

Summer 8-12-2017

The efficacy of D-mannose in the prevention of recurrent urinary tract infections compared to long-term antibiotic therapy

Kristine Stompro

Follow this and additional works at: <http://commons.pacificu.edu/pa>

Recommended Citation

Stompro, Kristine, "The efficacy of D-mannose in the prevention of recurrent urinary tract infections compared to long-term antibiotic therapy" (2017). *School of Physician Assistant Studies*. 610.
<http://commons.pacificu.edu/pa/610>

This Capstone Project is brought to you for free and open access by the College of Health Professions at CommonKnowledge. It has been accepted for inclusion in School of Physician Assistant Studies by an authorized administrator of CommonKnowledge. For more information, please contact CommonKnowledge@pacificu.edu.

The efficacy of D-mannose in the prevention of recurrent urinary tract infections compared to long-term antibiotic therapy

Abstract

Background: Recurrent urinary tract infections are a significant problem in women and the current mainstay of prophylactic therapy is long-term antibiotic use. Based on recent studies, there is a possible natural remedy that could reduce the use of antibiotics for preventative medicine in recurrent urinary tract infections. This would decrease the chance of antibiotic resistance and the side effects of the antibiotics to the user.

Methods: An exhaustive search of CINAHL, MEDLINE-Ovid, MEDLINE-PubMed, and Web of Science with the search terms “D-mannose” and “recurrent urinary tract infection” was performed. Eligible articles were assessed using the GRADE criteria.

Results: The search provided two pertinent articles comparing the efficacy of D-mannose to antibiotic therapy. Kranjcec et al⁴ demonstrated that there was no significant difference between nitrofurantoin and D-mannose therapy, but the side-effects of the antibiotic were considerable. Porru et al⁵ displayed a significant decrease in recurrence of urinary tract infections in the D-mannose group compared to the trimethoprim/sulfamethoxazole group.

Conclusion: D-mannose may become a useful prophylactic therapy for recurrent urinary tract infections, but further studies need to be performed to determine the efficacious dose and frequency of the therapy.

Keywords: D-mannose and recurrent urinary tract infections

Degree Type

Capstone Project

Degree Name

Master of Science in Physician Assistant Studies

Keywords

d-mannose, urinary tract infection

Rights

Terms of use for work posted in CommonKnowledge.

Copyright and terms of use

If you have downloaded this document directly from the web or from CommonKnowledge, see the “Rights” section on the previous page for the terms of use.

If you have received this document through an interlibrary loan/document delivery service, the following terms of use apply:

Copyright in this work is held by the author(s). You may download or print any portion of this document for personal use only, or for any use that is allowed by fair use (Title 17, §107 U.S.C.). Except for personal or fair use, you or your borrowing library may not reproduce, remix, republish, post, transmit, or distribute this document, or any portion thereof, without the permission of the copyright owner. [Note: If this document is licensed under a Creative Commons license (see “Rights” on the previous page) which allows broader usage rights, your use is governed by the terms of that license.]

Inquiries regarding further use of these materials should be addressed to: CommonKnowledge Rights, Pacific University Library, 2043 College Way, Forest Grove, OR 97116, (503) 352-7209. Email inquiries may be directed to: copyright@pacificu.edu

The Efficacy of D-mannose in the prevention of Recurrent Urinary Tract Infections Compared to Long-Term Antibiotic Therapy

Kristine Stompro



A Clinical Graduate Project Submitted to the Faculty of the

School of Physician Assistant Studies

Pacific University

Hillsboro, OR

For the Masters of Science Degree, 2017

Faculty Advisor: Annjanette Sommers, PA-C, MS

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Kristine Stompro moved to Hillsboro, OR from Boise, ID where she graduated from Boise State University with an Athletic Training degree. She practiced in a physical therapy office and a high school for three years before attending Pacific University. She enjoys hiking, camping, and anything that allows exploration of the beautiful Northwest.

Abstract

Background: Recurrent urinary tract infections are a significant problem in women and the current mainstay of prophylactic therapy is long-term antibiotic use. Based on recent studies, there is a possible natural remedy that could reduce the use of antibiotics for preventative medicine in recurrent urinary tract infections. This would decrease the chance of antibiotic resistance and the side effects of the antibiotics to the user.

Methods: An exhaustive search of CINAHL, MEDLINE-Ovid, MEDLINE-PubMed, and Web of Science with the search terms "D-mannose" and "recurrent urinary tract infection" was performed. Eligible articles were assessed using the GRADE criteria.

