QUINOLONES FOR UNCOMPLICATED ACUTE CYSTITIS IN WOMEN: A SYSTEMATIC REVIEW. PRELIMINARY DATA

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Background

Urinary tract infections (UTIs) are common with an estimated annual global incidence of at least 250 million cases. Acute cystitis is the most prevalent form of uncomplicated UTIs. Antimicrobials with proven efficacy in acute cystitis are co-trimoxazole, nitrofurantoin, quinolones, fluoroquinolones and phosphomycine trometamole. People diagnosed with acute cystitis are usually treated as outpatients and therefore tolerance and antimicrobial safety needs to be carefully considered. Adverse reactions may result in noncompliance, administration of another drug and, in some cases, hospitalisation. These factors lead to an increase in cost and reduction in quality of life. Hooton (1997) has suggested that clinically significant differences in safety and tolerance may exist between different quinolones.

Objectives of the study

1. To compare the efficacy, safety and tolerance of different quinolones in patients with acute, uncomplicated cystitis (AUC).
2. To compare different quinolones given as either a single dose, short course (three to seven days) or as a long course (seven to 14 days).

Methods

The literature search using search strategy by electronic database MEDLINE, EMBASE, the Cochrane Library, the trials register of the Cochrane Renal Group has been performed independently by two reviewers. Medline Search Strategy as defined in the Cochrane Renal Group's module, has been combined with the search strategy terms (box. 1)
The trials were identified by the following inclusion criteria:

Search strategy for identification of studies

1. urinary tract infections.me
2. UTI.tw
3. acute cystitis.tw
4. cystitis.me
5. Escherichia coli Infections.me
6. or/1-5
7. Anti-Infective-Agents-Fluoroquiolone.me
8. Anti-Infective-Agents-Quinolone$.me
9. Anti-Infective-Agents-Urinary$.me
10. or/7-9
11. 6 AND 10

Type of trial – randomised controlled design (RCTs).
Types of participants – non-pregnant women (>16 years), with symptoms of acute cystitis (dysuria, urgency, frequency or suprapubic pain). Significant positive urine culture: >= 1000 colony forming units/ml + pyuria >= 10 leukocytes/mmi or positive urine culture >= 10000 colony forming units/ml alone (ECLM 2000). Patients with pyelonephritis or complicating factors have been excluded.
Types of interventions – RCT comparing two or more quinolones.
Types of outcome measures. 1. Clinical response: cure, improvement, failure, reccurence, clinical success, sustain clinical success. 2. Bacteriological response: eradication, persistence, relapse, reinfection, sustained bacteriological success. 3. Overall success. 4. Adverse events: any adverse events, organ or system specific AE, serious adverse events, adverse events that require discontinuation of medication, adverse reactions, adverse laboratory events. 5. Frequency of quinolones withdrawal due to: clinical failure, adverse event, patient decision. 6. Development of pyelonephritis or urosepsis at any visit 7. Long-term mortality (all cause and related to UTI). 8. Average difference in the quality of life score (measured by any scale) between groups. 9. Number of people dropped out from the study after randomisation.
Studies selection. Two reviewers independently selected the trials to be included in the review. A third reviewer settled disagreements.
For dichotomous outcomes results were expressed as relative risk (RR) with 95% confidence intervals (95% CI). Data were pooled using the random effects model

Results

224 references have been identified and 40 studies have been selected. Among these 16 RCT evaluated ciprofloxacin, norfloxacin, ofloxacin, lomefloxacin, pefloxacin, rufloxacin, sparfloxacin, temafloxacin in different regimes were included, while 24 not, for various reasons (design of the study, type of participants etc). We could not find any relevant RCT compared primitive quinolones (e.g. nalidixic acid). We have not found two or more RCT compared the same pair of quinolones so we have not performed the data combining.
There was no statistically significant difference in clinical and microbiological efficacy between quinolones given in equivalent course. However significant differences in safety among these antimicrobials were been found (tab. 1). E.g. photosensitivity frequently occurred when used sparfloxacin as compared with ofloxacin (OR=15.77, p=0.008) and ciprofloxacin (OR=13.14, p=0.01); frequency of any adverse reactions (AE), skin AE and AE require discontinuation of medication when lomefloxacin was compared with norfloxacin (OR=2.06, p=0.01; OR=14.95, p=0.0002 and OR=7.0, p=0.01). The significant differences of adverse reactions and CNS AE were found when ofloxacin compared with ciprofloxacin (OR=0.59, p=0.007 and OR=0.29, p=0.005).

Table 1. List of the study and outcomes with significant test for overall effect p <0,05

Authors	Compared quinolones	Outcome	# of studies	# of participants	Effect size
Henry 1998	3D Sparfloxacin vs 3D Ofloxacin	Photosensitivity	1	419	15.77 [2.05, 121.04]
Del Rio 1996	SD Rufloxacin vs 3D norfloxacin	Any CNS AEs	1	203	27.46 [1.60, 470.38]
Henry 1999	SD Sparfloxacin vs 7D Ciprofloxacin	Relapse Sustained bacteriologic success Sustained overall success	1 1 1	308 325 407	2.40 [1.10, 5.26] 0.34 [0.17, 0.69] 0.42 [0.25, 0.70]
Henry 1999	3D Sparfloxacin vs 7D Ciprofloxacin	Pruritis Photosensitivity	1 1	780 780	2.81 [1.00, 7.87] 13.14 [1.71, 100.91]
Henry 1999	SD Sparfloxacin vs 3D Sparfloxacin	Relapse Sustained bacteriologic success Sustained overall success	1 1 1	306 330 406	4.06 [1.60, 10.31] 0.52 [0.28, 0.96] 0.46 [0.28, 0.76]
Neringer 1992	3D Lomefloxacin vs 7D Lomefloxacin	Persistence SAEs DAE	1 1 1	392 463 363	2.81 [1.08, 7.35] 0.14 [0.03, 0.62] 0.08 [0.02, 0.34]
Neringer 1992	3D Lomefloxacin vs 7D Norfloxacin	Persistence Skin AE Photosensitivity	1 1 1	391 451 451	2.80 [1.07, 7.31] 8.34 [1.89, 36.71] 19.35 [1.12, 334.42]
Neringer 1992	7D Lomefloxacin vs 7D Norfloxacin	Any AEs DAEs Skin AEs Photosensitivity	1 1 1 1	458 458 458 458	2.06 [1.33, 3.20] 7.00 [1.57, 31.16] 14.95 [3.52, 63.53] 51.78 [3.13, 856.85]
McCarty 1999	3D Ciprofloxacin vs 3D Ofloxacin	ARs CNS Aes Insomnia	1 1 1	458 458 458	0.59 [0.41, 0.87] 0.29 [0.12, 0.68] 0.12 [0.02, 0.99]
van Balen 1990	5D Norfloxacin vs SD Pefloxacin	Improvment Failure Clinical success GI AE	1 1 1 1	152 152 152 199	2.84 [1.10, 7.32] 0.11 [0.01, 0.93] 10.07 [1.24, 81.62] 0.24 [0.10, 0.60]
Auquer 2002	SD Ciprofloxacin vs 3D Norfloxacin	SAE	1	324	17.22 [0.99, 300.81]

SD – *single dose,* 3D – *3 days,* 5D – *5 days,* 7D – *7 days.* AEs – *adverse reactions,* DAEs – *any adverse events that require discontinuation of medication,* SAE – *any serious adverse events,* AR – *adverse reactions.*

Conclusion

There is not enough evidence to conclude that the same quinolones more effective than another one in patients with AUC but significant differences of drug safety and tolerability between quinolones were found.