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Oral D-mannose in recurrent urinary tract infections in women: a pilot study

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Abstract

Background: In recurrent urinary tract infections (UTIs) usual prophylactic antibiotic regimes do not change the long-term risk of recurrence. Our aim was to evaluate the efficacy of D-mannose in the treatment and prophylaxis of recurrent UTIs.

Methods: In this randomized cross-over trial female patients were eligible for the study if they had an acute symptomatic UTI and three or more recurrent UTIs during the preceding 12 months. Suitable patients were randomly assigned to antibiotic treatment with trimethoprim/sulfamethoxazole or to a regimen of oral D-mannose 1 g 3 times a day, every 8 hours for 2 weeks, and subsequently 1 g twice a day for 22 weeks. They received the other intervention in the second phase of the study, with no further antibiotic prophylaxis. The primary endpoint was evaluation of the elapsed time to recurrence; secondary endpoints were evaluation of bladder pain (VASp) and urinary urgency (VASu).

Results: The results for quantitative variables were expressed as mean values and SD as they were all normally distributed (Shapiro–Wilk test). In total, 60 patients aged between 22 and 54 years (mean 42 years) were included. Mean time to UTI recurrence was 52.7 days with antibiotic treatment, and 200 days with oral D-mannose ($p < 0.0001$).

Conclusions: Mean VASp, VASu score, and average numbers of 24-hour voidings decreased significantly. D-mannose appeared to be a safe and effective treatment for recurrent UTIs in adult women. A significant difference was observed in the proportion of women remaining infection free versus antibiotic treatment.

Keywords

Antibiotic treatment, cystitis, D-mannose, recurrent urinary tract infections, prophylaxis

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Introduction

Recurrent UTI (rUTI) is defined as three episodes of urinary tract infection (UTI) with three positive urine cultures in the previous 12 months or two episodes in the last 6 months.[1] Usual strategies include long-term low-dose prophylactic antimicrobial treatment or postcoital antibiotic treatment, but it seems that these strategies do not alter the long-term risk of recurrence. Patients with frequent UTIs who take prophylactic antimicrobial agents for extended periods decrease their infections during prophylaxis, but the rate of infection returns to pretreatment rates when

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prophylaxis is stopped.[2,3] Long-term antibiotics do not appear to positively affect the patient's basic susceptibility to infections.[4]

The cell wall of *Escherichia coli* bacteria has tiny finger-like projections that contain complex molecules called lectins on their surface. Lectins act as a cellular glue that binds the bacteria to the bladder wall so they cannot be easily rinsed out by urination, adhering to mannose receptors of the bladder wall.[5] D-mannose (Figure 1) is a simple sugar structurally related to glucose; it is found in several fruits and is also produced in the body.

We hypothesized that urinary D-mannose may be able to bind and eliminate bacteria such as *E. coli* by acting as a competitor for *E. coli* adhesion to bladder epithelial cells.[6-8]

In the management of rUTIs in women it is common practice to fight *E. coli* resistance by varying the type of antibiotic, or increasing the dose and duration of therapy. However, in doing so the bacteria become even more resistant to broad-spectrum antibiotics. It is likely that part of the old colony of bacteria in the urinary tract probably survive; some bacteria probably remain latent and are reactivated by various favourable conditions, therefore persistent recurrences may not be true re-infections.[9]

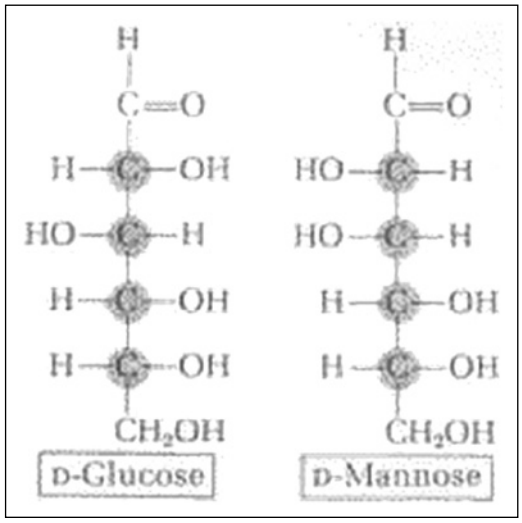

Figure 1. Chemical structure of D-glucose and D-mannose.

In this randomized cross-over study the aim was to evaluate if oral D-mannose could be used as a safe and effective treatment for UTIs and also as a prophylactic measure for rUTIs in adult women.

