

Letter to Editor:

The Forgotten Role of Methenamine to Prevent Recurrent Urinary Tract Infection: Urgency for Reuse 100 Years After Discovery



Falah Hasan Obayes AL-Khikani¹

1. Department of Microbiology, Faculty of Medicine, University of Babylon, Al-Shomali General Hospital, Babil, Iraq.

* Corresponding Author:

Falah Hasan Obayes AL-Khikani, PhD.

Address: Department of Microbiology, Faculty of Medicine, University of Babylon, Al-Shomali General Hospital, Babil, Iraq.

Phone: +964 (181) 7307280

E-mail: falahgh38@gmail.com

Dear Editor

Urinary Tract Infection (UTI) is the most prevalent bacterial infection worldwide. The increase in multidrug resistance is associated with a scarcity of new antimicrobials that reflect the demand for alternative drugs for UTI treatment. Maybe older antibiotics that were utilized in the past can be used again [1].

Methenamine was used as a urinary antiseptic agent for over 100 years but it has now been forgotten or overlooked by researchers and clinicians [2]. The main use of methenamine was treating acute and chronic UTIs, also it was utilized as a prophylactic agent. It is widely prescribed as a prophylactic drug for patients with recurrent UTIs [1, 3]. In recent years, bacterial infections such as UTI showed extensive antibiotic resistance by different mechanisms [4]. Thus using alternative therapeutic options such as formaldehyde compound is demanded that is an antiseptic and not an antibiotic. Besides, bacteria do not become resistant to it when formaldehyde compound is used at an adequate concentration and in an acidic environment. Thus methenamine does not present the risk of resistance development by organisms contrary to other common antibiotics [5, 6].

Methenamine is hydrolyzed to ammonia and formaldehyde in an acidic environment. Formaldehyde is considered the major metabolite of methenamine and possesses nonspecific antimicrobial activity via bacterial protein and nucleic acid denaturation [2, 5].

Methenamine use has been forgotten probably because of highly controversy on whether methenamine salts are effective in preventing UTI. In vitro studies suggest that a urinary pH below 5.5 is needed for bacteriostatic concentrations of free formaldehyde to be generated from methenamine hippurate. Some believe that it may be difficult to maintain urinary pH below this level with conventional techniques over a long period. Some also believe that in catheterized patients, the amount of time that any produced formaldehyde remains in the bladder may be insufficient to be clinically effective [7].

In adult renal transplant recipients, methenamine prophylaxis decreases the incidence of UTIs and the number of antibiotic days. This effect was seen even in patients with reduced creatinine clearance and patients with diabetes in retrospective study adult kidney transplant patients for one year that showed the incidence of UTIs per 1000 patient-days decreased significantly, from 9.66 to 3.24 ($P < 0.001$) [8].

Citation Obayes AL-Khikani FH. The Forgotten Role of Methenamine to Prevent Recurrent Urinary Tract Infection: Urgency for Reuse 100 Years After Discovery. *Pharmaceutical and Biomedical Research*. 2020; 6(4):247-250. <http://dx.doi.org/10.18502/pbr.v6i4.5110>

<http://dx.doi.org/10.18502/pbr.v6i4.5110>

Methenamine is an effective and safe choice to stop recurrent UTIs in older adults, for genitourinary surgical procedures, and in cases of long-term catheterization [5]. Methenamine must be utilized when commonly used antibiotics are unsuccessful to prevent recurrent UTIs, or there is a limitation because of the adverse effects resulting from other therapies [2, 9].

It is available in two salt formulations: 1) hippurate and 2) mandelate, both of which provide an acidic environment to promote formaldehyde formation [2, 5]. It has the capability of inhibiting many bacteria in UTIs, such as *Escherichia coli* that is the most common causative UTI-related pathogen [10, 11].

