

## $\beta$ blockers for asthma: a double-edged sword

The regulation of airway smooth muscle is balanced by sympathetic activity that produces relaxation and parasympathetic activity that produces constriction. Asthma was historically thought to be associated with an intrinsic defect of  $\beta_2$ -adrenoceptor function in airway smooth muscle that tipped the balance towards bronchoconstriction. Although acute exposure to  $\beta_2$ -agonists in people with asthma might induce beneficial bronchodilatory effects, chronic exposure can produce worsening of asthma control and airway hyper-responsiveness, with associated down-regulation and desensitisation of  $\beta_2$  adrenoceptors.<sup>1</sup>

$\beta$ -adrenoceptor antagonists ( $\beta$  blockers) are indicated for the treatment of cardiovascular diseases, including hypertension, ischaemic heart disease, and heart failure. They are contraindicated for patients with asthma because they can induce bronchoconstriction after acute dosing. This effect tends to be worse with non-selective drugs, such as propranolol or nadolol, which block both  $\beta_1$ -receptor and  $\beta_2$ -receptor subtypes, than with cardioselective drugs—ie, preferential  $\beta_1$  antagonists—such as atenolol or metoprolol which have less of a  $\beta_2$ -blocking effect.<sup>2</sup> Meta-analysis shows that single doses of cardioselective drugs significantly reduce forced expiratory volume in 1 s (FEV<sub>1</sub>) but, by contrast, chronic dosing does not cause such an effect or impairment of the acute response to salbutamol.<sup>3</sup>

Until recently,  $\beta$  blockers were contraindicated in heart failure because acute doses produced a deterioration in myocardial contractility and hence the possibility of tipping a patient into an acute decompensated state. Chronic dosing with  $\beta$  blockers

was subsequently shown to produce beneficial effects and reduce deaths in heart failure, and is now part of standard management guidelines.<sup>4</sup> This fundamental shift in thinking led to the proposition of use of  $\beta$  blockers for asthma—ie, a disconnect might exist between the beneficial effects with chronic dosing and negative effects with acute dosing. One cogent reason for use of  $\beta$  blockers in asthma was the known upregulation of  $\beta_2$  adrenoceptors with chronic dosing, by contrast with the downregulation and paradoxical worsening of asthma control that can occur with chronic exposure to  $\beta_2$  agonists.

Studies in ovalbumin-sensitised mice have shown that acute dosing with metoprolol or nadolol produced bronchoconstriction, whereas chronic dosing produced bronchoprotection against methacholine challenge—a cholinergic spasmogen which induces airway hyper-responsiveness<sup>5-7</sup> (panel). This bronchoprotective effect was associated with reduced inflammation and mucous metaplasia, upregulation of  $\beta_2$  adrenoceptors, and reduced expression of various spasmogenic proteins. These beneficial effects were thought to be mediated by the  $\beta_2$  adrenoceptor because they also occurred with the selective  $\beta_2$  antagonist ICI 118 581. Metoprolol, a preferential  $\beta_1$ -adrenoceptor antagonist, also conferred some bronchoprotection and associated  $\beta_2$ -adrenoceptor upregulation, which suggests that even a small amount of  $\beta_2$  blockade might be sufficient to elicit these benefits.

These findings in mice led to the first proof-of-concept open-label study from Nicola Hanania and colleagues in ten patients with mild steroid-naïve asthma (mean FEV<sub>1</sub> of 90%) who were given incremental doses of nadolol from 10 mg to 40 mg for 9 weeks in a chronic dosing protocol.<sup>8</sup> As expected, the first dose induced an acute fall in FEV<sub>1</sub>, but with chronic dosing this effect tended to ameliorate and airway hyper-responsiveness to methacholine challenge significantly improved (amounting to a 1.8 doubling-dilution shift in the PC20, the provocative dose of methacholine that leads to a 20% fall in FEV<sub>1</sub>). A 1–2 doubling-dilution shift in methacholine PC20 is about the same as would be achieved with inhaled corticosteroids or long-acting  $\beta_2$  agonists, and is also associated with reductions in exacerbations.<sup>9,10</sup>

### Panel: Effects of chronic nadolol in murine asthma model

- Reduced airway hyper-responsiveness to methacholine<sup>\*5,6</sup>
- Increased  $\beta_2$ -adrenoceptor density<sup>5,6</sup>
- Decreased total inflammatory cells and eosinophils<sup>7</sup>
- Decreased mucous metaplasia<sup>7</sup>
- Decreased mucin production<sup>7</sup>
- Decreased cytokines (interleukins 5, 10, and 13, and tumour growth factor  $\beta 1$ )<sup>7</sup>
- Decreased expression of phospholipase C- $\beta 1$ , phosphodiesterase 4D<sup>6</sup>

\*Also occurs in human beings with asthma.<sup>8</sup>

Ethical issues with respect to patients' safety need to be addressed, especially with the non-selective nadolol, before longer-term placebo-controlled studies can be started in patients with severe asthma. Patients exposed chronically to nadolol, even at low doses, might not respond to acute rescue therapy with salbutamol because of persistent  $\beta_2$ -adrenoceptor occupancy and antagonism.<sup>2,11</sup> A cardioselective drug, such as metoprolol, which possesses enough  $\beta_2$ -adrenoceptor antagonist activity to be effective but would be better tolerated on initial dosing than nadolol, might therefore be safer. One possibility might be to co-administer  $\beta$  blockers with a long-acting selective muscarinic type-3 receptor antagonist, such as tiotropium, which would theoretically prevent  $\beta$ -blocker-induced bronchoconstriction.<sup>12</sup>

Now is the time for taking the brave pills when trying to challenge current dogma and doing difficult clinical trials with  $\beta$  blockers for asthma—such pills might end up being the antagonists of  $\beta_2$  agonists.

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The Asthma and Allergy Research Group has received funding for clinical trials, postgraduate education, speaker's bureau, and consulting relating to asthma from AstraZeneca, Neolab, Cipla, Teva, Pharmaxis, Merck Sharp and Dohme, Nycomed, GlaxoSmithKline, Novartis, Schering Plough, Innovata, and Mundipharma.

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## International collaborative research on Charcot's disease

On Sept 17–18, the US National Institute of Diabetes, Digestive and Kidney Diseases and the Office of Rare Diseases of the National Institutes of Health hosted an international symposium on Charcot's disease of the foot (neuroarthropathy) in diabetes, in Bethesda, MD, USA. The intention was to bring together experts from different countries with the aim of promoting international collaboration to investigate the causes and best treatment of this uncommon, but potentially devastating, complication of diabetic neuropathy. Research has hitherto been hampered by the rarity of the condition, its protean manifestations, and the lack of any specific diagnostic marker. Indeed, it is a disease without even a formal definition, though it is one that is often easily recognisable by those with a high index of suspicion.

The timing is right, however, for such an initiative. Ideas concerning the causes of acute Charcot's disease were essentially stalled until the publication in *The Lancet* of a hypothesis suggesting that local inflammation played a key role in its development. Recognition of this hypothesis provided an explanation for clinical features which were superficially puzzling,<sup>1</sup> including the fact that the condition is both self-limiting as well as usually one-sided, whereas the underlying predisposing neuropathy is permanent and symmetrical. The suggested involvement of proinflammatory cytokines, such as tumour necrosis factor (TNF)  $\alpha$  and interleukin 1 $\beta$ , together with the RANKL-NF $\kappa$ B signalling pathway, also provided a potential explanation for the association of acute Charcot's disease with bone lysis and calcification of