CHEST

Pregabalin and Speech Pathology Combination Therapy for Refractory Chronic Cough

A Randomized Controlled Trial

Anne E. Vertigan, PhD; Sarah L. Kapela, BSpPath; Nicole M. Ryan, PhD; Surinder S. Birring, MB, ChB (Hons), MD; Patrick McElduff, PhD; and Peter G. Gibson, MBBS (Hons)

BACKGROUND: Chronic refractory cough (CRC) is a difficult problem to treat. Speech pathology treatment (SPT) improves symptoms but resolution is incomplete. Centrally acting neuromodulators also improve cough symptoms, but not cough reflex sensitivity, and the effect is short-lived. We hypothesized that combined SPT and centrally acting neuromodulators would have a superior outcome than SPT alone. Our goal was to determine whether combined pregabalin and SPT is more effective than SPT alone.

METHODS: Randomized placebo controlled trial. Forty patients with CRC were randomly assigned to receive either combined SPT and pregabalin 300 mg daily or combined SPT and placebo. Outcome measures were collected at baseline, end of treatment, and 4 weeks after the end of treatment. Primary outcome measures were cough frequency using the Leicester Cough Monitor, cough severity using a visual analog scale (coughVAS), and cough-related quality of life (QOL) using the Leicester Cough Questionnaire (LCQ).

RESULTS: Cough severity, cough frequency, and cough QOL improved in both groups. The degree of improvement in LCQ and coughVAS was greater with combined SPT and pregabalin than SPT alone; the mean difference in LCQ was 3.5, 95%CI of difference 1.1 to 5.8; the mean difference in coughVAS was 25.1, 95% CI of difference 10.6 to 39.6. There was no significant difference in improvement in cough frequency between groups. There was no deterioration in symptoms once pregabalin was withdrawn. Median capsaicin cough sensitivity improved from 15.7 to 47.5 μM with combined SPT and pregabalin and from 3.92 to 15.7 μM with SPT alone.

CONCLUSIONS: Combined SPT and pregabalin reduces symptoms and improves QOL compared with SPT alone in patients with CRC. CHEST 2016; 149(3):639-648

KEY WORDS: cough; dyspnea; hoarseness; vocal cord dysfunction; voice disorders

FOR EDITORIAL COMMENT SEE PAGE 613

ABBREVIATIONS: CAPE-V = Consensus Auditory Perceptual Evaluation Voice; C5dose = cough reflex sensitivity at C5; CRC = chronic refractory cough; DSI = Dysphonia Severity Index; LCQ = Leicester Cough Questionnaire; LHQ = Laryngeal Hypersensitivity Questionnaire; PLAC = placebo; PREG = pregabalin; QOL = quality of life; SP = speech pathology; SPT = speech pathology therapy; UTC = urge to cough; VAS = visual analog scale; VHI = Voice Handicap Index

AFFILIATIONS: From the Speech Pathology Department (Dr Vertigan and Ms Kapala and Prof Gibson), John Hunter Hospital, Hunter New England Health, Newcastle, Australia; Centre for Asthma and Respiratory Diseases (Dr Vertigan, Ms Kapela, and Prof Gibson), School of Medicine and Public Health, Hunter Medical Research Institute, The University of Newcastle, New South Wales, Australia; University of Newcastle (Drs Vertigan and McElduff and Prof Gibson), Newcastle, Australia;

Cough that is refractory to systematic assessment and medical management based on the anatomic diagnostic protocol occurs in up to 46% of referrals to specialty cough clinics.[1] Patients with chronic refractory cough (CRC) have marked hypersensitivity of the afferent limb of the cough reflex[1] and have features of central sensitization such as hypertussia, allotussia, and laryngeal paraeasthesiae.[2-4]

Treatment approaches for CRC include speech pathology (SP) treatment (SPT),[5] cough suppression therapy,[6] and centrally acting neuromodulatory drugs such as gabapentin[7] and morphine.[8] These therapies are limited by incomplete resolution of cough and cough recurrence once treatment is stopped.[7] Significant treatment-related adverse effects can also prevent dose escalation of neuromodulatory therapies; however, pregabalin (PREG) may be better tolerated in CRC than gabapentin because it can be prescribed in lower doses.[9] Additionally, although SPT reduces cough reflex hypersensitivity,[10] the neuromodulators do not improve this aspect of cough pathophysiology.[7,8,11] This suggests that neuromodulators and nonpharmacologic approaches act on different but potentially complementary aspects of the cough pathway in CRC. Therefore, we used a randomized controlled trial to test the hypothesis that a combination of SPT and neuromodulatory pharmacotherapy would lead to improved efficacy and complementary benefits on the cough mechanism compared with the individual therapies alone.

