges were carried out on seven such occasions in order to cover this range of citric acid concentrations. To assess the reproducibility of the curves for individual subjects four such dose-response curves (each with seven challenges) were carried out 1 h apart.

Study No. 2 (Codeine effect on dose-response curves) In the second part of the study ten different normal subjects aged 18 to 32 years without recent respiratory tract infections were studied. They received either 60 mg of codeine or matching placebo tablets in a double-blind randomised manner on two separate occasions at least 1 week apart. Citric acid challenges as described above were performed before taking any tablets and at 1, 2 and 3 h after taking the tablets.

The pre-gelled electrodes had to be removed after each day's challenges and replaced at the second occasion. Therefore exact repositioning with identical electrode/skin electrical contact was not possible. We therefore felt that analysis of the data in absolute figures was not possible and therefore we have also expressed the data for each sequence of challenges as a percentage of the control pre-drug EMG value on that particular occasion.

Results

1. *Correlation between integrated and peak EMG and cough flow and volume*

The data for the ten subjects, each of whom had produced 50 voluntary coughs, are presented in Table 1. From this it is evident that the highest correlation factors are between integrated abdominal EMG and cough volume (range 0.63–0.79). The relationship with cough flow was not so convincing (range 0.42–0.63) nor were the correlations between 'peak' EMG and cough volume (range 0.31–0.52) or cough peak flow (range 0.49–0.62).

2. *Correlation between integrated EMG and cough noise*

Here the correlation was good (range 0.61–0.84) as shown in Table 2.

Table 1 Correlation coefficients for comparison of integrated surface EMG and peak time filtered EMG against cough volume and the peak of the flow during the cough.

Subject	*Integrated abdominal EMG* vs *volume*	*Integrated abdominal EMG* vs *peak flow*	*Peak EMG* vs *cough volume*	*Peak EMG* vs *peak flow*
1 DLM	0.79	0.62	0.32	0.62
2 MCPA	0.78	0.63	0.51	0.54
3 IDC	0.63	0.48	0.34	0.63
4 LB	0.69	0.58	0.52	0.49
5 DB	0.72	0.42	0.49	0.52
6 RCAO	0.64	0.49	0.31	0.62
7 JP	0.68	0.46	0.36	0.52
8 PD	o,67	0.45	0.51	0.58
9 JB	0.63	0.52	0.31	0.59
10 KH	0.69	0.56	0.38	0.59

Table 2 Correlation coefficients for 10 subjects of integrated abdominal surface EMG against peak of noise level during cough.

Subject		*Correlation coefficient*
1	MCPA	0.73
2	IDC	0.61
3	KB	0.83
4	KH	0.74
5	PW	0.81
6	PR	0.83
7	NW	0.84
8	JB	0.79
9	PH	0.74
10	DB	0.74

Dose-response curves A repeated measures analysis of variance with concentration and time as factors was carried out on the response (taken as the integrated EMG) to the four highest concentrations of citric acid. The lower concentrations were excluded from this analysis due to the large number of zero responses. The results are shown in Table 3. Three subjects could not tolerate 20% citric acid. There was a highly significant effect of concentration but no effect of time and no time *vs* concentration interaction, i.e. there was a strong dose-response effect which remained constant over the 4 h. The coefficients of variation at those concentrations of citric acid inhaled by all subjects and producing an appreciable response are also shown in Table 3. They were all below 10%, being only 5% and 4% respectively at concentrations of 5% and 10% citric acid. Thus the dose-response curve of mean integrated EMG against citric acid concentration (on a log scale) appears to be very reproducible and the response to the highest concentrations (2.5, 5, 10 and 20%) almost linear (Figure 3).

Effects of codeine

The mean integrated EMG for the subjects after inhaling three of the four highest citric acid concentrations (*vide supra*) are shown in Table 4. Inspection shows that the values after codeine at all times tends to be less than after placebo. An analysis of variance was undertaken with subject and drug as factors for each post-drug time. The total EMG for all citric acid concentrations taken together was also compared after pretreatment with codeine or placebo. All the analyses showed a significant reduction in the EMG at 2 and 3 h after the administration of codeine. At 1 h only the total EMG for all citric acid concentrations and the response to 2.5% citric acid were significantly different to placebo. The effect of 60 mg of codeine on the mean of the integrated EMG recorded in the dose-response curve is shown in Figure 2 and illustrates the effect at 2 and 3 h and also the shift to the right shown by the drug.

