Lack of Effect of Methenamine in Suppression of, or Prophylaxis Against, Chronic Urinary Infection

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Methenamine is frequently prescribed for patients who have chronic urinary infection to suppress bacterial growth during active infection or to prevent recurrence once an infection has been brought under control. We have examined the effect of methenamine mandelate and ascorbic acid on bacteriuria in para- and quadriplegics from a spinal cord unit. Patients with indwelling urinary catheters and those on a program of intermittent catheterization were included. No suppressive or prophylactic effect of this regimen was observed in any of our patients. Methenamine does not appear to be an effective antimicrobial agent in subjects who have an indwelling urinary catheter or in patients with spinal cord injury who are on intermittent catheterization. Since there appears to be reason to question the efficacy of methenamine in situations in which it is usually prescribed, evidence should be sought for a therapeutic effect in other cases. If no benefit is observed, the drug should not be used.

Methenamine is frequently administered to patients who have chronic urinary infection, either for purposes of suppressing bacterial growth (reducing the number of bacteria per milliliter of urine) or for prophylaxis (keeping urine free of bacteria once it has been sterilized by some other antimicrobial agent). Considerations that favor the use of methenamine include: (i) its antibacterial effect *in vitro* (1-4), (ii) the lack of effect on gut flora, (iii) the apparent absence of bacterial resistance to low concentrations of formaldehyde (1, 3), (iv) its relatively low cost, and (v) its reported low degree of toxicity. Our clinical impression has been that this drug is not effective in patients for whom it is most often prescribed, namely, those with complicated histories of chronic urinary infection. We have found that methenamine is frequently administered to patients who have chronic infection and indwelling urinary catheters despite theoretical considerations that would suggest that, in the absence of adequate time to generate formaldehyde, it could not possibly be of value. In fact, this drug is frequently prescribed for these patients or for others who have chronic urinary infection without indwelling catheters, despite seemingly clear evidence for a lack of effect. The purpose of the present study was to examine the effect of methenamine in a small, homogeneous group of subjects who have a particularly high incidence of chronic urinary infection, namely para- or quadriplegics on a spinal cord unit.

MATERIALS AND METHODS

Patient selection. Thirty-two men who were para- or quadriplegic and who were inpatients on the Spinal Cord Unit at the Houston Veterans Administration Hospital were studied at various stages of their illness. Nine patients were studied on two or more separate occasions. All these patients had many previously documented episodes of urinary infection and had indwelling urinary catheters some time in the past and/or at the time of study. None had evidence of ureteral obstruction during the time the present study was in progress. All patients were afebrile, were not receiving antibiotics, and had serum creatinine of ≤ 1.2 mg/dl. None had a history of gastritis or peptic ulcer.

Suppression study. Twenty-seven episodes of established bacteriuria ($>10^5$ colony-forming units [CFU] per ml of urine on four successive determinations) were studied in two groups of patients: (i) those who had indwelling Foley or suprapubic catheters, and (ii) those who were on a program of intermittent straight catheterization. In each group, episodes were divided into those occurring with a urine pH of ≤ 6 or those with a pH of > 6 . A urine pH of > 6 was usually associated with infection due to one or more *Proteus* species, although, on occasion, other urease producers, such as *Klebsiella* or *Pseudomonas*, appeared to have been responsible for a modest degree of alkalinization. Urine was obtained, and CFU per milliliter, leukocytes (WBC) per milliliter, and pH were determined on 4 successive days, after which treatment with methenamine mandelate and ascorbic acid (each administered as 1 g every 6 h, orally) was begun. These same determinations were then made daily for the next 4 days.

Prophylaxis study. Fifteen episodes were studied

in which patients were initially shown to have uninfected urine ($<10^4$ CFU/ml, usually $<10^3$ CFU/ml) with a pH of <6 on several determinations. Patients were identified either at the time of admission to the Spinal Cord Unit or at the end of a course of appropriate antibiotic therapy for documented urinary infection. After treatment with methenamine mandelate and ascorbic acid (1 g of each every 6 h, orally) was begun urine was cultured two to three times weekly until two successive determinations showed $>10^5$ CFU/ml. These episodes were again divided into those occurring in patients who had indwelling catheters and those on intermittent catheterization.