Results: The search provided two pertinent articles comparing the efficacy of D-mannose to antibiotic therapy. Kranjcec et al⁴ demonstrated that there was no significant difference between nitrofurantoin and D-mannose therapy, but the side-effects of the antibiotic were considerable. Porru et al⁵ displayed a significant decrease in recurrence of urinary tract infections in the D-mannose group compared to the trimethoprim/sulfamethoxazole group.

Conclusion: D-mannose may become a useful prophylactic therapy for recurrent urinary tract infections, but further studies need to be performed to determine the efficacious dose and frequency of the therapy.

Keywords: D-mannose and recurrent urinary tract infections

Acknowledgements

To my family: Thank you for believing in me even when I didn't. You have been a consistent support that has truly gotten me to where I am today.

To *my partner, Ryan*: Thank you for all the love and support that you have shown through these last two years. You have put in just as much work, if not more, than I have and you deserve so much more recognition than this paragraph can offer.

Table of Contents

Biography	2
Abstract.....	3
Acknowledgements.....	4
Table of Contents.....	5
List of Tables	6
List of Appendices	Error! Bookmark not defined.
BACKGROUND	7
METHODS	8
RESULTS	9
DISCUSSION	12
CONCLUSION	15
References	16
Table I. Characteristics of Reviewed Studies	17
Table II. Summary of Findings	18

List of Tables

Table 1:	Quality Assessment of Reviewed Studies
Table 2:	Summary of Finding

List of Abbreviations

CDAD	Clostridium Difficile Associated Disease
UTI	Urinary Tract Infection
CFU	Colony Forming Units
LUTS	Lower Urinary Tract Symptoms
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation

The Efficacy of D-mannose in the Prevention of Recurrent Urinary Tract Infections Compared to Long-Term Antibiotic Therapy.

BACKGROUND

Urinary tract infections (UTI) are a frequent chief complaint for primary care visits. It is estimated that in 2007, 8.6 million people were treated for a UTI in medical centers across the United States, 60% of those being primary care settings.¹ In 2010, they estimated that the annual cost for treatment of urinary tract infections is approximately \$2.3 billion in the United States.² Of those that suffer from a urinary tract infection, many experience a recurrence. In a national study³ completed in 2016, 102 out of 100 000 females were found to suffer from recurrent urinary tract infections. This is defined as greater than 1 UTI in a 6-month period or 3 or more in a 12-month period.³⁻⁵ This translates into a greater number of primary care visits and higher prescription costs.

The current mainstay of treatment for this complaint is to prescribe long-term antibiotic therapy for prophylactic measures. The most commonly used are nitrofurantoin, trimethoprim/sulfamethoxazole (TMP/SMX), or ciprofloxacin.⁶ There are many negative outcomes with this treatment strategy such as *Clostridium difficile* associated disease (CDAD), decreased efficacy of birth control, and antibiotic resistance.⁷ Currently, the most commonly prescribed and safest antibiotic for prevention of recurrent urinary tract infections is Nitrofurantoin, which can cause acute pulmonary hypersensitivity or pneumonitis, liver damage, and blood dyscrasias.^{8,9} In 1980, a study⁹ in Sweden reported that Nitrofurantoin represented 10-12% of reports of adverse

reactions to medications with 48% of those being pulmonary reactions. An alternative therapy needs to be discovered due to the negative effects of antibiotics and the extensive medical and prescription costs.

This conclusion led to the study of a hypothesized treatment method: cranberry juice. This natural remedy has been studied for many years as a treatment or preventative method for urinary tract infections. The fruit is suspected to have properties that reduced bacterial adherence. However, studies did not form a consensus based on irregular results and the inability to determine effective formulation and dose. This led to the study of D-mannose, the sugar found in cranberries, as well as, other fruits.⁵ Bacteria have projections called pili that adhere to the wall of the urinary tract causing the infection. The sugar is thought to bind to the pili of the bacteria inhibiting it from adhering to the epithelial cells of the urinary tract.⁴ This allows the bacteria to be voided through the urine attached to excess D-mannose. However, before providers begin to recommend this therapy in place of the current standard antibiotic prophylaxis, the efficacy of D-mannose in the prevention of recurrent urinary tract infections in women compared to long-term antibiotic therapy needs to be determined.

METHODS

A comprehensive search of CINAHL, MEDLINE-Ovid, MEDLINE-PubMed, and Web of Science with the search terms “D-mannose” and “recurrent urinary tract infection” was performed. Due to the lack of relevant articles, an additional search was conducted using Google and the search terms “D-mannose” and “recurrent urinary tract infection.”

