
Correspondence

MONTELUKAST AND FLUTICASONE PROPIONATE

To the Editor:

I read with interest the recent article by Bukstein et al.¹ The authors conclude that montelukast and fluticasone propionate have similar outcomes in a “real-world” setting “probably as a result of the significantly better adherence with oral montelukast.” However, there are several caveats to the applicability of these results as representative of “real-world” effectiveness, including the dose (10 mg) of montelukast, the relevance of adherence to improved outcomes, lack of adequate power for infrequent events, and the fact that both groups had worsening of symptoms at a cost of 2.2 times more for montelukast.

In their article,¹ the authors state that “an adherence rate >50% appears to be critical in improving outcomes.”² Based on this statement, one would expect asthma control to improve in this “real-world” study in which the mean adherence rate was greater than 50% for the montelukast patients. However, the opposite effect is noted in that the mean symptom scores and β -agonist use increased during treatment for both groups. Furthermore, patients treated with montelukast filled significantly more oral prednisone prescriptions (0.94 ± 1.38) than those treated with fluticasone (0.44 ± 0.85 ; $P = .028$), and more montelukast patients were treated with prednisone (38% vs 27%, $P = .21$). These results also suggest that these patients warranted additional controller therapy or were inappropriately diagnosed as having mild persistent asthma at the beginning of the study.

Furthermore, the “Methods” section of the article indicates that the dose used in the study was 10 mg/d. If this information is correct, this amount is twice the recommended dose (ie, 5 mg/d) for the age range studied (6–15 years). Thus, the results would not represent an accurate evaluation of “real-world” efficacy. Even so, this dose did not result in decreased emergent visits compared with fluticasone and was associated with worsening asthma symptoms.

In this study, Bukstein et al identified the daunting task of developing a study that eliminates “unmeasured confounders and selection bias” of retrospective observational analyses. In their attempt to achieve this noble cause, they have designed an open trial that is underpowered to demonstrate differences of infrequent events and is confounded by observer bias. The first lesson of a clinical trial design is to power a study to demonstrate a difference in the primary outcome measure. The annual prevalence of an emergency department event and hospitalization in an asthma population is approximately 8% to 20% and 2% to 4%, respectively.³ Simple calculation would have told the authors that their study with 100 patients would never have demonstrated a difference and that the application of statistical methods to this comparison is inappropriate.

Open clinical trials have “real or perceived bias.” There were more than 50% fewer fills for oral prednisone ($P = .028$), suggesting greater asthma control in the fluticasone group. Use of prednisone has been identified as a means to reduce emergency department visits and hospitalizations. The authors propose that the greater use of oral prednisone by 7 patients, 14% of the population taking montelukast, may have skewed the results. However, the authors also state, “In the Dean Health Plan, prednisone is often written for more than one refill, and it can be prescribed based on a telephone call, which is not considered an office visit.”¹ Thus, prednisone refills by these patients, if accomplished without an urgent office visit or emergency department visit, could have potentially also skewed the primary outcome measurement by decreasing the number of emergent visits for montelukast.

Rather than focus on prednisone use, which may represent a treatment failure of asthma, the authors concentrate on the greater use of antibiotics in the inhaled corticosteroid group. They propose antibiotic use as a measure of asthma control. Since neither montelukast nor inhaled fluticasone has been demonstrated to alter the outcomes of sinusitis or other antibiotic-requiring illness in asthma, the cause-and-effect relationship between the asthma therapy and antibiotic use is unclear. The suggestion that montelukast’s effect on allergic rhinitis led to lower antibiotic use may in fact demonstrate inappropriate antibiotic prescribing rather than the failure of fluticasone therapy.

The authors also neglected to report the cost of therapy. Asthma therapy with montelukast costs \$382 (2.2-fold greater than fluticasone propionate) more per patient per year due to the greater average wholesale price of the medication and the greater compliance. This greater expenditure of resources was associated with no change in exacerbations but rather with an increase in symptoms and rescue medications.

Unfortunately, this study demonstrates that uncontrolled trials have significant limitations and real or perceived biases of investigators are sometimes difficult to overlook. These limitations can affect the ability to generalize the results to the patients who the physician may see in a true real-world setting.