Methods

Female patients were eligible for study if they were aged 18 years or older and had an acute symptomatic UTI and three or more UTIs documented with culture of midstream urine specimen at inclusion and in the preceding 12 months, had not taken antimicrobials within 4 weeks and were not pregnant or contemplating pregnancy. Exclusion criteria were: upper UTI and/or temperature higher than 38°C, flank/lumbar pain or tenderness, renal disease, anatomical abnormalities, prior gynaecological surgery, immunosuppressive medications or diseases (Table 1). All patients gave their written consent to the study. The work was conducted in accordance with the principles of the Declaration of Helsinki of World Medical Association. Each participant entering the trial was assigned to one of the following treatments in a random sequence: (a) A regimen of 5-day antibiotic therapy with trimethoprim/sulfamethoxazole 160 mg/800 mg twice a day, followed by a single dose at bedtime for 1 week each month in the following 23 weeks; (b) A regimen of oral D-mannose 1 g three times a day, every 8 hours for 2 weeks, and subsequently 1 g twice a day for 22 weeks. D-mannose activity is best when the urine has neutral pH; therefore, patients were instructed to measure urinary pH using dipsticks and use oral sodium bicarbonate 250 mg b.i.d. or potassium citrate 1 g b.i.d. as alkalinizing agents if pH was <7.

There were two groups of 30 patients; the first group received antibiotic first, and the second D-mannose first. The cross-over point was at 24 weeks in both groups A and B. Therefore patients in group A switched to group B at

Table 1. Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
female > 18 years	upper urinary tract infection and/or temperature > 38°C
acute symptomatic UTI	flank/lumbar pain/tenderness
≥ 3 UTIs with positive urine culture in the preceding 12 months	renal disease
no antimicrobials within 4 weeks	anatomical abnormalities
not pregnant/not contemplating pregnancy	prior gynaecological surgery
	immunosuppressive medications or diseases

Table 2. Results at 6, 12 and 24 weeks with treatment. Oral D-mannose treatment 1 g every 8 h in 60 patients. Number of patients with positive urine culture at time 0, 6, 12 and 24 weeks after starting treatment.

Urine culture	Time 0	6 weeks	12 weeks	24 weeks
E. Coli	40	28	20	10
Klebsiella pneumonia	10	12	6	2
Proteus	4	4	6	0
Streptococcus agalactiae	4	2	0	0
Enterococcus	2	0	0	0
No. of patients	60	46	32	12

week 24, and vice versa. Data of patients in both groups who had a symptomatic UTI and returned for at least one follow-up visit were included in the analysis of treatment outcome and adverse effects.

Main outcome measures

Bacteriuria with symptoms of UTI was defined as significant if voided urine culture was positive with at least 100,000 uropathogens per ml. Urine cultures were repeated whenever symptoms appeared and at the end of the study. The 24-hour number of voidings was obtained by completion of a voiding diary before and at the end of treatment in both treatment groups. The elapsed time to UTI recurrence (time to recurrence (TTR)) was evaluated and a comparison was made between the two groups of treatment; follow-up of the study was 12 months.

Primary outcome of the study was the TTR of UTI; the TTR after antibiotic treatment and with D-mannose treatment was appraised and compared. UTI was defined as an acute flare of urinary symptoms + positive urine culture. Secondary outcomes were visual analogue scale (VAS) pain and VAS urgency, both recorded during episodes of UTI.

Statistical analysis

The results for quantitative variables were expressed as mean values and SD as they were all normally distributed (Shapiro–Wilk test); *t*-test for paired data was used to analyse differences in TTR, VAS pain, VAS urgency and number of voidings between treatments.

Data analysis was performed with STATA statistical package (release 11.1, 2010, Stata Corporation, College Station, Texas, USA).

Results

In total, 60 patients aged between 22 and 54 years (mean 42 years) who visited at the outpatient clinic of our urology department were included in the study.

Table 3. Risk factors for UTIs in 60 patients.

Irritable bowel syndrome	5
Constipation	26
UTI 24–48 hours after intercourse	24

A significant difference in the elapsed time to develop an infection was found between patients on antibiotic treatment and those on treatment with D-mannose. The results of urine cultures of patients under treatment in both groups are shown in Table 2, and risk factors for UTIs are reported in Table 3.

Following antibiotic treatment, all patients had a negative urine culture 1 week after the end of treatment, and the mean time to UTI recurrence was 52.7 days (SD: 11.2; 95% Confidence Interval); under D-mannose treatment the mean TTR was 200 days (SD: 50.7) (Figure 2); the difference was statistically significant ($p < 0.0001$).

Of the 60 patients, 45 (75%) had one recurrence during the 24-week course of antibiotic treatment, 10/60 (16.6%) had two recurrences, and 5/60 (8.3%) had no recurrent infection. Twelve out of 60 patients (20%) had positive urine culture during treatment with D-mannose before completing the 24-week treatment, and 48 (80%) remained UTI free. Urine pH ranged between 6.5 and 7.5.

