

Stewardship opportunities in the treatment of urinary tract infection using oral fosfomycin

Aqtab Mazhar Alias, MBBS, Aina Salihah Shahrniza, MBBS, Helmi Sulaiman, MBBS, MIntMed

Department of Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

SUMMARY

Fosfomycin (FMT) was first isolated in 1969 and has gained popularity in the past few decades, specifically in the treatment of uncomplicated urinary tract infection (UTI). A retrospective study was undertaken to study the pattern of FMT use in our outpatient clinics. Subjects were divided into guideline compliant (GC) and non-guideline compliant (NGC) groups, based on available guidelines. More than half of the subjects (51, 51%) fall in the NGC group. Diabetes was an independent risk factor for inappropriate FMT prescription. This represented an opportunity for antimicrobial stewardship in treating diabetic patients with uncomplicated UTI when this agent is chosen.

INTRODUCTION

Fosfomycin (FMT) was first isolated following fermentation of *Streptomyces* strain in 1969.¹ It is a bactericidal phosphonic acid derivative which acts primarily by inhibiting bacterial cell wall synthesis.² Clinical trials showed that a single-dose of FMT is effective in the treatment of uncomplicated UTI.² It has broad activity against urinary pathogens including extended spectrum beta lactamase (ESBL) producing organisms. Hence, it is positioned as one of the primary treatment options for UTI in a few guidelines.^{3,4}

ORAL FOSFOMYCIN AS TREATMENT FOR UTI

We undertook a study looking at the appropriateness of the use of FMT in primary care setting for patients with UTI. This was a retrospective study carried out from April 2015 till May 2016 in primary care clinics of University Malaya Medical Centre (UMMC), Malaysia. We included subjects aged twelve years old and above who received FMT for UTI. Relevant data was collected via EMR, which include the types of UTI that patients had (i.e. complicated vs. uncomplicated UTI), the frequency and dose of prescribed FMT as well as baselines pathogens prior to the receipt of FMT when available. The subjects were divided into two groups; guideline compliant (GC) and non-guideline compliant (NGC) groups based on available guidelines^{3,4}. Subjects would fall into the GC group if they were:

- 1) female
- 2) received a single dose of 3 gram FMT and
- 3) diagnosed with uncomplicated cystitis.

Conversely, subjects fell into the NGC group if one was:

- 1) male or
- 2) had asymptomatic bacteriuria (ABU) or

- 3) had upper UTI or
- 4) complicated UTI.

We defined uncomplicated UTI as lower tract UTI (i.e. cystitis) in premenopausal and non-pregnant women, in the absence of congenital malformation or urinary tract obstructions.³ A complicated UTI is UTI that occurs in patients that do not fit the criteria mentioned above. The appropriateness of the investigations was also looked at in this study. The data was analysed using SPSS version 24.

COMPLIANCE AND STEWARDSHIP

Hundred subjects were recruited and female subjects predominate (81, 81%) with hypertension and diabetes being the common comorbidities in both groups (refer to table 1.0). Less than half of the cohort was treated according to guidelines (GC; 49%, NGC; 51%) with the main reason for non-compliance was inappropriate indication; complicated UTI (23, 45.1%), asymptomatic bacteriuria (18, 35.3%) and acute pyelonephritis (10, 19.6%) (refer to table 1.0). Of the 21 subjects on whom the urine culture were performed, the most common organism was *Escherichia coli* (8, 38%), followed by coliforms (2, 10%), *Streptococci* (2, 10%) and *Enterococcus* spp. (2, 10%). All urine cultures that grew *E. coli* and *Enterococcus* species had antibiotic susceptibility test performed. Of these, one expressed ESBL phenotype and the remaining *E. coli* isolates showed sensitivity towards augmentin (6), piperacillin-tazobactam (5), cefuroxime (5), ceftriaxone (4) and ciprofloxacin (4). Noteworthy, none of the isolates were tested against fosfomycin at the time of the study due to the unavailability of fosfomycin disc with glucose-6-phosphate.

In univariate analysis, factors that were found to be significantly associated with compliance status of FMT prescription were: presence of dysuria and abdominal pain as presenting symptoms as well as diabetes mellitus. However, only diabetes was found to be an independent risk factor for non-compliance (OR 4.67, 95% CI 1.103-19.77, P = 0.036) (refer to table 2.0).

We posit that diabetes mellitus status may introduce "framing bias" to prescribers as they may have associated its presence with plausible indicator of true UTI as well as infective complications even in those without infection in the first place (i.e. asymptomatic bacteriuria)⁶. This finding calls for further corroboration in larger studies and cohort. This too suggests an opportunity for antimicrobial stewardship that can be targeted towards diabetic patients.

