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Acute bronchitis, an illness frequently encountered by primary-care physicians, is an inflammation of the tracheobronchial tree that results from respiratory tract infection. It is characterized by persistent cough and sputum production and is occasionally accompanied by fever and/or chest pain. Acute bronchitis may have a viral or bacterial origin and is often treated with antibiotics. Four clinical trials were conducted to compare high and low doses of loracarbef, a new oral β-lactam antibiotic, with three agents commonly used to treat acute bronchitis: amoxicillin/clavulanate, cefaclor, and amoxicillin. Results of these studies indicated that loracarbef, 400 and 200 mg twice daily, had clinical and bacteriologic efficacy against the common respiratory pathogens *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella Branhamella cattarhalis* that was comparable with that of the comparative agents. Loracarbef was as well tolerated as cefaclor and amoxicillin; moreover, it produced a significantly lower incidence of diarrhea than did amoxicillin/clavulanate. Loracarbef may be considered a safe and effective alternative agent for the treatment of patients with acute bronchitis.

A cute bronchitis, an illness frequently encountered by primary-care physicians [1], is an inflammation of the tracheobronchial tree that results from respiratory tract infection [2]. Viruses as well as bacterial respiratory pathogens have been implicated in the etiology of acute bronchitis. Unfortunately, however, the identification of specific causative agents has been hampered by difficulties in obtaining reliable sputum samples for culture [1,3]; as a result, there is considerable controversy regarding the best course of treatment for this condition.

Patients with acute bronchitis that is suspected to be of viral origin are often treated with acetaminophen [4] and cough suppressants [3] for symptomatic relief. When bacterial origin is either suspected or documented, antibiotics are routinely used for treatment [1,5]. Newer antibiotics are currently being tested to determine their efficacy against such illnesses as acute bronchitis. This article reviews the etiology and treatment of acute bronchitis as well as the safety and efficacy results of four clinical trials designed to compare a new β-lactam antibiotic, loracarbef, with agents currently used as therapy for patients with this condition.

**SYMPTOMS AND ETIOLOGY OF ACUTE BRONCHITIS**

Patients with acute bronchitis generally have a persistent cough that is usually accompanied by sputum production and occasionally by fever, chest pain, or both. These symptoms develop quickly and are usually preceded by an upper respiratory tract infection [1–5]. Such factors as the age and general health of the patient, climate, exposure to air pollutants, and cigarette smoke contribute to the onset and severity of the illness [1,3,6].

The etiologic agents most likely to cause bronchitis vary with the age of the patient. Viral pathogens include respiratory syncytial virus, parainfluenza virus, rhinovirus, and influenza virus [3–5] as well as adenovirus [3,4], coronavirus [3,5], and rubella virus [3]. The extent to which bacterial infection is implicated in the development of acute bronchitis is controversial, in part because it is difficult to obtain sputum samples that are not contaminated with...
bacteria normally present in the nasopharyngeal tracts of healthy persons. Nevertheless, it is generally agreed that bacterial invasion may cause or prolong the illness.

It is now recognized that *Mycoplasma pneumoniae* [3,5] and *Bordetella pertussis* [3] are potential primary etiologic agents of acute bacterial bronchitis. Common respiratory bacteria, such as *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Staphylococcus aureus* may be responsible for secondary bacterial infections. Additional bacterial pathogens, such as *Moraxella* (*Branhamella*) *catarrhalis* and *Chlamydia psittaci*, may also play a role in the development of acute bronchitis.

**ANTIBIOTIC TREATMENT OF ACUTE BRONCHITIS**

To date, there have been only five randomized, placebo-controlled trials conducted to assess the efficacy of antibiotic therapy in acute bronchitis [7-11]. Results of these trials were mixed. In addition, their significance is unclear because rigorous diagnostic criteria for sputum purulence, pathogen isolation, and pathogen susceptibility testing were not applied, and four of the five studies had small sample sizes. Nevertheless, two of the studies [7,8] demonstrated a benefit for patients who received treatment: in both, symptoms improved and sputum production decreased, and in one, days lost from work also decreased [7]. Results of another study suggest that patients with chronic obstructive pulmonary disease and the associated risk factors of dyspnea, increased sputum production, and sputum purulence constitute a subgroup of patients with acute bronchitis who derive the greatest benefit from antibiotic therapy [12].

