A Comparative Clinical Trial Between Piromidic Acid And Nalidixic Acid

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ABSTRACT

A comparative randomized study on the efficacy and side effects of 2 urinary antiseptic agents were done. Fifty cases, divided equally between piromidic acid and nalidixic acid were studied. Twenty out of 22 cases or 90.9% on piromidic acid were cured while 19 out of 21 cases or 90.4% on nalidixic acid were also cured. Side effects with piromidic acid were increased appetite in 3 patients and headache in 1 patient. Among those on nalidixic acid, 2 complained of bitter taste and 1 had dizziness. *[Phil J Microbiol Infect Dis 1978; 7(1):23-30]*

Key Words: piromidic acid, nalidixic acid, urinary antiseptic, urinary tract infection

INTRODUCTION

Recurrent urinary tract infections present a challenging diagnostic and therapeutic problem. They posed a formidable problem both for the clinicians and researchers. They are extremely common, resistant to treatment and likely to recur. They rank second in frequency of occurrence only to upper respiratory tract infections.[1]

The incidence of chronic pyelonephritis in autopsy series varies from 2.8% to 15%, though the diagnosis prior to death was much less frequent.[2] This is because majority of people with urinary infections are asymptomatic and hence, unaware of its presence. Various laboratory methods and technics have been advocated for the diagnosis of urinary tract infections but the most valuable laboratory aid is still the quantitative urine culture.[3-7]

Familiar antimicrobials are still recommended for treatment.[8-10] Several modalities of treatment had been tried such as the short-term therapy,[11] intermediate therapy,[12-13] and long term therapy.[14] Regimen after regimen have been advocated but still the incidence of urinary tract infections has not abated. Newer drugs have been introduced, not necessarily to replace the older ones but either to improve or add to the long list of antimicrobials armamentarium used against such conditions.

To this list of new drugs is added piromidic acid, a 5, 8-dihydro-8-ethyl-5-oxo-2-pyrrolidinopyrido (2,3-d) pyrimidine-6-carboxylic acid, a congener of nalidixic acid, which is a 1-ethyl-7-methyl-4-oxo-1, 8-naph-thyridine-3-carboxylic acid (Figure 1). Piromidic acid is light yellowish white to yellow powder, which is odorless and tasteless. It is highly soluble in chloroform, very slightly soluble in dimethyl formamide and practically insoluble in water, ethanol and ether. It dissolves in sodium hydroxide solution.

The limited data about piromidic acid, which have been done mostly in Japan, revealed that the drug has a wide spectrum of activity against both gram-positive organism as *Staphylococcus aureus* and *Bacillus subtilis*, and gram-negative organism as *E. coli*, proteus, klebsiella, shigella and salmonella. Because of its high concentration in the urine, it is primarily recommended for urinary tract infections.

This paper therefore hopes to confirm these reports and at the same time compare its efficacy with a known proven antiseptic, nalidixic acid, in the treatment of acute and recurrent uncomplicated urinary tract infections.

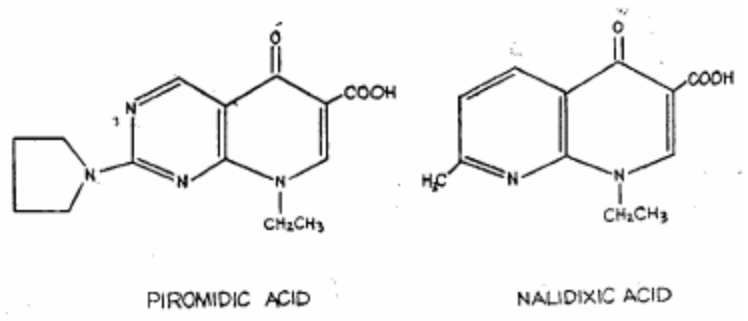


Figure 1

MATERIALS AND METHODS

Patient Inclusion

This study was conducted on patients examined and treated at the outpatient and service hospital of the UERMM Hospital in Quezon City, Philippines from March to September1977. Patients enrolled in the study were those with suspected or proven acute or recurrent uncomplicated urinary tract infections that have not received any antimicrobials within the past 3 days prior to inclusion to the study or start of therapy. The age, sex, primary or secondary conditions were all taken into consideration.

