

EFFECT OF ALKALINISATION OF URINE ON THE EFFICACY OF QUINOLONES IN TREATMENT OF URINARY TRACT INFECTION

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ABSTRACT

BACKGROUND

Physicians commonly prescribe an alkaliniser along with fluoroquinolones (FQ) in treatment of UTI. The combined effect of these two drugs in our body is unknown. So, we conducted two studies with two different FQ (Pefloxacin and Levofloxacin) with an alkali solution in two separate medical colleges at Kolkata to find out their efficacy in presence of alkali in the treatment of UTI.

MATERIALS AND METHODS

In our 1st study at SSKM Hospital Kolkata, patients with uncomplicated lower UTI were prescribed Pefloxacin 400 mg (Group-A) and Pefloxacin 400 mg + disodium hydrogen citrate (Group-B). In our 2nd study at RG Kar Medical college, Kolkata patients with uncomplicated lower UTI were prescribed Levofloxacin 250 mg (Group A) and Levofloxacin 250 mg + disodium hydrogen citrate (Group-B).

RESULTS

Pefloxacin and Levofloxacin can eradicate the uropathogens in more than 90% of cases when used alone but when Pefloxacin and levofloxacin were combined with disodium hydrogen citrate eradication rate reduced to 70% of uropathogens. The possible explanation of this reduced action of fluoroquinolones was that alkali solution may prevent the absorption of FQ from stomach or FQ and may precipitate in alkaline urine or both. So, the MIC of quinolones could not be reached in urine.

CONCLUSION

Fluoroquinolones should not be co-prescribed with alkali solution.

KEYWORDS

Fluoroquinolones, UTI, Alkali Solution.

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BACKGROUND

Urinary Tract Infection (UTI) is a very common disease affecting all age groups, especially in females. The reason is very short length of urethra in female (4 cm) compared to male urethra (20 cm) and also close proximity to anus in female. The female urethra is also exposed to menstrual blood loss and pathogenic vaginal organisms, especially during menstruation. Treatment of UTI has posed to be a challenge to the clinician due to emergence of resistance strains of bacteria to various antimicrobials used over the years. So, development of newer antibiotics and trial with them is going on for the treatment of UTI.¹ Fluoroquinolones

are very much effective in the treatment of UTI and newer fluoroquinolones are very much effective against these pathogenic organisms responsible for UTI.

In the treatment of UTI alkalinisation of urine is a common practice because this reduces the pain and burning sensation during voiding.² Pefloxacin and Levofloxacin two well-known fluoroquinolones often used for the treatment of UTI, found to be effective in most of the cases of uncomplicated UTI.³ However, when pefloxacin or levofloxacin is combined with disodium hydrogen citrate, a urinary alkalinising solution in treatment of UTI, the outcome may change. There is no clinical and Pharmacokinetic data available regarding the outcome of these combination in our population.⁴ These present studies were carried out to assess the effect of alkalinisation of urine on the efficacy of pefloxacin and levofloxacin, two prototype fluoroquinolones, in the treatment of uncomplicated UTI. The clinical responses were evaluated only in patients with symptoms and signs of uncomplicated lower urinary tract infections.⁵

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Aims and Objectives-

The aim of this study was to find out the clinical effect of alkalinisation of urine on the efficacy of fluoroquinolones in the treatment of UTI.

MATERIALS AND METHODS

Patients were mostly recruited from the outpatient department (General screening OPD) and gynaecology and obstetrics department of two different medical colleges at Kolkata, India. 1st clinical trial was conducted at Institute of Post Graduate Medical Education and Research at Kolkata and 2nd trial was at R.G. KAR Medical College, Kolkata.

- a. Inclusion Criteria- Patients with uncomplicated UTI aged between 15 to 45 years were included in the study.
- b. Exclusion Criteria- Pregnant and lactating mothers, any haematological diseases, diabetes mellitus (Type-1 & 2), any kind of malignancy, any urinary tract abnormality, known liver/kidney/cardiac disorders, known allergy to fluoroquinolones and history of any other antibiotic intake within 2 weeks prior to study and during study period.