In general, this drug is safe and quite-tolerated. However, there are some reported adverse effects such as rash, upset stomach, and nausea in less than 3.5% of total patients [12]. Also, its conversion to formaldehyde may cause dysuria [13]. Synergistic effect of methenamine with acetohydroxamic acid has been reported, especially in some bacterial urinary infection such as *Proteus* spp.; these bacteria produce a high amount of urease that make

the environment alkaline and prevent the formation of formaldehyde that considered the active metabolite of methenamine [14].

In the last few years, many old antibiotics have returned to the market. This revival is important to respond the urgent for novel therapeutic agents and treating infections such as complicated and uncomplicated UTIs. Anyway, we need more research for providing hard data and information regarding methenamine use in the era of drug resistance [1].

In conclusion, UTI is a globally distributed disease with the emergence of multidrug-resistant bacteria; thus, new drug discovery or activation of previously used drugs is an urgent issue. Methenamine has been suggested as a beneficial agent for UTI prevention as it works as a urinary antiseptic by safely producing formaldehyde to prevent bacterial growth while avoiding bacterial resistance that can be developed by the most known antibiotics. Methenamine can be utilized as an effective prophylactic agent in patients suffering from UTIs and help with the treatment of chronic recurrent UTIs as well as in re-

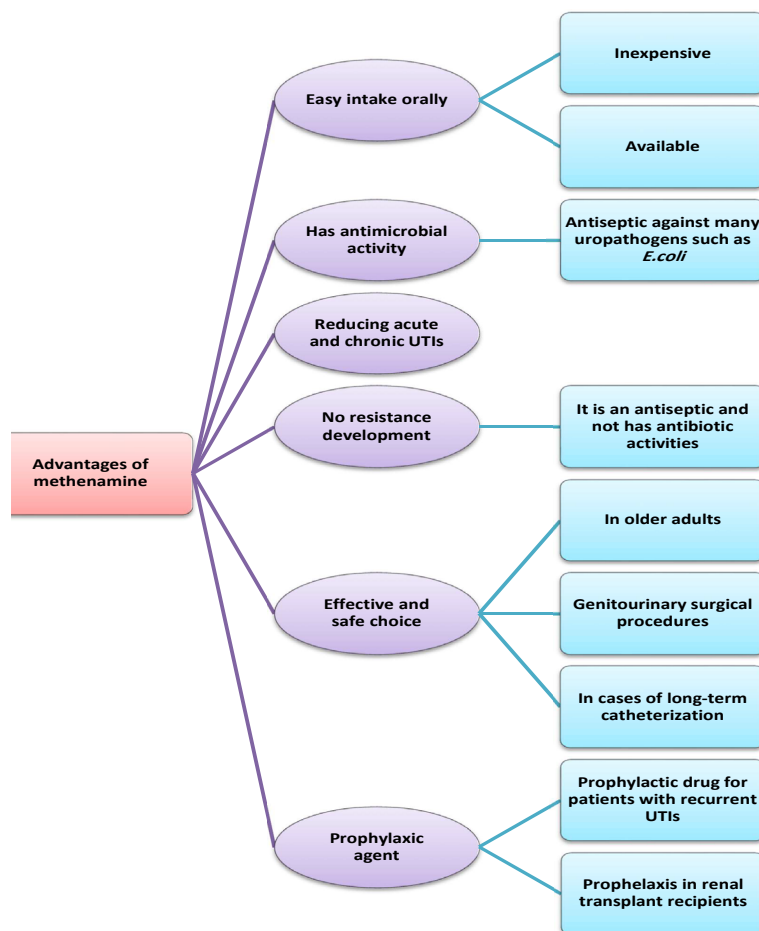


Figure 1. Some methenamine advantages

nal transplant recipients. This forgotten and overlooked antiseptic drug will become more important as bacteria continue to become resistant to antibiotics. These important advantages and unique properties of methenamine may encourage healthcare professionals to start using it (Figure 1).

Ethical Considerations

Compliance with ethical guidelines

All ethical principles are considered in this article.

Funding

This research did not receive any grant from funding agencies in the public, commercial, or non-profit sectors.

