Case in Point

Recurrent Multidrug Resistant Urinary Tract Infections in Geriatric Patients

Rebecca McAllister, MS, FNP-BC; and Janice Allwood, MS, ARNP, CUNP

Four case studies are presented, which suggest the safety and efficacy of methenamine hippurate to treat complicated urinary tract infections in geriatric patients.

Urinary tract infections (UTIs) account for 8.3 million doctor visits, 1 million emergency department (ED) visits, and 100,000 hospitalizations annually, with an estimated cost of $1 billion annually in the U.S.[1] UTIs are the most common bacterial infections found in nursing home residents, accounting for 50% of reported infections in Norwegian nursing homes, 30% to 50% in U.S. nursing homes, and 25% of all infections in the noninstitutionalized elderly in the U.S.[2-4] In the geriatric population, UTIs are often found incidentally at the time of hospitalization for other admitting diagnoses, such as mentation changes or falls.[5] Asymptomatic pyuria was found in 14.8% of community residents aged ≥ 80 years.[6] Woodford and colleague found that 37% of geriatric patients admitted through an ED diagnosed with UTIs had no dysuria or urinary frequency.[7]

The incidence of UTIs is higher in the elderly due to genitourinary abnormalities, urolithiasis, dehydration, and diabetes, among other causes. These are considered complicated UTIs, defined as those in the presence of factors that predispose to persistent or relapsing infection, such as foreign bodies (calculi, indwelling catheters), obstruction, renal failure, and urinary retention.[8]

In elderly men, prostate enlargement causes bladder outlet obstruction predisposing them to urinary stasis and UTIs.[2] UTIs are prone to recur when urinary tract abnormalities persist or treatment ineffectively eradicates resistant bacteria. UTIs are considered recurrent when ≥ 3 occur within 1 year or ≥ 2 occur in a 6-month period. The anticipated recurrence rate of complicated UTIs at 4 to 6 weeks following completion of therapy is 40% to 60%.[4]

Current practice standards recommend not treating asymptomatic UTIs to avoid contributing to bacterial antibiotic resistance.[9] The frequent use of antibiotics, such as quinolones, which are increasingly inactive against these organisms, contributes to the overgrowth of bacteria in the gastrointestinal tract and their appearance in the genitourinary tract.[10,11]

As UTI-causing bacteria become more resistant to available antibiotics, the need to explore new strategies for managing UTIs is clear.[12] The spread of extended spectrum beta-lactamase (ESBL), methicillin-resistant *Staphylococcus aureus* (MRSA), and vancomycin-resistant enterococci (VRE), among other emerging bacterial resistance factors, present increasing treatment cost and poor patient outcomes. This challenge is occurring at a time when the discovery and development of new anti-infective agents is slowing down.[13]

Methenamine hippurate, a drug developed 60 years ago, offers an option to the bacterial resistance challenge for select patients with recurrent, multidrug reistant (MDR) UTIs. The action of methenamine is novel—it converts to formaldehyde when it comes in contact with acidic urine. Formaldehyde destroys Gram-positive organisms by lysis of the bacterial cell wall. Gram-negative bacteria are destroyed when formaldehyde denatures enzyme proteins involved in vital metabolic processes.[14] Formaldehyde in dilute solutions has the ability to inhibit cell division, and higher levels are bactericidal.[15] Exposure to formaldehyde for ≥ 2 hours is necessary to achieve bacteriostatic effects.[16]

The European Commission Scientific Committee on Health and Environmental Risk reported that in

Ms. McAllister is a Community Living Center family nurse practitioner and **Ms. Allwood** is an advanced registered nurse practitioner in Urology Surgery, both at the Bay Pines VA Healthcare System in Florida.

patients receiving up to 4,000 mg/d methenamine for preventive long-term treatment of UTIs, no adverse effects (AEs) were noted (Figure).[17]

Complicated UTIs in the elderly are difficult to treat due to bacterial resistance. The off-label use of methenamine hippurate for treatment/prophylaxis of MDR-recurrent UTIs is a compelling option, explored further in the following case studies. Four case studies using methenamine for treatment and prevention of recurrent MDR UTIs in geriatric patients are presented.