Patients excluded in the study were: 1. pregnant patients and children 2. patients with renal failure 3. patients with known allergy to urinary antiseptics like nalidixic acid 4. diabetic patients 5. patients with chronic and complicated urinary tract infections in association with coexisting urinary calculi, carcinoma of the bladder, etc.

All patients included in the study were randomly assigned into 2 treatment groups using a randomized table.

Laboratory Examinations

Urinalysis and urine culture and sensitivity were done: 1. before treatment 2. during treatment or on day 3 of treatment 3. post-treatment or on day 16 after start of treatment. All patients were instructed on the aseptic, mid-stream collection of urine specimen. All patients with a urine culture of 10^5 col/ml before treatment were included in the study.

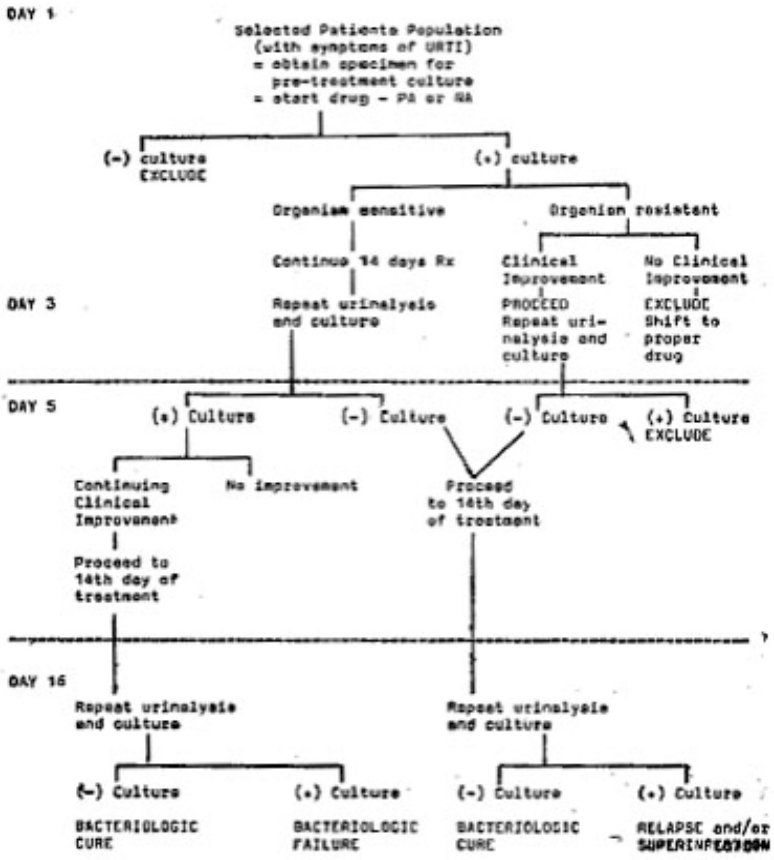
Drug and Dose Regimen

All patients were grouped into 2 treatment schedule - Groups A and B. They were randomly assigned to the 2 treatment groups by the use of random table. Group A received nalidixic acid in 500 mg tablets at a dose of 2 tablets 4 times a day or a total dose of 4 gms per day for14 days. Group B received piromidic acid in 250 mg capsules at a dose of 2 capsules 3 to 4 times a day or a total daily dose of 1.5 to 2 gms for 14 days. Patients were instructed to take the medicine as prescribed and requested to return on days 3, 5 and 16 for follow-up. All patients were just given enough medications until their next follow-up.

Evaluation of Patients

Patients were evaluated on days 3, 5 and 16 after starting therapy with day 1 as the first day of treatment. Follow-ups were extended to the 21st day if possible. Subjective and objective

parameters such as dysuria, polyuria, fever, chills and CVA tenderness were observed and charted. All bacterial isolates were subjected to sensitivity studies and side effects of either drug were carefully recorded. All patients with positive urine culture on day 1 and subsequent negative urine cultures on days 3 and 16 with clinical improvement were considered bacteriologically and clinically cured. All patients with positive urine culture on day 1 and persistently positive urine culture on day 3 but negative urine culture on day 16 with clinical improvement were also considered bacteriologically and clinically cured. All patients with persistent positive urine culture from days 1, 3 and 16 were considered bacteriologic failures. All patients with persistent positive urine cultures up to day 3 without clinical improvement were excluded and shifted to the proper drug according to sensitivity studies (see Treatment Schema).