The articles were chosen based on the eligibility criteria. This included defining recurrent urinary tract infections (UTIs) as 2 or more positive urine cultures in 6 months or 3 or more in 12 months, comparing D-mannose therapy to antibiotic therapy, and determining recurrences of UTIs during administration of the therapies. Other inclusion criteria included human studies and those published in English. Applicable articles were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE).

RESULTS

The search of the prominent databases produced 180 results. Out of these, 3 were repeats and 14 were deemed relevant. Three of the pertinent articles were in German and only 1 out of the 14 answered the clinical question. The Google search produced a relevant article from the Journal of Clinical Urology that was not found on any of the databases. Both chosen articles^{4,5} were randomized control trials, with the second being a cross-over study. See Tables 1 and 2.

Kranjcec et al

This study⁴ was a randomized control trial that compared a D-mannose therapy group, a nitrofurantoin therapy group, and a non-prophylaxis group. The authors wanted to look at both the rate and frequency of recurrence of UTIs, as well as the complications of the various therapies.⁴

All patients enrolled in the study were over 18, suffered from recurrent UTIs, and were currently diagnosed with acute cystitis. The diagnostic criteria included a clean void of 1 mL midstream urine with 10^3 or more colony forming units (CFU) along with at least 2 lower urinary tract infection symptoms (LUTS). These consisted of dysuria, frequency, urgency, suprapubic pain, nocturia, and hematuria. Patients were excluded from the study

if they were pregnant, trying to conceive, or breastfeeding; had symptoms of an upper urinary tract infection, systemic inflammatory involvement (fever or elevated white blood cell count), urinary tract anomalies, interstitial cystitis, or diabetes; were taking hormone therapy or contraception; or had already received antibiotics for their current acute cystitis. The 308 participants that met eligibility criteria were treated with ciprofloxacin 500 mg twice daily for 1 week and then identified *as treated* once their urine displayed less than 10^3 CFU and did not report any LUTS. They were then randomized into the 3 groups by throwing the dice.⁴

The first group was identified as the D-mannose group and received 2 grams of D-mannose powder diluted in 2 mL of water once daily in the evening, the second group received 50 mg of nitrofurantoin once daily in the evening, and group 3 received no prophylaxis. During the 6 months of the study, if a patient reported symptoms of a UTI, a clean urine sample was taken and the number of CFUs were identified. If the participant displayed greater than 10^3 CFU they were diagnosed with a UTI and were removed from the study to be treated with antibiotics.⁴

At the completion of the trial, there were 15 reported UTIs out of the 103 participants in the D-mannose group, 21 out of the 103 in the nitrofurantoin group and 62 out of the 102 in the no prophylaxis group. The study⁴ reported the difference in recurrence of the D-mannose and nitrofurantoin group as not significant. See Table 2. However, the reported side-effects were significantly lower in those taking D-mannose compared to those taking nitrofurantoin. Only 8 (8%) in the D-mannose group reported complications, all of which were diarrhea, where 29 (28%) in the nitrofurantoin group

reported various side-effects including diarrhea, nausea, headache, skin rash, and vaginal burning (RR of 3.5 and NNH of 5).⁴

Porru et al

This study⁵ was identified as a randomized control study with cross-over that was comparing the rate and frequency of UTI recurrence in a therapy group treated with D-mannose and one treated with trimethoprim/sulfamethoxazole (TMP/SMX).⁵

Eligibility criteria included females over 18 who currently have documented acute cystitis with greater than 10^5 CFUs and have had more than 3 UTIs in the past 12 months. Patients were excluded if they were pregnant or attempting to conceive; had an upper UTI, and/or temperature $>38^\circ$ C, flank/lumbar pain or tenderness, renal disease, anatomical abnormalities, prior gynecological surgery, or immunosuppressive medications or disease; or had taken antimicrobials in the last 4 weeks.⁵

There were 60 eligible participants that were randomly placed into 2 groups; a D-mannose group and a TMP/SMX group. The D-mannose group was instructed to take 1 g of oral D-mannose three times a day, separated by 8 hours, for 2 weeks, then the dose decreased to 1 g twice daily for 22 weeks. The TMP/SMX group had a regimen of 160 mg/800 mg tablets twice a day for 5 days, and subsequently 1 dose at bedtime for 1 week each month. The study wanted to maintain efficacy of the D-mannose which works the best at a neutral pH; therefore, the patients were instructed to measure urinary pH with dipsticks and adjust as necessary with sodium bicarbonate or potassium citrate if pH was <7 . After 24 weeks of the study, the participants switched groups and followed the other groups regimen in order to obtain a larger sample size.⁵

