Empirical use of Fosfomycin as a Single Dose Oral Treatment of Asymptomatic Bacteriuria: Randomized Control Trial

Thesis

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INTRODUCTION

Urinary tract infections (UTIs) are the most commonly occurring bacterial infections in women ***(Colgan R and Williams, 2011).***

Asymptomatic bacteriuria (AB) is a common complication during pregnancy, with a prevalence of 2–10%.It has been associated with a greater incidence of symptomaticurinary tract infection (UTI), as well as fetal and obstetric complications. Appropriate treatment reduces the incidence of UTI by 80–90%, as well as the risk of a premature birth and low-birth-weight baby ***(Mittendorf et al., 1992).***

Escherichia coli is the leading uropathogen responsible for uncomplicated UTIs, with other Enterobacteriaceae (e.g. Proteus mirabilis, Klebsiella pneumoniae),staphylococcus saprophyticus and Enterococcus faecalis alsocommonly implicated***(Gupta et al.,2011).***

The antibacterial agent fosfomycin was discovered in the late 1960s ***(Kahan et al., 1974)***. The original oral fosfomycin formulation was a calcium salt, which is poorly absorbed, and a derivative with greater bioavailability, fosfomycin trometamol

(fosfomycin tromethamine), was subsequently developed ***(Ferrari et al., 1981).***

Fosfomycin trometamol (Monuril, Monurol, Monural) is approved in numerous countries worldwide, including various European countries and the USA, mainly for the treatment of uncomplicated UTIs ***(Zambon, 2012).***

Fosfomycin is a phosphonic acid derivative that acts as a bacterial cell wall inhibitor, interfering with the first committed step in peptidoglycan biosynthesis. Specifically, fosfomycin inactivates the enzyme enolpyruvyl transferase, irreversibly inhibiting the formation of the peptidoglycan precursor N-acetylmuramic acid from N-acetylglucosamine and phosphoenolpyruvate ***(Karageorgopoulos et al., 2012).***

Fosfomycin has a broad spectrum of antibacterial activity, demonstrating good in vitro activity against Gram negative and Gram-positive organisms commonly isolated in UTIs ***(Karageorgopoulos et al., 2012).***

Fosfomycim is excreted unchanged in the urine and faeces and achieves high urinary concentrations.

Three trials compared the efficacy of single-dose fosfomycin trometamol with that of 3-day ***(Rafalskiy et al., 2009)*** or 5-day ***(Ceran et al., 2010)*** courses of ciprofloxacin or norfloxacin ***(Rafalskiy et al.,2009)*** in the treatment of women with uncomplicated lower UTIs.

A single dose of fosfomycin trometamol 3 g had similar efficacy to a 5-day course of ciprofloxacin 500 mg twice daily or a 3-day course of norfloxacin 400 mg twice daily in the treatment of women with uncomplicated lower UTIs. Clinical success rates did not significantly differ between fosfomycin trometamol and ciprofloxacin ***(Ceran et al., 2010)***or norfloxacin ***(Rafalskiy et al., 2009)*** recipients.

Oral fosfomycin trometamol was generally well tolerated, according to the results of a pooled analysis reported in the US prescribing information. The most commonly occurring drug-related adverse events in fosfomycin trometamol recipients included diarrhoea, vaginitis, nausea, headache, dizziness, asthenia and dyspepsia ***(Zambon, 2013).***

Single-dose regimen has potential for reduced costs and improved compliance, and limits the development of bacterial resistance ***(Nicolle, 2010).***

AIM OF THE WORK

This study aims to compare between the efficacy of empirical use of fosfomycin trometamol and the use of selected antimicrobials according to urinary culture and sensitivity in curing asymptomatic bacteriuria.

Study Hypothesis

In pregnant women with asymptomatic bacteriuria , Fosfomycin trometamol as a single dose oral treatment may be effective as antimicrobials given according to urine culture and sensitivity in treatment of this condition .

Study question

In pregnant women with asymptomatic bacteriuria, does Fosfomycin a single oral dose therapy effective as other oral antimicrobials according to urine culture and sensitivity in treatment in this condition?

