Original Article

Methenamine Hippurate As Good As Antibiotic Prophylaxis For Recurrent UTI

Isha Vedpathak[1*], Vijendra Rajan[2], Pragnesh Patni[3]

[1*, 2, 3] Khyati Collage of Pharmacy, plot no.-16 Palodiya, Ahmedabad

***Corresponding Author:** Isha Vedpathak

*Khyati Collage of Pharmacy, plot no.-16 Palodiya, Ahmedabad. Email: ishavedpathak3131@gmail.com
Doi: 10.47750/pnr.2022.13. S05.364

Abstract

Older persons frequently get urinary tract infections (UTIs), which can develop more serious, potentially diseases. It is belived that aging –related physiological changes are a cause in the higher frequency of UTI recurrence in older persons .unfortunately there aren't many ways toprevent UTI in older persons, and using Antibiotics to do so can have lot of unfavourable effect. Because it function as urinary antiseptic and produce safely formal ehyde to inhibit bacterial., methenamine has been suggested as a beneficial medication for the prevention of UTI.

Keywords: Aged, Antibiotic prophylaxis, older adult,methenamine, Urinary anti infective agents, urinary anti infective agent

INTRODUCTION

A urinary antibacterial drug called methenamine hippurate, sometimes referred to as hexaminehippurate, is meant to "suppress or eliminate urinary tract bacteria" [1]. Methenamine was originally used as a urinary antiseptic drug in 1894 It is also known as hexamine, hexamethylenetetramine, urotropine, and aminoform[2,3] the United States (US), urinary tract infection (UTI) accounts for almost 5% of all emergency department visits by adults 65 years and older[4]. A urinary tract infection can reduce an older person's quality of life, increase theirrisk of hospitalisation, and give rise to more serious, perhaps fatal illnesses[4]. Both in males and in women, the likelihood of getting a UTI rises with age. Over 10% of women aged 65 to 85 in the United States reported having a UTI over the previous 12 months, with that percentagerising to almost 30% for women 85 and older, according to a study that polled about 30,000 women in the country. Males between the ages of 18 and 24 were reported to have a 0.01 per person-year incidence of UTI; this rate rose with age to 0.05 per person-year for men betweenthe ages of 65 and 74, and finally to 0.08 per person-year for men 85 years and older[5, 6]. UTIs include both kidney-related upper urinary tract infections and lower urinary tract infections like cystitis (pyelonephritis[7]. Gram-negative rods like Escherichia coli, Klebsiella spp.,Pseudomonas aeruginosa, and Proteus spp., as well as Gram-positive cocci like Enterococcus faecalis, Streptococcus agalactiae, and Staphylococcus saprophyticus, are frequently the causeof UTI.[8] The US Food and Drug Administration (FDA) has licenced methenamine for the prevention of recurrent urinary tract infections (UTI) in patients aged 6 and older, and studies have shown that it is effective as an antimicrobial-sparing substitute in this patient population[9]Methenamine, an organic chemical that when given orally travels to the bladder and breaks down in the acidic environment to create formaldehyde and ammonia, was initially marketed as a urinary antiseptic in 1899.[10]By non-specifically alkylating the amino and sulfhydryl groups of proteins and the ring nitrogen atoms of purine bases, formaldehyde inactivates bacteria14[11.] While there is a dearth of information regarding the use of methenamine in transplant recipients, published data show that the drug is effective in preventing recurrent UTIin patients who are not transplant recipients. Methenamine may be useful in preventing cystitisin patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89),according to a meta-analysis of thirteen mixed-quality studies with 2032 participants. The studyalso found that overall methenamine adverse event rates, despite being poorly reported, were low[12]. Although hemorrhagic cystitis was one of the side effects that caused methenamine to lose popularity in the 1990s, it still presents a viable alternative to traditional targeted preventative antibiotics because it should be equally as effective and put less strain on the emergence of antibacterial resistance 16.[13] Although there is a lack of published data regardingthe use of methenamine in transplant recipients, there is published data demonstrating the effectiveness of methenamine in reducing recurrent UTI in patients who are not transplant recipients. Methenamine may be helpful in preventing cystitis in patients without renal tract abnormalities (symptomatic UTI: RR 0.24, 95% CI 0.07 to 0.89), according to a meta-analysisof 13 mixed-quality studies with 2032 participants. It was also found that, despite being poorlydescribed, methenamine's overall adverse event rate was low 15[14]. Although hemorrhagic cystitis and other side effects caused methenamine to lose popularity in the 1990s, it still presents an enticing alternative to standard targeted preventative antibiotics because it should be effective and ease the pressure on bacterial resistance.[15] Gram-negative rods like Escherichia coli, Klebsiella spp., Pseudomonas aeruginosa, and Proteus spp., as well asGrampositive cocci like Enterococcus faecalis, Streptococcus agalactiae, and Staphylococcus saprophyticus, are common pathogens that cause urinary tract infections.[16] Methenamine hasbeen shown in studies to be an effective antimicrobial-sparing option in this patient population,and the US Food and Drug Administration (FDA) has licenced it for the prophylaxis of recurrent UTI

