
Letters to the editor

CROSS-REACTIVITY OF CEPHALOSPORINS WITH PENICILLIN

To the Editor:

I recently received the Practice Parameters for Allergy Diagnostic Testing developed by the Joint Task Force on Practice Parameters.¹ I wish to call attention to one of the statements regarding penicillin and cephalosporin cross-reactivities that I believe is erroneous. On Page 550 in the last paragraph, this statement is made as follows:

"Cross-reactions to Cephalosporin family of drugs occur in 6% to 15% of patients who have both positive histories and positive skin tests to Penicillin."

It has been my understanding from the literature that 6% to 15% with positive histories for penicillin reactions demonstrate clinically significant cross-reaction with cephalosporins. If the patient, however, also has a positive skin test to penicillin, the cross-reactivity can be as high as 50%. It is my understanding that the apparent low cost reactivity of cephalosporin to penicillin among patients with only positive histories for penicillin reaction is due to the fact that many penicillin-allergic patients do lose their allergic sensitivity over time and thus could even receive penicillin without adverse reactions.

It appears that this statement in the Practice Parameters is misleading.

MICHAEL M. MILLER, MD
Knoxville, TN

REFERENCES

1. Bernstein IL, Storms WW, Blessing-Moore J, et al. Practice parameters for allergy diagnostic testing. *Ann Allergy Asthma Immunol* 1995;75:543-625.

Response:

As illustrated by Dr. Michael M Miller's letter, the issue of cross-reactivity between penicillin and cephalosporins often evokes brisk debate. First, the estimated 6% to 15% prevalence of cross-reactivity in the "Practice Param-

eters for Allergy Diagnostic Tests" may, in fact, have been overly generous as a consensus statement. In the early 70s, in vitro investigations suggested that there might be extensive cross-reactivity between penicillin and cephalosporins in penicillin skin test-positive patients.¹ Since that time, clinical experience has indicated that this original estimate of clinical cross-reactivity might have been overestimated because skin testing had been performed chiefly with the penicillin major determinant.^{2,3} The true incidence of cross-reactivity between penicillin and cephalosporin antibiotics is still not available because the minor determinants of cephalosporins have not yet been characterized and therefore no reliable skin testing method exists for comparable assessment of minor determinant reactions to both penicillin and cephalosporins.³ Several groups of investigators have shown that the vast majority of patients with positive skin test reactivity to penicillin may tolerate cephalosporin clinically without reactions.^{2,3} Further, because many patients have multiple antibiotic drug hypersensitivities, one would expect a reaction rate of 3% to 7% to cephalosporins in patients with penicillin allergies, even if no cross-reactivity could be demonstrated.⁴ Finally, considerable heterogeneity of cross-reactivity may exist even among different cephalosporin derivatives, as detected by RAST binding and inhibition experiments. Thus, allergenicity to second and third generation cephalosporins appears to be directed more toward side chain determinants rather than to the beta lactam ring structures.⁵

Having duly noted these facts, how does one evaluate this situation in an individual patient? Although the chance of developing anaphylaxis after administration of a first generation cephalosporin in a patient with a positive skin test to the minor determinant of penicillin is relatively small, it is not negligible. Further, it should be emphasized that the positive penicillin skin test itself may place the patient at

a higher risk of a cephalosporin reaction than a positive history alone. Unfortunately, however, a positive skin test to the native cephalosporin drug does not correlate with positive skin tests to either major or minor penicillin determinants. The risk/benefit decision about whether to use penicillin in a penicillin history, skin test-positive patient must be undertaken on a case-by-case basis and proper prophylactic measures for treatment of anaphylaxis should be in place.

I LEONARD BERNSTEIN, MD
Clinical Professor of Medicine and
Environmental Health Sciences
Co-Director of the Allergy Research
Laboratory
University of Cincinnati Medical
Center
Cincinnati, OH

REFERENCES

1. Assem ESK, Vickers MR. Tests for penicillin allergy in man. II: The immunological cross-reactivity between penicillin and cephalosporins. *Immunology* 1974;27:255-69.
2. Solley GO, Gleich GJ, Van Dellen RG. Penicillin allergy: clinical experience with a battery of skin-test reagents. *J Allergy Clin Immunol* 1982;69:238-44.
3. Saxton A, Beall GN, Rohr AS, Adelman DC. Immediate hypersensitivity reactions to beta-lactam antibiotics. *Ann Intern Med* 1987;107:204-15.
4. Smith JW, Johnson JE, Cluff LE. Studies on the epidemiology of adverse drug reactions. II. An evaluation of penicillin allergy. *N Engl J Med* 1966;274:998-1002.
5. Sullivan TJ. Drug allergy. In: Middleton E, et al, eds. *Allergy principles and practice*, 4th ed., St. Louis: CV Mosby, 1993:1726-46.

ROLE OF THEOPHYLLINE IN ASTHMA

To the Editor:

I read with interest the study as designed by Edwards et al.¹ Multiple international consensus panels have recommended the use of anti-inflam-

matory therapy early in the management of asthma and have recommended that β_2 agonists be used as rescue therapy only and as infrequently as possible.^{1,2} The benefit of this study in reducing the mean number of β_2 agonist puffs from 9.81 at baseline to 6.78 after 4 weeks of treatment (although an improvement over placebo) demonstrates continued poorly controlled asthma. Entry criteria into this study required continued need for at least eight puffs of "rescue" β_2 agonist inhaler despite concurrent use of anti-inflammatory agents. (These agents were used in only 44% of study patients). Instructions throughout the study were to take at least four puffs of β_2 agonist daily. The use of β_2 agonists is usually felt to be a measure of asthma control but the design of this study partially negates this measure.