Urine collection. In patients who had indwelling catheters, the catheter was clamped for several minutes. The distal area of the catheter was then cleansed with a 70% alcohol solution, and urine was aspirated from the lumen with a syringe and a 22-gauge needle. In patients who were on intermittent catheterization, the foreskin was retracted (if present), the meatus was cleansed with povidone-iodine skin cleanser, and the cleanser was wiped off before the introduction of a sterile catheter into the bladder.

Determinations of CFU, WBC, and pH. Immediately after urine specimens were obtained, the containers were placed in ice for transportation to the laboratory. For quantitative bacteriological studies, serial 10-fold dilutions of urine were made, and 10- μ l portions were plated on sheep blood, sheep blood containing colymycin and nalidixic acid, and MacConkey agar plates. WBCs were counted with a hemacytometer. This method does not detect $<10^3$ WBCs per ml. pH was determined with an Orion Research pH meter, model 701. Mean CFU and WBC counts were calculated by converting each determination to a logarithm in base 10 and then taking an average. Values of $<10^3$ were considered to equal 10^3 for purposes of averaging. Statistical analysis was done by Student's *t* test.

RESULTS

Suppression study. In patients who had indwelling urinary catheters and established urinary infection with acid urine (pH ≤ 6 ; mean, 5.54), the mean urine CFU per milliliter before the initiation of therapy was 6.4×10^6 and the mean WBC per milliliter was 1.2×10^5 . On treatment with methenamine mandelate and ascorbic acid, the mean CFU and WBC per milliliter were 8.5×10^6 and 1.4×10^5 , respectively (Table 1). Comparison of CFU and WBC per milliliter before and during treatment showed no significant difference ($P > 0.9$). Similar results were obtained in patients whose urine pH was >6 (Table 1). It should be noted that no decrease in urinary pH was observed in patients whose urine was originally acid (pH before treatment, 5.54; pH on treatment, 5.70) despite the administration of mandelic and ascorbic acids in generally rec-

ommended doses.

Because of the likelihood that methenamine would be effective in suppressing infection only in a closed urinary tract, where there is time to generate formaldehyde (9, 10, 15), patients who did not have indwelling catheters but who were on a program of intermittent straight catheterization two to four times daily were studied. The mean CFU and WBC per milliliter before treatment in patients with urine pH of <6 were 5.0×10^6 and 2.6×10^4 , respectively. On methenamine mandelate and ascorbic acid, the mean CFU per milliliter was 4.0×10^6 and the mean WBC per milliliter was 4.2×10^4 , unchanged from pretreatment results (Table 1). Once again, the mean urine pH did not decrease and, in fact, increased slightly, from 5.23 to 5.58, with treatment. In patients with established infection whose urine pH was initially >6 , a similar lack of response in CFU and WBC per milliliter and urinary pH was noted (Table 1).

Prophylaxis study. Even if methenamine failed to suppress an established urinary infection, perhaps it might prevent development of bacteriuria in patients whose urine was initially sterile (Table 2). In subjects with indwelling catheters, the initial CFU per milliliter was $<10^4$ and usually $<10^3$. The WBC per milliliter was $<10^3$. The mean urine pH was 5.58 at the time that methenamine mandelate and ascorbic acid were being given. Within 2 to 14 days (mean, 5.7 days), the urine had become infected, with mean CFU of 7.4×10^6 per ml and WBC of 4.6×10^4 per ml.

Similar results were observed in patients who were on intermittent catheterization. The initial CFU and WBC per milliliter were 2×10^3 and $<10^3$, respectively. Within 4 to 18 days (mean, 11.7 days), infection had appeared, with 1.5×10^6 CFU/ml and 4.7×10^4 WBC/ml, respectively. The initial mean urine pH was 5.9 at the time that infection was detected.

