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Effect of an anti-reflux medical device in the control of deflation cough: A placebo-controlled comparative study with an antacid drug in chronic coughers

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ABSTRACT

Background: Deflation cough (DC), i.e. the cough-like expiratory expulsive efforts evoked by maximal lung emptying, is partially inhibited by prior intake of an antacid. We wished to compare the effects of an anti-reflux medical device (*Gastrotuss*®) and of a widely used antacid drug (*Maalox*®) on the number of expiratory thrusts evoked by maximal lung emptying in chronic cough patients.

Methods: Twenty consecutive chronic cough outpatients also presenting DC attended the clinic on three separate occasions and were requested to inhale to near total lung capacity and then exhale maximally for at least 6 s. Trained investigators detected aurally the number of cough efforts evoked by maximal lung emptying prior to and 1, 5, 10, 30 e 60 min after administration of either *Maalox*®, or *Gastrotuss*® or placebo. The liking of the administered agents was also rated.

Results: In control conditions, maximal lung emptying was consistently accompanied by the appearance of DC. The number of efforts was unchanged after placebo whereas it was markedly ($P < 0.001$) reduced 1–10 min following *Maalox*® and *Gastrotuss*® administration. The value of liking for *Gastrotuss*® was greater ($P < 0.01$) than those of *Maalox*® and placebo.

Conclusions: Pre-treatment with anti-reflux agents with a substantially different composition are equally effective in inhibiting DC. The liking of the two compounds used in the present experiments differed considerably and may be important to improve adherence to treatment in patients undergoing long-term therapy for reflux-related symptoms.

1. Introduction

Recently, we have observed that during maximal lung emptying some patients with chronic cough and symptoms of gastro-oesophageal reflux produce one or more cough efforts that typically occur when lung volume is emptied to near residual volume [1,2]. The mechanism underlying this phenomenon, termed "deflation cough" (DC), appears to depend upon oesophageal acidification, since in the majority of patients DC is markedly reduced or even abolished by pre-treatment with a 40-ml Maalox® (Novartis International AG, Basel, CH), a solution containing aluminium hydroxide (3.25 g/100 ml) and magnesium hydroxide (3.65 g/100 ml) [1]. The hydroxides react with excess acid in the stomach, reducing its acidity [3,4]; the agent is commonly prescribed as an antacid to minimise the clinical symptoms of oesophageal acidification in patients with gastro-oesophageal reflux (GOR) [5] and its inhibitory action on DC was shown to be significantly stronger than that of placebo [1]. *Gastrotuss*® (Drugs Mineral and Generics, Pomezia, Rome, I) is a liquid preparation, registered as a medical device, largely employed in the control symptoms of GOR, including chronic cough [6]. The device is an association of different agents including simethicon – an anti-foaming agent that decreases the surface tension of gas bubbles – and magnesium alginate, i.e. the magnesium salt of alginic acid which is administered orally in the treatment of GOR [6]. After ingestion, the device combines with gastric acid to form a viscous gel, which floats on top of the gastric contents and acts as a physical barrier to reflux [6]. However, the effectiveness of *Gastrotuss*® in the control of DC has not been assessed. Thus, the primary objective of the study was to assess the effectiveness of *Gastrotuss*® in preventing or reducing DC

Abbreviations: DC, deflation cough; GOR, gastro-oesophageal reflux.

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in a group of outpatients with chronic cough. The secondary objective of the study was to compare the effectiveness of *Maalox*® and *Gastrotuss*® in the control of DC and to assess whether patients show any preferences regarding the liking of the agents employed.

2. Materials and methods

2.1. Patients

We recruited 20 consecutive outpatients (13 females, Table 1) with chronic cough of any origin and DC who attended the Cough Centre at the Azienda Ospedaliero Universitaria Careggi, Florence, Italy. Patients were non-smokers or ex-smokers (n = 6) for longer than 24 months, none of them reported recent (<4 weeks) airway infections. Patients were requested to be off any acid-suppressing therapy for at least 1 week before enrollment in the study. All procedures were in accordance with the Helsinki Declaration and the study was approved by the local Institutional Review Board (n. 869/13); patients gave their signed informed consent to participate.

2.2. Treatments

Maalox® (40 ml), or *Gastrotuss*® (40 ml) or placebo, i.e. a solution freshly prepared with 30 ml mineral water, 10 ml UHT milk and 10 drops of a multivitamin compound [1], were employed. A single dose of the active agents or placebo was randomly administered at each scheduled visit. The sequence of administered treatments was allocated according to an on-line randomization web site (www.randomization.com).

