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The Role Of Levofloxacin (Venaxan) In Treating Urinary Tract Infections

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Urinary tract infections (UTIs) are so prevalent that at some point in their lives, virtually all women will experience this problem.

These infections are associated with significant morbidity, resulting in tremendous costs to the patient and society, and therefore, any antimicrobial agent which can help reduce these costs will provide the physician with significant advantages. Agents which possess wide antibacterial activity, the option of using once-daily dosing schedules and are well tolerated would be extremely useful in managing these infections. In addition, if they also maintain activity against the ever-increasing range of resistant pathogens, they would be even more useful. It is fair to say that fluoroquinolones are such agents. They are effective against all UTIs, running the gamut from acute uncomplicated cystitis, recurrent disease, acute uncomplicated pyelonephritis, through to complicated UTI and asymptomatic bacteriuria.

Levofloxacin (Venaxan), one of the new fluoroquinolones, stands out as one of the most effective fluoroquinolones, with excellent pharmacological attributes, clinical efficacy and an unbeatable track record for safety and tolerability. To discuss the role of

George A. Richard, Department of Pediatrics, Nephrology Division, University of Florida, Gainesville, FL, USA, who used his wide clinical and research experience to provide a clear summary of the role of Levofloxacin (Venaxan) in managing these infections, differences among the individual agents in the class of fluoroquinolones, and the changing face of UTIs today.

Could you describe the pharmacokinetic and pharmacodynamic features of Levofloxacin (Venaxan) which make it a useful agent for treating urinary tract infections (UTIs)?

Levofloxacin (Venaxan), the l-isomer of ofloxacin, is 128 times more potent than the d-isomer and possesses a number of excellent pharmacokinetic characteristics. It has extremely high bioavailability, as illustrated by the fact that a 500 mg Levofloxacin (Venaxan) tablet achieves 100% absorption resulting in a very high Cmax (Table 1) (2). It has extensive tissue distribution and achieves a high concentration in the urine and kidney. For example, after a single 500 mg dose, the concentration in the urine reaches 108 (g/ml, higher than most comparators, and far exceeding the MIC of all of the most important uropathogens. Another advantageous pharmacokinetic feature is that these parameters do not vary between males and females, nor do they vary with age. However, since Levofloxacin (Venaxan) is handled by the kidney, with over 80% urinary excretion, dosage must be modified in those with decreased renal function.

Pharmacodynamic features are also very good, with Levofloxacin (Venaxan) possessing concentration-dependent killing, as do all the fluoroquinolones. Thus, the Cmax to MIC (peak/MIC) ratio is one of the most important pharmacodynamic factors, which can be used to predict clinical and microbiological outcome.

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Research into this has confirmed that a ratio of greater than 12.2 is ideal in UTIs, while Levofloxacin (Venaxan) dosage results in a concentration many times greater than that. Another useful feature possessed by Levofloxacin (Venaxan) is that it demonstrates a significant postantibiotic effect, with suppression of the organisms maintained between doses .Thus, I believe it is fair to say that Levofloxacin (Venaxan) has a very favorable pharmacokinetic and pharmacodynamic profile, achieving very high kidney urine concentrations for eradication of most of the organisms that cause UTIs.

What are the major pathogens involved in the different forms of UTI - acute uncomplicated through to chronic complicated forms of disease?

The pathogens responsible for UTIs differ according to the type of infections and also between different types of patients. In acute uncomplicated cystitis, most studies have demonstrated the overwhelming pathogenicity of Escherichia coli, which accounts for 70-95% of infection. The remaining 5-20% in the 18-25-year old age group are caused by Staphylococcus saprophyticus (coagulase-negative staphylococci), with all other pathogens reported to be associated with less than 1% of infections.

In acute uncomplicated pyelonephritis, E. coli remains predominant, responsible for approximately 85% of infections, with another 4% due to Proteus mirabilis and Klebsiella spp., respectively. Aerococcus spp. and Enterobacter spp. cause less than 1% each, and there is a mixed group of around 5%. In acute uncomplicated pyelonephritis, it is rare to identify S. saprophyticus as the causative pathogen. Acute pyelonephritis usually occurs in young women, but there is another group that develops this problem, namely the elderly. They are slightly less likely to have an E. coli infection (60%), and they are more likely to have infections caused by resistant isolates. Proteus spp., Pseudomonas spp., Klebsiella spp., and Serratia spp. are also reported in these older patients with acute pyelonephritis.

