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Concurrent coxibs and anti-platelet therapy unmasks aspirin-exacerbated respiratory disease

To the Editor:

Aspirin-exacerbated respiratory disease (AERD) is a clinical tetrad of chronic hypertrophic eosinophilic sinusitis, nasal polyps, asthma and sensitivity to any medication that inhibits cyclooxygenase (COX)-1, namely aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) [1].

The final metabolites of the degradation of arachidonic acid *via* COX-1 pathway are thromboxanes, prostacyclin and prostaglandins (PG); the most crucial ones are PGE_2 and PGD_2. According to the classical ''cyclooxygenase'' hypothesis, inhibition of COX-1, but not COX-2, triggers various mechanisms leading to asthmatic and/or nasal symptoms in AERD patients. The central mechanism was regarded as the deprivation of PGE_2 as a consequence of COX-1 inhibition, which would lead to an even more increased local and systemic generation of cysteinyl leukotrienes (LT). The overproduction of cysteinyl LT, due to upregulation of LTC_4 synthase and/or cysteinyl LT receptors in the airways, the hallmark of the disease, occurs at baseline as well, although at a much lower degree than after aspirin/NSAIDs intake [2].

After the introduction of the selective COX-2 inhibitors, casually referred to as coxibs, several well-designed studies reported the excellent safety profile of these new NSAIDs in patients with AERD [3, 4]. Nevertheless, shortly afterwards, as the use of coxibs extended, so did the number of case reports warning the clinicians that some AERD patients may not tolerate coxibs [5, 6]. In fact, all the position papers and updates on AERD evaluation and management recommend giving the first full dose of these drugs in the physician's office [7].

A recent study by Daham *et al.* [8] proposes a theory that might explain the underlying mechanism. These authors demonstrate that biosynthesis of PGD_2 (bronchoconstrictor and pro-inflammatory mediator) in patients with asthma (of which one-third had AERD), is increased at baseline, catalysed by constitutive COX-1 only, and is not inhibited by a short 3-day treatment with celecoxib. Meanwhile, whole body formation of PGE_2 (bronchodilator and anti-inflammatory) is predominantly COX-2 dependent and decreases progressively, with a reduction of $>50\%$ as compared to baseline, during coxib treatment.

Although none of the AERD patients in this study experienced bronchoconstriction throughout the coxib treatment, COX-2 inhibition definitely had a much lesser impact on the decrease in bronchoconstrictory PGD_2 than on protective PGE_2, thus creating an imbalance in the airway homeostasis, which seems to be generally well tolerated by most AERD patients, except perhaps for the small subset of them who do react to selective COX-2 inhibitors in real life. This minority supposedly includes those AERD patients suffering from a more severe form of the disease [1], and/or associating other pathogenic features, such as a reduced expression of the PGE_2 receptor E-prostanoid-2 on bronchial mucosal leukocytes [9], but the mechanisms underlying coxibs intolerance are not yet completely understood. Of course in real life nonselective COX inhibitors inhibit both COX-1 and -2 in a dose- and potency-dependent fashion, and other mechanisms, such as mast-cell degranulation, are involved, thus inducing reactions in all AERD patients [1, 2].

We herein report on an unusual case of AERD that supports and illustrates this hypothesis. The patient is a 75-year-old male with personal history of hypertension, dyslipidaemia and a stroke in 2001, for which he has been receiving treatment with acetylsalicylic acid (ASA) 100 mg per day. In 2006 he started to complain of perennial nasal congestion and occasional hyposmia, and has been followed up ever since by an ear, nose

TABLE 1 Oral challenge protocols

Meloxicam		
Day 1	3.75 mg; 7.5 mg	120-min interval
Day 2	15 mg	
Etoricoxib	30 mg; 60 mg	90-min interval

and throat specialist who recommended treatment with intranasal corticosteroids, with mild improvement. The allergological work-up revealed no sensitisation to common aeroallergens. Up until now, nasal polyps have never developed. The patient is a nonsmoker and, except for the isolated episodes further described, he has never experienced any asthma-like symptoms. The patient was referred to our Allergy Department (Hospital Universitario La Paz Institute for Health Research (IdiPaz), Madrid, Spain) in January 2011 because his GP had prescribed him dexketoprofen-trometamol 25 mg three times per day and omeprazole 20 mg per day in December 2010 for low back pain. He noted nasal congestion, dysphonia, dry cough, shortness of breath, chest tightness and wheezing 2 h after taking the first dose of dexketoprofen. The emergency room examination showed tachypnoea (respiratory frequency 22 breaths per minute), wheezing and mild hypoxia (arterial oxygen saturation 92%). His condition gradually improved after treatment with salbutamol 2.5 mg per nebuliser and hydrocortisone sodium phosphate 200 mg intravenously. He was discharged 3 h later. Afterwards, he continued his usual treatment with ASA 100 mg and omeprazole 20 mg per day, remaining asymptomatic, and took paracetamol 650 mg for his back pain, which was well tolerated.

