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Effect of Short-Term High-Dose Treatment with Methenamine Hippurate on Urinary Infection in Geriatric Patients with an Indwelling Catheter

IV. Clinical Evaluation

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Summary. An evaluation has been made of the clinical and laboratory effects of short-term (34 days), high-dose (2 g × 3 daily) treatment with methenamine hippurate (MH) of 14 geriatric patients with an indwelling catheter and clinical features of urinary tract infection. During MH treatment the number of catheter changes was halved, each catheter remaining in situ for an average of 12.0 days as compared to 6.2 days in the pre-treatment control period and 5.2 days in the post-treatment control period; the difference is significant ($p = 0.008$; Friedman two-way analysis of variance). Urine pH was reduced (pH 7.0–6.5–7.0; $p = 0.01$) and the standard bicarbonate in blood was slightly elevated (24.1–25.7–25.0 mmol/l; $p = 0.008$) during the MH treatment period, when compared to pre- and post-treatment control periods. It is suggested that MH treatment reduced the complications associated with indwelling catheters due to reduction in urine pH, bacteriuria, and pyuria. Blockage of catheters is thought to be due to intraluminal salt precipitations with trapping of clumps, and is primarily not correlated with urine viscosity.

Key words: methamine hippurate, urinary tract infection; indwelling catheter, geriatric patients

The basic nursing problem of treatment with an indwelling catheter, namely blockage of the catheter causing leakage, an odour and the need to change the catheter, is a major concern in geriatric wards. The complications of catheterization are thought to be due to (1) the catheter *per se,* because it is a foreign body in close contact with the urethral mucosa [3, 5]; and (2) ascending bacterial invasion of the urine and mucosal membranes from the perineal region by the luminal or periurethral routes [2]. As a result of the catheter and the bacterial unasion, salt precipitation and pyuria produce the characteristic cloudy urine of catheter patients. Formerly they received prophylactic long-term treatment with antibiotics.

Patients in the present study have been treated until 3 years previously with frequent short-term courses of nitrofurantoin and sulphonamides. Although these drugs were rarely prescribed in the preceding three years, the majority of bacterial strains in their urines are still resistant to them (Table 1). Methenamine hippurate (MH) has been reported to have a prophylactic and symptomatic rather than a curative effect on clinical urinary tract infection (UTI), even in patients with an indwelling catheter [4, 6, 9]. As a result of personal experience, some nurses had come to advocate prophylactic treatment of urinary tract infection in catheter patients with MH 1 g × 2 daily. When the value of this regimen was challenged, the nursing staff objected. It was decided to examine this question in a series of trials.

The present study was designed to evaluate the curative effect of short-term high-dose treatment with MH as the sole therapeutic agent for clinical distal UTI in geriatric patients with an indwelling

Table 1. Sensitivity to sulphonamides, nitrofurantoin, and ampicillin of bacterial isolates from quantitative urine cultures from 14 patients in the present study. From 42 (3 × 14) urine cultures. 94 bacterial strains were isolated, six of which were gentamycin-resistent (S. faecalis 3; E. coli 1; P. morgani 1; streptococcus-group B 1)

	Pre-treatment culture	Treatment culture	Post-treatment culture
Sulphonamides	2/14	2/14	4/14
Nitrofurantoin	0/14	4/14	1/14
Ampicillin	4/14	5/14	5/14

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Table 2. Urine pH in geriatric patients with an indwelling catheter before, during and after treatment with methenamine hippurate (MH) 2 g × 3 daily. Median pH value within each period. (Me: median of medians; Q_1–Q_3: interquartile range of medians; Rj: rank sums of the Friedman two-way analysis of variance [14] reflect relative changes in urine pH during days 1–73)

