

REPORT

The Effects of U-Tract, a Branded Form of D-Mannose, as a Practical Therapeutic Agent for the Management of Urinary Tract Infections.

Submitted to Progressive Laboratories, Inc.

by

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INTRODUCTION

Urinary tract infections are a very common clinical problem that are very gender specific, especially in women throughout their lifetime. Men become afflicted by urinary tract infections in the latter part of their years, mostly due to obstructive uropathy. Nationally, over ten million medical office visits a year are related to urinary tract infections, and up to 6% of all visits by women to primary care physicians are related to urinary symptoms. Statistically in the United States, 50% of the total female population will experience at least one urinary tract infection in their lifetime, half of which will be bacterial in origin with painful urination. Over 20% of women between the ages of 20 and 65 suffer one attack annually, and 2-4% of apparently healthy women who are asymptomatic have elevated levels of bacteria in the urine. Between the ages of 20 to 50, occurrence of urinary tract infections is 50 times greater in women than men. However, this gender gap narrows significantly after the age of 50.

Coliform bacteria cause 80 to 90% of all urinary tract infections with the leading bacterial cause being *Escherichia coli* (*E. coli*). Other bacterial causes are *Staphylococcus Saprophyticus*, *Klebsiella Pneumoniae*, *Proteus spp* and *Enterococcus spp*. The presence of *E. coli* normally found in the rectal or peritoneal area performs several bio-supportive functions in the bowel. However, when displaced to the wrong areas, the tendency of *E. coli* is to imbed itself in the hosts GU system. The symptoms of urinary tract infections are manifested in the host body attempting to rid itself of displaced *E. coli*. These symptoms may include painful, erratic and frequent bladder activity.

Current management of urinary tract infections consists of three or more days of antibiotic treatment. Typical prescription medications used today are Bactrim (sulfamethoxazole) Macrochantin (nitrofurantoin) or Cipro (fluoroquinolones). Antibiotics have provided excellent treatment for infections for some time, but there is a genuine concern of having an allergic reaction, failure of the antibiotic to control the infection, and the inducement of different bacteriological cell populations that may affect

the genitourinary systems in the form of bothersome vaginal infections or the development of gastrointestinal side effects. Of rising concern are generations of bacteria now evolving that are becoming resistant to available antibiotics due to excessive use. A recent roundtable (August 2002) presented by The Office on Women's Health of the United States Department of Health and Human Services focused exclusively on the impact of antibiotic resistance and the treatment of urinary tract infections in women. Conclusions from the conference confirmed acute urinary tract infections are a common health problem for women and increasing rates of antibiotic resistance are challenging traditional empiric therapies such as sulfamethoxazole. In addition new generations of antibiotics such as the fluoroquinolones (ie. CIPRO) are already reaching alarming resistance rates in some geographic areas, leading to recommendations limiting their empiric use in the management of uncomplicated infections and reserving their use for severe infection.

D-Mannose is a natural occurring simple sugar that appears to offer a safe practical alternative for the treatment of urinary tract infections. D-Mannose is absorbed 8 times slower than glucose, and when ingested, is not converted to glycogen or stored in the liver, but rather goes directly to the blood stream from the upper gastrointestinal tract. The greater part of D-Mannose is therefore immediately filtered through the kidneys and descends through the bladder. The bladder lining is comprised of polysaccharides, a form of glycoproteins or sugar molecules. When displaced E. coli bacteria is present in the bladder lining, finger-like projections of the E. coli adhere to these sugar molecules, imbedding in the bladder lining and initiating an infection.

In the presence of D-Mannose, certain bacteria including E. coli, exhibit a greater attraction to attach themselves to the D-Mannose molecule rather than to the mucous membrane of the bladder lining. Therefore, bacteria that are "Mannose positive" combine with Mannose to form a biochemical complex which is subsequently expelled with the next voiding.

For many years the unique properties of Mannose have been utilized as a diagnostic agent for the differentiation between aggressive, virulent, coliform bacteria and less aggressive, less pathogenic, coliform organisms. The practical consideration of using Mannose when confronted with symptoms of urinary tract infection is obvious, no prescription is required. Mannose is a natural substance that has few side effects, and most likely will work 80-90% of the time due to the fact that coliform organisms, the type disabled by Mannose, cause 80-90% of urinary tract infections. Whereas treatment with antibiotics induces a radical change in the bacterial populations, perhaps inducing fungal infections and/or gastrointestinal infections, Mannose removes bacteria by attachment and voiding, thus avoiding complete bacterial alteration. In addition to being readily available, D-Mannose is inexpensive.