Chapter (1)

Asymptomatic Bacteriuria

Asymptomatic bacteriuria is the presence of bacteria in the normally sterile urine of the bladder or kidneys, together with the absence of clinical signs or symptoms attributable to urinary tract infection ***(Nicolle et al., 2005)***. Asymptomatic bacteriuria is also referred to as asymptomatic urinary tract infection and, occasionally, bladder colonization.

Asymptomatic bacteriuria is very common, and is usually benign. An individual may have transient bacteriuria of any duration, or bacteriuria may persist for days to years with the same or differing organisms. Resolution of bacteriuria may occur spontaneously or as a consequence of antimicrobial therapy given for any indication. Recurrent bacteriuria is frequent. Bacteriuria has been associated with harmful outcomes in a few well-characterized populations, for whom screening and treatment of bacteriuria prevents adverse outcomes. On the other hand, antimicrobial therapy prescribed inappropriately to the many individuals with asymptomatic bacteriuria who are not at risk for adverse outcomes contributes to antimicrobial pressure, which

promotes the development of antimicrobial resistance. In addition, asymptomatic bacteriuria appears to prevent development of symptomatic urinary tract infection for some populations. This observation has stimulated exploration of the potential therapeutic benefit of establishing asymptomatic bacteruria with an avirulent strain to prevent recurrent symptomatic infection, referred to as bacterial interference ***(Nicolle et al., 2005)***.

Diagnosis of Asymptomatic Bacteriuria

Quantitative Urine Culture

Asymptomatic bacteriuria is diagnosed by isolation of one or more organisms meeting appropriate quantitative counts from a urine specimen collected in a manner that minimizes contamination (Table 1). For most patients, a voided urine specimen is obtained and the relevant quantitative count is $\geq 10^5$ colony-forming units (cfu)/ml. The groundbreaking studies of Kass ***(Kass, 1956)*** in the 1950s, confirmed the validity of a quantitative count of $\geq 10^5$ cfu/ml as the threshold to differentiate urinary infection from contamination and facilitated clinical and epidemiologic studies addressing asymptomatic bacteriuria. Two

consecutive urine specimens collected by in and out catheter from asymptomatic outpatients distinguished specimens growing either $<10^5$ cfu/ml (usually $<10^4$ cfu/ml) of bacteria, which seldom persisted in a second specimen, and $\geq 10^5$ cfu/ml, where E. coli was more likely to be isolated and tended to persist. Only 1% of patients had counts between 10^4 cfu/ml and 10^5 cfu/ml. Subsequent studies confirmed that growth of $\geq 10^5$ cfu/ml from a voided urine specimen correlated with a similar quantitative count in a catheter specimen ***(Kass, 1962)*** or suprapubic aspirate ***(Beard et al., 1965)***.

Table (1): Quantitative urine culture criteria for diagnosis of asymptomatic bacteriuria

Population	Quantitative count
Voided urine specimens	
Healthy women[a]	$\geq 10^5$ cfu/ml
Ambulatory men	$\geq 10^5$ cfu/ml
Catheter specimens	
In and out catheter	$\geq 10^2$ cfu/ml
Intermittent catheter	$\geq 10^3$ cfu/ml
Indwelling catheter	$\geq 10^5$ cfu/ml
Condom: elderly men	$\geq 10^5$ cfu/ml
Suprapubic aspirate	any number

[a]Two consecutive specimens preferred.

Voided Urine Specimens in women

Voided urine specimens collected from women are invariably contaminated with quantitative counts $\geq 10^2$ cfu/ml of one or more organisms which normally colonize the periurethral area or vagina ***(Platt, 1983)***. Rigorous collection methods using repeated periurethral cleaning or midstream collection do not decrease the frequency of contaminated specimens ***(Savage et al., 1967)***. In fact, use of the antiseptic chlorhexidine for vulvar cleansing prior to specimen collection resulted in falsely low quantitative counts of the infecting organism in the urine ***(Roberts et al., 1967)***. It is now accepted that collection of a clean catch voided urine specimen without perineal cleaning is appropriate for most women.