in individuals age 6 years and older[17]. Antibiotic prescriptions could be decreased if there were safe, efficient therapy options. Methenamine salts, such as methenamine hippurate, are an option that doesn't lead to antibiotic resistance and acts as a bacteriostatic agent by generating formaldehyde from hexamine in the urine. 3[18]. It is safe to use methenamine hippurate during pregnancy[19, 20]

RESULTS

RECURRENT URINARY TRACT INFECTION

Freeman 1968 In 122 males with persistent UTI, Freeman and colleagues assessed the effectiveness of continued therapy with urine-sterilizing drugs.[21] Patients qualified as having significant bacteriuria if they also had either a positive urine sediment or a renal biopsy that was consistent with the diagnosis of pyelonephritis. Significant bacteriuria is defined as the presence of > 105 organisms/ml of a single species or two cultures with 104 organisms/ml of the same Gram-negative rod. Patients first got antibiotic therapy based on the sensitivity of theurine culture. Patients were subsequently given one of four ongoing prophylactic choices on the final day of antimicrobial therapy: sulfamethizole 0.5 g four times per day, nitrofurantoin 50 mg four times per day, methenamine mandelate 1 g four times per day, or placebo four timesper day. Patients who participated in the analysis had therapy for at least 13 months and up to 25 months. Those who have a high creatinine. Results of culture tests and responders (sterile urine culture or less than 1000 organisms/ml) were used to track the effects of continuous prophylaxis. The prophylaxis with methenamine mandelate was associated with the greatest number of responders among all groups, according to the results of continuing therapy. Methenamine showed a considerable increase in both responders (75% versus 14%; p 0.001) and negative cultures (46% versus 3%; p 0.0005) when compared to placebo. Methenamine considerably outperformed nitrofurantoin and sulfamethizole in terms of the number of patientswho responded to treatment when compared to the other antimicrobial drugs examined (75% versus 43%; p 0.05). Negative cultural differences between agents, however, were nonexistent.Patients receiving methenamine had three incidences of adverse effects, including dyspnea, diarrhoea, and abdominal cramps.

1975, Freeman Expanding on the findings of the preceding 1968 study, Freeman and colleaguesassessed 249 men with symptomatic bacteriuria (defined as > 105 organisms/ml) in a prospective study of four continuous prophylactic regimens for 25 months: methenamine mandelate 1 g four times daily, nitrofurantoin 50 mg four times daily, sulfamethizole 0.5 g fourtimes daily, or placebo.[22]

Patients had to have "tissue infection" evidence, which was defined as either positive urine sediment or a kidney biopsy that supported the diagnosis of pyelonephritis. UTI recurrence and exacerbations, which are clinical infections characterised by inflammation of the urinary tractorgans, fever episodes necessitating antibiotic therapy, or both, were the main outcome. [23]

Bohensky investigated the potential of methenamine mandelate as a safe, well-toleratedtreatment for asymptomatic bacteriuria in elderly hospital patients. [24] 95 patients were enrolledin this trial, the majority of whom were catheterized and were not receiving immediate therapyfor an acute UTI. Patients received urinalysis prior to and during the trial period in order to identify the presence of bacteriuria using microscopic inspection and the triphenyl tetrazoliumchloride (TTC) test. A positive TCC test result for bacteriuria was characterised as a colour shift that occurs when large concentrations of urinary tract pathogenic organisms are present (organism concentrations not specified by the authors). Five patients stopped their therapy because their tastes changed. Prior to methenamine medication, 65 of the 90 individuals who completed the research tested positive for UTI, whereas 25 tested negative. Four times per day,each patient got 10 ml of methenamine mandelate suspension (1 g methenamine from a 100 mg/ml suspension. If their urine was alkaline, administering 2 g of ascorbic acid orally every day for the course of 3.5 weeks was used to acidify it. Before and during the trial, at 2 weeks and 3.5 weeks, a urinalysis was performed. Methenamine mandelate decreased the number of patients with bacteriuria, with 47 (72%) of those who had a positive urinalysis before starting medication changing it to a negative one by the end of the 3.5-week period. However, by the conclusion of the 3.5 week period, 13 of the 25 patients who had no substantial bacteriuria before to methenamine therapy developed a positive urinalysis. On these data, no statistical analysis was done. The authors did not discuss the development of bacteriuria leading in eithersilent or symptomatic UTI, or the occurrence of Prior to commencing methenamine for prophylaxis, ask individuals who had a negative TTC if they have bacteriuria. Furthermore, nonegative outcomes were reported.

