Brodimoprim in Upper Respiratory Tract Infections
Two Meta-Analyses of Randomised, Controlled Clinical Trials in Acute Sinusitis and Otitis Media

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Summary

Brodimoprim is a selective inhibitor of bacterial dihydrofolate reductase with a broad spectrum of antibacterial activity encompassing most common upper respiratory tract pathogens. The relative clinical efficacy of this agent was evaluated in 2 meta-analyses of randomised nonblind parallel-group studies of patients with upper respiratory tract infections. These analyses included 304 adults with acute sinusitis from 7 investigations and 594 children with acute otitis media from 14 investigations. Based on physician-rated global clinical efficacy in children with otitis media, brodimoprim showed superiority over ampicillin, erythromycin and cefalexin, and equivalence with amoxicillin and cefradine; pooled ratings again favoured brodimoprim. Global clinical efficacy among patients with sinusitis showed a slightly superior effect for brodimoprim over amoxicillin, and equivalence for brodimoprim and roxithromycin. No intergroup differences were apparent between brodimoprim and doxycycline or cefalexin in this setting, but small sample size precluded establishing equivalence. Pooled overall results, however, again (marginally) favoured brodimoprim. In both settings, brodimoprim was generally as well tolerated as any comparator agent, although better tolerated than ampicillin in patients with otitis media. These results demonstrate that brodimoprim is a worthwhile choice in the treatment of children with otitis media and adults with sinusitis.

Sinusitis and otitis media are two of the most common upper respiratory tract infections encountered by medical practitioners. Indeed, in the US, sinusitis may be one of the most common health-related problems per se, accounting annually for about 16 million medical consultations and at least 1 million working days lost in the adult population. Sinusitis and otitis media recorded for children aged < 5 years in the US in 1990 makes this the most frequently diagnosed bacterial illness of childhood in that country. Management of patients with otitis media or sinusitis has principally involved treatment with antibiotics where suspicion or evidence of bacterial infection exists. The utility of antibiotic therapy in
patients with acute bacterial sinusitis is accepted,[3] but it has been questioned in those with acute otitis media.[4] Recent meta-analysis, however, has shown a modest but significant impact of antibiotics on otitis media,[5] and these drugs are indicated to protect the minority (unpredictable in advance), who would otherwise experience progressive disease.[6]

Brodimoprim is a broad-spectrum antibacterial agent that selectively inhibits bacterial dihydrofolate reductases, including those with chromosomally and plasmid-mediated antibiotic resistance.[7] This drug also possesses in vitro activity against most common causative pathogens of otitis media and sinusitis,[7] and achieves high concentrations in the mucosa/secretions of the respiratory tract and effusions of the middle ear.[8]

In accordance with these characteristics, once-daily brodimoprim has shown clinical benefit in published results of clinical trials of adults with acute bacterial sinusitis[9-16] and children with otitis media.[12,17,18] Nevertheless, clinical studies of brodimoprim in these settings have often provided inconclusive results in terms of relative efficacy.

In an attempt to resolve these issues, 2 meta-analyses were conducted to more fully define the relative clinical efficacy of brodimoprim and standard comparator agents in adults with acute bacterial sinusitis and in children with acute otitis media. Tolerability was also assessed as a secondary end-point.

**Patients and Methods**

**Source of Study Materials**

All clinical studies performed during the clinical development of brodimoprim up to 1994 (including those that have been published) were reviewed for inclusion in the meta-analyses. To ensure that no studies were excluded from consideration, a literature search was performed using Medline and Excerpta Medica.

The fundamental criterion for inclusion was a similar overall study design. More specifically, studies meeting the following criteria were included in the meta-analyses:

- phase III comparative studies of brodimoprim versus active controls;
- randomised, parallel-group design;
- patients with acute infections of the upper respiratory tract;
- similar patient inclusion and exclusion criteria.

Once studies had been identified using the above criteria, only children aged between 0.1 and 14 years with a diagnosis of acute otitis media or adults aged between 16 and 75 years with a diagnosis of acute bacterial sinusitis were included in the analyses.

All studies were of similar design and were conducted to fulfil regulatory requirements. Consequently, no quality grading of the design and execution of the studies was performed.

Four studies were excluded from the meta-analyses for the following reasons:

- individual data unavailable and nonuniformity in the definition and grading of efficacy (3 studies);
- differences in diagnosis (1 study).

**Data Collection Methods**

Individual patient data were obtained from study reports. All data were recorded using an IBM personal computer and managed using a DBase IV software package (Ashton Tate Corp., Maidenhead, England). Encoded data were verified by a second individual.

**End-Points Reviewed**

The primary end-point used in these meta-analyses was the assessment of global therapeutic efficacy. This was evaluated by the physician at the end of treatment and categorised as cure (complete resolution of clinical signs and symptoms), improvement (clear regression of signs and symptoms) or failure (no apparent response to treatment or deterioration in condition).

Global efficacy evaluations were made on the basis of clinical examination results performed at baseline, midway through the scheduled period of therapy, and again at the end of treatment.