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Antitussive effect of carcainium chloride in patients with chronic cough and idiopathic interstitial pneumonias: A pilot study

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ABSTRACT

Background: Cough is a common presenting symptom in patients with idiopathic interstitial pneumonia (IIP); it is often disabling, and lacks effective treatment. Studies in animals suggest that carcainium chloride, a quaternary derivative of the local anesthetic lidocaine, is able to inhibit experimentally induced cough by a mechanism of action distinct from that of lidocaine.

Objective: To determine the effectiveness of aerosolised carcainium chloride (VRP700) in controlling cough in patients with IIP.

Methods: Eight female patients (mean age 71 years) with IIP were investigated in a double blind, randomised, placebo controlled crossover, adaptive contingency study design (EudraCT Number 2010-021350-19). The study consisted of a screening visit to assess the eligibility of patients, and two separated (48–72 h) study days. On the two study days, patients were randomised to receive either nebulized VRP700 (1.0 mg/kg) on the first study visit followed by nebulised placebo (sodium chloride 0.9%) on the second visit, or placebo on the first visit followed by VRP700 on the second visit. The primary endpoint was cough frequency over a 4-h assessment period; secondary endpoints were subjective cough-related level of discomfort as assessed by a visual analogue scale (VAS) and the subjective response to treatment as assessed by a quality of life question. Safety (ECG, spirometry, urine and blood tests) and adverse events occurring during the trial were also investigated.

Results: In all patients both VRP700 and placebo decreased cough frequency; however, mean decreases in cough frequency after treatment with VRP700 were significantly ($P < 0.001$) higher than with placebo. Similarly, mean reductions in VAS score were significantly ($P < 0.001$) higher after treatment with VRP 700 compared with placebo. All but one patient indicated that they felt better after receiving VRP700. No adverse events were reported during the study, nor were any changes in ECG variables, spirometry, urine and blood tests noted.

Conclusion: The results of this exploratory study indicate that nebulised VRP700 improved cough and quality of life in hospitalised IIP patients with no significant side effects. A larger trial is warranted to assess these promising results.

1. Introduction

Chronic cough remains a serious unmet medical need [1,2]. Cough is a nerve reflex involving the activation of vagally innervated receptors ultimately resulting in cough motor events [3]. Receptors (sensors) implicated in the cough reflex have been found on families of both thin myelinated (Aδ) and unmyelinated bronchial and pulmonary C sensory nerve fibres [4,5] Not surprisingly, therefore, local anaesthetics can inhibit coughing presumably via

Abbreviations: Cph, coughs per hour; IIP, idiopathic interstitial pneumonia; C_{max}, maximum plasma concentration; T_{max}, time to reach maximum plasma concentration; VAS, visual analogue scale.

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inhibition of conduction of these sensory nerve fibers [6], but they are known to interfere with other important protective reflexes such as the gag reflex [7], limiting their wider use in the clinic.

Carcainium chloride, that is structurally related to the local anaesthetic lidocaine [8], has been reported to reduce cough responses in guinea pigs and rabbits by selective inhibition of Aδ fibres when applied topically to the airways, whilst having no inhibitory effect on bronchial or pulmonary C-fibres, which were both inhibited by topical lidocaine [9]. To our knowledge, this selectivity for Aδ fibres has not been reported so far for other drug classes. However, to date no studies investigating the effect of inhaled carcainium chloride on cough responses have been reported in humans.

This pilot study, therefore, aimed to investigate the effectiveness of inhaled carcainium chloride (hereafter named VRP700) in controlling cough of patients with idiopathic interstitial pneumonia (IIP) [10]. Patients with IIPs were chosen since cough is a distressing and disabling symptom of this disease [10].

2. Methods

2.1. Study design and participants

This was a randomised, double blind, crossover, placebo controlled study performed according to an adaptive contingency design [11]. We enrolled adult, non-smoking inpatients with IIP and refractory chronic cough [12]. We excluded patients who reported <1 month respiratory tract infections, who were taking an angiotensin-converting enzyme inhibitor, or who had liver or renal dysfunction. Women breastfeeding or of childbearing age were also excluded. Written consent was obtained from each patient; the study was approved by the Ethics Committee of the Careggi Hospital (EudraCT number 2010-021350-19).

