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The Effect of Short-term High-dose Treatment with Methenamine Hippurate of Urinary Infection in Geriatric Patients with Indwelling Catheters

II. *Evaluation by means of a quantified urine sediment*

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ABSTRACT

The urine sediment of 12 geriatric patients with indwelling catheters was quantified by the glutaraldehyde-cytocentrifuge method prior to, during and after a clinical trial of methenamine hippurate (MH), 2 g x 3 daily given for 34 days as the sole therapeutic agent for urinary tract infection. The median leukocyte concentration in the urine of these patients was 100 cells/µl (Q_1 - Q_3 50-350), i.e. tenfold higher than the upper normal limits reported in healthy probands. The median bacteriuria in the control period was 12 x 10^5 bacteria/ml urine, interquartile range 10-60 x 10^5 bacteria/ml and extreme individual values 300-500 x 10^5 bacteria/ml. Hematuria, defined as $\geq$ 24 erythrocytes/µl urine, was not prominent and could not be correlated with MH treatment, nor with catheter changes. The reported observations suggest that short-term high-dose treatment with MH as sole therapeutic agent reduced pyruria and bacteriuria in the group of patients studied.

INTRODUCTION

The clinical relevance of bacteriuria and pyuria in patients with indwelling catheters is complex. These patients regularly acquire bacteriuria due to the ascension of gut microbes along the mucous layer surrounding the catheter (2, 6, 7, 8). The bacteriuria is thought to reflect the sum of bacterial infections of the urinary tract and bacterial growth in the urine (cf. 10).

Three factors are thought to contribute to the pyuria of patients with indwelling catheter: the reaction of the urethral mucosa to a large foreign body (3, 4, 15), the bacteria-induced inflammation of the urinary tract (11) and other chemical or physical irritants. The urine becomes cloudy and foul-smelling due to bacteriuria, pyuria, mucous secretions, bacterial products and salt precipitation.

It is reasonable to assume that the urine sediment reflects the total effect of foreign body, mucosal lesions, bacterial invasion and leukocyte emmigration. In a previous study (13), we reported a simple and rapid method of sampling, fixing, staining and quantifying the cells and bacteria of the urine from geriatric patients with an indwelling catheter. The aim of the present study was to elucidate the problems of quantifying the previously described glutaraldehyde-cytocentrifuge sediment and apply this urine sediment to the evaluation of short-term high-dose therapy with methenamine hippurate (MH) as the sole treatment of urinary infection in patients with indwelling catheters.

MATERIAL AND METHODS

The study involved 14 inpatients at the somatogeriatric wards of Saint Lars Hospital, Lund. They had all had indwelling catheters for a period of 6 months to several years before they entered the study (14). Urine was sampled twice a week during the pre-treatment control-period, days 10-17, during treatment with methenamine hippurate (MH, Hiprex^{R}, Riker Laboratories, Loughborough, Leicester. England), 2 g x 3, daily from day 18-52 and during the post-treatment control period, days 66-73, as described in the clinical report (14). During days 1-9 different cytocentrifuge preparations of the glutaraldehyde-suspended leukocytes and bacteria were evaluated (13). Two patients were excluded due to frequent blockage of the catheters after pre-sampling plugging, see below.

The catheter was plugged immediately after breakfast, 15-30 minutes before sampling. In patients no. 1, 3, 4 urine was obtained after plugging for 2 hrs before breakfast. The urine, approximately 15 ml, was collected in a sterile tube and thoroughly shaken in order to disperse the solids. The urine (0.1 ml) was then immediately transferred to 0.9 ml 2% glutaraldehyde (Taab Laboratories, Reading. England) in phosphate buffer, 0.135 M, pH 7.4. The glutaraldehyde-suspended cells and bacteria, 0.2 ml, were spun down on a slide 2-4 hrs after sampling by means of a cytocentrifuge (Shandon-Elliot Cytospin) at 1,000 r.p.m., 10 min., using twin preparations from each specimen. One of the preparations was always stained with the May-Grünwald-Giemsa stain (MGG) and the other with haematoxylin-eosin, periodic acid Schiff or Papanicolaou stain, as previously described (13).