The effectiveness of methenamine hippurate was assessed in 52 older females with chronic UTIby Parvio Parvio.[25] Each patient had a history of recurrent UTI and had been hospitalised in a long-term care facility for at least two years. In addition to long-term preventive antimicrobialtherapy substituted by methenamine hippurate at the beginning of the study, all patients received brief courses of antibiotic therapy for the treatment of UTI in the six months prior to the trial. Prior to prophylaxis with methenamine hippurate, patients had a urine analysis and were treated with antimicrobial drugs based on culture and sensitivity. Infection rates recordedin the 6 months prior to the experiment were compared to rates of re-infection during the 6- month course of therapy with methenamine hippurate 1 g twice daily. In addition, individuals with urine pH levels more than 5 received a daily dose of 2-4 g of oral ascorbic acid. Based onthe degree of incontinence and immobility (normal, partial, entire), patients were separated intothree groups for analysis. In comparison to no medication, methenamine hippurate prophylaxiswas linked with a lower risk of re-infection in all three patient groups: normal (0.45 against 2.82), partial (0.58 versus 4.33), and total (stated as total re-infection cases per person in each group over 6 months) (0.29 versus 5.24). No statistical evaluations of these findings were offered. Only 17 (42.5%) incidences of re-

infection occurred among the 40 patients who finished the 6-month course of medication, according to Parvio, which was objectively less than the 6-month period without therapy, in which there were 40 patients.

Allwood and McAllister A limited amount of further information about the security and effectiveness of methenamine hippurate in treating complex UTI in older adults is provided byfour case studies that McAllister and Allwood discuss. [26]

GENITORURINARY SURGICAL PROCEDURES

Guttu and Schiotz When administered prophylactically to surgical patients, Schiotz and Guttu discovered that methenamine hippurate dramatically decreased the incidence of postoperativebacteriuria and UTI [27]

Tyreman In 94 patients who underwent surgery for uterovaginal prolapse and had an indwellingcatheter inserted afterward, Tyreman and colleagues discovered that prophylactic methenaminehippurate dramatically decreased the rate of bacteriuria (defined as >105 organisms/ml of urine) at 3 days post-op.[28]
Wesolowski and colleagues conducted a study to compare the effectiveness of four antibacterial medications for preventing urinary tract infections in men having prostatectomy.[29]

Methenamine hippurate is typically administered orally twice day in doses of 1g for adults andchildren 12 years of age and older[30,31]. Hippuric acid keeps the pH of urine low, which promotes methenamine's conversion to formaldehyde and ammonia. For formaldehyde to exertbactericidal activity, urine must have a formaldehyde content of 25 micrograms per mL maintained for around 2 hours. Increased frequency, flow rates, and pH of the urine decrease formaldehyde production, concentration, and exposure time, and hence effect that is antibacterial Act of methenamine hippurate [32,33]. Methenamine was administered as a daily oral tablet dose of 1g with vitamin C. Although BID is advised for short-term methenamine treatment, we gave daily methenamine to improve patient compliance and convenience.[34] Methenamine is also given with ascorbic acid to assist acidify the urine since an acidic urine isnecessary for the conversion of methenamine into formaldehyde and some pathogens that breakurea and generate a more basic urine pH will have lower amounts of formaldehyde [35]. Manufacturers advise against using methenamine in individuals with severe renal failure (GFR10 ml/min) because of the possibility of hazardous serum levels.[36] dditionally, according to this meta-analysis, methenamine did not seem to be effective in people with neuropathic bladder 15.[36] While studies involving long-term exposure to methenamine have not yet beenestablished 21, studies involving formaldehyde have been extensively investigated in human carcinogen epidemiology involving lifetime occupational exposures.[37]

The following information on the pharmacological properties of methenamine hippurate is available in the Australian product information.
Methenamine is quickly absorbed after being taken orally. Twice-daily dose results in a peak plasma concentration of around 35 mg/L at steady state, which excludes drug accumulation.
Distribution: The average distribution volume is 0.56 L/kg, which is comparable to the amountof body water in adults
Metabolism: Stomach acid degrades a little amount of methenamine to formaldehyde. Antibiotic prescriptions may be decreased if there were safe, effective therapy options.[39,38]Methenamine salts, such as methenamine hippurate, are an option that doesn't lead to antibioticresistance and acts as a bacteriostatic agent by generating formaldehyde from hexamine in theurine [40]

