NALIDIXIC ACID—A NEW DRUG FOR URINARY INFECTIONS

(A Clinical Trial)

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Introduction

Urinary tract infection is quite common during postpartum and after pelvic surgery. Postoperative urinary tract infection is potentially a serious hazard as it may lead to chronic pyelonephritis (Simmons and WatsonBaker, 1963). Bladder drainage by indwelling catheter is a major causative factor in postoperative infections (Donald *et al,* 1962). Relationship between bacteriuria and pyelonephritis is still debated (Ingelfingeri *et al,* 1966). However, clearing the urine of bacteria seems reasonable enough, but this calls for adequate prolonged therapy. A number of antibiotics and chemotherapeutic agents have been recently introduced for the treatment of urinary tract infections. However, even now we often face a difficult task in controlling the chronic infections. Actually therapeutic failure in chronic urinary infections seems to be the rule. The rapidly increasing number of drug resistant organisms are responsible for such failures to a certain extent.

The search for newer effective drugs has been stimulated recently, partly due to the untoward effects of some antibacterial agents and partly due to the growing number of drug resistant organisms. Nalidixic acid, a Naphthridine derivative, is among the newest drugs. It is an orally active drug having pronounced antibacterial activity against gram-negative bacteria (Carroll, 1963). The drug was first described by Lesher in 1962, and is well absorbed from the gastrointestinal tract. It is excreted primarily in the urine and is found in therapeutically active concentrations. (Buchbinder *et al,* 1963; McChesney, E. W., 1964). The drug is well tolerated generally and is effective over the entire urinary pH range.

Keeping in view of the above the present study was undertaken to evaluate the effectiveness of Nalidixic acid in controlling the urinary infections, caused by E. Coli coliform organisms and B. Proteus, Furadantin, the most widely used drug in such infections was used as a control.

Material and Methods

One hundred female patients having urinary infections caused by E. Coli, Coliform organisms or B. proteus or both, and having sensitivity for both the drugs were selected for this study. Fifty patients were treated with Furadantin as

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Received for publication on 28-3-72.

controls, while fifty patients were treated with the drug under trial. Furadantin was given 300 mg., daily in divided doses for seven days and Nalidixic acid was administered for seven days in doses of 4 gm daily (2 caplets of 500 mg four times a day). At random selection of patients was made for either of the drugs.

Before the drugs were administered a detailed urological history along with the drugs already taken were noted. A fresh midstream specimen of urine was obtained after taking usual precautions. A second specimen was taken 10 days after and a third one 28 days after the first specimen. Medication was started after the first specimen was obtained. Microscopy of the specimens were performed and number of pus cells counted. Following studies were also undertaken along with the physical examination. Detailed blood picture, blood urea nitrogen, and liver function tests. These were repeated after 10 and 28 days. Blood counts were used as a guide for the evidence of any bone marrow depression. Blood urea nitrogen was used as an indicator for renal function, while liver function tests were used to judge heptocellular dysfunction.

Patients were not aware of the drug given and were asked to note the day of relief of symptoms. The results were not studied till the trial was complete and the principal authors were not aware of the drug on which the patients were. Response to drugs was determined clinically as well as bacteriologically. The latter was considered excellent if post-therapy urine cultures were negative and poor if there was no significant change or emergence of new strains was noted. Clinical response was considered excellent if the patient became asymptomatic, and good if there was notable improvement.

Results

Out of one hundred patients studied, six were dropouts. One was above 74 years age. Table I, shows the ages of the patients and the drug administered. Sixty patients were suffering from acute and forty were suffering from chronic infections. The latter patients had received some kind of medication in the past, including antibacterial agents. Thirty patients came from postpartum clinics. One patient, a 44 year old woman with chronic urinary tract infection had re-