A second specimen is recommended for women to confirm bacteriuria when $\geq 10^5$ cfu/ml of a potential uropathogen is isolated from an initial specimen. This recommendation was based on the observation of a 20% error rate in a single voided specimen compared with a catheter urine, but 96% accuracy with two consecutive voided specimens compared with the catheter specimen ***(Kunin et al., 1968)***. For school children, an initial specimen

with a gram-negative organism isolated at $\geq 10^5$ cfu/ml was confirmed by a second specimen obtained within 2 weeks in only 61% ***(Kunin et al., 1964)***. When three voided urine specimens were collected from pregnant women to confirm bacteriuria with the same organism at $\geq 10^5$ cfu/ml, the second urine specimen remained positive for 91% following an initial positive specimen, while 96% of third specimens remained positive following two consecutive positive specimens ***(Savage et al., 1967)***. However, in another study the prevalence of bacteriuria with a gram-negative organism in pregnant women decreased from 7.0% on a first specimen to 4.4% with a second specimen ***(Kaitz et al., 1961)***, while a Swedish study reported 15% of pregnant women had a negative second culture ***(Stenqvist et al., 1989)***. Only 42% of healthy, sexually active non-pregnant women aged 18–40 years had E. coli $\geq 10^5$ cfu/ml confirmed on a second urine specimen obtained one week or one month after the first ***(Hotoon et al., 2000)***. For these women, isolation of $< 10^5$ cfu/ml E. coli on a first specimen was followed by $\geq 10^5$ cfu/ml isolated on the next culture in only 3%. In a cohort of 40- to 64-year–old women in Finland, a second specimen obtained within 2 weeks confirmed bacteriuria in 90% ***(Takala et al., 1977)***.

Diabetic women of mean age 56 years, had persistence of an organism in 69% of repeat specimens obtained within 2 weeks ***(Harding et al., 2002)***, while 56% of 18- to 75-year–old diabetic women had persistent E. coli bacteriuria at 2–4 months ***(Geerlings et al., 2000)***. Swedish women resident in the community with a mean age of 83 years, had bacteriuria with a single gram-negative organism $\geq 10^5$ cfu/ml confirmed on a second urine specimen obtained within 2 weeks in 85% ***(Rodhe et al., 2008)***.

The variability in persistence of bacteriuria on a second urine specimen obtained from women following an initial positive specimen is likely attributable to differences in patient characteristics, the spectrum of species reported as bacteriuria, time elapsed between specimen collection, and any concurrent antimicrobial therapy. It seems likely, for most women, that a single appropriately collected voided urine specimen with E. coli or other gram-negative organism isolated at $\geq 10^5$ cfu/ml represents true bacteriuria, rather than contamination. A second positive specimen then identifies persistent bacteriuria. Many episodes of bacteriuria are likely transient, especially in sexually active young women ***(Rodhe et al., 2008)***.

Other Urine Specimens

Growth of any organism in any quantitative count from a urine specimen collected by direct puncture of the urinary tract, including suprapubic or renal pelvis aspiration, is diagnostic of bacteriuria ***(Beard et al., 1956)***. When urethral catheterization is used for specimen collection a small number of periurethral organisms may be introduced into the bladder. Evaluation of paired specimens collected by in and out catheter and suprapubic aspiration identified $\geq 10^2$cfu/ml as the most reliable quantitative count for identification of bacteriuria in specimens obtained by in and out catheter, including intermittent catheterization ***(Hotoon et al., 2010)***.

Indwelling urinary devices, including urethral catheters, nephrostomy tubes, and ureteric stents uniformly acquire biofilm on the device surface ***(Saint et al., 2003)***. Some organisms present in the biofilm but not in urine may contaminate a specimen collected through the device. When low counts of bacteria ($<10^2$ cfu/ml) are isolated from urine specimens collected through short term indwelling catheters, the quantitative count progresses to $\geq 10^5$ cfu/ml by 72 hours in 96% of patients who remain catheterized and do not