It has been estimated that >65% of patients with acute bronchitis are treated with antibiotics [1]. Historically, the most commonly used antibiotics have included erythromycin, tetracycline, and amoxicillin as well as ampicillin, trimethoprim/sulfamethoxazole, and cefaclor [5]. Additional drugs are currently being developed to enhance the efficacy and improve the safety of treatment of these patients.

Loracarbef, a member of the carbacephem class of β-lactam antibiotics, is a new oral agent that can be administered twice daily. The carbacephem class are chemically similar to the cephalosporins except that a sulfur atom has been replaced by a methylene group, which changes the dihydrothiazine ring of the cephalosporin nucleus to the tetrahydropyridine ring of the carbacephem nucleus. This substitution confers greater stability to the carbacephems [13,14]. Loracarbef has activity against a wide range of gram-positive and gram-negative bacterial pathogens [13,14], including those thought to play a role in acute bronchitis.

**RESULTS OF U.S. AND EUROPEAN TRIALS**

Four clinical trials (two in the United States, two in Europe) were initiated to study the relative effectiveness of loracarbef in treating acute bronchitis. Each trial was designed as a two-arm, randomized, parallel study comparing the efficacy of loracarbef with that of another antibiotic frequently used for treating acute bronchitis. The first study compared high-dose loracarbef (400 mg twice daily) with amoxicillin (500 mg three times daily) [Dere WH, unpublished data, 1991]. The second trial compared low-dose loracarbef (200 mg twice daily) with amoxicillin (500 mg three times daily) [Dere WH, unpublished data, 1991]. Of the remaining two trials, one compared low-dose loracarbef with the standard dose of cefaclor (250 mg three times daily) [15], and the other compared high-dose loracarbef with the standard dose of amoxicillin/clavulanate (500/125 mg three times daily) [16]. All regimens were administered for 7 days.

To be enrolled in any of these four studies, patients were required to have a diagnosis of acute purulent bacterial bronchitis. All of the patients had a cough that was productive of purulent sputum as confirmed by microscopic examination (≥25 white blood cells and <10 epithelial cells per high-power field). Furthermore, to ensure that the infection was acute, patients were required to have experienced a rapid onset of symptoms within 14 days of enrollment in the study. Patients who were diagnosed as having chronic bronchitis or who had an infiltrate on chest radiograph, renal impairment, or hypersensitivity to β-lactams were excluded from these trials. Pregnant and nursing women were also not eligible.

More than 2,000 patients were enrolled in the four studies: a total of 538 received high-dose loracarbef, 561 received low-dose loracarbef, 244 received amoxicillin/clavulanate, 159 received cefaclor, and 716 received amoxicillin [15; 16; Dere WH, unpublished data, 1991]. Many of the patients enrolled in these clinical trials did not qualify for clinical and bacteriologic evaluation; disqualification in most cases occurred because pretherapy evaluation of sputum cultures did not yield a known respiratory pathogen. Of 654 patients who were considered evaluable, 71% had pure or mixed cultures positive for one of the following four organisms: *H. influenzae*, *S. pneumoniae*, *M. catarrhalis*, and *Haemophilus parainfluenzae* (Table 1).

Resistance of respiratory pathogens to the antibiotics used was uncommon in both treatment
groups in all four studies (Table II) [15, 16; Dere WH, unpublished data, 1991]. These low rates of resistance to loracarbef, amoxicillin/clavulanate, and cefaclor were not unexpected; surprisingly, however, the level of resistance to amoxicillin, particularly of *H. influenzae*, although higher than for the other agents, was also relatively low. The explanation may likely be that the studies involving the amoxicillin treatment groups took place in Europe, where the prevalence of *H. influenzae* resistance to amoxicillin is generally lower than it is in the United States [17].

To determine the clinical and bacteriologic responses to antibiotic therapy, patients were evaluated within 3 days (posttherapy) and then 10–14 days (late-posttherapy) after the drugs were discontinued. The results of these studies are shown in Table III [15, 16; Dere WH, unpublished data, 1991]. From these data, it is clear that clinical and bacterial responses to both high-dose and low-dose loracarbef were virtually identical. In addition, loracarbef had comparable clinical and bacteriologic efficacy to each of the comparative agents.