Mean VAS pain was 4.4 (SD: 1.1) before D-mannose treatment and 2.2 (SD: 0.5) after its course. Mean VAS urgency score decreased from 4.6 (SD: 1.1) to 2.6 (SD: 0.7) before and after treatment (Figure 2). Mean number of voidings was 7.1 (SD: 1.7) before D-mannose, and 4.7 (SD: 1.0) at the end of D-mannose treatment (Figure 3). All differences were statistically significant ($p < 0.001$).

Discussion

Because of the need for alternatives to antibiotics in rUTIs, other treatment or prophylaxis regimens have been

suggested, such as intravaginal estriol, oral cranberry juice or lactobacilli vaginal suppositories.[10-12]

E. coli strains adhere to the normally sterile human urothelium using type 1 pili.[13] It has been observed that, initially, invasion of bladder superficial cells provides uropathogenic *E. coli* with a protective, but transient, environment in which the bacteria can replicate.[14] Subsequently, bacteria that manage to avoid rapid clearance from the urinary tract can invade the underlying epithelium,[15] where they can establish a more stable bacterial reservoir. This reservoir can persist for several weeks in a quiescent state, seemingly undetected by immune surveillance mechanisms and protected from antibiotics,[16] possibly by virtue of the permeability barrier maintained by the bladder epithelium. Intracellular uropathogenic *E. coli* appear to be better protected from a number of antibiotics, including cefuroxime, gentamicin, and trimethoprim-sulfamethoxazole.[17-19]

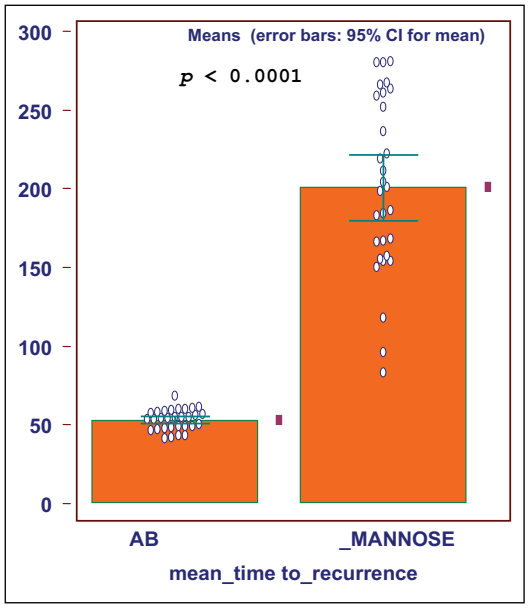

Figure 2. Time to recurrence in 60 female patients with recurrent UTIs with antibiotic treatment: 52.7 days (SD: 11.2), and with treatment with D-mannose for 24 weeks: 200 days (SD: 50.7). All differences were statistically significant ($p < 0.001$).

The chemical structure of D-mannose causes it to adhere to *E. coli* bacteria, perhaps even more tenaciously than *E. coli* adheres to human cells. Although the mechanism of action is complicated, we could hypothesize that if enough D-mannose is present in the urine, it may bind to the bacteria and prevent them from attaching to the urinary tract lining.[20]

Our trial compares two different treatment methods for addressing the issue of rUTIs in the female population, usually non-complicated UTIs, over a similar time-frame of 6 months. We randomly compared the results of D-mannose with antibiotics; our experience shows that D-mannose represents a useful choice to address the problem of treating acute UTIs and also preventing rUTIs. The justification for not performing a placebo-controlled crossover trial is that an acute UTI may result in severe clinical symptoms including pain, which may be addressed by one

