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Response to salbutamol in patients with mild asthma treated with nadolol

To the Editors:

β -blockers (inverse agonists) have an exactly opposite effect to β_2 -adrenoceptor (β_2 -ADR) agonists and are currently contraindicated in asthma. This results from the fact that the acute administration of these drugs can produce bronchoconstriction by blocking the bronchodilating effects of endogenous adrenaline, or by inactivating constitutively active β_2 -ADRs, and can worsen asthma symptoms [1]. In fact, published accounts have shown that acute β -blocker use can, but will not always, precipitate airway constriction in patients with asthma [2]. Nevertheless, there are compelling uses of β -blockers in asthmatics, such as in heart failure and after myocardial infarction. The effect of chronic administration of β -blockers in asthma has remained unknown until recently, when studies on a murine model of asthma showed that, while acute (single-dose) administration of β -blockers increased airway hyperresponsiveness (AHR), their chronic (28-day) administration had an opposite effect and decreased AHR [3]. Furthermore, recent data demonstrate that chronic β -blocker treatment produces broad anti-inflammatory effects, and especially dramatic effects on airway epithelium and mucous metaplasia [4, 5]. More recently, our group has further confirmed the pivotal role that β_2 -ADR has on mucous metaplasia using a β_2 -ADR null mouse [6]. Based on these findings in the murine asthma model, we investigated the role of chronic administration of

nadolol (a non-selective β_1 - and β_2 -blocker) on airway hyperresponsiveness in an open-label study of 10 subjects with mild asthma [7]. We demonstrated that nadolol produced a dose-dependent increase in the PC₂₀ (provocative dose causing a 20% fall in forced expiratory volume in 1 s (FEV₁)) methacholine when administered over 11 weeks. However, a concern that remained is whether these subjects treated with nadolol can still respond to short-acting β_2 -ADR agonists for rescue of bronchospasm [8]. In fact, one concern is that nadolol “may block bronchodilation produced by endogenous or exogenous catecholamine stimulation of β_2 receptors” (Corgard[®] product insert; King Pharmaceuticals, Inc., Bristol, TN, USA).

We have now completed our second open-label study of chronic nadolol in subjects with mild asthma who are not on controller therapy (n=10) (table 1). Both studies were approved by the Baylor College of Medicine Institutional Review Board (Houston, TX, USA) and informed consent was obtained from all subjects. Starting at a daily dose of 1.25 mg and ending at a maximum daily dose of 40 mg, nadolol dose was escalated on a biweekly basis based on predetermined safety, lung function, asthma control and haemodynamic parameters. Subjects were treated for a total of 13 weeks with nadolol (≥ 3 weeks on their final tolerated dose). Seven out of the 10 subjects were able to be escalated to 40 mg, one tolerated

TABLE 1 Baseline demographics and characteristics of study population

Subject no.	Sex	Age yrs	Race	Baseline FEV ₁ %	Baseline PC ₂₀	Final dose mg
1	F	48	Black	84	3.576	40
2	F	24	White	98	3.621	40
3	F	48	White	88	1.225	5
4 [#]	M	27	Hispanic	81	3.479	1.25
5	F	49	Hispanic	86	0.112	40
6	F	28	Black	99	2.11	10
7	M	29	White	83	0.349	40
8	F	26	Hispanic	91	0.471	40
9	F	18	Asian	83	0.372	40
10	F	29	White	114	6.418	40
Mean $\pm$ SEM		32.6 $\pm$ 3.6		90.7 $\pm$ 3.3	1.18 [†] $\pm$ 1.53 ⁺	29.6 $\pm$ 6

[#]: subject excluded because of an asthma exacerbation early in the study; [†]: geometric mean; ⁺: geometric SEM.

FIGURE 1. The effect of chronic treatment with nadolol on the PC₂₀ (provocative dose causing a 20% fall in forced expiratory volume in 1 s) metacholine in subjects with mild asthma. Data are shown for baseline visit and final visit. Final nadolol doses used for subjects based on dose-escalation are shown. Geometric mean $\pm$ SEM are shown ($\square$ and whiskers, respectively). $\bullet$: 40 mg nadolol (n=7); $\blacksquare$: 10 mg nadolol (n=1); $\blacktriangle$: 5 mg nadolol (n=1). Comparisons between V0 and V10 values were performed using paired t-tests. *: $p < 0.05$.

a 10-mg daily dose and one tolerated a 5-mg daily dose. One subject was excluded from the study because of an asthma exacerbation early in the study while on a dose of 1.25 mg. As demonstrated in our first study [8], we were able to show a significant effect on airway hyperresponsiveness with chronic nadolol dosing (fig. 1) with geometric mean $\pm$ SEM PC₂₀ at baseline and at final visit of 1.04 ± 1.54 and 3.61 ± 1.52 , respectively, and a doubling dose change $\pm$ SEM of 1.79 ± 0.44 ($p = 0.004$). No significant changes in lung function were observed (FEV₁ % predicted at baseline and final visit: 91.8 ± 3.4 and 87.1 ± 4.4 , respectively; $p = 0.165$). To address the effect of nadolol on the bronchodilator response to short-acting β_2 -ADR agonists, we evaluated the bronchodilator response after administering salbutamol by nebulisation (2.5 mg) immediately following methacholine challenge performed at the final visit in subjects from both studies (n=18). Spirometry was performed 20 min following salbutamol administration. As shown in figure 2, salbutamol was able to reverse methacholine-induced bronchoconstriction in all subjects who were on chronic treatment with nadolol.

