Urinary Formaldehyde Concentration After Methenamine Therapy in Patients on Intermittent Catheterization

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Although ascorbic acid is routinely used as a urinary acidifier in conjunction with methenamine therapy, it produces an inconsistent pH-lowering effect.[1-4] Cranberry juice has also been used for urine acidification, but its effect on urine pH is reported to be transient.[5,6] The effect of ascorbic acid and cranberry juice on urine pH and formaldehyde concentration in catheterized patients receiving methenamine mandelate was recently reported.[7] Although the urinary formaldehyde concentrations were higher in patients receiving urinary acidifiers compared with those receiving methenamine mandelate alone, the urine cultures remained positive in most patients. Each of these patients had an indwelling Foley catheter and the inefficacy of methenamine treatments can perhaps be explained, in part, by the continuous drainage of urine. Based on in vitro studies, it has been suggested that even in an acidic urine (pH 5 to 6), methenamine requires 30 to 90 minutes to generate inhibitory concentration of formaldehyde.[8,9] Two patients undergoing methenamine therapy and with intermittent urinary catheterization were studied, and markedly higher formaldehyde concentrations were found in these patients than in patients with indwelling Foley catheters.

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Methods

Two patients (a 22-year-old man and 30-year-old woman) with cerebral vascular accident and a history of chronic bacteriuria were enrolled into the study. The patients were catheterized for a period of 5 to 10 minutes every 6 hours and were to receive chronic methenamine therapy for prophylaxis of urinary infection. The patients were afebrile, and the bacterial cultures were negative. The patients did not have any known abnormality of the urinary tract and the serum creatinines were less than 1.1 mg/100 mL. Informed consent was obtained prior to the study. The patients did not receive any medication except for those on the study protocol for at least one week before and during the study, and a regular hospital diet was followed throughout.

The patients received the three treatments as follows: methenamine mandelate granules, 1 g four times daily alone (X); with ascorbic acid, 1 g four times daily (Y); and with ascorbic acid and cranberry cocktail (33 percent juice), 250 mL four times daily (Z). The drugs were administered about two hours before catheterization.

Each treatment was continued for five days. Two days were allowed to achieve the maximal formaldehyde concentration from the assigned regimen, and urine samples were obtained four times daily approximately two hours after each treatment and at the end of catheterization period during the remaining three days of therapy. The weekend served as a "washout" period before institution of the next treatment.

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Table 1. Comparative Effect of Methenamine Treatments on Urine pH and Formaldehyde Concentration in Patients Catheterized Intermittently and Those With Indwelling Catheter

	Intermittent Catheter				Patients With Indwelling Foley Catheter (n = 27)	
	Patient 1		Patient 2			
Treatment*	pH	Formaldehyde Concentration (μg/mL)	pH	Formaldehyde Concentration (μg/mL)	pH	Formaldehyde Concentration (μg/mL)
X	5.67 ± 0.22	118.8 ± 25.0	5.75 ± 0.61	64.3 ± 45.0	6.19 ± 0.50	19.6 ± 10.2
Y	5.99 ± 0.37	112.3 ± 50.0	5.51 ± 0.28	143.0 ± 77.0	6.08 ± 0.60	30.0 ± 16.3
Z	5.89 ± 0.20	102.0 ± 60.0	6.21 ± 0.53	92.9 ± 61.0	5.60 ± 0.50	39.4 ± 23.1

*X = methenamine mandelate 1 g four times daily; Y = methenamine mandelate 1 g and ascorbic acid 1 g four times daily; Z = methenamine mandelate 1 g, ascorbic acid 1 g, and cranberry cocktail 250 mL four times daily

All urine specimens were immediately refrigerated, and were tested within an hour for pH and within four hours for formaldehyde concentration. The preliminary studies showed that the urine pH and the formaldehyde concentration did not change during the storage period. A digital pH meter was used for pH measurements. The method of Chen and Chafetz[10] was used to determine formaldehyde as 3,5-diacetyl-1,4-dihydro-2,6-lutidine, formed by the Hantzsch reaction with acetylacetone and ammonia. The coefficient of variation for identical samples was less than 7 percent. Each subject's urine was analyzed 36 times for pH and formaldehyde concentration, 12 times on each of the three treatments. Urinary formaldehyde concentrations in the range of 10 to 28 μg/mL have been reported to be bacteriostatic, greater than 28 μg/mL bactericidal, and below 10 μg/mL subtherapeutic.[11] In vitro studies,[8,9] have suggested, however, that formaldehyde concentration above 25 μg/mL be considered bacteriostatic and above 50 μg/mL bactericidal, particularly with an exposure time of less than 2 hours.

Results

As shown in Table 1, the mean pH ranged from 5.67 to 5.99 in patient 1 and from 5.51 to 6.21 in patient 2. The lowest pH was seen with treatment X in one patient and with treatment Y in another. The mean urinary formaldehyde concentrations were substantially higher than the concentrations observed in the 27 patients studied previously.[7] In patient 1, the mean formaldehyde concentrations ranged from 102.0 to 118.8 μg/mL, and in patient 2 these values ranged from 64.3 to 143.0 μg/mL. The highest mean formaldehyde concentration of 118.8 μg/mL was observed with treatment X in patient 1 and 143.0 μg/mL with treatment Y in patient 2. Urinary formaldehyde concentrations were lower in both patients after treatment Z compared with treatment Y. The urinary formaldehyde concentrations in both patients were always in the bactericidal range, and the weekly urine cultures remained negative throughout the study.

Comment

The results suggest that the urinary formaldehyde concentration following methenamine treatments in patients catheterized intermittently may be two- to fivefold higher than in patients with indwelling Foley catheters.[7] It is important to consider the difference in the present and previous study conditions. First, the higher formaldehyde concentration in the present study may have been caused by the intermittent catheterization providing adequate time for the conversion of methenamine to formaldehyde. This is supported by in vitro observations[8,9] that the continuous drainage of urine in patients with indwelling Foley catheter does not provide the minimum of 30 minutes for adequate formation of formaldehyde. Second, the presence of urea-splitting Proteus microorganisms

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may alkalinize the urine and thus decrease the urinary formaldehyde concentration. This does not appear to account for the large observed difference because most patients with acidic urine pH in the previous study did not have Proteus species. The authors can find no published data to indicate that Escherichia coli and Klebsiella species substantially alkalinize the urine. Third, the two patients in the present study were young adults, while the patients in the previous study were elderly (aged 60 to 76 years). Although no data are available about the effect of age on the generation of formaldehyde from methenamine, it seems unlikely that age was related to the marked differences, as none of the patients in either study had renal dysfunction.

In this study, each of three methenamine regimens resulted in bactericidal formaldehyde concentration. Further long-term clinical studies are needed to demonstrate any therapeutic differences in regimens studied and in patients undergoing intermittent vs continuous urinary catheterization.

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The Relationship of Continuity of Care to Age, Sex, and Race

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Continuity of care has been identified as one of the distinguishing characteristics of good primary care.[1] Family medicine in particular regards continuity of care as a major ideal and seeks to teach and promote continuity in its educational programs.[2] These attempts to foster continuity should be paralleled by efforts to evaluate it, since the determinates of continuity and its influence on health outcomes are largely unknown.[3] A number of authors have sought to measure the overall continuity of care provided by a practice,[4-6] but their results have been difficult to compare because the authors used differing measures of continuity.

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