It is evident from the above description of the preparation of the urine sediment that the cell number on the slide should be linearly correlated to the number of cells in the original urine sample:

1. 20 ul urine was spun down on each slide (200 ul of a 10% urine suspension in glutaraldehyde).
2. The relation between the area of a high-power visual field of the Zeiss

Photomicroscope used (r=75 um) and the area of the cell preparation on the slide (R=3,000 um) was defined by:

$$\frac{r^2 \pi}{R^2 \pi} = \frac{1}{1,600}$$

The whole slide preparation was scanned under the x10 lens. The area with the highest cell density was further evaluated under the x100 lens, total magnification x1,000. The extreme ranges of cells per high-power field were noted and the average cell number was taken to represent the cellularity of the preparation except when the lower number was zero. Then one third of the highest cell number was approximated to represent the cell density as a correction for the heterogenous dispersion of cells. When twin specimens differed in cell density, the one with the higher cell density was recorded, since loss of cells during preparation appeared to be more likely than production of excess cells (13).

Statistics. The results were subjected to non-parametric analyses according to Siegel 1956 (17).

RESULTS

The transformation curve between cells per high-power field and cells per µl urine is shown in Figure 1 together with the normal limits for leukocyte concentration and erythrocyte concentration reported by Little 1964 (11).

The median leukocyte concentration of the present patients was 100 (Q_1 - Q_3 50 - 350) leukocytes/µl urine during the pre-treatment control period (Table 1), i.e. a tenfold higher leukocyte concentration than the upper limits of leukocyte concentration in healthy probands reported by Little 1964 (11). The rank sums suggested a relative reduction in pyuria during the late period of MH treatment (Table 1), but this tendency was not significant ($0.3>p>0.2$), as evaluated by the Friedman two-way analysis of variance.

The concentration of bacteria in the urine followed the same pattern as the leukocyte concentration although on a higher numerical level (Table 2). The median concentration during the pre-treatment control period was 1,200 bacteria/µl urine, interquartile range 1,000 - 6,000 bacteria/µl urine. The rank sums suggest a relative reduction in bacteria during the late period of MH treatment (Table 2), but this trend was not significant ($0.3>p>0.2$), when evaluated by the Friedman two-way analysis of variance.

In contrast to pyuria and bacteriuria, microscopic haematuria defined as ≥ 24 erythrocytes/µl urine was not a prominent feature in the patients studied (Fig.

Table 1. Leukocytes per high-power microscopic field (18 x 10^3 μm^2) in the glutaraldehyde-fixed cytocentrifuge-prepared quantified urine sediments of geriatric patients with indwelling catheters before, during and after treatment with methenamine hippurate (MH), 2 g x 3 daily. Median values within each period, based on 3-5 measurements on different days within the period (cf. 13). An individual measurement was based on double preparations from the same urine specimen. MM: median of medians. Q_1 - Q_3: interquartile range. R_j: the rank sums of the Friedman two-way analysis of variance (17) reflect the relative changes in pyuria during the period studied, days 1-73.

Pat.	Sex	Pre-treatment control period Days 10-17	Initial period of treatment Days 18-35	Late period of treatment Days 36-52	Post-treatment control period Days 66-73
1.	f	3.0	1.9	1.0	2.0
2.	m	0.3	6.9	2.2	1.7
3.	f	1.0	75.0	8.0	11.0
4.	f	1.3	0.9	0.7	1.7
5.	f	0.7	0.3	0.0	0.3
6.	f	5.0	2.5	4.0	5.0
7.	f	8.0	53.0	30.0	30.0
8.	m	0.7	2.2	1.0	0.7
9.	f	1.3	0.3	0.7	0.7
10.	f	7.0	5.0	4.0	9.0
11.	f	4.0	4.2	1.7	1.7
12.	f	0.3	3.9	0.7	1.7
MM		1.3	3.2	1.4	1.7
Q_1 - Q_3		0.7-4.5	1.4-6.0	0.7-4.0	1.2-7.0
R_j		30.0	32.5	23.5	34.0