After recruitment of patients from OPD, a detailed medical history were taken followed by thorough clinical examinations which include both general and systemic examination. This was followed by examination of urine i.e. routine urine examination (pH, pus cells, R.B.C., epithelial cells, albumin/cast) with culture and sensitivity. Routine laboratory investigations (Hb%, TC, DC, ESR, FBS, urea, creatinine, Liver Function Test) and imaging (straight x-ray abdomen/K.U.B, Ultrasonography) were done in selected cases.

The patients with UTI were screened from OPD with one/more of the following criteria- dysuria, increased frequency of urination, decreased amount of urine passed, high coloured or red urine, fever, supra-pubic tenderness, palpable bladder. These studies were randomized and assessor blind studies. Randomisation was done using randomization table. After screening, the patients fulfilling the selection criteria except the culture sensitivity report (which will be available after 72 hours) were randomized and

called for baseline visit on the same day. The first dose of study medication was given orally on this 1st day of visit. A mid-stream urine specimen was obtained at baseline for routine analysis and for culture /sensitivity testing before ingestion of the drug. On next visit, at 3rd day of treatment, clinical evaluation were done as well as bacteriological tests were repeated. Bacteriological and clinical effectiveness were reassessed on 6th day.

We analysed the collected data in both the studies by finding the p-value with Pearson’s two-sided Chi-square comparison.

In the 1st study at Institute of Post Graduate Medical Education and Research, Kolkata, the patients were put into the following two groups on the basis of treatment pattern irrespective of type of uropathogen detected. First group was treated with pefloxacin in doses of 400 mg twice daily orally for consecutive 5 days. Second group was treated with the same brand of pefloxacin in doses of 400 mg BD and alkali solution (disodium hydrogen citrate 1.4 gm/5 ml) 10 ml thrice daily orally for consecutive 5 days. Patients were evaluated bacteriologically and clinically accordingly.

In the 2nd study as, the patients were put into the two groups on the basis of treatment pattern irrespective of types of uropathogen detected. First group was treated with levofloxacin in doses of 250 mg once daily for 3 days. Second group was treated with levofloxacin in doses of 250 mg OD and alkali solution (disodium hydrogen citrate 1.4 gm/5 ml) 10 ml thrice daily for 3 days.⁶ Patients were evaluated bacteriologically and clinically accordingly and statistical analysis by chi square test.

RESULTS

In the 1st study, among the 70 patients in the study, 68 were female and 2 were male. The commonest symptom was dysuria followed by increased frequency.

The most common organism detected was Escherichia coli (82.86%).

Analysis of the clinical and bacteriological findings of these cases who had urinary symptoms were done. The results are shown in Table 1 and Table 2.

Nature of Symptoms	No. of Cases with (+ve) Clinical Findings	Urinary Findings		Microscopic & Bacteriological Observations in Positive Cases					
		+ve	-Ve	P	B	P+b	P+c	B+c	P+b+c
Dysuria	20	16	4	1	1	3	1	1	9
Increased frequency of Urination	12	10	2	0	1	1	0	1	7
Dysuria + increased Frequency	14	14	0	0	0	1	0	2	11
Dysuria + fever	7	7	0	0	1	2	1	1	2
Fever + frequency	4	3	1	0	0	0	0	1	2
Dysuria + frequency + fever	3	3	0	0	1	0	0	1	1
Pain	4	2	2	0	0	0	0	0	2
High colour urine	6	4	2	1	0	1	0	0	2
Total	70	59	11	2	4	8	2	7	36

Table 1. Analysis of the Clinical and Bacteriological Findings in 1st Study

P= Pus Cells, B= Bacteria, C = Culture.

Result of Culture of Urine- All 70 cases were confirmed as cases of urinary tract infection on the basis of culture of organism obtained from urine of the patients. The various organism isolated from the urine culture were as follows, Escherichia coli 58 (82.86%) cases, Klebsiella 6 (7.14%) cases, Proteus 3 (4.28%) cases, Pseudomonas 2 (2.85%) cases, Ureaplasma urealyticum 1 (1.42%) cases. This data is given in the following Table 2.

