TITLE: Probenecid Dosing When Given with Cefazolin: Guidelines and Clinical Effectiveness

DATE: 21 November 2008

RESEARCH QUESTIONS:

1. What is the evidence for the clinical effectiveness of the 1g dose of probenecid when given to prolong the half life of intravenous cefazolin compared to the 2g dose in outpatients with infection?

2. What are the guidelines for dosing of probenecid when given to prolong the half life of intravenous cefazolin in outpatients with infection?

METHODS:

A limited literature search was conducted on key health technology assessment resources, including PubMed, the Cochrane Library (Issue 4, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international health technology agencies, and a focused Internet search. Results include articles published between 1996 and January 2009, and are limited to English language publications only. No filters were applied to limit the retrieval by study type. Internet links are provided, where available.

The summary of findings was prepared from the abstracts of the relevant information. Please note that data contained in abstracts may not always be an accurate reflection of the data contained within the full article.

RESULTS:

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented.
first. These are followed by randomized controlled trials (RCTs), controlled clinical trials, observational studies, and evidence-based guidelines.

One systematic review, two RCTs, and one observational study were identified pertaining to the clinical effectiveness of probenecid when given to prolong the half life of intravenous cefazolin. No health technology assessments, controlled clinical trials, observational studies, or evidence-based guidelines were identified.

OVERALL SUMMARY OF FINDINGS:

One systematic review was identified that reviewed the pharmacokinetic and clinical evidence for the use of cefazolin and probenecid for the treatment of skin and soft tissue infections. Studies were included in the review if they evaluated pharmacokinetic and clinical outcomes such as the effect of probenecid on the pharmacokinetics of cefazolin, efficacy, and safety endpoints. Three pharmacokinetic studies were identified and each found that the addition of probenecid to cefazolin therapy increased the serum concentrations and prolonged the half-life of cefazolin. Two randomized controlled trials were included in the systematic review and were also identified in our literature search. Both trials used a probenecid dose of 1g per day and found that the combination of cefazolin and probenecid to be an effective treatment option for skin and soft tissue infections. Authors concluded that there is limited pharmacokinetic and clinical data, but that the limited evidence suggests that daily intravenous cefazolin (2g) and oral probenecid (1g) is effective in treating skin and soft tissue infections.

The first trial identified was a randomized double-blind equivalence trial of home-based therapy for cellulitis. Patients were randomized to either intravenous cefazolin (2g) plus oral probenecid (1g) or to intravenous ceftriaxone (1g) plus oral placebo. For the cefazolin/probenecid group, (n=59), clinical cure was obtained in 86% of patients and 96% of patients in the ceftriaxone/placebo group (n=57). The median antibiotic concentrations were 2.35 µg/mL for cefazolin and 15.45 µg/mL for ceftriaxone. Adverse reaction rates were similar in each arm. Authors concluded that the once daily regimen of cefazolin and probenecid was a practical and effective treatment option for cellulitis.

In the other included RCT, 194 patients presenting to the emergency department with a diagnosis of cellulitis or soft tissue infection were randomized to receive cefazolin (2g) and probenecid (1g) or ceftriaxone (2g) and probenecid (1g). There was no statistically significant difference between the ceftriaxone group (n=96) and the cefazolin group (n=98) group with regard to cause of infection, site of infection, duration of treatment, noncompliance, or the need for incision or drainage of the wound. Authors found that cefazolin and ceftriaxone in combination with 1g of probenecid are equally efficacious in the outpatient treatment of skin and soft tissue infections. They indicated the potential for cost savings of using cefazolin therapy over ceftriaxone for the treatment of such infections.

The only study to assess the effectiveness of probenecid at a dose of 2g/day (500g four times daily) was a prospective non-randomized unblinded study. A total of 26 patients received either 2g cefazolin every 8 hours, or 2g cefazolin once daily plus probenecid (500g four times daily). For patients given cefazolin once daily with probenecid, peak serum concentrations were 146.53mg/L on day one and 148.30mg/L on day five. In patients that received cefazolin every eight hours, day one peak serum concentrations were 122.15 mg/L and day five concentrations were 136.51 mg/L. Authors concluded that when given at a dose of 500g four times daily, probenecid was effective in maintaining therapeutic serum concentrations of cefazolin.
Overall, probenecid seems to be effective in maintaining therapeutic serum concentrations of cefazolin for the treatment of infection.\textsuperscript{1-4} The two RCTs used a probenecid dose of 1g, whereas the observational study used a 2g dose of probenecid. No studies were identified that compared probenecid at doses of 1g/day versus 2g/day. It is therefore unclear as to whether there are differences in the effectiveness of probenecid at those doses. No guidelines were identified for the dosing of probenecid.
REFERENCES SUMMARIZED:

Health technology assessments
No literature identified.

Systematic reviews and meta-analyses

Randomized controlled trials

Controlled clinical trials
No literature identified.

Observational studies

Guidelines and recommendations
No literature identified.

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APPENDIX – FURTHER INFORMATION:

Observational studies


Product information