TREATING UTI PATIENTS

Case Study 1

A man aged > 89 years, symptomatic with nocturia due to benign prostatic hypertrophy (BPH) with bladder outlet obstruction had 8 symptomatic UTIs over 15 months. His urine culture tested positive for MDR *Providencia stuartia* (resistant to ampicillin, chephazolin, gentamycin, tigecycline, tobramycin and sulfamethizole) and *Staphylococcus haemolyticus* (resistant to ciprofloxacin, levofloxacin, and nitrofurantoin). Postvoid residual urine was identified as the cause for his recurrent UTIs. Self-catheterization was recommended, but the patient declined. Due to his advanced age and preference, surgical intervention was not pursued. His renal function was within normal limits.

Treatment with methenamine hippurate 500 mg bid with 1,000 mg ascorbic acid to acidify the urine was initiated. This reduced dose of 500 mg bid (rather than 1,000 mg bid) was prescribed due to his advanced age and a choice to "err on the side of caution." Two months later, urinalysis was negative for leukocyte esterase and nitrates, and the growth culture tested negative. Three- and 6-month urinalyses also showed no growth. The patient's renal function remained stable. He experienced no AEs from the methenamine.

Due to his urinary retention, formaldehyde was able to collect in his bladder for longer than 2 hours, achieving bactericidal levels and effectively preventing recurrence of MDR UTIs.

Case Study 2

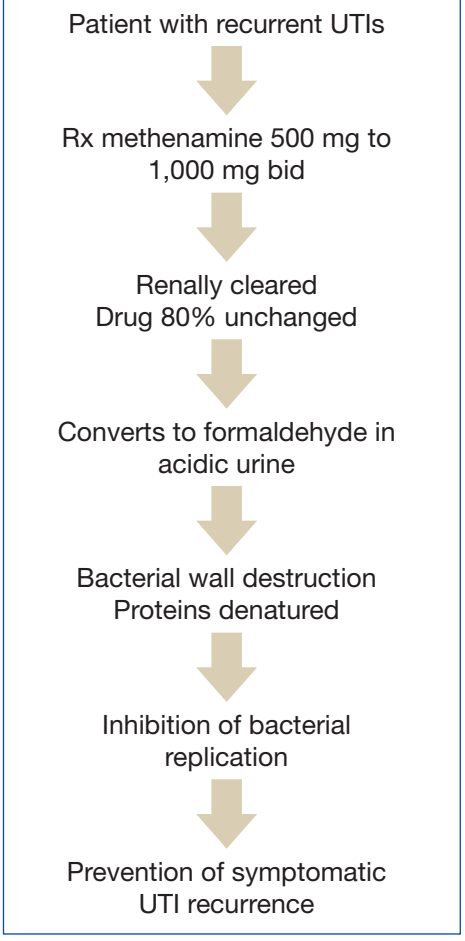
A man aged > 89 years with BPH and urinary incontinence managed with an external urinary device worn continuously had a history of 4 UTIs within a 6-month period. His renal function was normal with a creatinine clearance of 37 mg/dL. He was diagnosed with a symptomatic UTI culturing > 100,000 CFU *Proteus mirabilis* (resistant to ciprofloxacin, nitrofurantoin, and septra).

Due to resistance of the organism to available oral antibiotics, the patient's desire to avoid hospitalization, and his caregiver's inability to learn to administer IV antibiotics in the home, methenamine hippurate 500 mg bid was initiated. Within 21 days, the patient's urinalysis was negative, indicating no bacterial growth. He was treated for 4 months with no recurrence of a UTI. No symptomatic UTIs recurred during the ongoing methenamine treatment.

Case Study 3

A man aged > 89 years with end-stage renal disease and a history of bladder cancer declined dialysis, indicating that his goals for care were palliative. He was followed at home by a hospice team. He had 3 recurrent symptomatic MRSA UTIs in a 9-month period (resistant to ciprofloxacin, levofloxin, penicillin, and oxacillin). The antibiotics the bacteria was sensitive to, nitrofurantoin and septra, could not be given because his creatinine clearance was merely 8 mg/dL. He was prescribed 500 mg methenamine with 1,000 mg ascorbic acid bid. Within 4 weeks, his urinalysis had changed from > 100,000 CFU to > 50,000 CFU (< 100,000 CFU). One month later with the only treatment the methenamine and ascorbic acid, there was no bacterial growth in the patient's urine culture. He had no recurrence of a symptomatic UTI while receiving methenamine.

Figure. Action of Methenamine.