Pat.	Age	Sex	Pre-treatment control period Days 1–17	Initial period of treatment Days 18–35	Late period of treatment Days 36–52	Post-treatment control period Days 66–73
1	69	f	7.4	6.5	7.6	7.2
2	82	m	6.8	6.7	5.7	6.2
3	83	f	7.4	6.5	7.2	7.2
4	72	f	6.5	6.5	6.2	7.4
5	82	f	7.0	7.2	7.0	7.0
6	62	f	7.6	7.2	6.8	7.2
7	82	f	6.8	5.9	5.3	6.2
8	80	m	7.0	7.4	7.2	7.0
9	77	f	7.0	6.2	6.5	6.5
10	65	f	7.0	5.3	5.3	5.3
11	83	f	6.2	5.3	5.3	7.0
12	86	f	7.0	6.5	6.5	7.2
Me			7.0	6.5	6.5	7.0
Q_1–Q_3			6.8–7.2	6.1–7.0	5.5–7.1	6.4–7.2
R_j			43.0	33.0	26.0	38.0

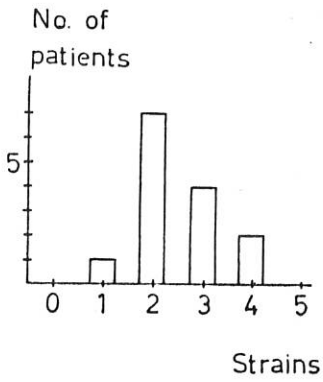

Fig. 1. Number of bacterial strains in urine from the catheter patients. N = 14

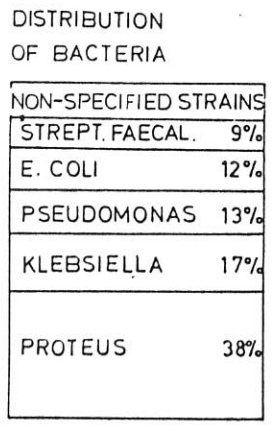

Fig. 2. Distribution of bacteria cultured from catheter urine: 14 patients, 42 quantitative cultures, 96 strains of bacteria

catheter. Since objective parameters of treatment effects were desired, quantitative examination of urine sediment and urine viscosimetry were performed, which have already been reported [7]. The clinical effect of a treatment is, nevertheless, of overriding importance, and this report is a review of both the laboratory and clinical findings.

Material and Methods

Patients. Patients with indwelling catheters from four somatogeriatric wards at Saint Lars Hospital, Lund, were selected for the study (Table 2). In each ward, the three or four patients with the heaviest urine infection, estimated by odour, cloudiness, encrustration, and frequency of catheter blockage, were chosen for short-term high-dose treatment with methenamine hippurate (MH, Hiprex, Riker Laboratories, Loughborough, Leicestershire, England); in all there were 14 patients. The patients would have had an antibiotic regimen if not admitted to the MH trial. Two male patients were excluded from the results of continuous urine analysis because of incomplete collection of specimens for periods of 10–14 days, due to repeated blockage of the catheter associated with pre-sampling plugging.

Design. The MH trial was designed with a pre-treatment control period on days 1–17, a treatment period on days 18–52, during which MH 2 g × 3 daily was given (corresponding to 85–170 mg per kg per day), and a post-treatment control period on days 53–73. Since some of the MH effects were not expected to become evident during the first two weeks of treatment [7], the treatment period was divided into an initial period on days 18–35 and a late period on days 36–52 (Table 2).

Catheter Treatment. The catheter treatment and fluid intake were standardized within the department by a group decision of the nurses. The fluid intake was set at 1800 ml a day. All patients had a closed drainage system with continuous flow of the urine into a bag. Only latex catheters nos. 12 and 14 Charrière were used (silicone-treated two-way Foley balloon catheters, Folimatic, Euromedical Industries Ltd, Rustington, West Sussex, England). The periurethral area was cleaned with sterile isotonic saline prior to catheterization. Catheters were routinely changed after 30 days or when blocked. Catheter rinsing was not performed.

Due to the standardization, it was possible to use catheter change as an objective parameter. Catheters which overlapped two periods were not counted,

unless the longer period ran to at least 85% of the time for which that particular catheter was in use. For medical and ethical reasons, catheters were not changed at the beginning of each period.

Urinalysis. In order to obtain urine for analysis the catheter was plugged for 20–30 min after breakfast. Then approximately 15 ml urine was collected in a sterile plastic tube. In patients 1, 3 and 4 the catheter had to remain plugged for 2 h before urine was obtained. Quantitative culture of urine bacteria (N = 14) and analysis of all isolated was performed in the pre-treatment, late treatment, and post-treatment periods. The urine was tested twice a week during days 1–52 and 66–73 for pH, cells, and bacteria [7, 8] and viscosity. Urine pH was measured with an indicator paper (Spezial-Indikator, Merck, Darmstadt, BRD).