Effect of methenamine on urine in the drainage bag in patients with indwelling catheter. It is possible that formaldehyde, which is generated in stagnant, acid urine in the collecting system, might suppress the growth of bacteria and, therefore, help to control the spread of infection in a hospital setting. Accordingly, we streaked urine obtained from the collecting bag for isolation and identification of bacterial species and measured CFU per milliliter daily for 4 days before and during administration of methenamine in five patients. There was no change in flora or reduction of overall bacterial counts during methenamine treatment in any case, despite a persistently acid pH (≤ 6) in three.

TABLE 1. *Methenamine mandelate and ascorbic acid in patients with established urinary infection^a*

Group	Time	CFU/ml ($\times 10^6$)	WBC/ml ($\times 10^4$)	pH
Indwelling catheter				
	pH ≤ 6			
	Before treatment	6.4	12	5.54
	On treatment	8.5	14	5.70
pH > 6	Before treatment	14	7.0	7.01
	On treatment	16	6.2	7.10
Intermittent catheterization				
	pH ≤ 6			
	Before treatment	5.2	2.6	5.23
	On treatment	4.1	4.2	5.58
pH > 6	Before treatment	7.9	8.1	6.72
	On treatment	6.3	8.1	6.86

^a Data reflect at least four determinations of CFU or WBC per milliliter or pH for each patient before and after institution of methenamine mandelate and ascorbic acid. There were 14 patients with indwelling catheters (7 with pH ≤ 6 and 7 with pH > 6) and 13 on a program of intermittent catheterization (8 with pH ≤ 6 and 5 with pH > 6). Each individual value was used for determining means; CFU and WBC per milliliter were first converted to $\log_{10}$. Statistical analysis to compare results before and during treatment was carried out using logarithmic values. Data were reconverted to standard forms of expression for inclusion in the table. There were no statistically significant differences between results before and during treatment ($P > 0.7$ for CFU and WBC per milliliter; $P > 0.3$ for pH).

TABLE 2. *Attempt to prevent emergence of urinary infection with methenamine mandelate and ascorbic acid*

Group	CFU/ml	WBC/ml	pH
Indwelling catheters			
	Initial (uninfected)	$< 10^3$	$< 10^3$ 5.58
	First infected ^a	7.4×10^6	4.6×10^4 6.32
Intermittent catheterization			
	Initial (uninfected)	2×10^3	$< 10^3$ 5.4
	First infected ^b	1.5×10^6	4.7×10^4 5.9

^a Mean days between initial (uninfected) specimen and first infected specimen was 5.7 (range, 2 to 14), average of data on six patients.

^b Mean days between initial uninfected specimen and first infected specimen was 11.7 (range, 4 to 18), average of data on nine patients.

DISCUSSION

Methenamine has been widely used to treat urinary infection since the beginning of the present century. The clearest indication for its use is as a prophylactic agent in otherwise healthy girls or women who have recurring urinary infection in the absence of structural abnormalities of the urinary tract (4, 5). Some benefits of prophylaxis may have been demonstrated for men as well (2). Methenamine has also been used to treat acute (1, 6) and chronic (1, 3, 7, 14) urinary infections, although these studies have generally included a heterogeneous group of patients, and careful analysis of the results suggests that the drug has not been

a highly effective agent. These reported successes in treating chronic infections, together with the fact that bacterial resistance to formaldehyde is thought not to develop (7, 13), have probably led to the adoption of methenamine as a "suppressant" drug for chronic urinary infection. Our experience has been that methenamine salts are regularly used to treat patients who have chronic urinary infection or as prophylaxis against relapse of chronic infection even in the presence of indwelling urinary catheters.