CONCLUSION:

The effectiveness of methenamine in preventing UTI in older persons, aswell as its tolerance and safety profile, are all demonstrated in this review. However, this studyprovides evidence in favour of the use of methenamine for prevention of UTI in various populations of individuals 58 years and older, despite the paucity of data regarding its use in older adults, particularly those with impaired renal function. To determine the optimal dose and duration of methenamine for the prevention of UTI in older persons, more research is required.

REFRENCES

1. Medsafe. 2019. Medsafe Product Detail: Hiprex Tablet 1g 31 May 2019. URL: https://medsafe.govt.nz/regulatory/ProductDetail.asp?ID=1248 (accessed 24 May 2022).
2. Altinoz MA, Ozpinar A, Ozpinar A, et al. 2019. Methenamine's journey of 160 years: Repurposal of an old urinary antiseptic for treatment and hypoxic radiosensitization of cancers and glioblastoma. Clinical and experimental pharmacology & physiology 46(5): 407-412. DOI: https://dx.doi.org/10.1111/1440-1681.13070 (accessed 20190227//).
3. Richardson MW. 1899. ON THE VALUE OF UROTROPIN AS A URINARYANTISEPTIC WITH ESPECIAL REFERENCE TO ITS USE IN TYPHOID FEVER. J Exp Med 4(1): 19-27. DOI: 10.1084/jem.4.1.19
4. Rowe TA, Juthani-Mehta M. Diagnosis and management of urinary tract infection in older adults. *Infect Dis Clin North Am* 2014; 28: 75–89.
5. Rowe TA, Juthani-Mehta M. Diagnosis and management of urinary tract infection in older adults. *Infect Dis Clin North Am* 2014; 28: 75–89.
6. 2. Rowe TA, Juthani-Mehta M. Urinary tract infection in older adults. *Aging Health* 2013; 9: 1–15. [Google Scholar]
7. Gupta K, Hooton TM, Naber KG, et al. International clinical practice guidelines for thetreatment 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: 103–120. [PubMed] [Google Scholar]
8. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections:epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; 13: 269–284. [PMC free article] [PubMed] [Google Scholar]
9. Lo TS, Hammer KD, Zegarra M, et al. Methenamine: a forgotten drug for preventing recurrent urinary tract infection in a multidrug resistance era. *Expert Rev Anti Infect Ther* 2014;12: 549–554. [PubMed] [Google Scholar] [Ref list]
10. Bartlett JG, Auwaerter PG, Pham PA, eds. Johns Hopkins ABX Guide 2012. Jones & Bartlett Publishers; 2011. 15. Lee BS, Bhuta T, Simpson

