NITROFURANTOIN IN CHRONIC URINARY INFECTION ASSOCIATED WITH RENAL CALCULI

BY

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In the recent literature there have been numerous references to the use of nitrofurantoin (N-(5-nitro-2-furfurylidene)-1-aminohydantoin; "furadantin") in the treatment of urinary infections. Many reports consist of series of cases of urinary infection, both acute and chronic, associated with varying complicating factors such as urinary stasis, prostatectomy, or urolithiasis, which greatly increase the difficulty in interpreting the results of therapy (Norfleet *et al.*, 1953; Kaplan and Hobgood, 1954; Draper *et al.*, 1954; Hasen and Moore, 1954; Waisbren and Crowley, 1955). In some reports an improvement in the patient's symptoms was claimed as evidence of successful treatment, although the urine was not rendered sterile. The only report of its use in Great Britain appears to be that of Heffernan *et al.* (1955), which gives the results of treatment in 12 cases of infection following prostatectomy or associated with carcinoma of the prostate, in none of which the urine was rendered sterile.

Nitrofurantoin has a wide spectrum of antibacterial activity against both Gram-positive and Gram-negative organisms. *In vitro* it is active against *Staph. pyogenes*, *Str. pyogenes*, *Str. faecalis*, *Str. mitis*, *C. diphtheriae* and diphtheroids, *A. aerogenes*, *E. coli*, and many strains of coliform organisms, many strains of *Proteus*, *Paracolon* species, *Salmonella*, and *Shigella*, and *N. gonorrhoeae*. Although some strains of *Ps. pyocyanea* show *in vitro* sensitivity, most workers have not found it clinically useful against infections with this organism. It has been used with success against infections with most other organisms which show *in vitro* sensitivity.

The results of nitrofurantoin therapy in 21 cases of urinary infection associated with renal calculi, or persisting after the removal of calculi, are reported here. The patients have been followed for a minimum period of three months after the end of treatment. Only those cases in which the urine was rendered sterile are regarded as successful. Sensitivity tests of the infecting organisms were carried out, and were repeated on cessation of therapy in the unsuccessful cases.

Selection of Cases

The patients were chosen arbitrarily from the out-patients attending the Stone Clinic, attached to this department. They all had a chronic urinary infection associated with the presence of a calculus (8 cases) or persisting after the removal of a calculus (13 cases). They had been observed by me to be infected with the same organism for periods varying from 3 to 24 months. In some patients the urine was known to have been infected before they came under my care, but this is not noted in Table I. All the patients had received adequate courses of sulphonamides and sometimes antibiotics without success, and in some cases these had been repeated several times. In the females a catheter specimen of urine, or a mid-stream boiled bottle specimen in the males, was obtained immediately before the treatment was begun. This was repeated on the last day of treatment, or the day following it, and again three months later. Two patients who did not attend at the end of the course of

nitrofurantoin have been excluded from the series. Details of the patients are shown in Table I. They were all ambulant and afebrile, and none complained of symptoms that could be directly attributed to the presence of infection.

Dosage

It was decided to give a large dose of nitrofurantoin despite the increased likelihood of toxic effects, because the infections had all proved resistant to treatment with other agents. The patients were weighed and given tablets to correspond to a dosage of 10 mg. per kg. body weight per 24 hours. They were instructed to take the tablets during a meal to prevent nausea, as has been recommended by Trafton *et al.* (1955). If nausea was severe or vomiting occurred the dose was gradually reduced until this was controlled, the treatment being continued at the highest level the patient could tolerate. Fourteen patients succeeded in taking the complete course of 10 mg. per kg. per day for 14 days. Three completed the course at a dose of 7 mg. or more per kg. per day. Two did not persist with