2). No evidence was found that either short-term treatment with high-dose MH, 2 g x 3 daily, or catheter changes increased the incidence of haematuria in patients with indwelling catheters. During 20 control days without MH, haematuria was noted in 13 out of 72 urine sediments (18%). During MH treatment for 34 days, haematuria was noted in 27 out of 106 urine sediments (25%). This difference was not significant ($0.3 > p > 0.2$), as evaluated by the x^2-test for two independent samples. Nor did the number of catheter changes in an individual patient correlate with the number of episodes of haematuria (N=11, Spearman's rho = +0.20).

DISCUSSION

The quantification of bacteria and cells in the urine of patients with indwelling catheters is difficult. One basic condition is that the concentration of bacteria and leukocytes appears to be dependent on urine production, i.e. excretion over time provides a better estimation than particle concentration

Table 2. Bacteria per high-power microscopic field (18 x 10^3 μm^2) in the glutaraldehyde-fixed cytocentrifuge-prepared quantified urine sediments of geriatric patients with indwelling catheters before, during and after treatment with methenamine hippurate (MH), 2 g x 3 daily. Median values within each period, based on 3-5 measurements on different days within the period (cf. 13). An individual measurement was based on double preparations from the same urine specimen. MM: median of medians. Q_1 - Q_3: interquartile range. R_j: the rank sums of the Friedman two-way analysis of variance (17) reflect the relative changes in pyuria during the period studied, days 10-73.

Pat.	Sex	Pre-treatment control period Days 10-17	Initial period of treatment Days 18-35	Late period of treatment Days 36-52	Post-treatment control period Days 66-73
1.	f	15	9	40	13
2.	m	150	105	12	105
3.	f	15	23	100	30
4.	f	125	30	2	15
5.	f	15	60	15	33
6.	f	8	12	8	55
7.	f	20	19	8	10
8.	m	10	35	15	13
9.	f	15	17	8	40
10.	f	7	7	15	35
11.	f	150	18	8	35
12.	f	15	9	6	55
MM		15	19	10	34
Q_1 - Q_3		13-73	11-33	7-15	14-48
R_j		30.5	31.0	23.0	35.5

(11, 16). Under the experimental conditions of the present study, the cell concentration per µl urine was expected to provide a close approximation of excretion per unit time (cf. 11).

The rheological properties of catheter urine are another stumbling-block. This urine resembles thin gruel, that is not a homogenous suspension. The corpuscles tend to concentrate in the clumps, much like cell concentration within a fibrin coagulum during blood clotting. It is obvious that the presence of a clump in the sample will produce an over-estimation of the corpuscularity of the urine and conversely the absence of a clump will produce an under-estimation.

Gram-stained smears of urine centrifugates have been reported to correlate with the numbers of viable organisms cultured from the same urine specimens (9). It is reasonable to assume that the present cytocentrifuge preparation further improved the correlation between urine organisms and organisms observed on the slide. This assumption is supported by the fact that the concentrations of urinary bacteria derived from these patients with indwelling catheters (Table 2) were in agreement with the bacterial concentrations found by previous authors by means of quantitative urine cultures (1), i.e. a median pre-treatment bacteriuria corresponding to 12 x 10^5 bacteria/ml urine, interquartile range 10 - 60 x 10^5