Conflict of interest

The authors declared no conflict of interest.

References

- [1] El Sakka N, Gould IM. Role of old antimicrobial agents in the management of urinary tract infection. *Expert Rev Clin Pharmacol.* 2016; 9:1047-56. [DOI:10.1080/17512433.2016.1189325] [PMID]
- [2] Lo TS, Hammer KD, Zegarra M, Cho WC. Methenamine: A forgotten drug for preventing recurrent urinary tract infection in a multidrug resistance era. *Expert Rev Anti Infect Ther.* 2014; 12:549-54. [DOI:10.1586/14787210.2014.904202] [PMID]
- [3] Keller LJ, Glauser J. Urinary tract infection updates and recent developments. *Curr Emerg Hosp Med Rep.* 2020; 8:41-4. [DOI:10.1007/s40138-020-00209-2]
- [4] AL Khikani FHO, Abadi RM, Ayit AS. Emerging carbapenemase *Klebsiella oxytoca* with multidrug resistance implicated in urinary tract infection. *Biomed Biotechnol Res J.* 2020; 4(2):148-51. [DOI:10.4103/bbrj.bbrj_165_19]
- [5] Chwa A, Kavanagh K, Linnebur SA, Fixen DR. Evaluation of methenamine for urinary tract infection prevention in older adults: A review of the evidence. *Ther Adv Drug Saf.* 2019; 10:2042098619876749. [DOI:10.1177/2042098619876749] [PMID] [PMCID]
- [6] Yang B, Foley S. Methenamine hippurate (Hiprex). In: Yang B, Foley S, Editors. *Female Urinary Tract Infections in Clinical Practice.* In Clinical Practice. Springer; 2019. [DOI:10.1007/978-3-030-27909-7]
- [7] Lee BS, Simpson JM, Craig JC, Bhuta T. Methenamine hippurate for preventing urinary tract infections. *Cochrane Database Syst Rev.* 2007; 4:43. [DOI:10.1002/14651858.CD003265.pub2]
- [8] Villacorta E, Acosta L, Myint T, Leedy N, Castellanos AL, Gedaly R. 2661. Sarcopenia increases risk of post-surgical infections in kidney transplant recipients. *Open Forum Infect Dis.* 2019; 6(Suppl 2):S931. [DOI:10.1093/ofid/ofz360.2339] [PMCID]
- [9] Quintero Cardona O, Hemmige VS, Puius YA. Methenamine hippurate may have particular benefit in preventing recurrent urinary tract infections in diabetic renal transplant recipients. *Transpl Infect Dis.* 2020; 22(2):e13247. [DOI:10.1111/tid.13247] [PMID]
- [10] AL-Khikani FH, Auda Ga, Ayit AS. Correlation study between urinary tract bacterial infection and some acute inflammatory responses. *Biomed Biotechnol Res J.* 2019; 3(4):236-9. [DOI:10.4103/bbrj.bbrj_122_19]
- [11] AL Khikani FH, Almosawey HS. Be conscious to be healthy: An initiative to prevent recurrent urinary tract infection in Iraqi women. *Hamdan Med J.* 2020. [DOI:10.4103/HMJ.HMJ_15_20]
- [12] HIPREX®. Product Information: HIPREX® oral tablets (methenamine hippurate oral tablets). Parsippany, NJ: Validus Pharmaceuticals LLC; 2017.
- [13] Ariens EJ, Hanselaar AG, Henderson PT, Simonis AM. Beware of formaldehyde in disguise. *Eur J Clin Pharmacol.* 1982; 23(4):373-5. [DOI:10.1007/BF00613624] [PMID]
- [14] Musher DM, Griffith DP, Tyler M, Woelfel A. Potentiation of the antibacterial effect of methanamine by acetohydroxamic acid. *Antimicrob Agents Chemother.* 1974; 5(2):101-5. [DOI:10.1128/AAC.5.2.101] [PMID] [PMCID]

This Page Intentionally Left Blank