TABLE I

Case No.	Calculus	Duration of Infection (Months)	Organism and Sensitivity	Previous Treatment	Nitrofurantoin Sensitivity	Results of Nitrofurantoin Treatment	
						Immediate	3 Months
1	-	6	Coliform PR, OR, CR, StR	Sul, C	2+	Unchanged	Unchanged
2	-	19	Enterococci PR, OS	Sul, O	2+	Coliform NR	Coliform
3	-	7	Coliform PR, OS	O	4+	Sterile	Sterile
4	+	12	Coliform PR, OR, StR, CS	Sul	2+	Proteus NS 2+	Coliform
5	-	8	Enterococci PR, OS	"	4+	Sterile	"
6	-	3	<i>Staph. pyogenes</i> (aureus) PR, OS	O, C	8+	"	Sterile
7	-	5	Proteus PR, OR, StR, CS	O, Sul	2+	Coliform NS 2+	Coliform
8	+	17	Coliform PR, OS	" "	1+	Enterococci Unchanged	Unchanged
9	+	15	Coliform PR, OS	Sul, O, sulphadimidine	8+	Coliform NS 4+	Coliform
10	+	6	Enterococci PR, OS	O, Sul	8+	Sterile	Sterile
11	-	8	Enterococci PR, OS, CS	C, Sul	2+	"	Enterococci
12	-	24	Coliform PR, OS	Sul	3+	Proteus NS 3+	Coliform
13	-	6	Coliform PR, OS, StS, CS	O, Sul	*3+	Unchanged	Unchanged
14	-	4	Coliform PR, OS	O, sulpho- phonamides	8+	Sterile	Sterile
15	+	21	Proteus PR, StS, CS, slightly OS	Sul, C, streptomycin	*2+	Unchanged	Unchanged
16	-	3	<i>Staph. pyogenes</i> (aureus) PS, OS	Penicillin	8+	Sterile	Sterile
17	-	18	Enterococci PR, OS	O, Sul	8+	"	"
18	+	17	Coliform (aerogenes)	Sul	1+	"	Coliform
19	+	8	Coliform PR, OS	C, sulphadimidine		Unchanged	
20	+	7	Coliform PR, OS	" Sulpha-triad "	4+	Sterile	Proteus 2 weeks later
21	-	6	Coliform	"		Diminished growth	Coliform

* Resistant colonies.

P, penicillin. O, oxytetracycline. St, streptomycin. C, chloramphenicol. Sul, sulphamethizole. R, resistant. S, sensitive. Sensitivity tests were carried out using the standard disk technique. Nitrofurantoin sensitivity: 1+, zone of no growth 2.5-5 mm. around 381 µg. disk; 2+, zone of no growth 2.5-5 mm. around 174 µg. disk; 3+ zone of no growth 2.5-5 mm. around 86 µg. disk; 4+, zone of no growth 2.5-5 mm. around 33 µg. disk; 5+, zone of no growth greater than 5 mm. around 381 µg. disk; 6+, zone of no growth greater than 5 mm. around 174 µg. disk; 7+, zone of no growth greater than 5 mm. around 86 µg. disk; 8+, zone of no growth greater than 5 mm. around 33 µg. disk.

the treatment after seven days, even at a reduced dose, because of severe vomiting. Two patients had 7 mg. or more per kg. for 9 days and 7 days respectively.

Bacteriology

Each urine specimen was taken in duplicate, and cultures were taken in the hospital laboratory and personally by me in an attempt to exclude the possibility of contaminated urine. In all cases the results were in agreement. No attempt was made to identify separate strains of the different organisms cultured, as this was not intended to be a bacteriological study. The standard disk method was used for determining the sensitivity of the organisms to nitrofurantoin, the disks containing 381, 174, 86, and 33 μ g. of nitrofurantoin respectively. An effort was made to make the inoculum as standard as possible, and the cultures were read at 6 hours and again at 18 hours, it being emphasized by Richards *et al.* (1955) that these factors influence the apparent *in vitro* sensitivity to nitrofurantoin.

Results

The results for individual patients are shown in Table I. Ten patients (48%) had sterile urine on the fourteenth or fifteenth day—that is, immediately after the conclusion of treatment. In four patients (19%) the original organism was replaced by another organism. In seven cases (33%) the original organism was still present at the end of treatment. In six patients (28%) the urine was sterile three months after the cessation of treatment. In one patient the original organism had reappeared, and two others had an infection due to a different organism. One patient reappeared with a urinary infection due to a different organism two weeks after the course of treatment. Two patients have been followed for five months. In one the original infection has recurred, although the urine was sterile at three months, but there is a large calculus in one kidney. The other patient's urine has remained sterile for five months, although she repeatedly relapsed after a few days when given courses of sulphonamides.

Bacteriology.—Nitrofurantoin appears to be particularly useful against infections with *Enterococcus*, *Staph. pyogenes*, and *Proteus*, as can be seen in Table II.