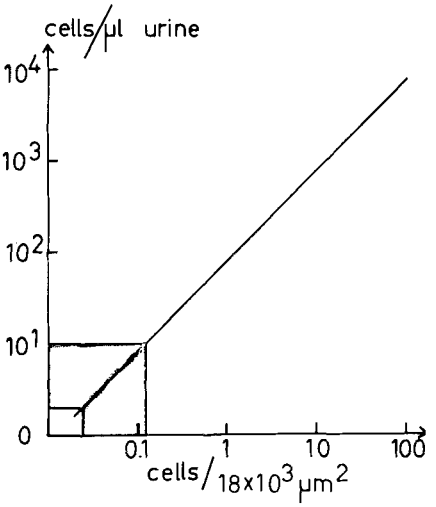

Fig. 1. The transformation curve between cells per high-power field (18 x 10^3 um^2) and cells per ul urine. The shaded area indicates the reference range of erythrocytes and leukocytes according to Little 1964 (11).

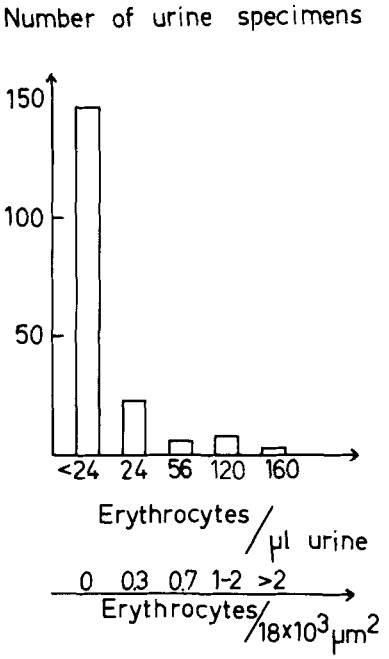

Fig. 2. Incidence and magnitude of haematuria in 12 geriatric patients with indwelling catheters prior to (days 10-17), during (days 18-52) and after (days 66-73) treatment with methenamine hippurate (MH), 2 g x 3 daily.

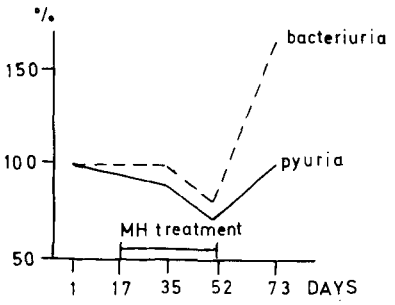

Fig. 3. Relative changes in bacteriuria and pyuria during treatment with methenamine hippurate (MH), 2 g x 3 daily, in per cent of control values. Median value based on the period medians given in Tables 1 and 2.

bacteria/ml, extreme values 300 - 500 x 10^5 bacteria/ml.

The incidence and magnitude of haematuria was moderate, considering that a large foreign body, the catheter, was in close contact with the mucosal membrane of the urinary tract and taking into account the persistent pyuria-bacteriuria.

MH has been thought to be of limited value in the treatment of established urinary tract infection (12). If it is assumed that MH reduces bacterial growth in the urine without affecting infection of the mucosa, MH treatment could not be expected to reduce bacteriuria and pyuria prior to the healing of the pre-existing mucosal infection, i.e. after MH treatment for at least 1 - 2 weeks. It is evident from Tables 1, 2 and Figure 3 that a relative reduction of bacteriuria and pyuria occured during the late period of MH treatment, If accordingly, the values from the pre-treatment control period and the initial treatment period are grouped together as one extended control period (Tables 1, 2), the pyuria was almost significantly reduced during the late MH treatment period ($p=0.014$), as evaluated by the Friedman two-way analysis of variance. The relative reduction of bacteriuria was still not significant ($p=0.14$).

In view of the size of the present material (N=12) and the dispersion of individual values, the risk of accepting a false null hypothesis (i.e. no curative effect of MH) seems great. It is more reasonable to assume from the central tendency described by the rank sums (Tables 1, 2) and the relativized medians (Fig. 3.), that short-term high-dose MH treatment reduced the bacteriuria and the pyuria in patients with indwelling catheters.

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