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REFERENCES

1. Bukstein DA, Luskin AT, Bernstein A. “Real-world” effectiveness of daily controller medicine in children with mild persistent asthma. *Ann Allergy Asthma Immunol.* 2003;90:543–549.
2. Luskin AT, Bukstein DA. Affect of partial adherence with controller therapy on asthma outcomes. *J Allergy Clin Immunol.* 2000;105:S95.
3. Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma—United States, 1980–1999. *MMWR Surveill Summ.* 2002;51:1–13.

Response:

As with any study, there are a number of critical points and limitations to understand, evaluate, and consider when drawing conclusions and generalizing the results of any observational data. Many of the points outlined by Dr. Nathan are critical ones to evaluate, because they represent elements of an accurate picture of what can be learned from observational studies. However, a close examination of the "Discussion" section of our article,¹ as well as a closer evaluation of the methods applied, would reveal that these have been, for the most part, preemptively addressed.

The "relevance of adherence to improved outcomes" seems clear in light of the enormous volume of literature that directly links adherence to therapy with improved outcomes. Perhaps the most elegant demonstration of this concept was completed by Suissa and Ernst² in which they unequivocally demonstrated that increased compliance with inhaled corticosteroid therapy led to decreased rates of death from asthma and, more recently, hospitalization rates.

Regarding prednisone fill rates, as clearly outlined in both the "Results" and "Discussion" sections, in a small pilot study such as this one, a few subjects who do disproportionately better or worse with any given therapy can misrepresent the overall mean data. Because this is an important confounding factor to appropriate data analysis, we included both the data represented as "group means" and "percent of any" to provide the most accurate picture possible. Our study in fact took deliberate care to clearly point out and address this problem. There was a difference noted in group mean prednisone fills for montelukast vs fluticasone ($P = .028$), which, as discussed, was due to a few patients skewing the mean in "group means" representation. However, when prednisone fills were expressed as "percent of any," there was no difference noted between therapies.

It is fundamentally incorrect to say that as per the Dean protocol "prednisone refills by these patients, if accomplished without an urgent office visit or emergency department visit, could have potentially skewed the primary outcome measurement by decreasing the number of emergent visits for montelukast." This contradicts the fundamental premise of statistical design. This was a randomized study, and as such the assumption is that any skewed measure of any outcome would be equally distributed between both groups.

Dr. Nathan then states, "These results suggest that these patients warranted additional controller therapy or were inappropriately diagnosed as having mild persistent asthma at the beginning of the study." This is precisely one of the key findings of real-world trials that we aim to uncover. Unfortunately, in the real world, patients' conditions are incorrectly diagnosed in terms of their severity or their disease may progress over time. Even more importantly, some patients with mild disease do well with monotherapy, whereas others may have their conditions substantially controlled with combination therapy. The variability of disease and limitations of the current categorizations are critical issues to address and

understand. This is not limited to any one group of patients (as suggested here, since patients' conditions were diagnosed before the patients were randomized, and both groups of patients demonstrated an increase in β -agonist use) but rather a finding from real-world trials that allows us as a specialty community to shed light on these issues and ensure appropriate education continues on accurate diagnosis and close monitoring of the disease over time.

The dose of montelukast reported¹ was inadvertently published erroneously, and a correction was sent to the *Annals* on June 10, 2003.³ The dose of montelukast used was consistent with standard institutional review board approval, with each patient receiving the recommended dose of montelukast consistent with their age per the Food and Drug Administration–approved packet insert.

Regarding the issue of appropriate powering, the primary outcome measured was an acute attack that required emergent care defined as any exacerbation-specific event that may lead to a visit, including acute care office visits and emergency department visits. The annual prevalences of emergency department visits and hospitalizations in an asthma population listed by Dr. Nathan as 8% to 20% and 2% to 4%, respectively, would in fact be underpowered to detect a change in approximately 100 patients. However, as discussed in the "Methods" section, our definition of an emergency visit in this population included both acute care office visits and emergency department visits, which in the Dean Health Plan population of patients with mild asthma is approximately 29%, and as such the study is significantly powered to detect emergent care utilization.