TABLE II

Organism	No. of Times Isolated	No. of Times Eradicated
Coliform	11	3
Coli (aerogenes)	1	1
Enterococci	5	5
<i>Staph. pyogenes (aureus)</i>	2	2
<i>Proteus</i>	2	1

Toxicity.—As might be expected from the relatively large dose of nitrofurantoin, toxic symptoms often occurred. These are shown in Table III. As already stated, only 14

TABLE III

Toxic Symptom	No. of Times
Nausea (slight)	5
.. (moderate to severe)	9
Vomiting	4
Headache	3
Flushing	2
Prostration	1
Skin rashes	0

of the 21 patients were able to tolerate the complete course. Seven patients did not notice any abnormality while taking nitrofurantoin. The toxic symptoms were similar to those reported by other workers, except for the occurrence of transient attacks of flushing in two patients. Toxic symptoms occurred more often amongst women. Although almost half the patients were women, none was free from toxic symptoms. The drug was given to one child aged 2½ years without any ill-effect. There were no instances of skin rash in this series, but rash has since occurred with two other

patients. In most cases toxic symptoms were controlled by slightly reducing the dosage, but in a few it was not possible to continue the treatment.

Discussion

In this study the number of cases was small and a detailed statistical analysis did not seem warranted. It was felt that the patients could form their own controls, since they had been continuously infected with the same organism for prolonged periods, and it was therefore unlikely that the infection would disappear spontaneously. The fact that the urine was sterile in one-third of the patients three months after the end of treatment increases the value of these results.

The cases in which the infecting organism was replaced by another organism have here been regarded as failures, although this has not been the practice of some other workers (Richards *et al.*, 1955). The replacement of a coliform infection by *Proteus*, for instance, is unlikely to prove beneficial to the patient. However, the occurrence of such cases suggests that the incidence of cure is likely to be higher in cases without the complicating factor of calculus damage.

The sensitivity of the infecting organism to nitrofurantoin, as would be expected, corresponded fairly well with the result of treatment. In all the successful cases except one the organism appeared to be very sensitive to nitrofurantoin; in the remaining case it appeared to be only slightly sensitive. It has also been noted by Mintzer *et al.* (1953) that *in vitro* tests may occasionally fail to correspond to the clinical effectiveness of the drug. In one unsuccessful case the organism appeared to be very sensitive *in vitro*, but there is a large calculus in one kidney.

In one of the unsuccessful cases the sensitivity of the organism appeared to have somewhat decreased after 14 days of treatment, but in the others the sensitivity was unchanged. In two cases resistant colonies were noted in cultures both at the beginning and at the end of treatment, although they did not seem to have increased in number. This suggests that two strains of the same organism of differing sensitivity were present or, alternatively, that there were resistant mutants of the same strain. The presence of such resistant organisms in an otherwise sensitive infection is of potential importance in cases in which it might be desirable to give a prolonged course of treatment.

In this group of patients infection had been present for long periods and had proved refractory to treatment with other drugs. The difficulty of eradicating urinary infection in the presence of a calculus is well recognized. The fact that infection frequently tends to persist, or occur for the first time, after the removal of a calculus is not often mentioned. In this type of patient it is particularly important to cure the infection, in view of the part it may play in increasing the incidence of recurrence of calculi. There is also the added danger of chronic pyelonephritis to the function of an already traumatized kidney. The urine became sterile in 48% of these cases, although only 28% remained sterile three months later. The high relapse rate, and the fact that in some cases the original infection was replaced by another one, does not detract from the therapeutic value of nitrofurantoin. They merely indicate that the damaged renal tract is especially prone to become infected. In cases of refractory urinary infection it would appear that nitrofurantoin is a drug of considerable value.

Summary

Nitrofurantoin was used in the treatment of 21 cases of refractory urinary infection associated with the presence of renal calculi or persisting after the removal of calculi. In 48% of cases the urine became sterile after 14 days. In 28% the urine remained sterile for three months.

The *in vitro* sensitivity of the organism corresponded fairly well with the result of treatment. Resistant colonies were observed in otherwise sensitive infections,

and the presence of such resistant organisms might prove to be of importance if it was desired to give prolonged treatment.

Toxic symptoms were often encountered, but could usually be controlled by slightly reducing the dosage.

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URINARY SYMPATHIN EXCRETION OF NORMAL INFANTS AND OF INFANTS WITH PINK DISEASE

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The condition known variously by the name of "pink disease" and by a number of other descriptive or eponymous titles was described by Feer (1923) as a disorder of the vegetative nervous system. The fact that he employed atropine in treatment, however, suggests that he may have failed to appreciate the full significance of his hypothesis.