There are over 14,000 citations in published literature about Mannose, and there have been numerous therapeutic utilization's, but prior to this study, no concentrated long range observations with urinary tract infections being treated with Mannose have been reported.

Statement of Purpose

The purpose of this study was to evaluate the effects of U-Tract, a branded form of D-Mannose, as a practical therapeutic agent for the management of urinary tract infections.

Subjects and Methodology of Investigation

All subjects involved in this study possessed two common characteristics:

1) they were long term patients of Dr. Michael Blue, board certified urologist, and 2) each patient had a history of reoccurring urinary tract infections.

The study consisted of forty two females, ranging in ages from 12 to 83 years old, and eighteen males, ranging in age from ___ to ___. Patients were selected on the basis of their subjective complaints and objective findings with a presumptive diagnosis of urinary tract infection. Each subject was initially cultured to determine specific bacterial cause, if any, and each subject was started on a daily regimen of D-Mannose (U-Tract) as the primary therapy. Subjects were fully advised about D-Mannose and it's potential therapeutic use.

All patient co-morbid conditions such as stones, tumors, and trauma eliminated potential subjects from study participation. The evaluation period for this investigation was June 1, 2002 to January 1, 2003.

Since all subjects had a long history of urinary tract infections under the treatment and supervision of Dr. Michael Blue, post genitourinary histories served as control(s) for this study. The only therapeutic change instituted with the study group was the use of D-Mannose (U-Tract) as directed by Dr. Blue.

Results

Any study about urinary tract infections reveals obvious gender differences; the results of this study reveals the same. As an overview of this study, few men responded as dramatically as the women. Obviously, the number of men represented in this study, 18 represented only 30% of the total subjects evaluated, so additional work on an expanded basis is suggested, including a significant evaluation of men suffering from prostatitis.

Several existing urological studies demonstrate that symptoms of urinary tract infections, when cultured, rarely reveal more than a 50% level of actual or clinical urinary tract infections. The findings of cultures performed in this study are similar, which underline the fact that not all painful conditions of bladders are infectious in origin.

It is typical of women to see numerous physicians from family practitioners, to gynecologists, to urologists for what they believe are repeated urinary tract infections. When not confirmed by culture, the diagnosis is deemed painful bladder syndrome, a condition that has numerous causes.

In this study involving 42 women, 24 were confirmed by urine culture to have a urinary tract infection, and its respective bacteria. In 19 cases, or approximately 80% of the cases, E. coli was the diagnosed cause. In 4

cases, the bacteria Klebsiella, was the diagnosed cause. In the remaining single case, a mixed bacteria was the diagnosed cause.

In this confirmed culture group the recommended course of action was 2 scoops of D-Mannose (U-Tract) daily for one week. Although every attempt was made to have urine re-cultured, 12 or 50% of this group returned for follow-up re-cultures. Eight of the 12 re-cultured were negative for growth. Patient feedback was generally that their symptoms had disappeared, and they did not require additional assistance.

Statistically, 17 of the 24 (71%) of the females in the confirmed culture group that were treated with D-Mannose (U-Tract) reported improvement in symptoms. Three of the 24 (12.5%) were unable to be contacted, but did not return for additional treatment. Only 4 of 24 (17%) reported no change or improvement in symptoms when undergoing use of D-Mannose.

Those females who were not confirmed by urine culture to have bacterial urinary tract infection, but had symptoms normally associated with urinary tract infection were classified into the group identified as the painful bladder syndrome ("PBS") group. This study had 18 females in its PBS group; all treated daily with 2 scoops of D-Mannose (U-Tract). Remarkably, 17 of 18 (94%) subjects reported symptom improvement; the lone case being a study subject unable to be contacted, but also not returning for treatment. Even more noteworthy is 80% became totally symptom free and requested additional D-Mannose (U-Tract) to be used preventively.

Eighteen males were involved in this study, 10 of whom were confirmed by urine culture to have a urinary tract infection. Seven men had neurogenic bladders from spinal cord injuries, three of the seven were on intermittent catheterization, and the remaining four had indwelling supra-pubic tubes.

