LETTERS TO THE EDITOR

RE: "RESPIRATORY ILLNESS, \(\beta\)-AGONISTS, AND RISK OF IDIOPATHIC DILATED CARDIOMYOPATHY: THE WASHINGTON, DC, DILATED CARDIOMYOPATHY STUDY"

In a recent paper, Coughlin et al. (1) sought to evaluate whether the association between asthma and cardiomyopathy is due to a causal effect of \(\beta\)-agonist therapy. They reported an association between \(\beta\)-agonists and cardiomyopathy, and concluded, "The results of this study suggest that use of \(\beta\)-agonists has an etiologic role in idiopathic dilated cardiomyopathy" (1, p. 395).

In drawing this conclusion, Coughlin et al. overlooked a simpler explanation for their findings. If asthma increases the risk of cardiomyopathy, it would follow that asthma therapies would also be associated with cardiomyopathy because of confounding by indication (i.e., asthma). Thus, after previously finding that asthma is related to cardiomyopathy (2), Coughlin et al. reported associations between cardiomyopathy and oral corticosteroids, Cromolyn, and theophylline medications, as well as \(\beta\)-agonists. In interpreting the association with theophylline, the authors reasoned: "The strong, persistent association with theophylline medications may be an indirect association since chronic use of theophylline products ... may simply be a marker for long-standing severe pulmonary disease" (1, p. 400). One could substitute for "theophylline" in the preceding sentence the name of any asthma treatment (e.g., \(\beta\)-agonists). Moreover, there is nothing in the results presented by Coughlin et al. to suggest that the association with \(\beta\)-agonists is causal and that the (stronger) association with theophyllines is confounded. Controlling for confounding by indication is notoriously difficult; nevertheless, we do not see how the analysis of Coughlin et al. can distinguish between the effects of asthma and the effects of asthma therapies.

REFERENCES


Stephan F. Lanes
Epidemiology Resources Inc.
New England Epidemiology Institute
Newton Lower Falls, MA 02162–1450

H. Michael Arrighi
Glaxo Wellcome Research and Development
Research Triangle Park, NC 27709

THE AUTHORS REPLY

We welcome the opportunity to respond to the letter by Lanes and Arrighi (1) concerning our case-control study of respiratory illness, \(\beta\)-agonists, and risk of idiopathic dilated cardiomyopathy (2). Before responding to Lanes and Arrighi's specific comments, we wish to point out that our conclusions were misquoted in their letter (1). The concluding sentence of our abstract actually states: "The results of this study suggest, but do not prove, that use of \(\beta\)-agonists has an etiologic role in idiopathic dilated cardiomyopathy" (2, p. 395) (emphasis added). The statement in the Discussion section of our paper reads: "The strong, persistent association with theophylline medications may be an indirect association since chronic use of theophylline products, particularly in combination with other respiratory medications such as corticosteroids, may simply be a marker for long-standing severe pulmonary disease" (2, p. 400) (emphasis added).

As Lanes and Arrighi point out (1), it is difficult to determine whether or not the observed associations between asthma and idiopathic dilated cardiomyopathy are accounted for by respiratory medication use. Nevertheless, the point estimates of the adjusted odds ratios for asthma (odds ratio (OR) = 1.9, 95 percent confidence interval (CI) 0.9–4.2) and asthma of \(\geq5\) years' duration (OR = 0.9, 95 percent CI 0.3–2.7) were substantially lower than the adjusted odds ratios for oral \(\beta\)-agonists (OR = 3.4, 95 percent CI 1.1–11.0), \(\beta\)-agonist inhalers or nebulization (OR = 3.2, 95 percent CI 1.4–7.1), oral corticosteroids (OR = 2.5, 95 percent CI 0.9–6.3), use of oral corticosteroids for \(\geq5\) years (OR = 8.0, 95 percent CI 1.5–44.3), and use of theophylline for \(\geq5\) years (OR = 2.1, 95 percent CI 0.7–6.3). Thus, we found little evidence of an association with asthma occurring prior to the onset or diagnosis of idiopathic dilated cardiomyopathy, and the associations with asthma were generally weak (2).

In a previous case-control study conducted in Baltimore, Maryland (3), bronchial asthma was significantly associated with idiopathic dilated cardiomyopathy after adjustment for hypertension, race, income, and other factors (adjusted OR = 6.3, 95 percent CI 1.2–32.4). A statistically nonsignificant association was observed with childhood asthma. Information biases or temporal trends in prescribing practices for asthma medications may explain this inconsistency across studies (2, 3). For example, asthmatic patients in the earlier study (3) may have been more likely to have received nonselective \(\beta\)-agonists such as ephedrine at some time in the past. Information about use of bronchodilators and history of emphysema and chronic bronchitis was not obtained in the Baltimore study.

With respect to the question of whether the focus should be on use of \(\beta\)-agonists or other respiratory medications such as theophylline, it is important to point out that about one fifth of the cardiomyopathy patients in the Washington, DC, Dilated Cardiomyopathy Study had a reported history of \(\beta\)-agonist inhaler use (2). Other respiratory medications,
such as theophylline and corticosteroids, were much less commonly prescribed. There is also substantial evidence from pharmacologic studies and clinical reports that β-adrenergic agonists are cardiotoxic in some individuals (4–7). Pharmacologic studies have suggested that interactive effects may occur between β-agonists and other respiratory medications, such as theophylline products (5).

In judging whether or not the association with β-agonist use is causal, the temporality of exposures should be considered (2). Since the onset of idiopathic dilated cardiomyopathy is often insidious and the latency period is poorly defined, we could not establish the temporality of exposures occurring shortly before the diagnosis of idiopathic dilated cardiomyopathy with any degree of certainty (2).

Taken overall, our findings and the weight of the evidence from all studies completed to date do suggest that β-agonists may have an etiologic role in idiopathic dilated cardiomyopathy. However, we certainly would not go so far as to conclude, on the basis of results obtained from a single case-control study, that the association between β-agonist use and idiopathic dilated cardiomyopathy is causal.

REFERENCES


Steven S. Coughlin
Catherine Metayer
Frances J. Mather
School of Public Health and Tropical Medicine
Tulane University
New Orleans, LA 70118

Ellen P. McCarthy
School of Medicine
Boston University
Boston, MA 02215

Richard E. Waldhorn
Bernard J. Gersh
School of Medicine
Georgetown University
Washington, DC 20037

Kenneth L. Baughman
School of Medicine
The Johns Hopkins University
Baltimore, MD 21205