Discussion

Previous methods of assessing cough have relied on the recognition of the coughs by the sound of individual coughs. This has allowed investigators to count the number of coughs produced in response to a stimulus or to determine the threshold of coughing to increasingly irritant stimuli. These methods have been widely used and can give valuable information. However they are limited as they treat all coughs as equal. In this way changes of cough intensity may occur which may pass

Table 3 The mean values of the integrated abdominal EMG in the 10 subjects at different concentrations of citric acid over a 4 h period. The coefficients of variation are also given for the three concentrations of citric acid inhaled by all subjects.

Time (h)	*Concentration of inhaled citric acid (%)*						
	0.3	*0.6*	*1.25*	*2.5*	*5*	*10*	*20*
1	0	0	14	47	90	123	156
2	0	0	13	47	102	127	146
3	0	0	15	59	97	124	157
4	0	0	12	62	95	121	157
s.e. mean	–	–	–	4.7	5.6	5.2	
Coefficient of variation				8%	5%	4%	

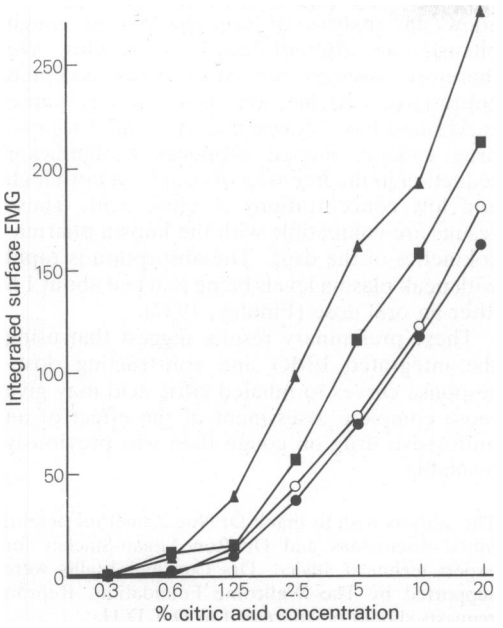

Figure 2 Dose-response curves to increasing concentrations of citric acid using integrated surface EMG as a measure of the response. Constructed from the mean values in Table 3. The effects of codeine 60 mg. ▲ pre-drug, ■ 1 h, ○ 2 h, ● 3 h.

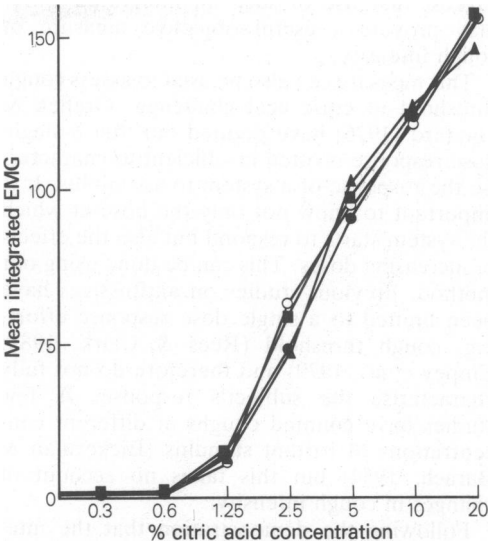

Figure 3 Dose-response curves with concentration of citric acid plotted against absolute values of the mean integrated EMG for the 10 subjects. The four curves were recorded at hourly intervals as described in the text. ▲ 1 h, ■ 2 h, ○ 3 h, ● 4 h.

unnoticed. A method of assessing cough which takes into account the intensity of the coughs will allow a more precise analysis of the changes in cough in response to treatment.

The driving force of the cough mechanism is the contraction of the abdominal muscles and in particular the lateral abdominal muscles (Floyd & Silver, 1950; Strohl *et al.*, 1981). While sitting quietly as our subjects were, these muscles are relaxed, but on contraction they raise intrabdominal pressure. The EMG of this contraction can be recorded from electrodes overlying the muscles. It is this contraction initially against a closed glottis that produces the sudden rapid airflow through the bronchial tree with the associated noise. We have recorded the EMG of these muscles during coughing and have measured the integrated surface EMG. This provided an assessment of the use of the integrated surface abdominal EMG as a measure of the intensity of cough. Our results

Table 4 The mean integrated EMG for the subjects at 2.5%, 5% and 10% citric acid and the total EMG across all concentrations, expressed as a percentage of pre-drug EMG on both occasions.

