CHOICE OF QUINOLONES FOR TREATMENT UNCOMPLICATED UTI: SAFETY PROFILE MAY BE THE KEY FACTOR

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Background

Urinary tract infections (UTIs) are common with an estimated annual global incidence of at least 250 million cases (Ronald, 2001). Uncomplicated infections account for the greatest number of UTIs. Acute cystitis is the most prevalent form of uncomplicated UTI. The percentage of women who have at least one episode of acute cystitis is estimated to be 40-50% (Kunin, 1994).

The organisms most often responsible for UTIs are the enteric gram-negative bacteria of the group Enterobacteriaceae. *Escherichia coli (E. coli)* causes approximately 80% of UTIs (Johnson, 1989). Antimicrobials with proven efficacy in acute cystitis are co-trimoxazole, nitrofurantoin, quinolones, fluoroquinolones and phosphomycine trometamole (Warren, 1999; Naber, 1999; Naber, 2000, JAC). Increased resistance to co-trimoxazole, however, may reduce its effectiveness in the treatment of uncomplicated acute cystitis as there has been shown to be a correlation between resistance and eradication of *E. coli* (Minassian, 1998). Quinolones have a good activity against *E. coli*, achieve high urinary concentrations and have minimal effect on the natural vaginal protective flora (lactobacilli and anaerobes) (Anderson, 1999). People diagnosed with acute cystitis are usually treated as out-patients and therefore tolerance and antimicrobial safety needs to be carefully considered. Adverse reactions may result in non-compliance, administration of another drug and, in some cases, hospitalisation. These factors lead to an increase in cost and reduction in quality of life. Reviews by Warren, 1999 and Echols, 1999 have focused on the microbiological efficacy and factors influencing therapy outcomes of several different antimicrobials. However neither looked at the adverse reactions of quinolones. Hooton, 1997 has suggested that clinically significant differences in safety and tolerance may exist between different quinolones.

Objective

To compare efficacy and safety of quinolones for acute uncomplicated cystitis (AUC).

Methods

The literature search for randomized controlled design (RCT) using search strategy was performed in electronic databases MEDLINE, EMBASE, Cochrane Library and others (Kidney Disease A Bibliography Of Randomised Controlled Trials; Academic Search Premier + Health Source: Nursing/Academic Edition + Health Source – Consumer Edition; 8, 9, 10, 11, 12, 13 European Congress of Clinical Microbiology and Infectious Diseases (ECCMID) 1997, 1999, 2000, 2001, 2002, 2003; Blackwell Synergy – online journal database; Wiley InterScience; 21 International Congress of Chemotherapy (ICC) 1999; 35, 36, 37, 38, 39, 40th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), 1995-2000).

Table 1. Search strategy for different bibliographical databases

Cochrane Library	Embase	Cochrane Library
(urinrandomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR ("clinical trial" [tw]) OR ((singl* [tw] OR doubl* [tw] OR trebl* [tw] OR tripl* [tw]) AND (mask* [tw] OR blind* [tw])) OR ("latin square" [tw]) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [mh] OR evaluation studies [mh] OR follow-up studies [mh] OR prospective studies [mh] OR cross-over studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animal [mh] NOT human [mh]) AND (urinary tract infections[MH] OR UTI*[TIAB] OR acute cystitis[TIAB] OR cystitis[MH] OR Escherichia coli Infections[MH]) AND (Quinolone[MH] OR Anti-Infective Agents, Urinary[MH] OR Quinolon*[TIAB] OR Fluoroquinolon*[TIAB] OR (ciprofloxacin OR norfloxacin OR lomefloxacin OR levofloxacin OR ofloxacin OR pefloxacin OR rufloxacin	1. clinical article/ 2. clinical study/ 3. clinical trial/ 4. controlled study/ 5. randomized controlled trial/ 6. major clinical study/ 7. double blind procedure/ 8. multicenter study/ 9. single blind procedure/ 10. phase 3 clinical study/ 11. phase 4 clinical study/ 12. crossover procedure/ 13. placebo/ 14. or/1-13 15. allocat$.ti,ab 16. assign$.ti,ab 17. blind$.ti,ab 18. ((clinic$ adj25 (study or trial)).ti,ab 19. compar$.ti,ab 20. control$.ti,ab 21. cross?over.ti,ab 22. factorial$.ti,ab 23. follow?up.ti,ab 24. placebo$.ti,ab 25. prospectiv$.ti,ab 26. random$.ti,ab 27. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab 28. trial.ti,ab 29. (versus or vs).ti,ab 30. or/15-29 31. 14 or 30 32. human/ 33. nonhuman/ 34. animal/ 35. animal experiment/ 36. 33 or 34 or 35 37. 32 not 36 38. 31 not 36 39. 31 and 37 40. 38 and 39 41. (urinary tract infections).me,ti,ab. 42. UTI#.ti,ab. 43. (acute cystitis).ti,ab. 44. cystitis/ 45. (Escherichia coli Infections)/ 46. 41 or 42 or 43 or 44 or 45 47. Anti-Infective-Agents-Fluoroquiolone$/ 48. Anti-Infective-Agents-Quinolone$/ 49. Anti-Infective-Agents-Urinary/ 50. ciprofloxacin.ti,ab. 51. norfloxacin.ti,ab. 52. lomefloxacin.ti,ab. 53. levofloxacin.ti,ab. 54. ofloxacin.ti,ab. 55. pefloxacin.ti,ab. 56. rufloxacin.ti,ab. 57. moxifloxacin.ti,ab. 58. gatifloxacin.ti,ab. 59. gemifloxacin.ti,ab. 60. sparfloxacin.ti,ab. 61. fleroxacin.ti,ab. 62. enoxacin.ti,ab. 63. nalidixic acid.ti,ab. 64. or/47-63 65. 46 and 64 66. 40 and 64	(urinary tract infections[MH] OR UTI*[TIAB] OR acute cystitis[TIAB] OR cystitis[MH] OR Escherichia coli Infections[MH]) AND (Quinolone[MH] OR Anti-Infective Agents, Urinary[MH] OR Quinolon*[TIAB] OR Fluoroquinolon*[TIAB] OR (ciprofloxacin OR norfloxacin OR lomefloxacin OR levofloxacin OR ofloxacin OR pefloxacin OR rufloxacin OR moxifloxacin OR gatifloxacin OR sparfloxacin OR fleroxacin OR enoxacin OR Nalidixic Acid)[TIAB])

