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Review

Optimal dosage and duration of pivmecillinam treatment for uncomplicated lower urinary tract infections: a systematic review and meta-analysis

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SUMMARY

Objective: To compare the efficacy and safety of different pivmecillinam (PIV) regimes for uncomplicated lower urinary tract infections (UTIs).
Methods: The MEDLINE, Embase, and Cochrane Library databases were searched. Randomized controlled clinical trials (RCTs) involving adults or children with symptoms suggestive of uncomplicated UTI and that compared different PIV regimes or PIV versus other antibiotics were included. Meta-analyses were conducted to obtain direct and indirect efficacy estimates. PIV regimes were categorized into high total dosage, moderate total dosage, and low total dosage. The risk of bias was evaluated using the Cochrane tool.
Results: Twenty-four RCTs were identified. No difference in clinical cure was found for the high vs. moderate (short-term: risk ratio (RR) 1.01, $p = 0.813$; long term: RR 1.09, $p = 0.174$) or high vs. low dosage comparisons (mean difference 0, 95% confidence interval −0.44 to 0.45, $p = 1$). For bacteriological cure, comparisons of high vs. moderate dosage (short term: RR 1.05, $p = 0.056$; long term: RR 1.05, $p = 0.131$) and high vs. low dosage (short term: RR 1.02, $p = 0.759$; long term: RR 1.13, $p = 0.247$) showed a trend in favor of the high dosage treatment. Results for relapse, re-infection, and failure were inconclusive and not statistically significant. Patients treated with high dosages were 40% ($p = 0.062$) and 44% ($p = 0.293$) more likely to report mild to moderate adverse events.
Conclusions: There is insufficient evidence to support the use of an optimal combination of dosage, frequency, and duration of PIV therapy for the treatment of uncomplicated lower UTI. Evidence is limited due to the high risk of bias, poor reporting, and heterogeneous study data.

Contents

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Introduction

Urinary tract infections (UTIs) are among the most prevalent bacterial infections and affect men and women of all ages (Nicolle, 2003; Warren et al., 1999). There are up to 150 million cases of nosocomial and community-acquired infections per annum worldwide, accounting for considerable morbidity and health care costs (Graninger, 2003). Women are more often affected by UTIs than men (Nicolle, 2008; Hooton, 2012; Nicolle, 2013) More than 30% will experience a UTI during their lifetime (Nicolle, 2008). Recurrent episodes are frequent and affect patient quality of life considerably.

A wide variety of oral antimicrobial agents (i.e., penicillin, cephalosporins, β-lactam antibiotics, trimethoprim, sulfonamides, and fluoroquinolones) are available. Pivmecillinam (PIV) is a β-lactam antibiotic and is the pro-drug of mecillinam (Graninger, 2003). The clinical and bacteriological efficacy of oral PIV monotherapy for the treatment of uncomplicated lower UTIs has been documented consistently, with evidence from clinical trials that have been published since the 1970s (Ferry et al., 2007; Pitkajarvi et al., 1990; Menday, 2002; Ferry et al., 2004; Skinner et al., 1984; Sutlieff, 1982; Hansen et al., 1981; Donald and Rimmer, 1980; Marsh and Menday, 1980; Place, 1981; Bresky, 1977; Richards, 1984; Gupta et al., 2011). PIV is recommended by the Infectious Diseases Society of America, the European Society for Clinical Microbiology and Infectious Diseases (Gupta et al., 2011), and by the European Association of Urology (Menday, 2002). In Scandinavian countries, PIV is increasingly prescribed for the treatment of community-acquired UTIs (Andre et al., 2008; Christoffersen et al., 2014). In Germany, the UK, and France, clinical guidelines recommend PIV for the treatment of uncomplicated acute cystitis (Ferry et al., 2007; Wagenlehner et al., 2011; Etienne et al., 2014; Neuzillet et al., 2012).

Nevertheless, treatment recommendations for the optimal PIV regime vary substantially across countries. The optimal dosage, duration, and frequency of an effective PIV therapy remain unknown. The emerging problem of antibiotic resistance increases the need to determine the optimal usage of currently available antibiotics to reduce overtreatment, ineffective antibiotic prescriptions, and unnecessary adverse events (Dewar et al., 2014). Therefore, the aim of this study was to identify the available information from clinical trial evidence and to compare the efficacy and safety of different PIV regimes to optimize PIV therapy in the management of uncomplicated lower UTIs.

Methods

This systematic review is registered in PROSPERO (CRD42016038241). Discrepancies between the protocol and the present review are listed in the **Supplementary Material (Table S1)**.

Search strategy

A search was performed of the MEDLINE and Embase databases via OvidSP from 1946 and 1947 onwards, as well as of the Cochrane Central Register of Controlled Trials (CENTRAL); no language or time restriction was set, and the last search was performed in April 2016. The reference lists of identified reports were also screened, and experts from the German UTI guideline development group were contacted to identify gray literature. In addition, the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; http://www.who.int/ictrp/en/) and ClinicalTrials.gov (http://www.clinicaltrials.gov/) were searched to identify unpublished or ongoing trials (**Supplementary Material Table S2**).

Study design and patients

Randomized and quasi-randomized controlled clinical trials (RCTs) on adults or children with symptoms suggestive of an uncomplicated lower UTI (cystitis or urethritis or asymptomatic bacteriuria) were included. Studies on complicated forms of UTI were only considered if the results were reported separately for uncomplicated UTIs or if those patients made up less than 5% of participants. Studies were included if patients received treatment for an uncomplicated lower UTI that had been acquired in the outpatient setting and if there was at least one treatment arm including PIV.

Interventions and comparisons

Possible comparisons were PIV vs. another PIV regime, vs. another antibiotic, or vs. placebo. The parameters that define a PIV regime include a certain combination of dosage, frequency, and duration of administration. Thus the PIV interventions could differ in dosage range (e.g., 200 mg, 400 mg), frequency of dosage (e.g., once a day, twice daily, or three times daily and four times daily), and duration (e.g., 3 days, 7 days).