	Time post-drug (h)	*Placebo*	*Codeine*	*s.e. of difference*	*Two-tailed P-value*
2.5% citric acid	1	79.2	54.6	7.79	0.012
	2	87.3	40.0	11.48	0.003
	3	85.5	36.4	4.90	<0.001
5% citric acid	1	97.3	76.4	10.99	0.090 (NS)
	2	100.7	53.0	6.59	<0.001
	3	91.8	47.6	9.09	<0.001
10% citric acid	1	107.6	82.9	13.44	0.099 (NS)
	2	111.2	64.8	9.07	<0.001
	3	99.6	61.1	10.61	0.006
Total (0.3–20% citric acid)	1	99.1	74.7	4.70	<0.001
	2	99.3	56.8	4.30	<0.001
	3	92.9	52.1	3.67	<0.001

suggest that use of such an integrated EMG may provide a useful objective measure of cough intensity.

This measure can also be used to assess cough threshold to citric acid challenge. Orehek & Gayrard (1976) have pointed out that a single dose response is often insufficient to characterise the response of a system to a stimulus. It is important to know not only the dose at which the system starts to respond but also the effects of increasing doses. This can be done using our method. Previous studies on antitussives have been limited to a single dose response effort, e.g. cough threshold (Rees & Clark, 1983; Empey *et al.*, 1979) and therefore do not fully characterise the subject's response. A few studies have counted coughs at different concentrations of irritant stimulus (Bickerman & Barach, 1954) but this takes no account of changes in cough intensity.

Following the demonstration that the integrated abdominal EMG was a measure of cough intensity we used it to assess the cough response to inhaled citric acid. The dose-response curves so constructed are reproducible over a 4 h period. Such dose-response curves allow an analysis of the changes in cough intensity at different levels of stimulus. We therefore assessed the effect of an accepted antitussive, codeine, on these dose-response curves and have shown that at 2 and 3 h post-drug codeine indeed produces a significant reduction in the intensity of coughs at both high and low concentrations of citric acid. These results are compatible with the known pharmacokinetics of the drug. The absorption is rapid with peak plasma levels being reached about 1 h after an oral dose (Findlay, 1977).

These preliminary results suggest that using the integrated EMG and constructing dose-response curves to inhaled citric acid may give more complete assessment of the effect of an antitussive drug on cough than was previously available.

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References

Bickerman, H. A. & Barach, A. L. (1954). The experimental production of cough in human subjects induced by citric acid aerosols. Preliminary studies on the evaluation of antitussive agents. *Am. J. clin. Sci.*, **228**, 156–163.

Bickerman, H. A., German, E., Cohen, B. M. & Itkin, S. E. (1957). The cough response of healthy human subjects stimulated by citric acid aerosol: Evaluation of antitussive agents. *Am. J. clin. Sci.*, **234**, 191–206.

Bigland, B. & Lippold, O. C. J. (1954). The relationship between force, velocity and integrated electrical activity in human muscles. *J. Physiol.*, **123**, 214–224.

Empey, D. W., Laitinen, L. A., Young, G. A., Bye, C. E. & Hughes, D. T. D. (1979). Comparison of the antitussive effects of codeine phosphate 20 mg, dextromethorphan 30 mg and noscapine 30 mg using citric acid induced cough in normal subjects. *Eur. J. clin. Pharmac.*, **16**, 393–397.

Findlay, J. W., Butz, R. F. & Welch, R. M. (1977). Codeine kinetics as determined by radioimmunoassay. *Clin. Pharmac. Ther.*, **22**, 329–446.

Floyd, W. F. & Silver, P. H. S. (1950). Electromyographic study of patterns of activity in the anterior abdominal wall muscles in man. *J. Anatomy*, **84**, 132–145.

Gravenstein, J. S., Devloo, R. A. & Beecher, H. K. (1954). Effect of antitussive agents on experimental and pathological cough in man. *J. appl. Physiol.*, **7**, 119–139.

Loudon, R. G. & Romans, W. C. (1967). Cough monitoring equipment. *Med. Res. Eng.*, **6**, 25–26.

Orehek, J. & Gayrard, P. (1976). Non-specific bronchial provocation tests in asthma. *Bull. Eur. Physiopath. Resp.*, **12**, 565–598.

Rees, P. J. & Clark, T. J. H. (1983). Assessment of antitussive effects by citric acid thresholds. *Br. J. dis. Chest*, **77**, 94–97.

Strohl, K. P., Mead, J., Banzett, R. B., Loring, S. H. & Kosch, P. A. (1981). Regional differences in abdominal muscle activity during various manoeuvres in man. *J. appl. Physiol.*, **51**, 1471–1476.

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