This article was accepted: 2 July 2019

Corresponding Author: Dr. Aqtab Mazhar Alias

Email: aqtab_mazhar@um.edu.my

Table I: Subject demographics and clinical characteristics

Variable	Guideline compliant (GC)	Non guideline compliant (NGC)	Total (GC + NGC)
	(N, %)	(N, %)	
Sex:			
i) Male	0	(19, 19)	(19, 19)
Prescriber:			
i) Medical officer (MO)	(48, 48)	(46, 46)	(94, 94)
ii) Lecturer	(1, 1)	(5, 5)	(6, 6)
Total (N, %)	(49, 49)	(51, 51)	(100, 100)
Comorbidities (57, 57)	(25, 25)	(32, 32)	(57, 57)
i) Hypertension (40)	16	24	(40)
ii) Diabetes mellitus (35)	11	24	(35)
Symptomatology:	(49, 49)	(33, 33)	(82, 82)
i) Dysuria (52)	41	11	52
ii) Frequency (40)	24	16	40
iii) Abdominal pain (22)	19	3	22
iii) Fever (14)	8	6	14
iv) Loin pain (13)	0	13	13
Without symptoms- ABU	0	(18, 18)	(18, 18)
Total (N, %)	(49, 49)	(51, 51)	(100, 100)
Initial investigations (90):	(46, 46)	(44, 44)	(90, 90)
i) Urinalysis (87)	45	42	87
ii) Urine culture (21)	9*	12	21
iii) Full blood count (13)	3	10	13
iv) Renal profile (8)	1	7	8
iii) Ultrasound of kidney (4)	0	4	4
Without initial investigation (10)	(3, 3)	(7, 7)	(10, 10)
Total (N, %)	(49, 49)	(51, 51)	(100, 100)
Type of UTIs:			
i) Uncomplicated cystitis	(49, 49)	0	(49, 49)
ii) ABU	0	(18, 18)	(18, 18)
iii) Acute pyelonephritis	0	(10, 10)	(10, 10)
iv) Complicated UTI	0	(23, 23)	(23, 23)
Total (N, %)	(49, 49)	(51, 51)	(100, 100)
Risk factors of complicated UTI:	0	16 (16)**	(16, 16)
Urinary retention (6)	0	6	6
Catheterization (5)	0	5	5
Neurogenic bladder (3)	0	3	3
Without risk factor	(49, 49)	(35, 35)	(84, 84)
Total (N, %)	(49, 49)	(51, 51)	(100, 100)

Table II: Analysis using logistic regression to assess factors altering NGC group

Univariate analysis Variable	Odd ratio	95% CI	P-value
Prescriber:			
Medical officer (MO)	0.192	0.022- 1.704	0.138
Comorbidities:			
Hypertension	1.833	0.814- 4.128	0.143
Diabetes mellitus	3.071	1.290- 7.312	0.011
Symptomatology:			
i) Dysuria	0.054	0.020- 0.147	< 0.001
ii) Frequency	0.476	0.211- 1.075	0.074
iii) Abdominal pain	0.099	0.027- 0.362	< 0.001
Multivariate analysis			
Variable	Odd ratio	95% CI	P-value
Comorbidities:			
Diabetes mellitus	4.670	1.103- 19.765	0.036

CONCLUSION

Majority of the prescribing physicians in our primary care clinics did not conform to the available guidelines, especially in diabetic patients. We believe continuous education targeting UTI management as well as development of local guideline and proforma for clients with UTI may help improve this suboptimal prescribing behaviour.

REFERENCES

1. Popovic M, Steinort D, Pillai S, Joukhadar C. Fosfomycin: an old, new friend? *Eur J Clin Microbiol Infect Dis* 2010; 29(2): 127-42.
2. Patel SS, Balfour JA, Bryson HM. Fosfomycin Tromethamine. *Drugs* 1997; 53(4): 637-56.
3. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, Miller LG, et al. International Clinical Practice Guidelines for the Treatment of Acute Uncomplicated Cystitis and Pyelonephritis in Women: A 2010 Update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. *Clin Infect Dis* 2011;52(5): e103-20.
4. Grabe M, Bartoletti R, Bjerklund Johansen TE, Cai T, Çek M, Köves B, et al. Guidelines on Urological Infections. European Association of Urology 2015. Available from https://uroweb.org/wp-content/uploads/19-Urological-infections_LR2.pdf
5. Falagas ME, Vouloumanou EK, Samonis G, Vardakas KZ. Fosfomycin. *Clin Microbiol Rev* 2016; 29(2): 321-47.
6. Nitzan O, Elias M, Chazan B, Saliba W. Urinary tract infections in patients with type 2 diabetes mellitus: review of prevalence, diagnosis, and management. *Diabetes Metab Syndr Obes* 2015; 8: 129-36.