JM, Craig JC. M
11. Bartlett JG, Auwaerter PG, Pham PA, eds. Johns Hopkins ABX Guide 2012. Jones & Bartlett Publishers; 2011.
12. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2012; 10:CD003265.
13. Ross RR Jr., Conway GF Hemorrhagic cystitis following accidental overdose ofmethenamine mandelate. Am J Dis Child. 1970; 119(1):86–87. [PubMed: 5410299]
14. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2012; 10:CD003265. 16. Ross RR Jr., Conway GF Hemorrhagic cystitis following accidental overdose of methenamine
15. 6. Ross RR Jr., Conway GF Hemorrhagic cystitis following accidental overdose of methenamine mandelate. Am J Dis Child. 1970; 119(1):86–87. [PubMed: 5410299] http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/
16. Flores-Mireles AL, Walker JN, Caparon M, et al. Urinary tract infections:epidemiology, mechanisms of infection and treatment options. *Nat Rev Microbiol* 2015; 13: 269–284. [PMC free article] [PubMed] [Google Scholar] [Ref list]
17. Lo TS, Hammer KD, Zegarra M, et al. Methenamine: a forgotten drug for preventing recurrent urinary tract infection in a multidrug resistance era. *Expert Rev Anti Infect Ther* 2014;12: 549–554. [PubMed] [Google Scholar]
18. Mayrer AR, Andriole VT. Urinary tract antiseptics. *Med Clin North Am.* 1982; **66**(1):199–208. [PubMed] [Google Scholar]
19. Christopher LJ, Thompson GR. A trial of hippramine in the treatment of bacteriuria of pregnancy. *Ir J Med Sci.* 1969; **2**(7):331–337. [PubMed] [Google Scholar]
20. Furness ET, McDonald PJ, Beasley NV. Urinary antiseptics in asymptomatic bacteriuria of pregnancy. *N Z Med J.* 1975;**81**(539):417–419. [PubMed] [Google Scholar]
21. Freeman RB, Bromer L, Brancato F, et al. Prevention of recurrent bacteriuria with continuous chemotherapy. *Ann Intern Med* 1968; 69: 655–672. [PubMed] [Google Scholar]
22. Freeman RB, Smith WM, Richardson JA, et al. Long-term therapy for chronic bacteriuria in men. U.S. Public Health Service cooperative study. *Ann Intern Med* 1975; 83: 133–147. [PubMed] [Google Scholar]
23. Freeman RB, Smith WM, Richardson JA, et al. Long-term therapy for chronic bacteriuria in men. U.S. Public Health Service cooperative study. *Ann Intern Med* 1975; 83: 133–147. [PubMed] [Google Scholar]
24. Bohensky FB. Suppression of bacteriuria by methenamine mandelate in aged hospital patients with chronic disease. *J Am Geriatr Soc* 1969; 17: 394–396.
25. Parvio S. Methenamine hippurate ('Hiprex') in the treatment of chronic urinary tract infections: a trial in a geriatric hospital. *J Int Med Res* 1976; 4: 111–114. [PubMed] [Google Scholar] [Ref list]
26. McAllister R, Allwood J. Recurrent multidrug resistant urinary tract infections in geriatric patients. *Fed Pract* 2014; 31: 32–35.
27. Schiotz HA, Guttu K. Value of urinary prophylaxis with methenamine in gynecologic surgery. *Acta Obstet Gynecol Scand* 2002; 81: 743–746. [PubMed] [Google Scholar]
28. 28.] Tyreman NO, Andersson PO, Kroon L, et al. Urinary tract infection after vaginal surgery.Effect of prophylactic treatment with methenamine hippurate. *Acta Obstet Gynecol Scand* 1986; 65: 731–733. [PubMed] [Google Scholar] [Ref list]
29. Wesolowski S, Wencel J, Czaplicki M, et al. Antibacterial prophylaxis in patients after prostatectomy. *Int Urol Nephrol* 1977; 9: 241–244. [PubMed] [Google Scholar] [Ref lis
30. Micro Labs Pty Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – APOHEALTHURINARY TRACT ANTIBACTERIAL methenamine hippurate 1 g tabletamine hippurate1 g tablet 3 December 2021. URL: https://www.ebs.tga.gov.au/ (accessed 17 May 2022).
31. Micro Labs Pty 6 Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – HEXAMINE MICROmethenamine
32. Micro Labs Pty Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – APOHEALTHURINARY TRACT ANTIBACTERIAL methenamine hippurate 1 g tabletamine hippurate 1g tablet 3 December 2021. URL: https://www.ebs.tga.gov.au/ (accessed 17 May 2022).
33. Micro Labs Pty Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – HEXAMINE MICRO methenamine
34. 17. Methenamine. Lexi-Comp, Inc.; 2018. http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/ 7265. Accessed September 28th,2018.
35. .Nahata MC, Cummins BA, McLeod DC, Butler R. Predictability of methenamine efficacy based on type of urinary pathogen and pH. J Am Geriatr Soc. 1981;29(5):236–239. [PubMed: 7014695]
36. . Bartlett JG, Auwaerter PG, Pham PA, eds. Johns Hopkins ABX Guide 2012. Jones &Bartlett Publishers; 2011. 15. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippuratefor preventing urinary tract
37. Lee BS, Bhuta T, Simpson JM, Craig JC. Methenamine hippurate for preventing urinary tract infections. Cochrane Database Syst Rev. 2012; 10:CD003265. 16. Ross RR Jr., Conway GF Hemorrhagic cystitis following accident
38. URL Micro Labs Pty Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – APOHEALTH URINARY TRACT ANTIBACTERIAL methenamine hippurate 1 g tabletamine hippurate 1 g tablet 3 December 2021. URL: https://www.ebs.tga.gov.au/ (accessed 17 May 2022).
39. Micro Labs Pty Ltd. 2021. AUSTRALIAN PRODUCT INFORMATION – HEXAMINE MICRO methenamine hippurate 1 g tablet 3 December 2021: https://www.ebs.tga.gov.au/(accessed 17 May 2022).
40. Mayrer AR, Andriole VT (1982) Urinary tract antiseptics. *Med Clin North Am* **66**, 1, 199–208.