Our study has several limitations. We studied steroid-naïve patients with mild asthma. In patients with severe disease and inflammation, it is unknown whether chronic nadolol treatment would also show a preserved response to β_2 -ADR agonists. In addition, it is not known whether the observed effects may be seen with the use of lower doses of salbutamol. While we believe that our findings can be explained by the high degree of inverse agonism of nadolol, future work needs to explore this further and compare these effects using β -blockers with different levels of inverse agonism.

In summary, we demonstrated that in subjects with mild asthma, chronic dosing with an inverse agonist, nadolol, is accompanied by attenuation of airway hyperresponsiveness, and administration of salbutamol is able to reverse methacholine-induced bronchoconstriction in these subjects. These findings suggest that β_2 -ADRs may not be completely blocked with

FIGURE 2. Response to salbutamol (2.5 mg by nebulisation) administered after methacholine challenge at final visit in subjects with mild asthma treated with nadolol from both studies (n=18). Forced expiratory volume in 1 s (FEV₁) % predicted values pre- and post-challenge and values 20 min following salbutamol administration (recovery) are shown. Mean values for each time period with 95% CI are also shown ($\square$ and whiskers, respectively).

chronic nadolol dosing, and are supportive of the data from patients with hypertension and anxiety, which suggested that the use of the β -blocker propranolol in these populations was associated with increased β_2 -ADR bronchodilating function contrary to that which would be expected [9, 10]. The significance of our findings, if confirmed in larger controlled trials, may provide a paradigm shift in the chronic management of asthma and in the way we view the pathology of asthma.

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Endobronchial metallic clips to guide high-dose external-beam radiotherapy in radio-occult lung cancer

To the Editors:

As a result of the increased sensitivity of videobronchoscopy (including narrow-band and video autofluorescence imaging) and a specific interest in surveillance of pre-invasive lesions, an increase in diagnosis of radiographically occult lung carcinoma (ROLC) can be anticipated. Described for the first time in the late 1970s by MARTINI and MELAMED [1] and in the early 1980s by CORTESE *et al.* [2], surgery still remains the treatment of choice for ROLC [3]. However, patients can be functionally inoperable due to comorbidity, advanced age, multiple primary lesions or irresectable, centrally localised tumours, or because they refuse surgery [2]. Therefore, varieties of endoscopic techniques, such as photodynamic therapy, cryotherapy, laser therapy, electrocautery and brachytherapy, were developed as alternatives to surgery [3–5]. The combination of high-dose external-beam radiotherapy (EBRT) with intraluminal radiotherapy (IR) using low [6–8], middle [9] and high dose-rate [10] iridium-192, has been investigated in ROLC with promising results. EBRT has obvious advantages to surgery, as it is less invasive and better tolerated by the patient. A major issue is, however, the localisation of the tumour for the guidance of EBRT, since these tumours are radiologically occult. Previously, in those studies combining EBRT with IR [6–10], localisation of tumour was determined under fluoroscopy using the tip of the bronchoscope. Radiation was given using small anterior-posterior opposed portals. Obviously, this is less reliable, precise and comfortable, as might be anticipated. To overcome this problem, we hypothesised that metallic clips, the same as used in gastroenterology to obtain haemostasis, could be used as beacons to locate the tumour during EBRT. In a post-operative setting, the same principle is often used to orient EBRT in incomplete resections. Radiation fields are collimated using metallic clips placed by the surgeon.

In a prospective pilot series (June–October 2008) we assessed the feasibility and safety of EZ-Clips HX 610-090 (Olympus, Aartselaar, Belgium) in inoperable patients with ROLC to

guide high-dose EBRT. The standard length of these clips is 6 mm when deployed, and when opened the angle of the jaws is 90° (fig. 1). Patient characteristics and tumour locations are summarised in table 1. All four patients were male, smokers with a median age of 68 yrs and fitted the criteria for ROLC as described by the Japan Society of Lung Cancer [8]. They underwent white light and autofluorescence video bronchoscopy (fig. 1) because of haemoptysis (case 1), persistent infiltrate (case 2), screening for second primary (case 3) and persistent cough (case 4). Pathology of the endobronchial biopsies was invasive squamous cell carcinoma for all patients. One was staged cT2N0M0 and three were cT1N0M0. Staging was performed according to the 6th edition of the TNM (tumour, nodes, metastasis) Classification of Malignant Tumours [11]. Patients 1, 2 and 4 received brachytherapy with one fraction of 10 Gy at 1 cm from the catheter. Patient 3 did not receive endobronchial brachytherapy because of a concurrent supraglottic tumour. Before EBRT, the patients underwent a second bronchoscopy to place two endobronchial metallic clips: one on the proximal carina and one on the distal carina, relative to the ROLC (fig. 1). This was performed under local anaesthesia and was well tolerated by all patients. The time needed to place the clips was estimated to be no longer than an ordinary flexible bronchoscopy with biopsies. Although one clip loosened immediately after placement, it could be removed using biopsy forceps. No other complications occurred. As can be seen in figure 1, the clips are radiographically identifiable. The clips were used for delineation of the clinical target volume on the treatment planning system (fig. 1). In addition, the clips served as beacons facilitating the correct positioning of the patient with cone-beam computed tomography (CT) during hypofractionated radiation therapy (8 × 7.5 Gy EBRT).

3–4 weeks after EBRT, the patients underwent another bronchoscopy to remove the endobronchial clips by means of biopsy forceps. In cases 1 and 4, both clips were easily retrieved. In case 2, one of the clips was missing, and in case 3 both clips had disappeared. Thorough examination of all