There is no evidence that methenamine prevents or eradicates infection in patients with suprapubic or Foley catheters (3). In fact, an understanding of the mechanism of action of methenamine would suggest that this drug could not be effective under these circumstances; even in an acid medium (pH 5 to 6), it takes 30 to 90 min to generate inhibitory concentrations of formaldehyde (9, 10, 14). Methenamine might have been thought to be more effective in patients who have neurogenic bladders and are on a program of intermittent catheterization because urine remains in the bladder for prolonged periods of time. Although such patients may have chronically infected foci, methenamine might still have been thought to reduce bacterial counts or to prevent establishment of bacteriuria.

In the present study, we investigated the effect of methenamine as it is usually administered, namely, as a salt of an organic acid that is said to be bacteriostatic (mandelic acid) together with another organic acid that is said to acidify the urine (ascorbic acid). Previous studies in vivo showed only a slight antibacterial

effect of mandelic acid despite extraordinary doses (12 g/day) (12). In vitro studies in our laboratory have shown that mandelic, hippuric, and sulfosalicylic acids have approximately equivalent, and minimal, bacteriostatic effects (D. M. Musher and G. B. Templeton, unpublished observations). The acidifying effect of ascorbic acid (4 g/day) has been questioned by previous investigators (16); our data showed no urinary acidification at this dosage. The possibility that substantially higher doses might produce urinary acidification cannot be excluded. However, because of effective renal buffering mechanisms, this acidification is expected to be short-lived; a lasting effect on urine pH would result only from doses that produce metabolic acidosis.

In the present study, methenamine mandelate was shown to have no effect on bacterial colonization of the urine in any group of patients studied. As was anticipated, this drug did not suppress bacterial counts in patients with established urinary infection and indwelling catheters. Similar results have previously been reported by Gerstein et al. (3). Moreover, it was of no value prophylactically, in that it did not prevent rapid acquisition of infection in patients with indwelling catheters whose urine was initially sterile. It was, perhaps, more surprising to observe that methenamine did not suppress bacteriuria in patients on intermittent catheterization who had infected urine and an acid urine pH, although data on CFU in collecting systems and previous in vitro studies (D. M. Musher, unpublished observation) suggest that a large bacterial inoculum may evade the antibacterial effect of achievable concentrations of formaldehyde. Most disconcerting was the finding that methenamine did not prevent the rapid emergence of infection in patients whose urine was initially sterile and acid, even in the absence of indwelling catheters.

The patients selected for our study were different from groups that have been studied in the past in that all were inpatients who were under care for para- or quadriplegia and associated complications. They were hospitalized on the Spinal Cord Unit, where nursing and medical personnel are particularly aware of problems related to urinary infection and where careful techniques are used to prevent acquisition of infection. The rapidity with which infections developed in patients with indwelling catheters in the prophylaxis study is a result of chronic focuses of infection that are not eradicated by systemic antibiotics, such as chronic urethritis or prostatitis and/or of recolonization by endogenous or hospital bacte-

rial flora. In those with closed urinary tracts, chronic bacterial prostatitis was usually thought to have been responsible, this condition having resulted from prolonged instrumentation at sometime in the past. Our patients did not have kidney stones, and the presence of a higher focus of infection was excluded by cystoscopy and urethral catheterization in several during the study.

As we have shown previously, there was a high degree of correlation between WBC count and bacteriuria in these patients, suggesting that bacteriuria in the catheterized patient reflects infection rather than simple colonization (11). Methenamine had no effect on reducing WBC in established infection or on prevention of acquisition of pyuria together with bacteriuria in patients whose urine was initially free of infection. We did not study a control group of patients who did not receive methenamine; however, the rapidity with which infection was reacquired in our patients suggests that such a control group was not necessary.

Our patients may be more severely affected than others who have chronic urinary infection, and this could contribute to the failure of methenamine to suppress and/or prevent infection. However, our data, together with previous studies in vitro and in vivo (9, 14, 15), would suggest that methenamine should simply not be used in patients who have indwelling catheters. Methenamine appears to have been of no value in treating the patients in this study group who had chronic urinary infections without indwelling catheters. In any case, continued administration of this drug either in the absence of an observed effect on bacterial colonization or if a transient initial effect has been followed by recolonization should be discouraged.

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