The relative safety of loracarbef in comparison with the other antibiotics was also addressed in these studies. In the study comparing loracarbef with amoxicillin/clavulanate, a similar proportion of patients in each group reported experiencing nausea, vomiting, or both as well as rash or other cutaneous manifestations of hypersensitivity (Table IV) [16]; the proportions of patients who discontinued therapy were also comparable. However, a significantly greater number of patients in the amoxicillin/clavulanate group reported experiencing diarrhea. In the study in which loracarbef was compared with cefaclor, the safety profiles of the two drugs were similar for all event categories (Table V) [15]. This was also true for adverse reactions reported by patients who received treatment with high-dose loracarbef, low-dose loracarbef, or amoxicillin (Table VI) [Dere WH, unpublished data, 1991].

In summary, recent clinical trials designed to evaluate the use of loracarbef in treating acute bronchitis have shown that loracarbef had clinical as well as bacteriologic efficacy similar to that of the comparative drugs against such major respiratory pathogens as *H. influenzae*, *M. catarrhalis*,

**Table I**
Number of Isolates, by Organism, from Pretherapy Sputum, by Treatment Group, in Evaluable Patients with Acute Bronchitis

| Organisms                        | Loracarbef 200 mg b.i.d. (n = 149) | Loracarbef 400 mg b.i.d. (n = 179) | Cefaclor 250 mg t.i.d. (n = 56) | Amox/Clav t.i.d. (n = 99) | Amox t.i.d. (n = 171) | Total (n = 654) |
|---------------------------------|-----------------------------------|-----------------------------------|--------------------------------|--------------------------|----------------------|-----------------|
| *Haemophilus influenzae*        | 38                                | 54                                | 10                             | 17                       | 63                   | 182             |
| *Streptococcus pneumoniae*      | 36                                | 34                                | 7                              | 24                       | 39                   | 140             |
| *Moraxella* (Branhamella) *catarrhalis* | 17                              | 13                                | 4                              | 11                       | 19                   | 64              |
| *Haemophilus parainfluenzae*    | 9                                 | 9                                 | 8                              | 6                        | 10                   | 42              |
| Mixed culture with one or more of the above | 7                              | 11                                | 3                              | 4                        | 12                   | 37              |
| *Staphylococcus aureus*         | 8                                 | 10                                | 3                              | 4                        | 8                    | 33              |
| *Streptococcus pneumoniae*      | 7                                 | 9                                 | 9                              | 7                        | 0                    | 32              |
| Group A streptococci           | 6                                 | 7                                 | 5                              | 5                        | 2                    | 25              |
| *Klebsiella pneumoniae*        | 3                                 | 11                                | 1                              | 7                        | 0                    | 22              |
| Other mixed cultures*           | 4                                 | 5                                 | 0                              | 4                        | 0                    | 13              |
| Other single-organism cultures  | 14                                | 16                                | 6                              | 10                       | 18                   | 64              |

Amox = amoxicillin; Amox/clav = amoxicillin/clavulanate.

*Combination of Streptococcus pyogenes, group A streptococci, *S. aureus*, *K. pneumoniae*, Klebsiella sp, Haemophilus sp, Aerococcus sp, Neisseria sp, and group D streptococci.

**Table II**
Resistance of Selected Organisms to Drugs Used in Patients with Acute Bronchitis in Four Clinical Trials

| Organism                        | *Haemophilus influenzae* | *Streptococcus pneumoniae* | *Moraxella* (Branhamella) *catarrhalis* |
|---------------------------------|--------------------------|---------------------------|----------------------------------------|
| Drug                            | n %                      | n %                       | n %                                    |
| Loracarbef                      | 4/257                    | 5/197                     | 2.5 / 0.90                             |
| Amoxicillin/ clavulanate        | 2/49                     | 0/56                      | 0/25                                   |
| Cefaclor*                       | 0/25                     | 1/17                      | 1/14                                   |
| Amoxicillin                     | 11/191                   | 7/124                     | 5.6 / 9.51                             |

*Cephalothin disk was used to test susceptibility to cefaclor.*

**Table III**
Resistance of Selected Organisms to Drugs Used in Patients with Acute Bronchitis in Four Clinical Trials

| Organism                        | *Haemophilus influenzae* | *Streptococcus pneumoniae* | *Moraxella* (Branhamella) *catarrhalis* |
|---------------------------------|--------------------------|---------------------------|----------------------------------------|
| Drug                            | n %                      | n %                       | n %                                    |
| Loracarbef                      | 4/257                    | 5/197                     | 2.5 / 0.90                             |
| Amoxicillin/ clavulanate        | 2/49                     | 0/56                      | 0/25                                   |
| Cefaclor*                       | 0/25                     | 1/17                      | 1/14                                   |
| Amoxicillin                     | 11/191                   | 7/124                     | 5.6 / 9.51                             |

