CASE REPORT

Reversible bronchospasm with the cardio-selective beta-blocker celiprolol in a non-asthmatic subject

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Summary
Beta (β)-blockers are widely used in the treatment of cardiovascular disease but are well recognised for causing bronchoconstriction in asthmatic subjects. The third-generation cardio-selective β-blocker celiprolol is a selective β1-adrenergic blocking agent with β2-agonist properties and would therefore be a preferred β-blocker if an asthmatic subject required treatment with β-blockers for cardiovascular disease. We present the case of a 79-year-old man with ischaemic heart disease and hypertension but no preceding respiratory disease who developed significant bronchoconstriction on celiprolol, which resolved completely on drug cessation alone with no relapse of respiratory symptoms two years after cessation of treatment.

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Introduction
β-blockers are widely used in the treatment of cardiovascular disease, including hypertension, angina, myocardial infarction, arrhythmias and heart failure. β-blockers bind to β-adrenoceptors, thereby blocking the effects of epinephrine and norepinephrine. Some β-blockers, not only prevent binding of sympathoamines to the β-adrenoceptor but also partially activate the β-adrenoceptor, and are thus said to possess intrinsic sympathomimetic activity (ISA).

Early β-blockers are non-selective, in that they block both β-1 (cardiac) and β-2 (bronchial) adrenoceptors and can lead to unwanted β-2-blockade effects such as airflow obstruction. Newer β-blockers such as celiprolol are relatively cardio-selective but are not cardio-specific. Celiprolol additionally possesses vasodilator properties through blockade of vascular alpha-adrenoceptors.

Celiprolol has been widely reported as being non-bronchoconstrictive both in subjects with asthma and propranolol-induced bronchoconstriction.

We report a case of significant bronchospasm in a patient taking celiprolol with no previous history of airway disease, which resolved completely on cessation of the drug.

Case report
A 79-year-old man presented with a 3-year history of wheeze, especially at night. There was no dyspnoea or
He gave up smoking 30 years ago after 15 pack years’ consumption. He had ischaemic heart disease and hypertension, for which he took celiprolol 200 mg twice daily and had been for the preceding 10 years. There was no history of atopic disease, no family history of asthma and he had no occupational exposures.

Physical examination revealed a clear chest with normal breath sounds and no added sounds. Peak expiratory flow rate (PEFR) 274 L/min. Spirometry did not demonstrate airflow obstruction with forced expiratory volume in 1 s (FEV1) 2.04 L, forced vital capacity (FVC) 2.24 L (ratio 91%). Chest X-ray revealed a cardiothoracic ratio of 18/29 cm with clear lung fields.

A PEFR diary [Fig. 1(a)], whilst continuing celiprolol, showed a peak of 460 L/min and trough of 300 L/min (diurnal variation 35%). Following this observation, celiprolol was stopped and a repeat PEFR diary [Fig. 1(b)] was recorded after cessation of celiprolol for 3 months. This showed a peak of 460 L/min and trough of 420 L/min (diurnal variation 9%). Coincident with this improvement in PEFR was complete resolution of all respiratory symptoms. During a 2-year period of follow-up there was no recurrence of any respiratory symptoms.

**Discussion**

β-blocker induced bronchoconstriction in asthma is widely reported, even with the cardio-selective β-blocker atenolol. However, β-blocker induced bronchoconstriction in non-asthmatic subjects is exceedingly rarely reported and then, only with non-cardio-selective agents such as propranolol. To the best of our knowledge there are no reported cases of celiprolol-induced bronchoconstriction in non-asthmatic subjects. In fact, celiprolol has been widely reported as being non-bronchoconstrictive both in subjects with asthma and propranolol-induced bronchoconstriction.

What makes this case even more interesting is that celiprolol is regarded as providing a greater margin of respiratory safety than other cardio-selective β-blockers due to its β2 agonist and intrinsic sympathomimetic activity (ISA).

Celiprolol is a third-generation β-adrenoceptor blocker with selective β1-antagonist, partial β2-agonist and mild alpha-2-antagonist actions, with less risk of vasoconstriction, bronchoconstriction and myocardial depression due to
its ISA. Whilst not being previously described as causing bronchoconstriction, celiprolol is reported to cause hypersensitivity pneumonitis with a lymphocytic alveolitis, which resolves completely on celiprolol cessation.\textsuperscript{10}

When celiprolol is directly compared to another cardioselective \(\beta\)-blocker (atenolol) in asthmatic subjects, it has been shown that atenolol is associated with bronchoconstriction but that there is no difference in day-to-day asthma control, as judged by PEFR diary, inhaler use and symptom scores.\textsuperscript{7}

Our patient fulfilled the criteria for diagnosing asthma according to the British Thoracic Society/Scottish Intercollegiate Guidelines Network (BTS/SIGN) British guideline on the management of asthma 2008. There was significant diurnal variation in PEFR clearly demonstrated whilst taking celiprolol, which completely resolved on cessation of the drug. Follow-up for 2 years of celiprolol failed to demonstrate any recurrence of respiratory symptoms.

One common feature of most published data involving \(\beta\)-blocker usage in asthma is the relatively small number of patients recruited in each study, emphasising the need for a larger scale study in this area.

Conclusions

We present the first case of celiprolol-induced bronchospasm in a non-asthmatic subject, which resolved completely on celiprolol cessation alone. Although celiprolol is cardio-selective we would still urge caution and close observation for the development of respiratory adverse effects when initiating cardio-selective \(\beta\)-blockers, even in patients without a preceding history of Asthma.

We would also like to emphasise that the development of respiratory symptoms can be delayed, and hence the need to consider drugs in new onset respiratory symptoms.

Learning points

- \(\beta\)-blocker induced bronchospasm can develop in non-asthmatic patients even with cardio-selective agents such as celiprolol.
- The onset of adverse effects from \(\beta\)-blockers is not necessarily temporally related to the initiation of treatment.

Conflict of interest statement

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References