2.3. Study design and protocol

This was a randomized, placebo-controlled, double blind, cross-over study. Blindness was guaranteed by the fact that all treatments were administered by indistinguishable syringes into the patient's mouth, the identity of which were blinded to patients and investigators. Patients attended the clinic on three occasions separated by a time interval of 48–72 h. Food intake was withheld 3 h prior to each study day. At the clinic, patients underwent a general clinical assessment and the assessment of DC as described in the literature [1]. In brief, patients inhaled to near total lung capacity and then exhaled slowly down to near residual volume. During the manoeuvre patients wore a nose clip and breathed freely through a mouthpiece to prevent pursing of the lips, a phenomenon that in our experience may affect the appearance of DC. Patients were trained to exhale maximally as in an attempt at emptying out the lung as much as possible for at least 6 s. Trained investigators detected aurally the number of cough efforts evoked by maximal lung emptying prior to (i. e., at baseline) and 1, 5, 10, 30 e 60 min after each treatment and noted for subsequent analyses. At baseline, the manoeuvre was repeated 3–5 times, and a 5 min recovery period was allowed between each expiratory effort. After completion of each trial, patients were requested to rate the liking of the administered agent according to a method described previously [7]. In brief, patients rated the taste using a 10 cm long visual analogue scale. The extremes of the scale were classified from 0 (extremely poor) to 10 (excellent).

2.4. Data analysis

Based on the results of a previous investigation [1], the sample size was chosen to design the study to have a 80% statistical power of detecting a 50% reduction in baseline DC frequency with the use of one-way repeated measure analysis of variance (ANOVA) and a significance level of 0.05. All expulsive efforts recorded during each maximal expiration were considered. Deflation cough frequency was taken as the number of expiratory efforts recorded during each maximal expiration. The number of DC events recorded at baseline was pooled and averaged for subsequent calculations. Comparisons between DC frequencies recorded at baseline and after placebo, *Maalox*®, and *Gastrotuss*® administration were performed by two-way, nonparametric, repeated-measure ANOVA followed by post-hoc tests. Treatments (i. e. *Gastrotuss*®, *Maalox*® and placebo) and the time intervals after administration of each drug were factors in the ANOVA. This statistical analysis allowed us to investigate, for each subject, interactions between drugs and the time course after their administration. Ratings of anti-reflux agents' taste obtained at the end of each trial were compared by one-way ANOVA followed by Dunn's multiple comparisons test. All reported values are means ± standard deviations (SD); a P value <0.05 was taken as significant.

Table 1
Patients' anthropometric, functional and clinical characteristics.

Pt. no.	Sex	Age (years)	BMI	FEV_1/FVC	Cough duration (months)	Most prominent associated symptoms	Ongoing treatment
1	M	55	29.07	80	72	Regurgitation	PPI
2	F	59	21.36	75	96	Dyspnoea, dysphonia, heartburn regurgitation	LAMA, PPI
3	F	51	20.81	79	12	Dysphonia, indigestion	None
4	M	23	19.59	77	24	Heartburn, indigestion	None
5	F	57	25.40	79	12	Dysphonia, regurgitation, thoracic pain	None
6	M	67	31.25	81	11	Dysphonia, indigestion	None
7	F	40	22.59	73	60	Dyspnoea, indigestion, regurgitation	PPI
8	F	70	25.39	79	24	Dysphonia, dyspnoea, regurgitation	ICS, PPI
9	F	66	23.83	77	10	Dysphonia, heartburn	PPI
10	M	62	25.26	72	36	Heartburn, indigestion, regurgitation	None
11	M	37	24.38	79	9	Dysphonia, heartburn	PPI
12	F	67	29.64	77	10	Dysphonia dyspnea, indigestion	None
13	M	55	25.10	86	8	Dysphonia, heartburn	None
14	F	29	24.50	80	9	Heartburn, regurgitation	None
15	F	61	27.18	81	12	Dyspnoea, heartburn	LAMA, PPI
16	M	60	27.12	77	84	Heartburn, regurgitation	None
17	F	65	28.09	73	72	Dysphonia, dyspnoea, regurgitation	PPI, LABA, ICS
18	F	68	25.71	79	7	Heartburn, thoracic pain	PPI
19	F	50	25.10	81	100	Heartburn, indigestion, regurgitation	PPI, prokinetics
20	F	70	24.91	74	96	Dyspnoea, heartburn, thoracic pain	ICS, LABA, PPI
Mean	–	55.60	26.79	77.95	38.20		
SD		13.65	3.23	3.39	35.35		

BMI, body mass index; FEV_1, forced expiratory volume at 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; LABA, long-acting β_2 agonists; LAMA, long-acting muscarinic antagonist; Pt, patient; PPI, proton pump inhibitors.