Fosfowash: Early proof of concept study investigating intravesical fosfomycin for recurrent urinary tract infections

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Introduction

Patients with neurogenic lower urinary tract dysfunction (NLUTD) rate urinary tract infections (UTIs) as one of the most bothersome problems.(1) This is a frustrating, multifactorial problem that often arises due to the use of catheters, abnormal bladder compliance, coexisting neurogenic bowel dysfunction, multidrug resistant organisms, and specific deficiencies in host defense mechanisms.(2) The management of NLUTD patients who are plagued by an abnormally high frequency or severity of UTIs and are using clean intermittent catheters (CIC) may require tertiary treatment options to try and prevent UTIs. Clinicians often struggle with the potential harms of continuous oral antibiotic prophylaxis (such as antibiotic resistance) and this approach is often considered as a last resort.(3,4)

Intravesical antibiotic bladder instillation is an alternative option that is well suited to patients already using CICs. Previous studies have generally focused on the use of gentamicin(5–7), however, it an expensive medication, it is cumbersome to obtain for patients, and in recent years it has been the victim of manufacturing delays and drug shortages. Our objective was to investigate if fosfomycin tromethamine, a readily available oral antibiotic that comes in powder form, may be a suitable agent for intravesical bladder instillation therapy.

Methods

Fosfomycin tromethamine is a bactericidal antibiotic with a broad range of activity against gram positive and negative aerobic bacteria (such as *Escherichia coli*, *Enterococcus*, *Klebsiella*, *Proteus*, *Serratia*, Pseudomonas and *Citrobacter*) that are commonly associated with UTIs. It has *in vitro* antimicrobial activity against Extended Spectrum Beta Lactamase (ESBL) producing bacteria and can penetrate biofilms. It inactivates the enolpyruvyl transferase enzyme (which inhibits bacterial cell wall synthesis) and reduces adherence of bacteria to the urothelium.(8,9) We conducted two *in vitro* experiments using fosfomycin. We tested three solutions: reconstituted fosfomycin (created by mixing a commercially available package of fosfomycin tromethamine (JAMP Pharma Corporation, Quebec Canada) in 125mL of distilled water), tobramycin 160mg in 1L normal saline (positive control), and buffered saline (negative control).

The objective of our first experiment was to determine if reconstituted fosfomycin tromethamine was bactericidal in the absence of metabolism by the human gut (where it is normally metabolised to its free acid, fosfomycin). We added 10µL of the fosfomycin solution to a tryptic soy agar (TSA) plate of 10^5 colony forming units (CFU) of urinary isolate, *E. coli* 67, and the plate was incubated at 37°C aerobically overnight.

The objective of our second experiment was determine the minimum inhibitory concentration of the fosfomycin and tobramycin solutions. 1mL of each of the solutions was added to 1.5mL eppendorf tubes in triplicate using the following dilutions based on the original solutions (100%, 50%, 25%, and 12.5%). Then $1x10^5$ CFU of *E. coli* 67 was added to each tube. Tubes were incubated over night at 37°C and agitated at 170rpm. Bacterial survival was assessed the next day by dilution series and drop plating on TSA plates.

Results

The fosfomycin solution had a similar pH (5.5) to the tobramycin solution (6.5). In the first experiment, fosfomycin and tobramycin were effective at inhibiting the growth of *E. coli* 67 with a zone of inhibition of 31mm and 20mm respectively. This result was replicated after 1 week of storage at 4°C, showing that there is no loss of efficacy over this time period (data not shown). In our second experiment, all four dilutions of both the tobramycin and the fosfomycin inhibited all bacterial growth of *E. coli 67*; the negative control series had high growth of bacteria (Fig. 1).

Discussion

A recent systematic review identified 11 previous studies of intravesical antibiotic therapy and found that this approach was generally efficacious at both treatment and prevent of UTIs, with minimal side effects.(10) This conclusion supports the need to develop further feasible intravesical options. To our knowledge, this is the first investigation into the use of fosfomycin as an intravesical antibiotic. We have shown promising, preliminary data that supports the further investigation of fosfomycin as an intravesical antibiotic agent for patients with NLUTD and frequent UTIs. As both the fosfomycin and tobramycin achieved complete bacterial kill in

all the tested dilations, we know the minimal inhibitory concentration for *E. coli* 67 is less than a 12.5% dilution (equivalent to 1 satchel of commercial fosfomycin in 1L of water).

Ideally intravesical antibiotics are instilled before bedtime at the time of the last catheter of the day and allowed to dwell overnight. Potential advantages of fosfomycin as a bladder instillation include the ability of patients to obtain it from any outpatient pharmacy, the ease of storing a reconstituted satchel in the fridge for use over the course of a week (for example reconstituting in a 500mL or 1000mL of commercial bottled water), and the wide antimicrobial spectrum of fosfomycin. Fosfomycin has often been used as a once per week oral therapy for recurrent urinary tract infections, however, using it as an intravesical therapy may have benefits of avoiding systemic side effects, reducing bacterial resistance in the gut flora, and improved patient acceptance compared to continuous oral use. Three patients with NLUTD who were unable to access intravesical aminoglycosides due to the current pandemic switched to using fosfomycin instillations due to lack of alternatives. Anecdotally, they found it to be tolerable and to have a similar efficacy to their previous tobramycin instillations.

Limitations of this work include the use of a single UTI-relevant bacterial strain, no direct assessment of potential cytotoxic effects (although it is typically well tolerated orally), and the potential for resistance to develop with long-term use. Further basic science and clinical studies will be necessary to determine clinical efficacy and safety and to test different dilution options and instillations schedules.

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Figures and Tables

Fig. 1.