Organisms	No. of Cases	%
E. Coli	58	82.86
Klebsiella	6	7.14
Proteus	3	4.28
Pseudomonus	2	2.85
Ureaplasma Urealyticum	1	1.42
Total	70	100

Table 2. Various Organism Isolated from the Urine in 1st Study

This table shows that Escherichia coli was the commonest organism isolated from urine samples followed by Klebsiella.

Result of Treatment- Clinical and bacteriological evaluation were done after 5 days of therapy. It was seen that all the 35 cases treated with pefloxacin alone were eradicated (100%) and other group of 35 patients, treated with pefloxacin and alkali solution eradication was 16 (45.71%) cases.

Cases were designated bacteriologically as eradicated, when urine samples were found to be sterile and persistent when the urine specimens showed bacteria microscopically or growth on culture or both. This data is given in Table 3.

Treatment	No. of Cases	Eradication	No. of Cases Persistent
Pefloxacin alone	35	35 (100%)	0
Pefloxacin + Alkali solution	35	16 (45.71%)	19 (54.29%)
Total	70	51 (72.86%)	19 (27.14%)

Table 3. Result of Initial Treatment in 1st Study

- P<0.001 by Pearson’s two-sided Chi-square comparison.
- It can be seen that after 5 days of therapy, eradication is 100% with pefloxacin alone and only 45.71% with pefloxacin + alkali solution.

Result of Retreatment- Those cases which were not eradicated by pefloxacin plus alkali solution were again subjected to 5 days therapy with pefloxacin alone. It is seen that all the cases which failed to show eradication by treatment with pefloxacin with alkali solution could be eradicated by another 5 days therapy with pefloxacin alone.

Bacteriological Outcome in Vitro- All the micro-organism isolated in MacConkey’s culture medium were moderately sensitive to pefloxacin 20 mcg /bio-disc.

Statistical Analysis- Finding the p-value with Person’s two-sided Chi-square comparison, we can find the significance of difference of clinical outcome results between pefloxacin and pefloxacin + alkali solution was p<0.001 which denotes that the observation is statistically significant.

Result of Second Study- Among the 80 patients in the study, 76 were female and 4 were male. Many clinically diagnosed cases of UTI were excluded from our study when result of urine analysis were negative for microscopic as well as culture.

Analysis of the clinical and bacteriological findings of these cases who had urinary symptoms were done. The results are shown in Table 4.

Result of Culture of Urine- All 80 cases were diagnosed as cases of UTI on the basis of culture, Pus cells and Bacteria obtained from urine of the patients. Various organisms isolated from the urine culture were as follows, Escherichia coli 73 cases, Klebsiella 3 cases, Pseudomonas 3 cases and Proteus 1 cases given in the following Table 5.

This table shows that Escherichia coli was the commonest organism isolated from urine samples and Proteus is the least one.

Result of Treatment- All our study population received levofloxacin empirically. Clinical and bacteriological evaluation were done after 3 days of therapy. It is seen that the 40 cases treated with Levofloxacin alone 37 became clinically cure (93%) and the other group of 40 patients treated with Levofloxacin and alkali solution cure rate was (70%) 28 cases.

Cases were designated bacteriologically as eradicated, when urine samples were found to be sterile and persistent when the urine specimens showed bacteria microscopically or growth on culture or both. This is shown in Table-5.

Result of Retreatment- Those 12 cases which were not eradicated by Levofloxacin plus alkali solution treatment for 3 days were again subjected to another 3 days therapy with levofloxacin 250 mg alone. It is seen that out of 12 patients, 10 cases who failed to show eradication by treatment with levofloxacin with alkali solution could be eradicated by another 3 days therapy with levofloxacin alone. It was also seen that three (03) patients in group A and two (02) patients in group B failed to be eradicated by another 3 days of therapy with 250 mg levofloxacin and they were prescribed other antibiotics.

Bacteriological Outcome in Vitro- All the micro-organism isolated in MacConkey’s culture medium were moderate to highly sensitive to levofloxacin 5 mcg /bio-disc.

Statistical Analysis- Finding the p-value with Pearson’s two-sided Chi-square comparison, we found the significance of difference of clinical outcome results between levofloxacin

(group A) and levofloxacin + alkali solution (group B). The p value was $p < 0.001$ which denotes that the observation is statistically significant.