On the first appointment in our department the spirometric parameters were normal (forced vital capacity (FVC) 3.68 L (97%), forced expiratory volume in 1 s (FEV_1) 3.12 L (109%) and FEV_1/FVC 85%), and no changes after inhalation of salbutamol metered dose inhaler 400 µg were observed. The diagnosis of AERD seemed somehow doubtful, especially with the patient tolerating daily ASA. Subsequently, an oral challenge with meloxicam was programmed. Our usual challenge protocols are detailed in table 1. On the day of the challenge, physical examination and lung function were normal at baseline; therefore, 3.75 mg of meloxicam was administered. 30 min later, the patient reported nasal congestion, chest tightness, dyspnoea and then started to cough. Pulmonary auscultation revealed bilateral wheezing, and an 8% drop in FEV_1 was observed. He was treated with salbutamol 200 µg metered dose inhaler which was administered with an inhaler spacer device. 15 min later, as the symptoms did not subside, the dose of short-acting β_2-agonist was repeated and 100 mg of hydrocortisone sodium phosphate were administrated intravenously, with clinical and spirometric improvement within 1 h. Even though the drop in FEV_1 was $<$15%, the clinical picture was pretty convincing, bearing in mind that this is not an asthmatic patient, so we stopped meloxicam and scheduled an oral challenge with etoricoxib 1 month later. After recording normal baseline conditions, 30 mg of etoricoxib were administered and 45 min later the patient experienced the same symptoms mentioned above, evidencing again bilateral dispersed wheezing and a fall in FEV_1 of 12%. We eventually diagnosed him with AERD and, given that his rhinitis was mild and the risk of new vascular events was high, we decided to maintain the anti-platelet therapy with ASA of 100 mg per day, recommending paracetamol or tramadol and the rest of the opiates for analgesia.

This is an uncommon case of AERD, not only because of its late onset, but also since we seem to be dealing with an ''extra-mild'' form of the disease one would expect this patient to tolerate coxibs. Even more so, the patient tolerated low doses of ASA and only had bronchospasm when challenged with coxibs (except of course for the original episode with dektetoprofen, not surprising *a posteriori*), while usually this occurs the other way around, due to accidental self-administration of over-the-counter NSAIDs. It appears that he tolerated his chronically decreased PGE_2 production due to the daily treatment with low doses of ASA, but the equilibrium was disrupted when the COX-2 inhibitors additionally diminished the biosynthesis of PGE_2, leaving the lower airway without any protection against cysteinyl LT [2]. Maybe if ASA was suspended, this patient might tolerate coxibs; nevertheless, we consider that this case brings us a small step closer to understanding the complex mechanisms of aspirin hypersensitivity, which still remain unclear despite over 30 years of intensive research.

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Oral challenge with coxibs diagnosed an "extra-mild" AERD subphenotype in a patient tolerating 100 mg of aspirin http://ow.ly/nPVko

Irina Bobolea[1], Rosario Cabañas[1], Jesús Jurado-Palomo[2], Ana Fiandor[1] and Santiago Quirce[1]
[1]Dept of Allergy, Hospital La Paz Institute for Health Research (IdiPAZ), Madrid, and [2]Dept of Allergy, Nuestra Señora del Prado General Hospital, Talavera de la Reina, Spain.

Correspondence: I. Bobolea, Dept of Allergy, Hospital Universitario La Paz, Paseo La Castellana 261, 28046 Madrid, Spain. E-mail: irinabobolea@yahoo.com

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The safety and feasibility of the inhaled mannitol challenge test in young children

To the Editor:

The mannitol challenge is an indirect challenge that increases airway surface liquid osmolality resulting in bronchoconstriction [1, 2]. Mannitol challenge tests are used clinically to diagnose asthma and, in particular, exercise-induced broncoconstriction (EIB) in adults and children above 6 years of age [3]. To date, mannitol has not been used as a challenge agent in children under 6 years of age and the feasibility and safety of its use in this age group is unknown.

The assessment of bronchial responsiveness in young children is difficult and limited by the cooperation of the child. The standardisation of lung function tests suitable for use in young children, such as the interrupter technique or the forced oscillation technique (FOT), provide an opportunity to assist in the assessment of bronchial responsiveness in young children and a variety of challenge tests using FOT have been reported in young children [4].

The aim of this preliminary study was to assess the feasibility and safety of the mannitol challenge test in young children using the FOT as the objective outcome measure.

20 children aged 3–7 years were recruited; 10 of these children were healthy and 10 children had a history of parentally reported exercise-induced symptoms (EIS) in the past year. The mannitol challenge test (Aridol; Pharmaxis, Frenchs Forest, Australia) was performed as previously published [2], with the exceptions that the respiratory resistance at 8 Hz (R_{rs8}) from the FOT was used as the primary outcome and the definition of a positive response was altered, as detailed below.

Prior to the mannitol challenge test the children were trained on the use of the mannitol dry powder inhaler using an inspiratory flow meter (In check; Clement Clarke International, Harlow, UK) configured to ensure that inhalation ranged between 30 and 50 $L \cdot min^{-1}$ to optimise deposition of mannitol. An examination including chest auscultation, baseline heart rate (HR), arterial oxygen saturation measured by pulse oximetry (S_{pO_2}) and lung function using FOT (I2M; Chess Medical; Ghent, Belgium) was performed in all children. During the mannitol inhalation challenge FOT was performed 1 min after each stage and 15 min after salbutamol inhalation at the end of the challenge. For baseline, control and post-salbutamol