Two men in the study group had been incapacitated with recurrent sepsis, retention, and obstructive uropathy. Both men underwent insertion of supra pubic tubes. Once released from the hospital, both were placed on a daily regimen of D-Mannose (U-Tract). Improvement was evidenced by their ability to avoid additional hospitalization.

In the group diagnosed with urinary tract infection caused by E. coli and treated with D-Mannose (U-Tract), significant improvement was reported. Due to the composition of the male study group, fewer of them responded as dramatically as the female group.

Significant Findings of this Study

1. All studies involving urinary tract infections reveals obvious gender differences. The results of this study reveals the same.
2. Consistent with existing literature, approximately 50% of those reporting symptoms of urinary tract infections were actually confirmed by urine culture to possess bacterial infection. The therapeutic use of D-Mannose (U-Tract) on acute urinary tract infection in this study was significantly effective in eliminating or substantially improving symptoms.
3. In addition to the significant therapeutic benefits exhibited by D-Mannose (U-Tract) on specific bacterial causing agents (ie: E. coli), D-Mannose (U-Tract) produced remarkable results for Painful Bladder Syndrome Group. More than 80% of this group became symptom free using D-Mannose (U-Tract). Over the six months of this study, three females with different issues presented most noteworthy responses to Mannose (U-Tract). The first is a fifty-year old lady with neurogenic bladder and incontinence suffering from a documented urinary tract infection every month. Endoscopically, her bladder revealed numerous areas compatible with recurrent urinary tract infections. After three months of D-Mannose (U-Tract), her urine was completely sterile and her bladder mucosa returned to normal. The second had been under my care for twenty years. Her main complaint was bladder pain for which she received numerous therapeutic attempts, none of which were successful.

After one week of D-Mannose (U-Tract) her pain ceased. The third lady presented an E. coli infection and pronounced structural findings in her bladder called Cystitis Cystica, all which disappeared after three months on D-Mannose (U-Tract).

4. Interstitial Cystitis ("IC") is a treatable but essentially incurable condition manifested by chronic pelvic pain and urinary frequency, occurring in the absence of any known etiology and remains an enigma to urologists. Since there is considerable information about IC, but a paucity of knowledge, there are no diagnostic or therapeutic absolutes. Challenges remain because most studies on IC are not controlled. For example, hydrodistention of the bladder under anesthetic, is diagnostic, but could be therapeutic.

D-Mannose (U-Tract) may have a place in the treatment for IC since one of the findings in IC is the abnormality in the mucus layer over the bladder wall. Under normal conditions our bladders are not exposed to urine and remain "dry". The lining of the bladder is a complex carbohydrate called the "gag" layer, which coats the bladder mucosa. Any breach of this layer allows urine to be in contact with the mucosa of the bladder. Many believe this may be the initial event in IC development, therefore, therapy has been directed along this line. To repair the "gag" layers, has consisted of intravesical heparin, which is complex carbohydrate. Some patients respond well to heparin, but because this is a predominately female disease, chronic use of heparin is contraindicated because of the possibility of osteoporosis. An oral pentosanpolysulfate is used for IC with modest results. It's very expensive, not overly efficacious, and must be taken for 6 to 9 months.

D-Mannose (U-Tract) may be a viable alternative to sodium sulfated pentosanpoly sulfate since it is a pentose sugar with some affect on the mucous layer of the bladder. Part of my thoughts evolved out of the positive response of patients with painful bladder syndromes ("PBS"). These patients who came in with symptoms of a UTI, but whose urine was sterile, were initially placed on D-Mannose (U-Tract) - 2 scoops BID. Patients with PBS responded well to D-Mannose (U-Tract) in the absence of a documented UTI. An unexpected benefit for many of these patients was the resolution of pain, frequency, and a decreased sense of voiding pressure. Some demanded to stay on D-Mannose (U-Tract).

Why does D-Mannose (U-Tract) therapy relieve bladder symptoms when no infection is present? I believe it interacts with the "gag" layer to resolve mucosal irritation, reduce afferent nerve stimuli, and possibly reduce chemotaxis or inflammatory cellular stimulation.

Summary

The majority of subjects were female, which was expected. In summary, D-Mannose (U-Tract) appears to have considerable efficacy for simple uncomplicated UTI's. D-Mannose (U-Tract) may be utilized in Interstitial Cystitis and for patients with painful bladder syndrome. The role for D-Mannose (U-Tract) on male subjects requires more examination in terms of both numbers as well as specifics.