Nature of Symptoms	No. of Cases with (+ve) Clinical Findings	Microscopy Urinary Findings		Microscopic, Bacteriological and Culture in Positive Cases					
		+Ve	-Ve	P	B	P+B	P+C	B+C	P+B+C
Dysuria	31	26	5	6	8	3	2	3	4
Increased frequency of urination	15	10	5	3	3	1	1	1	1
Pain lower abdomen	13	10	3	2	2	2	1	0	3
Dysuria + increased Frequency	7	7	0	2	1	1	1	1	1
Dysuria + fever	5	5	0	2	0	0	0	1	2
Fever + frequency	5	4	1	1	1	0	0	1	1
Dysuria+ Frequency + fever	3	3	0	0	0	0	0	1	2
Urine high coloured	1	1	0	0	0	0	0	0	1
Total	80	66	14	16	15	07	05	08	15

Table 4. Analysis of the Clinical and Bacteriological Findings in 2nd Study

P= Pus Cells, B= Bacteria, C = Culture.

Organisms	Number of Cases	Percentage
E. Coli	73	91.25
Klebsiella	3	3.76
Pseudomonas	3	3.76
Proteus	1	1.25
Total	80	100

Table 5. Various Organism Isolated from the Urine in 2nd Study

Treatment	Number of Cases	Eradication	Number of Cases Persistent
Levofloxacin alone (GR-A)	40	37 (93%)	3 (7%)
Levofloxacin + Alkali solution (GR-B)	40	28 (70%)	12 (30%)
Total	80	65 (81%)	15 (37%)

Table 6. Result of Initial Treatment after 3 Days in 2nd Study

DISCUSSION

Urinary tract infection is common ailment affecting predominantly females between ages of 20 to 45 years. In this study female: male ratio was 10.67:1 which corroborates well with the text book figure though incidence varies at different stages of life. Of the 35 patients (50%) in the group treated with alkali solution + pefloxacin, only 16 (45.71%) were found to be eradicated. The patients where eradication failed were then subjected to a further treatment of 5 days with pefloxacin alone and showed complete eradication of the organism.

In the 1st comparative study at SSKM (IPGME & R) Hospital at Kolkata it was shown that 100% of patients were relieved of symptoms and signs when pefloxacin alone was used, whereas only 45.71% of patients receiving pefloxacin + alkali mixture showed eradication and clinical cure. Therefore, we can say that antibacterial efficacy of pefloxacin in vivo showed diminution of action in the presence of alkali in urine.

In the 2nd study at R.G. Kar Medical College & Hospital, Kolkata it was found that comparative study of bacteriological and clinical efficacy of Levofloxacin that 93% (37/40) of patients were relieved of symptoms and signs

when levofloxacin was used alone (Group A), whereas only 70% (28/40) of patients who received levofloxacin + alkali mixture (Group B) showed eradication and clinical cure. In the group B patients, in whom eradication failed (12/40) they were prescribed to a further treatment of 3 days of levofloxacin and showed about 88% eradication of the organism. Therefore, we can say that antibacterial efficacy of levofloxacin in vivo is reduced in the presence of alkalisation of urine in this study.

There is no specific explanation of this reduced efficacy of quinolones in presence of alkali mixture. It is postulated that when quinolones like pefloxacin or levofloxacin when taken with anta-acids, combine to form insoluble salts that are difficult to absorb from the intestines. Peak serum concentrations of pefloxacin and levofloxacin may be reduced by 90% or more, which can prevent the fluoroquinolones from working.^{7,8} However, no specific pharmacokinetic or pharmacodynamics drug-drug interaction between fluoroquinolones and alkali is found in any literature. Lacey et al. (1987) observed the presence of crystals of fluoroquinolones in the alkaline urine.⁹ This may also occur following administration of pefloxacin and levofloxacin with alkali mixture. So, when fluoroquinolones

like pefloxacin or levofloxacin co-administered with alkali mixture the minimum antibacterial concentration (MIC) may not be reached in urine.

CONCLUSION

It may be concluded that fluoroquinolones and alkali mixture should not be co-administered.

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