The sampling, handling, and analysis of urine was performed by the nursing staff of the wards after individual instruction and training. Thus 16 nurses participated in the trial.

Blood Analyses. Blood-standard bicarbonate and base excess, and serum creatinine were measured in the pre-treatment, late treatment, and post-treatment periods.

Statistical Analysis. The statistical data were analysed according to Siegel [12].

Results

Bacteriological Background. Repeated quantitative urine cultures demonstrated a mixed bacterial flora (Fig. 1) of the type usually found in the urinary tract of inpatients with an indwelling catheter (Fig. 2), i. e., predominance of *BB. proteus, Klebsiella,* and *Pseudomonas,* which comprised 68% of the strains isolated. Only a small minority of patients harboured strains which were susceptible to sulphonamides, furadantin, and ampicillin (Table 1). Six gentamycin-resistant strains were isolated (Table 1). The number of bacterial strains decreased during the study (35-30-29) but the difference was not significant (p = 0.092; Friedman two-way analysis of variance). Other shifts in bacterial flora and bacterial properties during the MH trial were not suitable for statistical analysis, the numbers being too small.

Urinalysis. The bacteriuria and pyuria of catheter patients appeared to be reduced during MH treatment [7]. Urine viscosity fell continuously, with a significant reduction in the post-treatment control

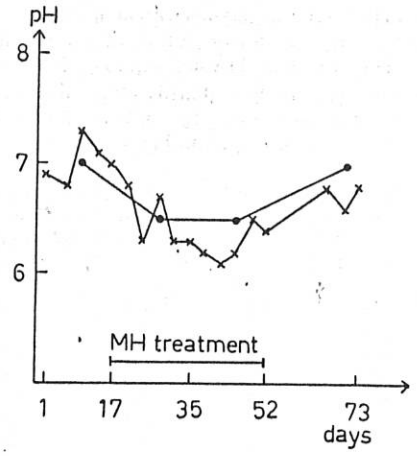

Fig. 3. Influence of short-term high-dose treatment with methenamine hippurate (MH) on urine pH. The acid shift in urine pH during the treatment period was significant.
×——× arithmetic mean each day of sampling
●——● median of individual period medians

Table 3. Time (in days) between catheter changes in 8 patient during short-term high-dose treatment of urine infection with methenamine hippurate (MH) 2 g × 3 for 34 days. Patients 3, 5, 6, 7, 10 and 14 were excluded as nonevaluable due to infrequency of catheter changes and overlap of same catheter by more then 15% from period to period. In patients 10 and 14 the prolonged catheter time occurred in the post-treatment control period

Patient	Pre-treatment control period Days 1–17	Treatment period Days 18–52	Post-treatment control period Days 53–73
1	6.7	16.5	3.3
2	13.0	25.0	8.0
4	8.5	28.0	5.5
8	2.5	4.0	4.6
9	8.0	12.0	8.3
11	3.5	14.0	4.3
12	14.0	33.0	10.5
13	4.5	6.7	4.0
$\tilde{x}$	6.2	12.0	5.2

period (unpublished data). The urine pH was lowered during MH treatment and increased again in the post-treatment control period (Fig. 3); these differences were not significant (Table 2; p = 0.066; Friedman two-way analysis of variance). Analysis of differences between isolated periods by the Wilcoxon matched-pairs signed-ranks test revealed, however, that the reduction in pH from the pre-treatment control period to the initial treatment period was significant (p = 0.010), and so was the fall in pH between the pre-treatment control period and the late treatment period (p = 0.010). These two-tailed probabilities should, however, more correctly be

replaced by the corresponding one-tailed probabilities ($p = 0.005$), since MH treatment was not expected to increase the pH of the urine.

Blood Analyses. Standard bicarbonate in blood was raised during treatment with MH 2 g × 3 daily ($N = 14$, $\bar{x} = 25.7$ mmol/l, S. D. ± 1.7), as compared to the pre-treatment control period ($\bar{x} = 24.1 \pm 0.98$ mmol/l), and post-treatment control period ($\bar{x} = 25.0 \pm 1.98$ mmol/l). The changes were significant ($p = 0.008$; Friedman two-way analysis of variance). Serum creatinine was not affected by MH treatment.