TABLE I

Age Groups of Patients and the Drug Administered

Age group	Furadantin	Nalidixic Acid	Total
16 to 25, years	11	9	20
26 to 35, years	16	20	36
36 to 45, years	10	8	18
46 to 55, years	7	5	12
56 and above	6	8	14
Total	50	50	100

ceived many drugs including true antibiotics (Sulfas, chloramphenicol, Furadantin, penicillin G, ampicillin, kanamycin sulphate, methenamine hippurate, etc.) and also a 14 days course of Nalidixic acid without substantial improvement. However, she was again kept on Nalidixic acid and seven days after therapy was begun she reported marked diminution of frequency and strangury. However, the symptoms re-occurred after 15 days. The medication was continued and she became asymptomatic after further treatment for ten days. This was the only patient in the series who was kept on Nalidixic acid knowingly. The infecting organism was Escherichia Coli in the first and second cultures and no growth was seen in the third one. But the medication was continued till she was on the drug for 40 days in all. She has no recurrence till one year after the discontinuation of the therapy and nothing abnormal was reported from the blood and liver function studies. The details of the infections and the drugs used are indicated in Table II.

TABLE II

Infections and the Drugs Administered

Infection site	No. of cases	Nalidixic Acid	Furadantin
Pyelonephritis	28	20	8
Cystitis (no evident cause)	42	19	23
Postpartum infections	30	11	19
Total	100	50	50

Clinical response was excellent in 12 cases. They became asymptomatic within six days of the therapy. In twenty cases, response was considered good; they became asymptomatic within 10 days of the treatment. Nineteen patients recovered within 14 days and one recovered after 28 days as mentioned. Six of the patients dropped out and no follow up was possible. Two patients having Nalidixic acid had urticaria which responded to antihistamine. Four patients having Furadantin and one having Nalidixic acid, complained of nausea. One patient having Nalidixic acid complained of dryness of mouth. A few patients on both the drugs complained of drowziness. The relief from symptoms was noticed as early as 48 hours in 12 cases. Table III, shows the onset of relief of symptoms after commencement of medication. Table IV shows the onset of adverse reactions.

The urine specimens obtained 10 days after the start of medication showed the effectiveness of treatment, while the specimens obtained on 28th day of medication helped in assessing the results. Nalidixic acid was found more effective in reducing the pyuria. It is notable that six of the urine specimens taken on 28th day showed the presence of E. Coli. Four of these patients were on the control drug. However, these patients have shown the absence of the organisms in the urine collected on 10th day. Effectiveness of Nalidixic acid as compared with Furadantin in reducing pyuria is shown in Table V.

TABLE III
Onset of Relief of Symptoms

Onset of relief (Symptomatic)	Nalidixic Acid	Furadantin	Total
Before 48 hours of starting medication	12	—	12
6th day or before	28	2	30
10th day or before	4	16	20
14th day or before	1	18	19
15th to 28th day	1	—	1
Drop outs	3	5	8
Failure of therapy	1	9	10
Total	50	50	100

TABLE IV
Onset of Adverse Reactions

Adverse Reactions	Onset days	Fura-dantin	Nalidic acid	Remarks
Cholestasis	—	—	—	
Dizziness and vertigo	3, 4, & 5	—	—	
Drowsiness	3, 5	4	2	5th day with nalidixic acid
Eosinophilia rise	—	—	—	
Haemolytic anaemia	—	—	—	
Headache	3 & 4	1	1	3rd day with nalidixic acid
Leukopaenia	—	—	—	
Nausea and vomiting	2, 3rd	3	1	
Paresthesia	—	—	—	
Peripheral neuritis	—	—	—	
Photosensitivity	12th day	—	1	
Pruritus	—	—	—	
Skin rash	3rd day	1	—	
Thrombocytopaenia	—	—	—	
Urticaria	6, 7th day	—	2	Responded to antihistamine. But the medication was discontinued.
Visual disturbances	—	—	—	

TABLE V
Results of Urine Microscopy

Day on which Specimens were collected after medication was started	Patients on Nalidixic Acid	Patients on Furadantin
10th, day		
Pyuria	12	26
Negative for pus cells	38	24
28th, day		
Pyuria	2	9
Negative for pus cells	45	36
Dropouts	3	5

Discussion

Bacterial infections of the female urinary tract occurs quite frequently. Acute infections can be manifested in mild symptoms that gradually increase in severity. Adequate and prolonged therapy is needed to control such infections. This calls for a drug which can be given for long periods, should not develop intolerance nor should interfere with the use of other chemotherapeutic agents. Unfortunately, very few drugs meet this requirement of long term therapy. And then there is the problem of resistant strains.