*Cephalothin disk was used to test susceptibility to cefaclor.*

**Table IV**
Resistance of Selected Organisms to Drugs Used in Patients with Acute Bronchitis in Four Clinical Trials

| Organism                        | *Haemophilus influenzae* | *Streptococcus pneumoniae* | *Moraxella* (Branhamella) *catarrhalis* |
|---------------------------------|--------------------------|---------------------------|----------------------------------------|
| Drug                            | n %                      | n %                       | n %                                    |
| Loracarbef                      | 4/257                    | 5/197                     | 2.5 / 0.90                             |
| Amoxicillin/ clavulanate        | 2/49                     | 0/56                      | 0/25                                   |
| Cefaclor*                       | 0/25                     | 1/17                      | 1/14                                   |
| Amoxicillin                     | 11/191                   | 7/124                     | 5.6 / 9.51                             |

*Cephalothin disk was used to test susceptibility to cefaclor.*

**Table V**
Resistance of Selected Organisms to Drugs Used in Patients with Acute Bronchitis in Four Clinical Trials

| Organism                        | *Haemophilus influenzae* | *Streptococcus pneumoniae* | *Moraxella* (Branhamella) *catarrhalis* |
|---------------------------------|--------------------------|---------------------------|----------------------------------------|
| Drug                            | n %                      | n %                       | n %                                    |
| Loracarbef                      | 4/257                    | 5/197                     | 2.5 / 0.90                             |
| Amoxicillin/ clavulanate        | 2/49                     | 0/56                      | 0/25                                   |
| Cefaclor*                       | 0/25                     | 1/17                      | 1/14                                   |
| Amoxicillin                     | 11/191                   | 7/124                     | 5.6 / 9.51                             |

*Cephalothin disk was used to test susceptibility to cefaclor.*

**Table VI**
Resistance of Selected Organisms to Drugs Used in Patients with Acute Bronchitis in Four Clinical Trials

| Organism                        | *Haemophilus influenzae* | *Streptococcus pneumoniae* | *Moraxella* (Branhamella) *catarrhalis* |
|---------------------------------|--------------------------|---------------------------|----------------------------------------|
| Drug                            | n %                      | n %                       | n %                                    |
| Loracarbef                      | 4/257                    | 5/197                     | 2.5 / 0.90                             |
| Amoxicillin/ clavulanate        | 2/49                     | 0/56                      | 0/25                                   |
| Cefaclor*                       | 0/25                     | 1/17                      | 1/14                                   |
| Amoxicillin                     | 11/191                   | 7/124                     | 5.6 / 9.51                             |
**TABLE III**
Clinical and Bacteriologic Responses in Evaluable Patients with Acute Bronchitis in Four Clinical Trials

| Drug                  | Posttherapy* | Bacteriologic Success† | Late-Posttherapy* | Bacteriologic Success† |
|-----------------------|--------------|------------------------|-------------------|------------------------|
|                       | Total        | Clinical Success%      |                   | Total                   | Clinical Success%      |
| High-dose loracarbef§ | 179          | 172 (96.1)             | 152 (84.9)        | 112                     | 104 (92.9)             |
| Low-dose loracarbef§  | 149          | 141 (94.6)             | 130 (87.2)        | 138                     | 135 (97.8)             |
| Amoxicillin/clavulanate| 99           | 96 (97.0)              | 92 (92.9)         | 60                      | 59 (98.3)              |
| Cefaclor              | 56           | 53 (94.6)              | 52 (87.2)         | 47                      | 41 (82.7)              |
| Amoxicillin           | 171          | 163 (95.3)             | 147 (88.0)        | 60                      | 55 (91.7)              |

*Posttherapy evaluation occurred 3 days after therapy was discontinued; late posttherapy, 10-14 days after therapy was discontinued.
†Clinical success refers to elimination of or improvement in symptoms.
‡Bacteriologic success refers to documented elimination or presumed elimination (in patients who had clinical success and a repeat culture was not possible or indicated—sputum production resolved) of the pathogen.
§High-dose loracarbef = 400 mg twice daily; low-dose loracarbef = 200 mg twice daily.
Data from [15, 16; Dere WH, unpublished data, 1991].

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