A very severe case of pink disease which was admitted to the Royal Edinburgh Hospital for Sick Children in October, 1953, appeared to one of us (J. W. F.) to show so many suggestive features of an overacting sympathetic nervous system that it was thought justifiable to embark on the determination of the infant's urinary sympathin (adrenaline and noradrenaline) excretion. The result was of sufficient interest to stimulate the investigation of further cases and of control subjects.

Method of Investigation

Urine was collected accurately for 24-hour periods from 19 healthy infants, most of whom were resident in nurseries under the care of the local authority, usually because of some temporary dislocation of family life. A number were

convalescing from minor illnesses in hospital, and in these cases the collections were obtained over the 24 hours immediately before discharge. Urine was collected similarly from four infants who presented the undoubted clinical features of pink disease.

All the control subjects and three of the affected infants were males in whom accurate urine collection was possible by means of small-sized latex colostomy tubing which was strapped to the penis and allowed to drain into a specially prepared collecting bottle. The fourth patient with pink disease was a female, and great difficulty was experienced in obtaining an accurate collection of urine despite the use of an indwelling catheter.

The urine was collected in bottles containing 5 ml. of 2N H₂SO₄ and 0.5 ml. of chloroform to stabilize the sympathin. Aliquots of the measured 24-hour specimen were used for assay. One aliquot (50–100 ml.) was submitted to acid hydrolysis by heating at pH 2 (adjusted with 2N H₂SO₄) for 20 minutes in a boiling-water bath. This treatment releases some (Euler and Hellner, 1951) but not all of the catechol amines excreted in a conjugated form (Euler and Orwén, 1955). The sympathin excreted in the free state was determined, using another aliquot of the urine which was not submitted to acid hydrolysis.

The sympathin determinations on the hydrolysed and unhydrolysed urine were carried out by a method to be described in detail elsewhere by Crawford and Law. It consists essentially in the extraction of the sympathin by passage of the diluted urine at pH 7 through a column of a weak cation exchange resin "amberlite IRC-50" previously buffered to pH 7–7.5. The adsorbed sympathin is recovered from the column by elution with dilute sulphuric acid. Most of the inorganic salt in the eluate, brought to pH 3.5 with dilute sodium hydroxide, is precipitated by the addition of 2–4 volumes of a mixture of equal volumes of acetone and ethanol. The supernatant is evaporated to dryness at 35° C. under reduced pressure. The residue is dissolved in distilled water (3 ml.) to give the "final urine extract." The sympathin content of this solution is determined fluorimetrically, using Lund's (1949, 1950) method modified in such a way that equal quantities of adrenaline or noradrenaline or mixtures of the two amines give similar intensities of fluorescence (Crawford and Law, unpublished).

When individual determinations of adrenaline and noradrenaline in the urine extract were required, separation of the two amines was effected by submitting an aliquot of the final urine extract to paper chromatography (Crawford and Outschoorn, 1951, modified as described by Vogt, 1954). The concentrations of the separated amines in the eluates from the appropriate paper strips were determined fluorimetrically.

The method of extraction of urinary sympathin described by Euler and Hellner (1951) was used in the first case of pink disease investigated (Table III). The sympathin in the urine aliquot is adsorbed on to aluminium hydroxide formed in the urine by the addition of aluminium sulphate followed by adjustment of the pH to 7.5 with dilute sodium hydroxide. The separated precipitate is dissolved in dilute sulphuric acid and the inorganic salts are removed by precipitation with acetone-ethanol mixture (see above) after adjusting the pH to 3.5. The supernatant is evaporated to dryness under reduced pressure at 35° C. The residue was dissolved in 0.9% (w/v) sodium chloride and the sympathin concentration in terms of noradrenaline determined by bio-assay, using the rat's blood pressure preparation (Crawford and Outschoorn, 1951).

A recovery of 82% (S.D. 6) was obtained by the amberlite IRC-50 method in 51 experiments in which adrenaline or noradrenaline (3–30 µg.) was added to urine. No significant difference ($P=0.05$) in the recoveries of adrenaline or noradrenaline, or in the recoveries from hydrolysed and unhydrolysed urine, was found. Similar control experiments in which the two amines were separately determined following extraction by the amberlite IRC-50 method and separation by paper chromatography showed a recovery of 50%