Dr. Nathan's most confusing comment lists "investigator bias" as an issue needing to be considered but provides no specific examples in support of his claim. Again, a careful review of the study would reveal that there is no opportunity for investigator bias, because patients were seen by a specialist at the time of randomization; however, "During the subsequent observation period, the subject's medical management was identical to that provided to similar patients in the same managed care organization; specifically, no additional follow-up contacts were initiated by either the study physician or any other health care professional." Most patients, consistent with typical practice, were followed up by their primary care physician (including administration of the Asthma Therapy Assessment Questionnaire), and data were collected via medical record analysis of identified patients when they used health care services. In other words, there was no physician analysis incorporated into the primary end point. This is one of the strengths of randomized, observational trials, and a clear understanding of the methods behind this trial would negate most concerns of investigator bias.

We do not lend weight to antibiotic use over prednisone fills as a better marker of asthma control; however, antibiotic use represents an important marker not only in overall allergic disease cost but also as a surrogate to asthma control in the real world. The link between asthma, allergic rhinitis, sinusitis, and otitis media (possible sources of antibiotic utilization) is now

better understood, and it is important to look at a broad picture of the impact of therapy on all associated costs. Because these antibiotics can affect asthma control, it is important to look at overall asthma costs in the context of dollars spent on antibiotics (among many other things). From this perspective, we are confirming previous reports that montelukast has an antibiotic-sparing effect, possibly due to its systemic effects on target organs; however, the assumption that this is "because of a failure of fluticasone" was not drawn.

In summary, we have agreed that there are many strengths and limitations of any type of clinical trial.⁴ Because randomized controlled trials have significant limitations, observational studies possess equal but different limitations. This study attempts to improve on some of the limitations of observational studies by randomizing patients before the observational period and clearly defining the patient group. We are very conscious of the limitations of this type of trial design and have attempted to address nearly all of the issues outlined by Dr. Nathan in our article.

Dr. Nathan's comments seem clearly designed to focus on a small piece of this picture, therapy selection in favor of fluticasone. Although therapy selection is critical, and the results here suggest that in the real world fluticasone and montelukast provide similar efficacies, in this group of mild asthmatic children there is a bigger picture to be seen for practitioners, which I believe can serve to elevate our specialty and the care we provide to patients. This bigger picture includes the strengths and limitations of all trial designs and a demand for numerous trial design types, the serious effect of compliance on outcomes, misclassification of patient severity, the inability of peak expiratory flow rate to lead patients to comply with their asthma action plan (almost no montelukast patients filled their as-needed fluticasone prescriptions as ordered), the impact of asthma on other allergic diseases and vice versa, and understanding the variability of disease regardless of severity classification. It is hoped that a focus on all of these topics can provide value to practitioners and ultimately the patients we serve.

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REFERENCES

1. Bukstein DA, Luskin AT, Berenstein A. "Real-world" effectiveness of daily controller medicine in children with mild persistent asthma. *Ann Allergy Asthma Immunol.* 2003;90:543-549.
2. Suissa S, Ernst P. Use of anti-inflammatory therapy and asthma mortality in Japan. *Eur Respir J.* 2003;21:101-104.
3. Bukstein DA. Erratum to " 'Real-world' effectiveness of daily controller medicine in children with mild persistent asthma." (*Ann Allergy Asthma Immunol.* 2003;90:543-549). *Ann Allergy Asthma Immunol.* 2003;91:308.
4. Ray J. Evidence in upheaval, incorporating observational data into clinical practice. *Arch Intern Med.* 2002;162:249-254.