The antibiotics comprise a large and growing group of effective and reliable antibacterial drugs They have a wide antimicrobial range. However, these drugs have marked adverse reactions, such as overgrowth of resistant bacteria, fungal infection of the mouth, gastro-intestinal tract and vagina neurotoxic effects allergic reactions, etc. Tetracyclines and penicilins, including the synthetic preparations, are contraindicated for prolonged use (Martin, W. J., 1966). Chemical antibacterial drugs are well tolerated, are effective and are relatively safe. Sulphonamides were probably most used in early 60's for long term therapy of urinary tract infections. However, there is always the risk of development of bacterial resistance and an ever present danger of serious toxic reactions. (Finland and Weinstewl, 1953; Goodman and Gilman, 1965). The methenamine products have the disadvatage of needing supplemental urinary acidification in order to be effective. Even the widely used nitrofuradantin is known to produce side effects, such as megaloblastic anaemia, peripheral neuropathy (Bass, 1963; Asbury, 1963: Willett, 1963) and allergic reactions (Bayer *et al*, 1965; Robinson, B. R., 1964). Anaphylactoid reaction has also been reported by Khorsandian *et al*, 1963 and Satter, 1966.

Nalidixic acid, a new chemotherapeutic agent is particularly potent against gram-negative organisms and is unrelated to sulfonamides, antibiotics, etc. It is effective over the entire urinary pH range, and is rapidly absorbed from the gastro-intestinal tract and most of the excretion occurs within first eight hours, from the kidneys (McChesney *et al*, 1965). The drug can be given to patients for very long periods and is well tolerated by children (Dulow, 1965). It has been given to patients having severe renal damage without additional impairment (Carroll, 1963). Nalidixic acid is generally well tolerated but side effects like nausea, and diziness have been reported. The drug should not be used in the first trimester of pregnancy and should be used with caution in patients having severely impaired kidney function. Resistance to the drug has been observed both in vivo and in vitro, which is rare for an antibacterial agent.

The present report is of a limited study based on the results of 50 patients. Nalidixic acid was compared with Furadantin as a control, in the treatment of urinary tract infections. No severe toxic effects were encountered in the study. Response was excellent to good clinically. One patient was for more than 40 days on the trial drug and no abnormality was discovered in her blood picture and liver function tests were normal. No neurogical side effects were noted. However, the administration of Nalidixic acid has been associated with increased intracranial pressure. Bilateral palsy of the 6th nerve and papilloedema following administration of 43.5 gm of the drug over a 58 day period have been reported (Anderson, *et al*, 1971). Papilloedema in a 9

year old child and increased intracranial hypertension has also been reported (Borevsk and Sundstrom, 1967).

The significant finding of the present study is that Nalidixic Acid is a drug of choice for the long term therapy of urinary tract infections. In cases of chronic infections due to resistant strains of gram-negative organisms the drug is unique. It can also be of use when the organisms are resistant to other antibacterial agents. Its place in gynaecological surgery can be judged from the fact that the authors found 14% of women admitted for gynaecological surgery having urinary tract infections. Tomlison in 1968 gave a 6.9% rate of infection in such cases.

Summary and Conclusions

The study represents 50 patients who have been treated with Nalidixic acid. The majority of the patients have shown subjective and objective clinical improvements. Furadantin was used as a control on 50 patients. The study indicated that Nalidixic acid is a safe non-toxic antibacterial which can be administered for longer periods and is effective in certain type of urinary tract infections, particularly those due to E. Coli and Proteus. Authors conclude that this drug can be a valuable adjunct in the treatment of acute as well as chronic urinary tract infections, specially in the later.

Acknowledgements

Authors are grateful to Dr. M. L. Sharma, Professor of Pathology for his help and guidance in this study, Prof. S. I. Jacob, F.R.C.O.G., Head of the Department of Gynec. & Obstet. and Supdt. Zanana Hospital Jaipur for allowing to publish this study, The Drug Controller India for the Test Licence and Messers Winthrop Products, Inc. New York for suppling 500 x 500 mg. caplets of Nalidixic Acid (NEGRAM) through there associates in India.

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