CORRESPONDENCE

Angiotensin II blockers in obstructive pulmonary disease: a randomised controlled trial

To the Editors:

In a recent issue of the *European Respiratory Journal*, ANDREAS *et al.* [1] explored the effect of the angiotensin II type-1 receptor blocker irbesartan on skeletal and respiratory muscle strength in Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III and IV chronic obstructive pulmonary disease (COPD) patients.

Although I agree that there is only sparse evidence of any systemic or pulmonary effect of angiotensin-converting enzyme (ACE) inhibitors in COPD, there are some indications that increased rennin–angiotensin system activity may contribute to the pathogenesis and progression of COPD. Captopril, at a dose of 25 mg, is associated with lower exertional pulmonary artery pressure, lower pulmonary vascular resistance, higher mixed venous oxygen saturation, and lower lactate levels in selected COPD patients [2]. In several studies, KANAZAWA and co-workers [3–5] demonstrated that these effects might be ACE genotype dependent. Based on the presence (insertion) or absence (deletion) of some alleles, they demonstrated that increased pulmonary arterial pressure is associated with the angiotensin deletion allele, which was confirmed by an independent Slovakian group [6]. The deletion allele is also associated with greater quadriceps strength in COPD patients [7].

So if we want to study the effects of angiotensin-converting enzyme blockers on the exercise capacity in chronic obstructive pulmonary disease patients, we should not only power the study to detect modest changes in maximal oxygen uptake, but also stratify for angiotensin-converting enzyme gene polymorphism as this could potentially effect the oxygen delivery to the working muscle.

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From the authors:

I would like to thank M. Meysman for raising the interesting aspect of the angiotensin-converting enzyme (ACE) genotype in chronic obstructive pulmonary disease (COPD) patients. I fully agree that the activation of the rennin–angiotensin system is likely to contribute to inflammation, cachexia, pulmonary hypertension and skeletal muscle dysfunction in COPD [1]. M. Meysman cited interesting studies by KANAZAWA and co-workers [2, 3] and HOPKINS *et al.* [4] pointing to an effect of the ACE genotype on pulmonary hypertension and muscle strength in COPD patients.

My study group evaluated the effects of an angiotensin-receptor blocker in patients with COPD and found no significant effect on the primary end-point, maximum inspiratory pressure. However, total lung capacity and haematocrit were affected [5]. It was reasoned that well-known cardiovascular drugs can produce unanticipated effects in COPD patients. Pulmonary haemodynamics were not evaluated because this was a noninvasive study. However, echocardiography was used without noticing a significant effect of angiotensin I inhibition on right ventricular dimension. Furthermore, the rennin–angiotensin system is unlikely to be a major determinant of pulmonary vascular pathology in therapeutic trials [6].

Albeit it must be acknowledged that there is a clear benefit of angiotensin-converting enzyme and angiotensin I inhibition in

large randomised cardiovascular trials, pharmacogenomics probably help to improve individual tailored therapy. Thus, I value the suggestion to assess the effect of angiotensin-converting enzyme genotype in further therapeutic studies on chronic obstructive pulmonary disease patients.

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Delirium induced by clarithromycin in a patient with community-acquired pneumonia

To the Editors:

We would like to describe the case of a patient who was treated with clarithromycin for community-acquired pneumonia (CAP). She presented with an episode of agitation and delirium while taking the clarithromycin, but this disappeared when the clarithromycin was stopped. This case is interesting because of the low frequency of symptoms of the central nervous system during the treatment.

The patient was a 63-yr-old female, with pathological history of arterial hypertension. She was treated with angiotensin-converting enzyme inhibitor and a pacemaker for atrial block and had no previous psychiatric history. The patient went to the emergency department in a poor general state; she had had a fever for 7 days and developed chills. Once at home, she was treated with paracetamol. A physical examination revealed a fever (39°C), blood pressure of 120/60 mmHg and heart frequency of 70 beats·min⁻¹. She had crepitations at the left hemithorax and cardiac arrhythmic tones without left ventricular failure. The abdomen was not painful and neurological examination was normal. The right thorax showed an alveolar pattern of the superior lobe in the left lung. The analytical results were as follows: glucose 104 mg·dL⁻¹; creatinin 0.91 mg·dL⁻¹; aspartate aminotransferase 118 UI·L⁻¹; sodium 140 mEq·L⁻¹; potassium 4.6 mEq·L⁻¹; leukocytes 6,200·μL⁻¹; haemoglobin 10.9 g·dL⁻¹; and platelets 265,000·μL⁻¹. The arterial blood gas results were: pH 7.57; carbon dioxide tension 4.38 kPa; partial pressure of oxygen 10.37 kPa; and HCO₃ 24 mEq·L⁻¹.

The ECG showed an atrial fibrillation. The diagnosis was severe CAP and the patient was treated with 2 g intravenous ceftriaxone every 24 h and 500 mg intravenous clarithromycin

every 12 h. The patient also received sodium heparin for the atrial fibrillation. On the third day of treatment, the patient presented with an acute episode of agitation and delirium, which required administration of antipsychotics (haloperidol). A cranial computed tomography (CT) scan was carried out, which didn't show any alterations. The current authors suspected that the delirium was induced by clarithromycin as when treatment with the drug ceased the symptoms disappeared. The patient was observed by the psychiatric service and was diagnosed with delirium induced by clarithromycin in resolution phase. The patient presented with good evolution of CAP and outside hospital control she was asymptomatic.

Clarithromycin is an antibiotic belonging to the macrolide family with a structural ring of 14 atoms. The bacterial effect of the macrolides is due to the inhibition of protein synthesis, and the ability to administer it orally and intravenously. Clarithromycin is metabolised by hepatic metabolism and the majority is eliminated biliary, in faeces and in a smaller portion in urine. It is active against Gram-positive cocci, *Legionella* and *Chlamydia* and is indicated in the treatment of severe CAP associated with cephalosporin (cefotaxime or ceftriaxone) [1].

Adverse effects of clarithromycin in the central nervous system include dizziness, ototoxicity and headaches, but delirium is very uncommon with few cases being reported in previous literature. In our case, it is obvious that there is a relationship between delirium and clarithromycin as the patient did not have any psychiatric history and delirium disappeared completely when the drug was removed. Other delirium causes were also excluded as the neurological exploration did