Case Study 4

An 89-year-old man with BPH and recurrent MRSA UTIs had 3 hospitalizations within 1 year. He had stage 3 chronic kidney dis-

ease with a creatinine clearance of 43 mg/dL. The patient had a symptomatic UTI > 100,000 CFU MRSA. He was treated with 500 mg methenamine and 1,000 mg ascorbic acid bid. Urinalysis results 2 months later revealed the bacterial count had dropped to the colonization range (< 50,000 CFU). His urinalysis was positive for leukocyte esterase with high white blood cell (WBC) counts, but it was negative for nitrites. He continued without recurrent UTIs while receiving the medication.

DISCUSSION

Patients with similar profiles to those discussed in this report were treated with less dramatic results. Several remained free of symptomatic UTIs with urine cultures showing bacterial counts in the colonization range of < 50,000 CFU, as noted in case 4. Frequently, patients treated with methenamine have urinalyses with negative nitrites, positive leukocyte esterase, high WBCs, and few bacteria, but cultures show no growth. Some patients who did not reliably take medications as prescribed had recurrent symptomatic UTIs. Some had a subsequent UTI culturing a different organism or a change in the sensitivity profile of the same organism. This phenomenon suggests that formaldehyde disrupts the manufacture and transmission of the proteins and enzymes responsible for bacterial resistance factors.

Freeman and colleagues conducted a prospective study of 249 men with bacteruria followed for up to 10 years.[18] Continuous therapy with methenamine delayed recurrence of bacteruria. Nilsson found that recurrent UTIs were reduced by 25% with long-term treatment (> 3 months) with methenamine.[19]

Bacteria do not develop resistance to methenamine.[20] Reports of AEs are low, and drug interactions are limited to sulfamethizole, which can cause crystallization in the urine. Daily dosing used in studies ranged from 1 g to 4 g daily.[21] Nilsson conducted research over 16 months with geriatric patients and found no changes in renal function or crystallization in urine.[19]

Severe hepatic impairment is also a contraindication, as methenamine can be hydrolyzed to ammonia. Studies have shown a reduced effectiveness with lower urinary tract abnormalities, although those studies administered the medication for short periods of time.[21] Because the action of the medication relies on ≥ 2 hours of exposure to urine in the bladder, patients with indwelling catheters or patients who urinate frequently experience little benefit.[22] Ideal candidates for methenamine are those with urinary retention and recurrent UTIs.

Although the use of methenamine has increased in Norway and Sweden by 24% since 2000, the use of methenamine in the U.S. remains low, perhaps because of conflicting reports in the literature regarding effectiveness and use with limited populations (ie, noncatheterized patients, those able to retain urine for ≥ 2 hours, and a creatinine clearance > 50 mg/dL).[3]

Some health care providers use methenamine for UTI prophylaxis, but this practice is less common in the U.S. than it is in Scandinavian countries.[3] However, no published studies have explored the action of methenamine on MRSA, ESBL, and VRE bacteria or on the enzymes and proteins that enable and transmit bacterial resistance factors.

Elderly patients with complicated recurrent UTIs due to resistant bacteria are often left with no oral antibiotic options. Costs escalate rapidly when IV antibiotics are given. Administration generally requires hospitalization with close monitoring of renal function and drug levels and the placement of a PICC or midline IV access. If there is no caregiver, then hospitalization followed by an admission to a skilled nursing facility is required.

Lee and colleagues concluded that there is a need for further studies to explore long-duration therapy with methenamine.[21] No studies have addressed its use in the geriatric population for long-term use of prevention of recurrent UTIs. No studies have been done on its use for primary treatment of MDR UTIs. The benefits of this drug with a low AE profile and low cost ($60/month for 1 g bid), which has been proven to reduce the incidence and/or delay recurrence of UTIs, is well worth further examination.

CONCLUSION

Multiple studies over 60 years have shown methenamine hippurate to be a well-tolerated and safe medication. Little data are available about the use of this medication in the elderly in the U.S., despite its wide use in Scandinavian countries. Use of methenamine for MDR UTIs in the geriatric population has been shown to be safe and effective, as presented in these case studies. Substantial cost savings were realized with the use of methenamine in these geriatric patients by reducing hospitalizations and complications due to recurrent MDR UTIs. The use of methenamine for treating MDR UTIs and the prevention of recurrent UTIs in the geriatric population warrants further clinical use and research.

The very interesting changes noted in sensitivity of the same bacteria in subsequent UTIs in patients treated with methenamine raises questions about the action of formaldehyde in the bladder on bacterial resistance factors. Given the worldwide increase in bacterial resistance to currently available antibiotics, this is a most compelling action that demands further study. ●

Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

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