The study's primary outcome measurement was the time to recurrence of UTI in the 2 groups, and the secondary outcome was the visual analogue scale for pain and urgency (VAS). If a participant complained of UTI symptoms both a urine culture and VAS were taken. If the culture displayed greater than 100 000 CFU, the urine was considered positive.⁵

Only 12 out of the 60 (20%) cross-over participants in the D-mannose group had a positive urine culture following the 24 weeks of the study and 45 out of the 60 (75%) participants that took TMP/SMX had one recurrence, 10/60 (17%) had two, leaving 5/60 (8%) who did not have a recurrence. The mean time to recurrence for the D-mannose group was 200 days, while it was 52.7 days for the antibiotic group. This study displayed a significant difference between the D-mannose group and the antibiotic group.⁵

DISCUSSION

Due to the data in these studies,^{4,5} there is significant evidence to argue for D-mannose to be used as a prophylactic agent in those who suffer from recurrent urinary tract infections. Both TMP/SMX and nitrofurantoin are common antibiotics prescribed for prevention of recurrent urinary tract infections and the data presented from each study demonstrates that D-mannose, when taken regularly, is comparably effective for decreasing recurrence or limiting side-effects from the treatment.

D-mannose is also a cost effective approach to treatment compared to the cost of prescription drug use. The current cost of a 4-month supply of D-mannose is \$36.42 at a drug store in comparison of between \$300 to \$400 for a 3-month supply of nitrofurantoin and \$77.70 for TMP-SMX.¹⁰⁻¹² This does not include the frequent physician visits needed

to obtain prescription refills increasing the annual cost of antibiotic treatment depending on insurance coverage.

According to the reviewed studies^{4,5} there is very little risk with chronic D-mannose use, especially when compared to long-term antibiotic use. According to a study⁷ that examined *Escherichia coli* in urine from over 200 United State laboratories from 2000 to 2010, they found TMP/SMX resistance increased from 17.9% to 24.4% and nitrofurantoin 0.8% to 1.6% in 10 years. These results do not appear to display a rapid growth in resistance; however, these were not the most prescribed antibiotics for urinary tract infections. Ciprofloxacin with its broad spectrum coverage, was the most frequently prescribed antibiotic for UTIs and consequently had the highest growth in resistance.⁷ In the 10 year study,⁷ *Escherichias coli*'s resistance to ciprofloxacin increased from 3% to 17.1%. This has led to a shifting treatment paradigm from ciprofloxacin to TMP-SMX and nitrofurantoin creating a concern for similar resistance of these two medications.

Despite, the remarkable findings listed in this review, each study has its limitations. Kranjcec et al⁴ excluded diabetic patients from the study, but Porru et al⁵ did not mention the use or exclusion of diabetic participants. The use of D-mannose in diabetic mellitus (DM) patients needs to be further evaluated. Considering that the supplement is a simple sugar, research needs to be conducted to establish safety of use in patients with DM. This factor is essential for providers to be aware of before recommending it to their patients.

The only limitation identified in Kranjcec et al⁴ was the lack of blinding of both the participants and the data collectors as there was no mention of matching the

medications including adding the use of a placebo for the no prophylaxis group.

However, because of the reliability of urine cultures, it is not a serious limitation.

Other limitations were identified in the Porru et al⁵ study during appraisal. Because it was a cross-over study, there should have been a washout period. Therefore, the participants did not begin the second 24 weeks with the same eligibility criteria of acute cystitis. There is an understanding that not all patients would immediately get acute cystitis once the treatment was stopped, and it would not be feasible or humane to cause this to occur. Additionally, due to this limitation, there should have been separate data presented for each 24-week period. This would have revealed whether the greatest recurrence of urinary tract infections occurred in the first 24 weeks or the second for each group. The only data given identifying a difference in timing is the mean time to recurrence.⁵

The final limitation to Porru et al⁵ is the lack of treatment of the participant's acute cystitis prior to starting the trial. Kranjcec et al⁴ treated the acute cystitis prior to administration of the therapy allowing the study to focus on the prophylactic nature of D-mannose. Porru et al⁵ did not separate treatment from prophylaxis; therefore, it cannot identify whether D-mannose is better at treating or preventing recurrence of the urinary tract infection. The results of the study⁸ demonstrate a significant enough difference making it a less serious limitation.