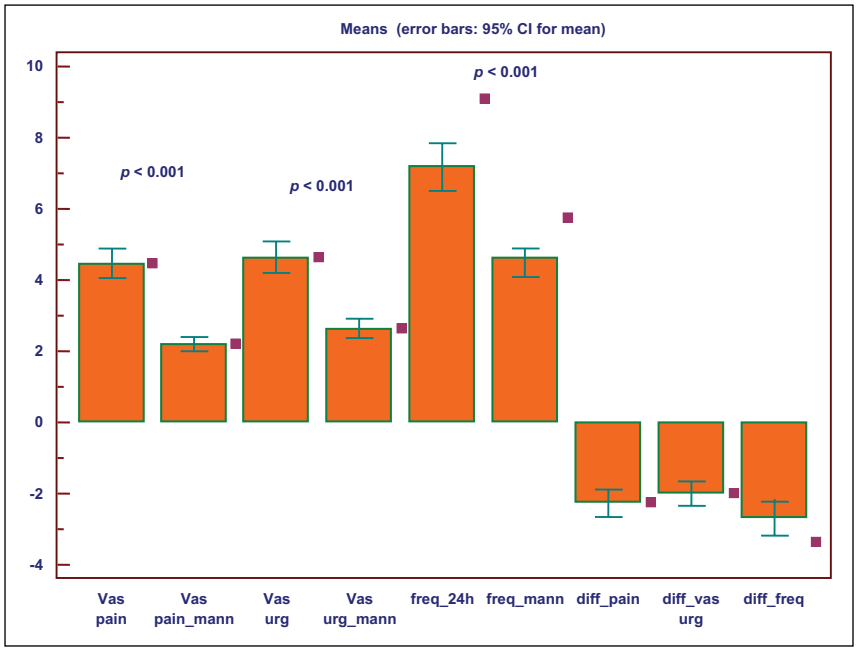

Figure 3. VAS pain, VAS urgency and 24-hour frequency with antibiotic treatment and during 24-week treatment with oral D-mannose. Mean VAS pain from 4.4 (SD: 1.1) to 2.2 (SD: 0.5). Mean VAS urgency score from 4.6 (SD: 1.1) to 2.6 (SD: 0.7). Mean number of voidings from 7.1 (SD: 1.7) to 4.7. All differences were statistically significant ($p < 0.001$).

the two treatment methods chosen. There are no comparable studies with the same characteristics using D-mannose; when examining previous results[21-23] we should question whether long-term antibiotic prophylaxis has real advantages over a prolonged regimen with D-mannose, possibly promoting further representative studies.

As control group we thought that a continuous daily prophylactic antibiotic for 6 months, more commonly used,[21] would probably "sterilize" urine by eliminating microorganisms; however, its continuous and prolonged use would probably also reduce normal vaginal and intestinal bacterial flora, facilitating new UTI recurrences in patients at risk.[24] Therefore a weekly intermittent administration of trimethoprim/sulfamethoxazole was chosen in the control group, based on previous experience;[25] limited evidence suggests that weekly prophylaxis is better than monthly prophylaxis.[26]

Mannose is involved in an extensive series of metabolic transformations, being incorporated into glycoproteins and glycolipids or formed into fructose that is then incorporated into glycoproteins. The primary source of mannose is glucose. Mannose occurs as the free sugar in peaches, apples, and oranges but is absorbed from the gastrointestinal tract of rats at only about 12% of the rate of glucose.

Our data reveal that D-mannose provides both preventative and therapeutic effects, and we think its properties can be greatly improved. We know that mannose has no bactericidal properties, and it might well be that the dosage and duration of therapy have to be individualized according to bacterial growth and replication speed in the bladder and urinary tract. It has been described that the majority of ingested mannose works by binding to bacteria concentrated in infected urine, and perpetuating infection, by binding to the mannose receptors of urothelial bladder cells.[5] This mechanism is the one involved in most cases of recurrences of UTIs.

In most cases recurrences are wrongly regarded as reinfections: it is likely that the clinical results of d mannose are obtained with the elimination of progressive bacterial loads in urine, "alive" albeit inactivated, motionless, and devoid of pathogenic potential due to mannose linked to them.[18,19] This is the main reason for performing a cross-over trial with a sufficiently long D-mannose treatment period; a much longer time is required for D-mannose than for antibiotic treatment in order to improve its effectiveness and obtain an adequate infection-free time period. Further studies should clarify the positive effect of reducing the rate of recurrences of microorganisms other than *E. coli*, such as Klebsiella and Proteus (Table 2), which are not known to act by means of pili on urothelial tissues.

No significant side effects limiting long-term consumption of mannose have been reported. D-mannose has been shown to reduce bacteria in rats in a dose-dependent manner. Basic microbiological data from *in vitro* experiments are lacking. However, D-mannose was found to significantly reduce bacteria in 1 day,[23,27,28] and in a murine cystitis model the potential of ligand-based design of antagonists of UTIs is determined by structural mimicry of natural epitopes, and extends into blocking of bacterial invasion, intracellular growth and capacity to fluxing and of recurrence of the infection.[23]

Conclusions

In our study oral D-mannose appeared to be a safe and promising treatment choice for acute and recurrent UTIs in adult women, which represent a significant burden on their sexual life. This was the first experience in the clinical setting, the previous data coming from animal studies. A statistically significant difference was seen in the proportion of women remaining infection free during an average course of 24-week treatment, both for treatment of acute episodes and as a safe, preventative therapy of UTI recurrences, compared with targeted antibiotic treatment.

Future research and clinical studies are needed in a wider population to establish and confirm D-mannose as a practical, safe, and effective therapy.

Conflict of interest

None declared.

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Note

1. ClinicalTrials.gov Identifier: NCT01808755. https://register.clinicaltrials.gov/prs/app/action/SelectProtocol?sid=S00043DV&selectaction=Edit&uid=U0001954&ts=5&cx=ht023

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