Brodimoprim in upper respiratory tract infections: two meta-analyses of randomised, controlled clinical trials in acute sinusitis and otitis media

Rahlfs V W, Macciocchi A, Monti T

Authors' objectives
The authors aimed to assess the clinical efficacy of brodimoprim and standard comparator agents in adults with acute bacterial sinusitis, and in children with acute otitis media.

Searching
All clinical studies performed during the development of brodimoprim up to 1994 were reviewed for inclusion. MEDLINE and Excerpta Medica were also searched for relevant literature.

Study selection
Study designs of evaluations included in the review
Individual patient data (IPD) from randomised controlled trials (RCTs) were included.

Specific interventions included in the review
Oral brodimoprim was compared with amoxicillin, cefalexin, doxycycline, roxithromycin, ampicillin, cefradine or erythromycin. In all studies, brodimoprim was initially administered as a 400 mg (adults) or 10 mg/kg (children) loading dose, and at a dosage of 200 mg/day (adults) or 5 mg/kg per day (children) thereafter; the dosages of the comparators were listed in the review.

Participants included in the review
Children aged between 0.1 and 14 years with a diagnosis of acute otitis media, or adults between 16 and 75 years with a diagnosis of acute bacterial sinusitis, were eligible for inclusion. All studies excluded patients with bacterial isolates resistant to the study drugs at baseline, patients hypersensitive to trimethoprim or similar agents, and those receiving concomitant antimicrobial therapy, from study entry. Among the adult population with sinusitis, patients with concomitant upper respiratory tract infections and females who were pregnant or lactating were also excluded.

Outcomes assessed in the review
The primary outcome used was global therapeutic efficacy. This was 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). Doctors conducted the assessments at the end of the treatment period. Tolerability was also evaluated, based on the incidence of adverse events spontaneously reported by the patient or elicited by indirect, non-specific questioning.

How were decisions on the relevance of primary studies made?
The review did not mention whether the trial investigators were contacted to verify the eligibility of the data.

Assessment of study quality
All studies that met the inclusion criteria were included in the meta-analysis. Studies were excluded when IPD were unavailable (n=3), or there were differences in diagnosis (n=1).

Data extraction
IPD were obtained from study reports and managed using a dBASE IV software package. A second reviewer verified the encoded data.
Methods of synthesis

How were the studies combined?
Two separate meta-analyses were performed to evaluate the effects of brodimoprim and other antibiotics, in adult patients with sinusitis and in children with otitis media. For binary data, standard odds ratios (ORs) or their logarithms were calculated; for data with more than 2 classes, generalised odds or hazard rates were calculated with 95% confidence intervals (CIs) for each study.

The studies were pooled across strata using the Mantel-Haenszel method, according to Cochran (see Other Publications of Related Interest), along with the Cox-Mantel estimator for the variance of the odds or hazard ratio. Pooled measures with 95% CIs were calculated for studies evaluating brodimoprim and the same comparator agent.

How were differences between studies investigated?
No statistical tests of heterogeneity were reported, although it was stated that there were no intra-study differences in baseline demographic variables or the duration of treatment.

Results of the review

Twenty-one single-centre RCTs were included. None of the studies were blinded: 14 evaluated children with acute otitis media (n=594) and 7 examined adults with bacterial sinusitis (n=304).

Otitis media.

Brodimoprim was compared with amoxicillin (4 studies), ampicillin (4 studies), erythromycin (4 studies), cefradine (1 study) and cefalexin (1 study). With regard to the global clinical efficacy rating, the pooled data showed brodimoprim to be statistically significantly superior to erythromycin (OR 1.99, 95% CI: 1.02, 3.90, P=0.044), ampicillin (OR 4.20, 95% CI: 2.26, 7.80, P<0.0001) and cefalexin (OR 12.38, 95% CI: 2.86, 53.61, P=0.0008). No statistically significant difference was demonstrated between brodimoprim and either amoxicillin (shown to be equivalent) or cefradine.

Overall, brodimoprim was significantly superior to the comparator agents when global efficacy ratings were pooled and compared (OR 2.55, 95% CI: 1.82, 3.56, P<0.0001). No inter-group difference in the tolerability profile of brodimoprim versus that of its comparator agents was demonstrated (OR 0.81, 95% CI: 0.50, 1.30, P<0.0001).

Sinusitis.

Brodimoprim was compared with amoxicillin (2 studies), doxycycline (3 studies), cefalexin (1 study) and roxithromycin (1 study). A statistically significant difference in global clinical efficacy ratings was demonstrated in favour of brodimoprim when compared with amoxicillin (OR 3.20, 95% CI: 1.20, 8.55, P=0.0202). No statistically significant differences were demonstrated for any other comparator agent, although equivalence of brodimoprim with roxithromycin was proven.

No overt differences were demonstrated in the tolerability data from either individual or pooled investigations.

Authors’ conclusions

The results of the meta-analysis showed that brodimoprim is at least as efficacious and well-tolerated as a variety of antibacterial agents in children with acute otitis media and adults with acute sinusitis.

CRD commentary

The review lacked a description of the trials included and a description of the regulatory requirements. The meta-analysis was weakened by the inherent problems of the primary studies, e.g. small sample sizes and variation in settings. With regard to the tolerability of the drugs for the treatment of sinusitis, Figure 4 appeared to demonstrate a significant difference between brodimoprim and doxycycline, with doxycycline showing fewer adverse events; this was not reflected in the text.
Implications of the review for practice and research
Practice: The authors stated that brodimoprim should be considered a worthwhile alternative to traditional antibacterial drugs for adults with acute sinusitis and children with acute otitis media.

Research: The authors did not state any implications for further research.

Funding
Helsinn Healthcare SA.

Bibliographic details

Other publications of related interest

Indexing Status
Subject indexing assigned by CRD

MeSH
Respiratory Tract Infections /drug therapy; Trimethoprim /therapeutic use

AccessionNumber
11996000589

Date bibliographic record published
31/07/2004

Date abstract record published
31/07/2004

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.