Future studies do need to be completed. The dosing of D-mannose is not fully established. The Kranjcec et al⁶ study used 2 g once daily while the Porru et al⁸ study used 3 g in divided doses daily and both demonstrated efficacy in preventing recurrent UTIs. Additionally, it is not clear whether or not D-mannose is safe or effective in

patients with diabetes or children. Lastly, longitudinal studies would be beneficial in evaluating if there is a similar relapse to recurrency of UTIs as compared to antibiotic prophylaxis.

CONCLUSION

According to the studies evaluated, D-mannose could be used as a prophylactic measure for recurrent urinary tract infections. There is no evidence for the use of D-mannose as a treatment of urinary tract infections, but once treated, these studies suggest a positive response for use to prevent recurrence. However, more studies need to be performed to determine the appropriate dose and frequency of the therapy. Long-term follow-up would also be beneficial to demonstrate any adverse effects of D-mannose. Overall, the current research establishes D-mannose as an efficacious therapy for prevention of recurrent urinary tract infections and can be recommended to patients as a cost-effective and low-risk option for prevention of uncomplicated recurrent urinary tract infections.

References

- 1 Schappert S, Rechtsteiner E. Ambulatory medical care utilization estimates for 2007. *Vital and Health Statistics* [35 leading primary diagnosis]. 2011;13:1--45.
- 2 Foxman B. The epidemiology of urinary tract infection. *Nature Reviews*. 2010;7:653--660.
- 3 Suskind A, Saigal C, Hanley J, Lai J, Setodji C, Clemens J. Incidence and Management of Uncomplicated Recurrent Urinary Tract Infections in a National Sample of Women in the United States. *Urology*. 2016;90:50--55.
- 4 Kranjcec B, Papes D, Altarac S. D-mannose powder for prophylaxis of recurrent urinary tract infections in women: a randomized clinical trial. *World J Urol*. 2014;32:79-84.
- 5 Porru D, Parmigiani A, Tinelli C, et al. Oral D-mannose in recurrent urinary tract infections in women: a pilot study. *Journal of Clinical Urology*. 2014;7:208.
- 6 Fihn SD. Acute Uncomplicated Urinary Tract Infection in Women. *N Engl J Med*. 2003;349:259-266.
- 7 Sanchez G, Master R, Karlowsky J, Bordond J. In Vitro Antimicrobial Resistance of Urinary Escherichia coli Isolates among U.S. Outpatients from 2000 to 2010. *AAC*. 2012;56:2181--2183.
- 8 McKinnell J, Stollenwerk N, Jung C, Miller L. Nitrofurantoin Compares Favorably to Recommended Agents as Empirical Treatment of Uncomplicated Urinary Tract Infections in a Decision and Cost Analysis. *Mayo Clinic Proc*. 2011;86:480--488.
- 9 Holmberg L, Boman G, Bottiger IE, Eriksson B, Spross R, Wessling A. Adverse Reactions to Nitrofurantoin Analysis of 921 Reports. *American Journal of Medicine*. 1980;69:733--738.
- 10 Walmart. Solaray D Mannose with Cranactin 1000 mg Vegetable Capsules, 120 Count. Available at: <https://www.walmart.com/ip/Solaray-D-Mannose-with-Cranactin-1000-mg-Vegetable-Capsules-120-Ct/146362891?wmlspartner=wlp&selectedSellerId=0&adid=2222222227041760255&w0=&w1=q&w2=c&w3=61289724218&w4=pla-101342079218&w5=9033084&w6=&w7=&w8=&w9=pla&w10=8175035&w11=online&w12=146362891&w13=&veh=sem>. Accessed April 17, 2017.
- 11 Truven Health Analytics. Red Book Online: Nitrofurantoin Macrocrystals. Available at: <http://www.micromedexsolutions.com.proxy.lib.pacificu.edu:2048/micromedex2/librarian/PFActionId/evidencexpert.ShowRedBookSearchResultsForActiveIngredient?SearchTerm=Nitrofurantoin>

[oin,%20Macrocrystals&navResults=relatedProductLookupRedBook](#). Accessed April 17, 2017.

- 12 Truven Health Analytics. Red Book Online: Sulfamethoxazole/Trimethoprim. Available at: <http://www.micromedexsolutions.com.proxy.lib.pacificu.edu:2048/micromedex2/librarian/PFActionId/evidencexpert.ShowRedBookSearchResultsForActiveIngredient?SearchTerm=Sulfamethoxazole/Trimethoprim&navResults=relatedProductLookupRedBook>. Accessed April 17, 2017.