Methods

This study was a randomized, double-blind, placebo (PLAC)-controlled trial that was approved by the Hunter New England Research Ethics Committee (approval number 11/11/16/3.04) and registered with the Australian and New Zealand clinical trials register (12611001186943). All participants gave written informed consent.

Participants

Inclusion criteria were age between 18 and 80 years and unexplained cough (ie, no associated diagnoses) or refractory cough (ie, cough that persisted after treatment of associated diagnoses of asthma, rhinitis, gastroesophageal reflux disease, angiotensin-converting enzyme inhibitor use). Exclusion criteria included cough productive of purulent sputum, current smoking, pregnancy/breast-feeding, other active respiratory disease, respiratory tract infection during the month before randomization, significant psychiatric or neurologic disorder, and previous SPT for cough or dysphonia within the past 12 months. Previous medical treatment for cough was assessed and patients who had not completed their treatment were excluded from the study until they had appropriate investigations and treatment.

Procedure

Participants attended seven study visits (Fig 1). Visit 1 was a screening visit. Visit 2 involved assessment and randomization in which eligible participants were randomly allocated to combined SP + PREG (maximum dose 300 mg/day; Table 1) or combined SP + PLAC for 14 weeks. Visits 2 to 6 were treatment visits. Pharmacological treatment was tapered following visit 6. Visit 7 was a follow-up visit conducted when off treatment. In addition, all patients received five sessions of SPT for chronic refractory cough (visits 2-6), as previously described.[5] Medication adherence was assessed by tablet counts at each session and medication diary review. SPT was provided by two speech pathologists with previous experience treating CRC. A standardized SPT treatment program was used (see e-Appendix 1).[5]

Randomization and Blinding

We used concealed random allocation and double-blind pharmacotherapy. The randomization list was generated by the data manager using the Randomization Generator Software (Randomization Generator Version 1.0, Jonathan Goddard, Medical Statistics, Health Care Research Unit, University of Southampton, UK). Treatment was randomized using permuted blocks of six with stratification according to sex. Pregabalin and matching PLAC capsules were prepared and packaged into identical bottles (Stenlake Pharmaceuticals). The hospital pharmacy dispensed the study medication to participants. Matching PLAC capsules contained lactose and aluminium potassium sulphate to provide a matching bitter taste. The investigators had no access to the randomization schedule during the study. Both participants and investigators were blinded to the intervention.

Outcome Measures and Data Analysis

The outcome assessments for cough were cough-related QOL using the Leicester Cough Questionnaire (LCQ),[12] cough severity using a cough visual analog scale (VAS),[13] 24-hour cough frequency using the Leicester Cough Monitor[14] capsaicin cough reflex sensitivity,[15] and the patient's rating of their urge to cough using the urge to cough scale[16] at the end of cough reflex sensitivity testing. Capsaicin concentration ranged from 0.98 to 500 μM in doubling doses. Outcome measures for laryngeal function included the Laryngeal Hypersensitivity Questionnaire (LHQ),[17] Voice Handicap Index (VHI),[18] Consensus Auditory Perceptual Evaluation Voice (CAPE-V),[19] and Dysphonia Severity Index (DSI)[20] (e-Table 1).

The geometric mean value of each outcome and 95% CI were calculated at each time point and are presented as high-low-close graphs. Change in each outcome was calculated for posttreatment (visit 6) and follow-up (visit 7) as change from the pretreatment value (visit 2) and is presented graphically as mean and 95% CIs.

Department of Toxicology & Pharmacology (Dr Ryan), The University of Newcastle, Calvary Mater Newcastle, Newcastle, Australia; Department of Respiratory & Sleep Medicine (Prof Gibson), John Hunter Hospital, Newcastle, Australia; and Division of Asthma, Allergy and Lung Biology (Dr Birring), King's College Hospital, London, England.

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CORRESPONDENCE TO: Anne E. Vertigan, PhD, Speech Pathology, John Hunter Hospital, Locked Bag 1, Hunter Region Mail Centre, NSW, 2310, Australia; e-mail: anne.vertigan@hnehealth.nsw.gov.au

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