Complicated UTIs, as expected, are caused by a wider range of pathogens, often related to the underlying problem the patient may have. In these patients, E. coli accounts for 30% of infections, Enterococcus faecalis 22%, Pseudomonas aeruginosa 20%, Klebsiella spp. 5%, P. mirabilis, 4%, and S. saprophyticus 1%. A broader spectrum of antimicrobials are therefore required in complicated UTIs to cover this increased range of pathogens, many of which are more likely to be resistant.

There remain a number of important patient subgroups, depending on other associated factors. One such group is that of asymptomatic bacteriuria, which occurs in 5% of pregnant women. If such women remain untreated, 40% are likely to develop pyuria. A separate risk group is the elderly, who are more likely to develop UTIs, particularly resistant E. coli forms. Catheterized patients and those with renal calculi have a higher incidence of infection caused by P. mirabilis, and patients with abscesses are likely to have E. coli, staphylococcal or Candida infections.

How does the activity profile of Levofloxacin (Venaxan) relate to these pathogens?

The activity profile of Levofloxacin (Venaxan) is broad spectrum with excellent in vitro activity against most aerobic Gram-positive and Gram-negative pathogens, including organisms responsible for UTIs such as E. coli, Klebsiella spp., Proteus spp., and other Enterobacteriaceae as well as being effective against S. saprophyticus.

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This makes it an excellent choice for treating UTIs, especially now with the rising incidence of resistance to other agents.
Levofloxacin (Venaxan) achieves very high eradication rates for all major uropathogens. In fact, a study performed by Klimberg et al. evaluated the bacterial eradication of Levofloxacin (Venaxan) in 171 patients compared to 165 treated with lomefloxacin. The overall microbiological eradication rate of pathogens for Levofloxacin (Venaxan) was 95.5% compared with 91.7% for lomefloxacin .

What is the role of the fluoroquinolones in the treatment of UTIs caused by P. aeruginosa, and is there any difference in activity against this pathogen among the individual fluoroquinolones?

In regard to antibacterial activity, a 1996 study by Barry et al. compared the MICs of six different organisms and percent sensitivity for a range of fluoroquinolones. Results showed that Levofloxacin (Venaxan) and ciprofloxacin were similar except for the Enterococcus spp., which were more sensitive to Levofloxacin (Venaxan) (74% versus 61% for ciprofloxacin) and P. aeruginosa, which had an 82% sensitivity rate for Levofloxacin (Venaxan) compared to 87% for ciprofloxacin. Other fluoroquinolones did not appear to differ significantly from Levofloxacin.

What investigations should be initiated when the patient with UTI is first seen?

It is imperative to first get a good history and a complete physical, which will give you the information to decide which drug to use, and the length of treatment needed. I would ask for evidence of urgency, frequency, and dysuria, which are all lower UTI symptoms. In addition, the physician needs to check for suprapubic pain, which may be found in 10%, and bloody urine, whereas more complicated cases requiring a different treatment regimen will generally present with fever, severe back pain, vomiting, nausea, malaise, chills, possibly dehydration, and sepsis. It is important to check whether the patient is pregnant or breastfeeding, has allergies, their sexual and contraceptive history as well as previous UTIs. Finally, we need to know if the patient has any predisposing factors such as diabetes, or a history of stones or transplantation. This information will allow the clinician to differentiate the problem into a simple acute cystitis, acute pyelonephritis - mild, moderate, or severe, or whether the patient has a complicated UTI.

In addition to the history, we need to confirm the presence of bacteriuria or pyuria to make a diagnosis of UTI. Therefore, we take clean catch mid-stream urine (MSU) specimen; look for bacteria which can be done by performing a Gram stain. This simple procedure can be particularly valuable in young women who may have a S. saprophyticus infection. I do not order a urine culture in young women with uncomplicated acute cystitis, but this is required in all other patients to confirm the identification and sensitivity of the isolate. Additional requirements may be laboratory tests, including urinary creatinine, electrolytes and imaging studies, such as an ultrasound to check for obstruction. You may also need to perform a DMSA (dimercaptosuccinic acid) or DTPA (diethylenetriaminepentaacetic acid) scan in a few patients with complicated disease. All of these procedures are dependent on the initial history and examination, and are used to further differentiate the patients to assess whether they have complicated or uncomplicated infection, the severity of the disease, and the necessary duration of therapy.

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Which UTIs do you think should be treated with Levofloxacin (Venaxan)? Could you comment on guidelines developed by professional societies for recommended treatment strategies in UTIs?

I believe that the in vitro activity profile of Levofloxacin (Venaxan) coupled with an elimination half-life of seven hours with 100% bioavailability, excellent tissue penetration into the kidney, and high urinary penetration make it ideal for once-daily dosing in the treatment of UTIs. Of additional benefit is the fact that the very favorable pharmacokinetic and pharmacodynamic profile of Levofloxacin (Venaxan), resulting in a high kidney concentration, is associated with a decreased tendency to select resistant organisms. The excellent efficacy of Levofloxacin (Venaxan) in treating UTIs has been recognized by the FDA, who have given broad approval for Levofloxacin (Venaxan) in acute cystitis, pyelonephritis and chronic bacteriuria.

