

EFFECT OF NITROFURANTOIN ON BACTERURIA OF INFECTION FOLLOWING PROSTATIC OPERATION

JOHN W. DRAPER, ROBERT ZUFALL, LEON T. ROSENBERG
AND VERNON KNIGHT

*From the Departments of Surgery (Urology) and Medicine, Cornell University
Medical College, and Cornell Surgical (Urology) and Medical Divisions,
Bellevue Hospital, New York, N. Y.*

The purpose of this paper is to present the results of a study of the effect of nitrofurantoin (furadantin*) in the treatment of chronic urinary tract infection. Studies of this agent by Mintzer, Kadison, Schlaes and Felsenfeld¹ revealed that it inhibited many gram negative and gram positive bacterial species *in vitro* in concentrations ranging from 7.3 to 62.7 mcg. per ml. (0.7 to 6 mg. per 100 ml.). Their studies also indicated that the drug was well absorbed after oral administration, and was excreted in urine in concentrations as high as 400 mcg. per ml. (40 mg. per 100 ml.). These investigators, and Norfleet and his associates,² found it to be of value in the treatment of infections of the urinary tract in man.

Evaluation of the effectiveness of therapy of urinary tract infection is difficult because of the diverse nature of the infectious lesions, and because of the presence of many factors of noninfectious origin which may modify the course of the disease. In the present study of nitrofurantoin, an effort was made to minimize the influence of these factors in determining the effect of treatment.

This was accomplished by selecting for study chiefly patients with chronic urinary tract infection which had followed prostatic operation. In addition, quantitative as well as qualitative bacteriologic observations on the urine were made, based on a method described earlier in a study of the effect of methenamine mandelate in a similar group of patients.³

PLAN OF STUDY

Clinical material. In the study, therapeutic observations were made of the effect of nitrofurantoin in the treatment of 43 patients. Three patients were retreated following recurrence of infection, so that a total of 46 infectious episodes were observed. The 43 patients were all elderly males, of whom 42 had had prostatic operation for prostatic obstruction. The remaining patient had chronic urinary tract infection associated with nephrolithiasis. The patients were followed for the most part on an ambulatory basis in the out-patient department. None

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¹ Mintzer, Sidney, Kadison, E. R., Shales, W. H. and Felsenfeld, Oscar: Treatment of urinary tract infections with a new antibacterial, nitrofurantoin. *Antibiotics and Chemotherapy*, **3**: 151-157, 1953.

² Norfleet, C. M., Beamer, P. R. and Carpenter, H. M.: Furadantin in infections of the genito-urinary tract. *J. Urol.*, **70**: 113-118, 1953.

³ Knight, Vernon, Draper, J. W., Brady, E. A. and Attmore, C. A.: Methenamine mandelate: Antimicrobial activity, absorption and excretion. *Antibiotics and Chemotherapy*, **2**: 615-635, 1952.

were acutely ill, although they all had pyuria and some degree of dysuria, frequency and nocturia. None were febrile, and in none were instruments passed during the period of nitrofurantoin administration or post-treatment observation.

Nitrofurantoin was given to each patient in four equally divided doses totalling 400-600 mg. per day for a period of 2 weeks. Urine cultures were taken before treatment, at weekly intervals during treatment, and once each week for two weeks after treatment was stopped. In the course of the study, blood counts were made before, during, and after treatment in 30 of the above patients and in 12 additional hospital patients for evidence of hemic toxicity. These latter 12 patients were kept on continuous treatment for periods up to 5 weeks.

In addition, three young men with profuse urethral discharge containing many gram negative intracellular diplococci, considered to be gonorrheal urethritis, were given nitrofurantoin. The dosage used was similar to that above, except that it was continued for only 3 days.

Methods. Urine specimens were collected without catheterization and inoculated into differential media, and in several dilutions into nutrient agar pour plates. From these cultures, the different species present and the total number of viable bacterial units per ml. of undiluted urine were determined. These procedures have been described in greater detail in a previous publication.³

RESULTS

Clinical observations. Following therapy with nitrofurantoin, almost all patients in this study showed some degree of improvement in their infection. Since the symptoms in a number of cases were not severe, this improvement did not always represent a pronounced change over the pre-treatment status. The best results