LEVALBUTEROL

To the Editor:

The review article in the June 2003 issue of the *Annals* by Dr. Berger concludes, "Levalbuterol . . . offers a safe, well tolerated, and efficacious bronchodilator." That is unquestionably an accurate statement. However, Dr. Berger also states, "Levalbuterol should be considered as first-line therapy in situations in which a short-acting β -agonist is warranted." That latter statement can be equally applied to albuterol (salbutamol), pirbuterol, terbutaline, or levalbuterol (R-albuterol, R-salbutamol). Since levalbuterol nebulizer solution costs about 3 times as much as albuterol nebulizer solution (drugstore.com) and more than 10 times as much as a therapeutically equivalent dose of albuterol from a metered-dose inhaler, Dr. Berger's conclusion regarding the pharmacoeconomic benefit of levalbuterol is not supported by an objective examination of the data. Despite intriguing preclinical data, S-albuterol, whether administered alone or with R-albuterol as the racemate, has been associated with no detrimental effect in clinical studies.¹⁻³ The references used to support therapeutic advantage of the single enantiomer, levalbuterol, in the acute care setting (Dr. Berger's references 43, 56, 57, and 61) are abstracts that are not available as peer-reviewed publications, and his reference 60 claiming cost saving was based on a comparison of different patient mixes of asthma and chronic obstructive pulmonary disease during 2 different 6-month periods in which different treatment protocols for the racemic albuterol and levalbuterol were used.

Inhaled bronchodilators are used most commonly and appropriately in ambulatory patients for relief of acute symptoms on an occasional basis. When used for this purpose, racemic albuterol is not associated with clinically important adverse effects. Patients who require frequent use should receive additional treatment, either a course of an oral corticosteroid if symptoms are acute or an inhaled corticosteroid if symptoms are persistent. Scheduled daily use of albuterol (either as the single enantiomer or the racemate), as was done in the clinical studies of levalbuterol for ambulatory patients, has no clinical indication.⁴ If levalbuterol has potential for advantage over albuterol when higher doses than those studied are used, as may occur for patients in the emergency department or hospital, this needs to be established with further study using appropriate methods. However, there appears to be no compelling reason to use levalbuterol for ambulatory patients rather than any other preservative-free albuterol aerosol. The albuterol metered-dose inhaler is the most economical formulation; it matches the efficacy of nebulizer administration and when used with a valved holding chamber can be administered effectively even to young children.⁵

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REFERENCES

1. Cockcroft DW, Swystun VA. Effect of single doses of S-salbutamol, R-salbutamol, racemic salbutamol, and placebo on the airway response to methacholine. *Thorax*. 1997;52:845–848.
2. Cockcroft DW, Davis BE, Swystun VA, Marciniuk DD. Tolerance to the bronchoprotective effect of β_2 agonists: comparison of the enantiomers of salbutamol with racemic salbutamol and placebo. *J Allergy Clin Immunol*. 1999;103:1049–1053.
3. Ramsay CM, Cowan J, Flannery E, McLachlan C, Taylor DR. Bronchoprotective and bronchodilator effects of single doses of (S)-salbutamol, (R)-salbutamol and racemic salbutamol in patients with bronchial asthma. *Eur J Clin Pharmacol*. 1999;55:353–359.
4. Cook D, Guyatt G, Wong E, et al. Regular versus as-needed short-acting inhaled beta-agonist therapy for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2001;163:85–90.
5. Wildhaber JH, Dore ND, Wilson JM, Devadason SG, LeSouef PN. Inhalation therapy in asthma: nebulizer or pressurized metered-dose inhaler with holding chamber? in vivo comparison of lung deposition in children. *J Pediatr*. 1999;135:28–33.

Response:

The opinions expressed by Drs. Weinberger and Hendeles appear to be based on a misunderstanding of the purposes of the studies and a misinterpretation of the useful data they provide.¹ They state, “Scheduled daily use of albuterol (either as the single enantiomer or the racemate), as was done in the clinical studies of levalbuterol for ambulatory patients, has no clinical indication.” I would respond that the original regulatory studies with racemic albuterol, required for Food and Drug Administration approval, were conducted in the same manner. In fact, use of racemic albuterol as rescue medication only (vs scheduled therapy) is not supported by its label, but that is clearly the way it is currently being used by physicians who follow widely accepted guidelines for the treatment of patients with asthma.