RESULTS

This comparative open trial was conducted on a total of 81 patients from which 31 dropped-out for various reasons. Fifty patients completed the final evaluation - 25 patients each under Group A nalidixic acid and Group B piromidic acid. There were a total of 39 females and 11 males. Age ranges from 16 to 72 with an average of 44 years (Table 1).

Of the 25 patients under Group A nalidixic acid, 19 out of the 21 patients became asymptomatic and had negative urine cultures on the 5th day of therapy giving a cure rate of 90.4%. There were 2 clinical and bacteriological failures. Four were excluded and shifted to the drug of choice because of resistance to nalidixic acid and persistence of symptoms (Table 2). In Group B piromidic acid, 20 of the 21 patients had clinical and bacteriological cure with a cure

rate of 90.9%. Two were declared failures and 3 were excluded and shifted to the drug of choice (Table 2).

Table 3 shows the different urinary isolates, which responded to nalidixic acid and piromidic acid. As expected *E. coli* was the most commonly isolated with 10 out of 11 cases responding to piromidic acid and 15 out of 19 cases responding to nalidixic acid. Of the klebsiella group, 4 out of 6 cases responded to nalidixic acid and 4 out of 8 cases responded to piromidic acid. There was about equal response for both *Enterobacter sp* and *Staphylococcus aureus*.

Table 1

		Sex	
	Age Range	F	M
Nalidixic Acid	20 - 72	18	7
Piromidic Acid	16 - 67	21	7

Table 2

Regimen	Total Patients	Bacteriologic Cure	Cure Rate	Bacteriologic Failure	Excluded
Piromidic Acid	25	20	90.9%	2	3
Nalidixic Acid	25	19	90.4%	2	4

Table 3

Isolates (cured cases)	Nalidixic Acid	Piromidic Acid
E. coli	15	10
Klebsiella	4	4
Enterobacter sp	5	7
Staphylococcus aureus	4	7
Proteus	0	1
	28*	29*

* some patients had 2 isolates

Side effects for both drugs were minimal. Of those on piromidic acid, 3 patients had increased appetite and 1 patient had headache. Among those on nalidixic acid, 2 complained of bitter taste and 1 had dizziness.

DISCUSSION

This study shows that the efficacy of piromidic acid and nalidixic acid are highly comparable in urinary tract infections caused by sensitive common pathogens. The piromidic group showed a cure rate of 90.9% as compared to the 90.4% cure rate of the nalidixic group. These results are comparable with the results of the clinical trials done mostly in Japan.

Clinical trials in Japan showed that piromidic acid has been proved effective in 81.3% cases of urinary tract infections caused by gram-negative bacteria. Controlled trials between piromidic acid and nalidixic acid reveal that for infections with staphylococci only and mixed infections with staphylococci and gram-negative organism, the efficacy rate of piromidic acid was 90% while that of the nalidixic acid was 53.3%.[15]

Piromidic acid is absorbed well from the intestinal tract with bacteriologically active substances excreted into the urine in high concentrations. It is reported that its main rnetabolite, B-hydroxypiromidic acid, has more antibacterial activity than the parent compound, piromidic acid. These could explain the high cure rate of piromidic acid in this study. Other possible explanations to this high cure rate are: 1. synergistic effect between piromidic acid and its metabolite, B-hydroxypiromidic acid 2. their high concentration in the urine 3. most of the bacterial isolates

were sensitive to piromidic acid and its metabolite. Reports showed that some of the bacteria sensitive to piromidic acid are *E. coli*, klebsiella, *Staphylococcus aureus* and proteus.[15-16]

CONCLUSIONS

From this study we can conclude that:

1. Piromidic acid is effective for urinary tract infections caused by sensitive gram-positive and gram-negative bacteria;

2. There is no significant difference in the efficacy between piromidic acid and nalidixic acid; and

3. Piromidic acid may be a promising urinary antiseptic but requires further clinical trial.

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