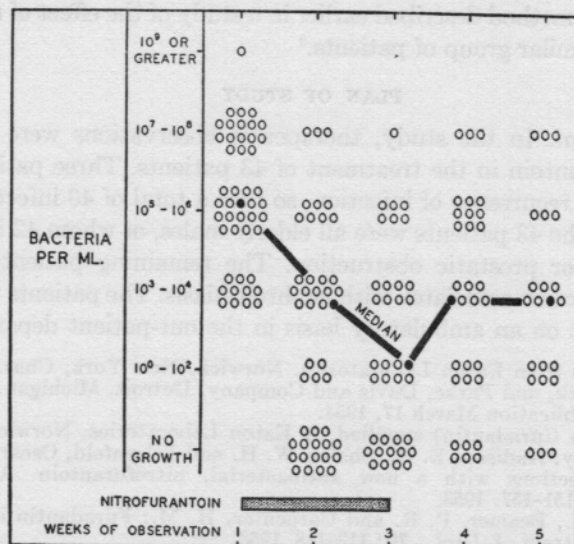


FIG. 1. Circles represent individual urine cultures. Weekly medians indicated by filled in circles. Nitrofurantoin treatment was associated with pronounced drop in number of urine bacteria which persisted with only slight rise for 2 weeks after treatment was stopped. Thirty-seven per cent of all specimens taken during treatment contained no bacteria on culture.

were obtained in those cases whose urine was later reported to be cleared of bacteria. Virtually all of these patients were completely relieved of symptoms of urinary infection. A definite but somewhat lesser degree of improvement was observed among patients whose urinary bacterial counts were reduced with treatment. The least improvement, and in some cases, no change from their pretreatment situation, was observed in the group of patients who had mixed infections or infection caused by *Pseudomonas aeruginosa*. In these patients, little or no reduction occurred in the number of urine bacteria during treatment.

Bacteriological observations. Effect of nitrofurantoin on the degree of bacteruria: The results of the enumeration of bacteria in the urine in the course of treatment of 43 patients (46 episodes of infection) are presented in figure 1. Before treatment, the number of bacteria ranged from a few thousand to 100 million organisms per ml. of urine. The greatest number fell in the range from 10,500 to 10 million with a median value of 1 million bacteria per ml.

After one week of treatment, more than one-third of the 45 specimens cultured showed no growth, and the median count dropped to 1,000 organisms per ml. of urine. In the second week of treatment, again about one-third of the cultures were sterile, and the median number of bacteria was only 100 organisms per ml. of urine.

In the 2 weeks after treatment, the median number of organisms per ml. rose slightly, and the proportion of cultures showing no growth was reduced to about one-fifth of the total patients cultured.

These studies, therefore, clearly revealed an abrupt fall in the number of urine bacteria in the majority of cases during treatment with nitrofurantoin, which persisted with only slight increase for a period of two weeks of post-treatment observation.

Effect of nitrofurantoin on infections caused by various bacterial species: In table 1 are described the results of those cases in which only a single bacterial species was isolated in the pre-treatment culture. Of the 15 cases from which *E. coli* were isolated, cultures from 8 showed no growth during treatment, and the remaining 7 had reduced numbers of organisms in comparison to their pretreatment bacteruria. Following treatment, the urine from 4 of the patients again showed counts as high as those present before treatment. Six showed bacteruria, but of a degree less than was present before treatment, while in one patient no growth occurred. Of considerable interest, however, is the fact that, of all the specimens which contained bacteria during or after treatment, only 2 were due to the continued presence of *E. coli*. All of the others were new species which appeared in the course of treatment. This point will be discussed later.

Of the 6 patients with *Ps. aeruginosa* infection, 4 continued to have this organism present during treatment, with no reduction in number in 3. In one, *Ps. aeruginosa* disappeared from the urine but was replaced by a new species in high count. The remaining patient had *Ps. aeruginosa* eliminated from the urine, which remained free of all bacteria during treatment. Following treatment, one of the four patients studied continued to have *Ps. aeruginosa*, one had sterile urine, and two had high counts of new species present.