Our first concern is always for our patients’ well-being, and we are all dedicated to providing the best medication for their treatment, particularly for those with severe disease who tend to be the most difficult to control. It is also necessary that, as physicians, we listen to the concerns of our patients about their asthma and the treatment that they are receiving. Providing them with reasonable choices regarding their therapy is critical to a successful outcome. Prescribing physicians can no longer maintain the outdated perspective that the physician is always right about what is best for patients. Unmistakably, our patients are telling us otherwise. They frequently avoid their medications if side effects are a problem.

There are now 3 studies that have evaluated patients’ preference for levalbuterol compared with racemic albu-

terol.^{2–4} All have been presented as abstracts at major asthma and allergy meetings and are currently in the process of being written for publication (personal communications). All show that patients prefer levalbuterol over racemic albuterol, and many patients claim better efficacy and fewer side effects as their reason for this preference. Many patients state that they do not want to use racemic albuterol after trying levalbuterol.

Side effects do matter to patients. White and Sander⁵ showed that approximately one third of adults and one fourth of children are bothered by side effects to the point that they reduce or skip doses of racemic albuterol to avoid these side effects. However, studies show that reducing the dose of racemic albuterol does not provide the same improvements in bronchodilation as lower doses of levalbuterol (0.31 mg in children or 0.63 mg in adults).^{6,7} Advising our patients to use a decreased dose of racemic albuterol, in an attempt to reduce or alleviate β -mediated side effects, may, in fact, be putting them at risk for a worse exacerbation. Without a doubt, better acceptance of a drug leads to better compliance with its use.

Although it is true that all inhaled, short-acting β -agonists are considered first-line therapy for treatment of acute symptoms, our clinical experience has taught us that their therapeutic profiles differ and, overall, clinicians have chosen to prescribe one (racemic albuterol) over the others. Just as we have seen with inhaled corticosteroids, antihypertensives, antiulcer drugs, and many other classes of drugs, improvements are made over time. Clearly, the newer inhaled corticosteroids offer advantages to patients in better efficacy, safety, and convenience. Similarly, levalbuterol provides advantages to patients in efficacy, side effects (at lower doses), and the convenience of fewer doses.

Furthermore, the purpose of the study by investigators Truitt et al⁸ (reference 60 in my review) was to objectively examine real-world use of racemic albuterol vs levalbuterol. They performed a retrospective comparison of the outcomes that resulted from the way these 2 drugs are used clinically (ie, racemic albuterol, 2.5 mg once every 4 hours, compared with levalbuterol, 1.25 mg once every 8 hours). Their findings showed that levalbuterol could be given on a less frequent basis without increasing the need for as needed (PRN) rescue therapy. Patients who received racemic albuterol more frequently required the same number of PRN rescue treatments, demonstrating that levalbuterol provided better control of their symptoms.

Further studies with levalbuterol, (S)-albuterol, and racemic albuterol are currently being conducted. Clearly, this ongoing research represents a significant increase over the amount of work that was previously performed in this field at the time racemic albuterol was introduced to the market and will certainly continue to add to our knowledge of this important therapeutic area of asthma management.

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REFERENCES

1. Berger WE. Levalbuterol: pharmacologic properties and use in the treatment of pediatric and adult asthma. *Ann Allergy*. 2003; 90:583–592.
2. Ohar JA, Grogan DR, Schaefer K. Physicians and patients prefer levalbuterol to racemic albuterol. Abstract presented at the Annual Meeting of the College of Asthma, Allergy, and Immunology; November 16–21, 2001; Orlando, FL.
3. Portnoy JM, Noonan MJ, Chipps BE. Patients and physicians prefer levalbuterol over racemic albuterol: a comparison preference study. Abstract presented at the Annual Meeting of the College of Asthma, Allergy, and Immunology; November 3–8, 2000; Seattle, WA.
4. Berger WE, Ames D. Patient satisfaction survey comparing levalbuterol to racemic in children. *J Allergy Clin Immunol*. 2003;111:S214.
5. White MV, Sander N. Asthma from the perspective of the patient. *J Allergy Clin Immunol*. 1999;104:S47–S52.
6. Milgrom H, Skoner D, Bensch G, et al. Reply. *J Allergy Clin Immunol*. 2002;110:325–328.
7. Milgrom H, Skoner DP, Bensch G, et al. Low-dose levalbuterol in children with asthma: safety and efficacy in comparison with placebo and racemic albuterol. *J Allergy Clin Immunol*. 2001; 108:938–945.
8. Truitt T, Witko J, Halpern M. Levalbuterol compared to racemic albuterol: efficacy and outcomes in patients hospitalized with COPD or asthma. *Chest*. 2003;123:128–135.