Given the continued concerns about asthma morbidity and mortality and the virtually uniform international recommendations that anti-inflammatory therapy be used as the cornerstone of asthma management in the 1990s, studies designed such as this, contribute no new knowledge to contemporary asthma management. Conceivably, a comparative study between patients taking inhaled corticosteroids versus sustained released theophylline might be perceived as a comparative study between two different types of anti-inflammatory agents. The current study does not add any information about anti-inflammatory action of theophylline and certainly didn't result in adequate control of asthma at the end of the study. Theophylline can contribute to improved asthma control in asthmatic patients even when high doses of inhaled corticosteroids are used concurrently.³ Although I believe theophylline continues to have an important therapeutic role in asthma, this study does little to define further the current role of theophylline in the management of mild-to-moderate asthma.

R N RIVINGTON, MD, FRCP(C)
Chief, Division of Respiriology
Ottawa Civic Hospital
Ottawa, Ontario, Canada

REFERENCES

1. Edwards TB, Dockhorn RJ, Wagner DE, et al. The efficacy of once daily

extended-release theophylline in decreasing the use of inhaled β_2 -agonists in stable, mild-to-moderate asthma patients. *Ann Allergy Asthma Immunol* 1995;75:409–16.

2. Global strategy for asthma management and prevention. NHLBI/WHO Workshop Report. National Institutes of Health Publication # 95-3659 January, 1995. Bethesda Maryland.
3. International Consensus Report on Diagnosis and Treatment of Asthma. *Clin Exp Allergy* 1992;(Supp 1):1–72.
4. Rivington RN, Boulet LP, Cote J, et al. Once daily theophylline (Uniphyll) and theophylline plus salbutamol are superior to salbutamol alone in asthmatics on high dose inhaled corticosteroids. *Am J Respir Crit Care Med* 1995;151:325–32.

Response:

The comments of Dr. Rivington regarding the statistically significant decrease in short-acting β_2 agonist use in patients treated with theophylline in our placebo-controlled, multicenter, randomized, single-blind study illustrate several important points. This study was designed to evaluate clearly defined endpoints, primarily the use of inhaled short acting β_2 agonists in theophylline-treated patients in a real world setting. Although it was not designed for evaluation of anti-inflammatory activity, recent evidence indicates that theophylline^{1–3} and other investigational selective phosphodiesterase inhibitors may have anti-inflammatory properties,⁴ perhaps in part by molecular mechanisms involving adhesion molecules.⁵

Given the documented concern over tolerance,⁶ overuse, and compliance^{7,8} with inhalational asthma therapies, the clinical implications and advantages of oral nonsteroidal therapy are substantial. Although 44% of the patients in this parallel design study were under treatment with inhalational corticosteroids, there was no difference in the extent of the reduction of β_2 agonist usage between steroid-treated and untreated groups. Further, there were no major safety issues in the study utilizing standard doses of theophylline consistent with the product label.

Therefore, Dr. Rivington's thoughtful analysis of this study with clearly defined endpoints (excluding inflam-

mation) must be considered in light of both the past, present and future. We stand by our reminder that theophylline is a well established treatment option for asthma. In selected patients, the early use of theophylline therapy will reduce the need for rescue β_2 agonists and maintain acceptable control of asthma. A longer term study of theophylline therapy might show improvement in asthma control and indices of inflammation such as bronchial hyperreactivity as assessed by inhalational challenge. A successful partnership between patients and physicians in realizing cost containment through the use of lower doses of complementary therapeutic options that promote safety and efficacy is the key to this actively evolving focus of disease management.

THOMAS B EDWARDS, MD
Albany, New York

REFERENCES

1. Sansone G, Matin A, Wang SF, et al. Theophylline blocks the spontaneous release of nitric oxide in vitro in mononuclear cells from asthmatic patients. *J Allergy Clin Immunol* 1996;97:290.
2. Sullivan P, Bekir S, Jaffer Z, et al. Anti-inflammatory effects of low dose oral theophylline in atopic asthma. *Lancet* 1994;343:1006–8.
3. Ward AJM, McKenniff M, Evans JM, et al. Theophylline—an immunomodulatory role in asthma? *Am Rev Respir Dis* 1993;147:518–23.
4. Martin RJ. Selective phosphodiesterase inhibitors and theophylline: anti-inflammatory action. Presented at the AAAAI, March, 1996.
5. Ohta K, Sawamoto S, Nakajima M, et al. Theophylline induces apoptosis in eosinophils surviving with interleukin-5 in vitro [Abstract]. *J Allergy Clin Immunol* 1994;93:200.
6. Grove A, Lipworth, BJ. Bronchodilator subsensitivity to salbutamol after twice daily salmeterol in asthmatic patients. *Lancet* 346:201–6.
7. Abbosh JM, Anderson JA. Not all asthmatics are carrying their rescue therapy inhalers. [Abstract] *J Allergy Asthma Immunol* 1996;76:83.
8. Kaiser HB. Compliance and Noncompliance to Inhaled Corticosteroids in Chronic Asthma [Abstract]. *Ann Allergy Asthma Immunol* 1996;76:112.