The trials were identified by the following criteria:

- *Type of trial* – randomized controlled design.
- *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 or asymptomatic bacteriuria and urinary tract infections in men have been excluded.
- *Types of interventions* – RCT comparing two or more quinolones.
- *Types of outcome measures.* 1. Clinical response: cure, improvement, failure, recurrence, clinical success, sustain clinical success. 2. Bacteriological response: eradication, persistence, relapse, reinfection, sustained bacteriological success. 3. Overall success. 4. Adverse events (AE): any adverse event, 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's 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 randomization.
- *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

7124 references have been identified and 50 studies have been selected. 28 RCT evaluated ciprofloxacin, gatifloxacin, gemifloxacin, lomefloxacin, levofloxacin, norfloxacin, ofloxacin, pefloxacin, rufloxacin, sparfloxacin, temafloxacin in different regimes were included, while 22 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 did not find two or more RCT compared the same pair of quinolones so we did not perform the data combining. There was no statistically significant difference in the clinical and microbiological efficacy between quinolones given in the equivalent course. However significant differences in safety among these antimicrobials were found (table 2).

Table 2. 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]
Neringer 1992	7D Lomefloxacin vs 7D Norfloxacin	Any AEs	1	458	2.06 [1.33, 3.20]
		DAEs	1	458	7.00 [1.57, 31.16]
		Skin AEs	1	458	14.95 [3.52, 63.53]
		Photosensitivity	1	458	51.78 [3.13, 856.85]
McCarty 1999	3D Ciprofloxacin vs 3D Ofloxacin	AEs	1	458	0.68 [0.47, 0.98]
		ARs	1	458	0.59 [0.41, 0.87]
		CNS AEs	1	458	0.29 [0.12, 0.68]
Richard 1998	3D Levofloxacin vs 3D Ofloxacin	ARs	1	591	0.43 [0.20, 092]
Richard 2002	3D Gatifloxacin vs 3D Ciprofloxacin	Sustained bacteriological success	1	402	2.35 [1.08, 5.09]
Iravani 1993	7D Flerofloxacin vs 7D Ciprofloxacin	Insomnia	1	645	4.69 [1.76, 12.56]

3D – 3 days, 7D – 7 days. AEs – adverse events, DAEs – any adverse events that require discontinuation of medication, ARs – adverse reactions.

The frequency of AEs:

- *Photosensitivity:*

Sparfloxacin > ofloxacin (OR=15.77, p=0.008)

Lomefloxacin > norfloxacin (OR=51.78, p=0.006)

- *Frequency of any adverse reactions, skin AE, AE require discontinuation of medication and photosensitivity:*

Lomefloxacin > norfloxacin (OR=2.06, p=0.01; OR=14.95, p=0.0002; OR=7.0, p=0.01 and OR=51.78, p=0.006).

- *Frequency of any adverse reactions, adverse events, CNS AE:*

Ofloxacin > ciprofloxacin (OR=0.59, p=0.007; OR=0.68, p=0.04 and OR=0.29, p=0.005).

- *Frequency of any adverse reactions:*

Ofloxacin > levofloxacin (OR=0.43, p=0.03)

Conclusion

There is not enough evidence to conclude that any quinolone is more effective than others for AUC but significant differences of drug safety and tolerability between quinolones exist.