Frequency of Replacement of Catheter. Short-term high-dose treatment with MH doubled the average interval between changes of catheter as compared to the control period ($\bar{x} = 6.2$–12.0–5.2 days per catheter); the effect was significant ($N = 8$, $p = 0.008$; Friedman two-way analysis of variance). Only patients with frequent catheter changes could, however, be included in the evaluation, because of the short observation period in the present study (Table 3).

Discussion

The present study has provided evidence that short-term high-dose treatment with methenamine hippurate (MH) reduced the complications associated with an indwelling catheter. The interval between catheter changes was doubled during MH treatment (Table 3). It is reasonable to assume that the doubled catheter life was due to the release of formaldehyde and hippuric acid in the urine of patients, with secondary effects on bacteriuria [7], pyuria [7], urine viscosity and urine pH (Table 2). In view of the difference in lumen between catheters and capillary viscosimeters, we suggest that catheter blockages were caused by intraluminal salt precipitation with trapping of clumps rather than primarily by increased urine viscosity.

The beneficial effect of short-term high-dose MH treatment on UTI in geriatric patients with closed indwelling continuous-flow catheters is in agreement with the findings of previous authors at lower dose levels; prophylactic, low-dose, long-term MH treatment doubled catheter life and reduced antibiotic consumption by geriatric patients with closed indwelling intermittent-flow catheters [9].

The high-dose MH treatment produced a statistically significant but clinically negligible increase in blood-standard bicarbonate, presumably due to systemic release of hippuric acid [11, 13]. The slight acid shift in urine pH persisted throughout MH treatment without evidence of activity of compensatory mechanisms (Fig. 3). This observation supports the idea that the MH-induced decrease in urine pH was mainly a peripheral phenomenon, i. e., localized to the urinary tract.

The observed effect of MH on UTI in patients with a continuous-flow catheter is interesting, since bladder incubation of acid urine has been thought to be a pre-requisite for the splitting of methenamine to release formaldehyde, the antibacterial activity of which is independent of the pH. Methenamine cleavage, however, would be a matter of seconds rather than minutes, i. e., an acid milieu at any level from the glomerular tuft to the bladder should permit de production of formaldehyde in the urine [11, 13].

It is apparent that the attitude of the nursing staff could influence the results of an open study of the present type. This source of error was minimized by the co-operation of 16 observers with varying attitudes and by the use of several objective parameters. Standardization of catheter management within the department was instituted because of the reported influence of cleaning and sampling on the specimens obtained [10]. Only latex catheters of one type were used throughout this study, since different catheters have been reported to have different effects on UTI [3, 5].

The subjects selected formed an extreme group of catheter patients, because each had several bacterial strains resistant to most common antibiotics. Further antibiotic treatment would have increased the development of bacterial resistance with built-in risks for patients and for staff. The results of the study suggest that short-term high-dose MH treatment may provide a useful alternative to antibiotics in the treatment of clinical UTI in afebrile patients with an indwelling catheter and no suggestion of renal involvement. There was only one febrile patient with UTI who was treated with short-term high-dose MH. It was an 89-year-old male with a catheter crisis, manifested by fever for 3 days (38.2 °C), sludged urine, and frequent catheter blockage. MH 2 g × 3 daily was started on day 2. Then the fever tapered off and the urine cleared.

The present dosage of MH is moderate in comparison with the doses of its constituent substances previously prescribed; methenamine 5–20 g daily and hippuric acid 8–16 g daily [1, 13]. Treatment with MH 2 g × 3 daily was introduced in Sweden for the treatment of distal UTI of catheter patients by Edman and Månsson in 1971, with satisfactory clinical results. It seems reasonable to conclude from the present study that short-term high-dose therapy with MH provides an alternative to antibiotics in the treatment of clinical distal UTI of geriatric patients with

an indwelling catheter. Since the effect of short-term high-dose therapy with MH, like antibiotic treatment, is only transient in clinical distal UTI of patients with an indwelling catheter, we suggest that the high-dose MH course is followed by prolonged low-dose MH treatment [9].

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