2.2. Protocol and recording procedures

After screening, each patient was examined on two separate (48–72 h) occasions (Fig. 1). On each occasion, patients randomly inhaled 1.0 mg/kg VRP700 or placebo (sodium chloride 0.9%) by means of a DeVilbissUltraNeb 3000 nebuliser set to produce 2 mL/min of aerosol. Administration continued until nebulisation occurred; a ~1.2 mL residue remained in the nebuliser cup after each nebulisation. After study completion, patients were followed up for a further 12–24 h. On all occasions, the cough frequency was recorded at baseline and for 4 h after the completion of each inhalation period by means of a cough recorder (PulmoTrack® 2010 W-Holter, Karmelsonic) [13] and expressed as coughs per hour (cph). Cough-related level of discomfort was investigated by a 10-cm visual analogue scale (VAS), with the extremes indicating no discomfort (0 cm) or extreme discomfort (10 cm). Patients' subjective response to treatments was also assessed 4 h post treatment asking the patients: "how do you feel: worse, same or better following treatment?" Similarly, physicians' judgement (i.e. superior, same, inferior) of individual patient responses in terms of anti-tussive actions compared to baseline was also obtained. Vital signs, ECG and spirometry variables were recorded at baseline and 15, 20, 40, 60, 90, 120 min, 3 and 4 h after drugs administration. Concomitant medication changes and adverse events were reported. Blood and urine samples were collected for standard safety laboratory assessments; blood samples were also taken at baseline, at 20, 40, 60, 90, 120 min and 3, 4 h after VRP700 inhalation to calculate the maximum plasma concentration (C_{max}) and time to reach C_{max} (T_{max}) [14].

2.3. Data analysis

The primary outcome variable was cough frequency over a 4-h assessment period measured before and after VRP700 and placebo administration; secondary outcome variables were VAS scores, patients' subjective response and physicians' judgement. Categorical data were expressed as percentages, whereas normal distributed data were presented as mean ± SD. For efficacy parameters, all tests for a difference between the two treatments have been two-sided and performed at the 5% significance level.

3. Results

Eight female patients (Table 1) completed the study with no significant changes in vital signs, ECG variables, spirometry, as well as in any parameters measured in blood or urine. Preliminary CT scans indicated that six patients suffered from usual interstitial pneumonia, one had non-specific interstitial lung disease, and another one had an unclassifiable IIP. No patients reported adverse events during the study. However, they consistently coughed more during the 1st or 2nd minutes of nebulisation of active drug, followed by a marked decrease in cough over the rest of nebulisation period. As the cough monitor was not started until after inhalation had completed, these initial coughs have not been recorded.

In the patients as a group, C_{max} for VRP700 ranged from 2.26 to 37.7 ng/mL with a T_{max} of 20 min.

VRP700 significantly decreased cough frequency from 57.75 ± 15.51 cph to 13.13 ± 9.62 cph 4 h after VRP700 administration ($p < 0.001$, Fig. 2). With placebo, the same variable decreased from 46.06 ± 10.70 cph to 37.38 ± 19.34 cph (NS).

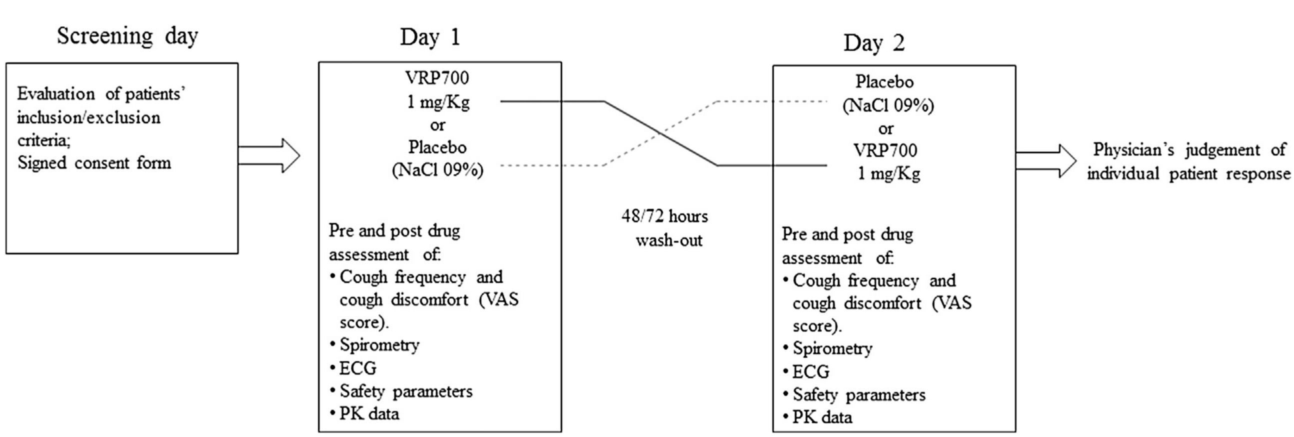

Fig. 1. Study flow chart. PK, pharmacokinetic; See text for details.