TOLERABILITY OF CYCLOOXYGENASE 2 INHIBITORS AND THE ADVISABILITY OF ORAL CHALLENGE

To the Editor:

Urticaria and angioedema commonly occur after taking non-steroidal anti-inflammatory drugs (NSAIDs). It is believed that inhibition of cyclooxygenase 1 (COX-1) is the main determinant of such hypersensitivity. Therefore, anti-inflammatory drugs with highly selective COX-2 inhibition properties, such as celecoxib and rofecoxib, are preferred in patients with NSAID sensitivity.¹ Herein, we describe a patient who presented with hypersensitivity to several NSAIDs, as well as to celecoxib, although he uneventfully tolerated mefenamic acid and rofecoxib.

A 28-year-old man sought treatment at an allergy clinic because of several episodes of generalized urticaria after ingestion of diclofenac, acetylsalicylic acid, and paracetamol. He had no family or personal history of atopy or chronic urticaria.

After written consent was obtained from the patient, a single-blind, placebo-controlled challenge with paracetamol was performed. Initially, a full-day placebo challenge gave a negative result. One week later, a grade dose challenge with paracetamol gave a positive result: generalized urticaria appeared 20 minutes after a 125-mg, oral dose.

Ten days afterward, a single-blind oral challenge test to celecoxib was performed (20, 200, and 200 mg), and gener-

alized urticaria appeared again approximately 20 minutes after the first dose of 200 mg. Ten more days later, a new single-blind oral challenge test to rofecoxib (6.25, 25, and 25 mg) was performed with good tolerance. Although the patient was warned to use no NSAIDs in the future, he decided to take mefenamic acid, 250 mg twice daily for several days, because of headache, with good tolerance.

Adverse reactions to NSAIDs are frequent, and the need to find a safe anti-inflammatory drug for affected patients is a common problem in clinical practice. The recently developed COX-2 inhibitors are generally considered safe in patients with NSAID-related urticaria and angioedema.²

Rofecoxib inhibition of COX-1 is minimal, whereas etodolac, meloxicam, and nimesulide are in the same range of celecoxib.³ The partial COX-1 inhibition that celecoxib seems to produce might explain the development of urticaria after the oral challenge in the described patient.^{3,4} On the other hand, no explanation was found for the patient's tolerance of mefenamic acid, a potent COX-1 inhibitor. However, patients have been described who tolerate some NSAIDs, such as mefenamic acid or piroxicam, but not others, such as diclofenac, acetylsalicylic acid, and paracetamol.⁵

This case suggests that COX-2 inhibitors might not be as safe as generally considered. In our opinion, cautious oral challenge is still invaluable to evaluate the tolerance of anti-inflammatory drugs in patients with NSAID hypersensitivity.

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REFERENCES

1. Valero A, Baltasar M, Enrique E, et al. NSAID-sensitive patients tolerate rofecoxib. *Allergy*. 2002;57:1214–1215.
2. Sánchez Borges M, Capriles-Hulett A, Caballero-Fonseca F, Pérez CR. Tolerability to new COX-2 inhibitors in NSAID-sensitive patients with cutaneous reactions. *Ann Allergy Asthma Immunol*. 2001;87:201–204.
3. Nettis E, Di Paola R, Ferrannini A, Tursi A. Tolerability of rofecoxib in patients with cutaneous adverse reactions to non-steroidal anti-inflammatory drugs. *Ann Allergy Asthma Immunol*. 2002;88:331–334.
4. Cryer B, Feldman M. Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Am J Med*. 1998;104:413–421.
5. Quirarte J, Blanco C, Castillo R, Delgado J, Carrillo T. Intolerance to nonsteroidal antiinflammatory drugs: results of controlled drug challenges in 98 patients. *J Allergy Clin Immunol*. 1996;98:678–685.