Treatment of 5 cases of *Aerobacter aerogenes* infection resulted in complete

TABLE 1. Summary of treatment of 32 cases of urinary tract infection with nitrofurantoin

Pretreatment Cultures	Cultures during Treatment (2 weeks)			Cultures after Treatment (2 weeks)			Cases Lost from Study
	Bacterial counts (compared with pretreatment)		No growth	Bacterial counts (compared with pretreatment)		No growth	
	No change	Reduced		No change	Reduced		
<i>E. coli</i> (15 cases)	—	1* 6 (new species)	8	2 3 (new species)	6 (all new species)	1	3
<i>Pseudomonas aeruginosa</i> (6 cases)	3	1 1 (new species)	1	1 2 (new species)	—	1	2
<i>Aerobacter aerogenes</i> (5 cases)	3	—	2	2	1 (new species)	—	2
<i>B. proteus</i> (3 cases)	—	—	3	—	2 (new species)	1	—
<i>Paracolon bacillus</i> (1 case)	1 (new species)	—	—	—	1 (new species)	—	—
<i>Str. faecalis</i> (1 case)	—	—	1	—	—	—	1
Unidentified gram neg. bacillus (1 case)	—	—	1	1	—	—	—
<i>Total</i> (32 cases)	7	9	16	11	10	3	8

* Number of cases

clearing of the urine during treatment in 2 cases, and no change in 3. After treatment, 2 continued to have large numbers of *Aerobacter aerogenes* in the urine, and another had a new species present.

All three patients with *Proteus* infection in pure culture cleared completely under treatment, although after treatment new species were found in two cases. *Paracolon bacillus* disappeared from one patient during treatment, to be replaced later by a new species. *Streptococcus faecalis* was eliminated during treatment in one patient, and an unidentified gram negative bacillus disappeared from one patient, to return after treatment was stopped.

Among this group of 32 patients, new species appeared in the urine of 18 during or after treatment. These new species were principally divided among *Corynebacterium* sp. (diphtheroids), staphylococci (predominately *S. albus*), and *Ps. aeruginosa*. Except for *Ps. aeruginosa*, the numbers of these new species were never great, and they did not cause severe symptoms.

Thus, in the group of 32 patients with infection caused by a single species, treatment was followed by complete elimination of urine bacteria in 16. Nine patients had urinary bacterial counts reduced, while in seven, pretreatment counts were maintained. In many of the patients, new bacterial species were the cause of bacteruria during or after treatment.

In table 2 are described the results of treatment of 14 cases of mixed bacterial urinary tract infection. In this group, no patient's urine was completely freed

TABLE 2. Summary of treatment of 14 cases of mixed bacterial urinary tract infection with nitrofurantoin

Pretreatment Cultures	Cultures during Treatment (2 weeks)			Cultures after Treatment (2 weeks)			Cases Lost from Study
	Bacterial counts (compared with pretreatment)		No growth	Bacterial counts (compared with pretreatment)		No growth	
	No change	Reduced		No change	Reduced		
<i>Pseudomonas aerug.</i> , <i>B. proteus</i> et al. (5 cases)	2* (<i>B. proteus</i> eliminated)	3 (<i>B. proteus</i> eliminated)	—	1 2 (<i>B. proteus</i> eliminated)	1 (<i>B. proteus</i> eliminated)	—	1
<i>Pseudomonas aerug.</i> , <i>Aerobacter aerogenes</i> (2 cases)	1 (<i>Aerobacter</i> eliminated)	1	—	—	—	—	2
<i>Pseudomonas aerug.</i> , <i>E. coli</i> (1 case)	—	1 (<i>Coli</i> eliminated)	—	1	—	—	—
Other mixed infections, including <i>E. coli</i> , <i>B. proteus</i> , <i>Pseudomonas</i> , staphylococci, diphtheroids, paracolon bacillus (6 cases)	4	2	—	2	1	—	3
Total (14 cases)	7	7	0	6	2	0	6

* Number of cases

of bacteria, although the count was reduced in 7 during treatment. Following treatment, there was little further change in the 8 patients observed. It was of interest, however, that in mixed infections which included *B. proteus*, these species were almost always eliminated, a result which corresponded to the effect of nitrofurantoin against infection with pure cultures of this organism. In contrast, *Ps. aeruginosa* was rarely eliminated as a component of mixed infection, and, as previously noted, it usually persisted after treatment in patients in which it was the only infecting species.

Therapy of gonococcal urethritis. Three patients with gonococcal urethritis were treated with nitrofurantoin for a period of 72 hours. In one patient the amount of urethral discharge had decreased by the third day of treatment, although gram negative intracellular diplococci were still readily demonstrable in a stained smear of the exudate. In the other two patients, there was no reduction of discharge or other evidence of improvement in the infection.

In view of the little or no improvement, penicillin treatment was begun after 3 days, and within 24 hours the infection in all three patients had completely subsided.

Toxicity and intolerance of nitrofurantoin. Among the 42 patients in whom blood cell counts were made in the course of treatment, eosinophilia in excess of 5 per cent was observed in 17 (41 per cent). No patient's count showed more than 16 per cent eosinophiles, and most were in the range of 6-10 per cent. The eosinophilia was greatest after the second week of treatment, and subsided promptly after treatment was stopped. Three patients with eosinophilia also had a

mild, generalized erythematous and exfoliative skin rash. The rash cleared in all three soon after treatment was discontinued. In two of these patients, re-administration of a test dose of nitrofurantoin was followed by re-appearance of the rash. No other signs of hematologic toxicity or allergic manifestations have been observed.

Nausea and vomiting were severe enough in two cases to require stopping treatment, and were present to a lesser degree in two additional patients. In other patients, gastro-intestinal intolerance such as anorexia, nausea, and occasional vomiting caused some difficulty in continuing treatment. Reducing the dose, or giving of milk with doses, diminished these symptoms.

DISCUSSION

In the studies which have been described, the effect of nitrofurantoin has been tested under uniform conditions of treatment and observation in a series of patients, most of whom had urinary tract infection following prostatectomy. Following the start of treatment, there was an abrupt and progressive fall in the number of bacteria which could be cultured from the urine of the 43 patients studied. The median number of bacteria per ml. dropped from several million to a few hundred by the end of the second week of treatment, and at this time more than one-third of the specimens tested were completely free of bacteria. The drug possessed potent activity against strains of *E. coli* and *B. proteus*, and was somewhat less effective against *A. aerogenes*. Infections with *Pseudomonas aeruginosa* and mixed infections of which this species was a part, responded least well, but in special patients whose mixed infection included *B. proteus*, this organism disappeared with treatment.

Another phenomenon of interest was that, among the patients whose urine was not cleared of bacteria during or after administration of nitrofurantoin, approximately one-half were caused by new species which appeared in the course of drug therapy or post-treatment observation. These new species were about equally divided among diphtheroids, staphylococci (predominantly *S. albus*), and *Ps. aeruginosa*. Although these invaders reached high counts in some specimens, only those containing *Pseudomonas* strains were associated with any important symptomatology of infection. None of these patients had instruments passed during the period of observation.

The effect of nitrofurantoin in urinary tract infection appears to even greater advantage when it is compared to the urinary antiseptic, methenamine mandelate, which was previously studied by similar techniques.³ Although it was found that methenamine mandelate was inhibitory against several pathogenic bacterial species, it was quantitatively much less active in the treatment of urinary tract infections than nitrofurantoin. For example, in 61 specimens of urine obtained from 20 patients during treatment with methenamine mandelate, the mean number of bacteria per ml. was approximately 100,000, and no specimens were completely freed of bacteria, although these values represented a significant drop over the pre-treatment counts of the methenamine mandelate treated patients.

Despite the fact that the number of cases treated in which *B. proteus* was present in the urine was not large, the effect of nitrofurantoin against this organ-

ism was most impressive. Since this species is frequently highly resistant to other antimicrobial agents, nitrofurantoin may be of unique value in treatment of *B. proteus* infections of the urinary tract.

It should be pointed out that none of these patients had bacteremia or systemic manifestations of infection. Since serum concentrations of the drug after usual doses are extremely low, and presumably tissue concentrations are also at this level, it would be logical to expect less benefit from the treatment of systemic infections with this agent.

The eosinophilia observed in this study was not high, and in itself was not considered a contra-indication to treatment. The occurrence of a skin rash in 3 cases did necessitate discontinuance of treatment, although the rashes were not severe. The finding that a small but significant number of patients manifested a sensitivity reaction to the drug (eosinophilia and skin rash) constitutes a warning that this agent should be administered to patients with a history of allergic disorders with the greatest caution, and only under circumstances when other treatment might not be effective.

SUMMARY

Nitrofurantoin has been found to be highly effective in the treatment of chronic urinary tract infection following prostatectomy. Treatment resulted in an abrupt fall in the number of bacteria in the urine, and, in almost one half of the patients, sterile urines were obtained during treatment. The drug was most effective against infections with *E. coli* and *B. proteus*.

A moderate eosinophilia occurred in 17 patients (41 per cent), and was associated with a skin rash in 3. Eosinophilia and skin rashes subsided soon after treatment was stopped.

Three patients with gonococcal urethritis were not appreciably benefited in three days of treatment with nitrofurantoin.