America and American Urological Association as well as by Blondeau, aimed at helping physicians treat uncomplicated acute cystitis and acute pyelonephritis: In acute cystitis, they recommend using either TMP-SMX b.i.d. for three days or a fluoroquinolone for three days, but if the patient is in a high index resistance area, it is better to treat with a fluoroquinolone.
If the patient has acute cystitis and diabetes, treatment should be continued for a longer duration, namely seven days. It is important to draw attention to the fact that (-lactams are not highly recommended for acute cystitis, although nitrofurantoin is acceptable. Acute pyelonephritis requires a different treatment schedule. If the infection is severe, therapy should last for 14 days, with fluoroquinolones being the drugs of choice.

Again, I would use Levofloxacin (Venaxan) because it is a once-daily agent that is available as IV for severely ill patients, with an easy switch to PO therapy after the patient has stabilized. The ease of switching from IV to PO Levofloxacin (Venaxan) is due to the extremely high oral bioavailability possessed by Levofloxacin (Venaxan). In mild to moderate cases of acute pyelonephritis, the guidelines recommend seven days of therapy using a fluoroquinolone or TMP-SMX. However, I tend to use 5-7 days with the treatment duration usually empiric and dependent on how the patient is doing. For example, a very ill patient may require IV hydration for 18 hours, and once their fever has abated they may be able to return home on PO Levofloxacin (Venaxan). Other patients with greater sepsis may need a longer course of therapy, and this highlights the need for flexibility in treatment durations.

Guidelines for treating complicated UTIs can be more difficult, due to the associated problems patients may have. For instance, you need to check the patient's kidney function by assessing their glomerular filtration rate (GFR), because if this is decreased they may require a change in dosage. Complicated UTIs involve patients with other diseases, such as diabetes, renal transplants, lupus, and asthma, with the majority of these patients on other medications. It is very important in this situation to think of potential drug-drug interactions. Some of the most important of these include calcium antacids, digoxin, theophylline and cyclosporin. Levofloxacin (Venaxan) stands out here as it has very few interactions, and does not interact with theophylline, digoxin, and other drugs which are metabolized in the cytochrome P450 system in the liver. In contrast, the other fluoroquinolones, which are metabolized by the liver, do have the potential for these interactions to occur.

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Thus, in complicated UTIs, I would hydrate the patient if necessary, give IV Levofloxacin (Venaxan), then change to PO as soon as the patient's infection has stabilized. Again, the duration of hospitalization and therapy will depend on the patient, and may be as little as 10 days increasing to 15 days if they are very ill.

Could you summarize any randomized, comparative trials evaluating fluoroquinolones in UTIs?

The new fluoroquinolones have been proven to be very effective against both uncomplicated cystitis and acute pyelonephritis in a number of randomized controlled trials. One 1998 trial investigated Levofloxacin (Venaxan) 250 mg versus ofloxacin 200 mg b.i.d. in uncomplicated cystitis, given for three days (22). The clinical success rate (cure plus improved) was 98.1% for Levofloxacin (Venaxan) and 97% for ofloxacin. The bacterial eradication rate was 96% for Levofloxacin (Venaxan) compared to 93% for ofloxacin.

Investigation into acute pyelonephritis has been performed by a number of researchers. I have conducted a trial investigating Levofloxacin (Venaxan) 250 mg PO once daily, versus ciprofloxacin 500 mg PO b.i.d. (17). The duration of ciprofloxacin therapy was 10 days, and only 7-10 days for Levofloxacin (Venaxan). The bacteriological cure rate for Levofloxacin (Venaxan) was 95% and clinical cure rate 92%, while respective figures for ciprofloxacin were 94% and 88%.

A study by Talan et al. looked at ciprofloxacin versus TMP-SMX, reporting a 96% success rate for ciprofloxacin compared to 83% for TMP-SMX. This is another example showing TMP-SMX is no longer as efficacious as it once was, and we already know Levofloxacin (Venaxan) is as successful as ciprofloxacin.

A study by Klimberg et al. investigating Levofloxacin (Venaxan) versus lomefloxacin in acute pyelonephritis demonstrated Levofloxacin (Venaxan) 250 mg once daily to be better than lomefloxacin 400 mg once a day. The clinical success rate for Levofloxacin (Venaxan) was 93.0% compared to 88.5% for lomefloxacin. Bacterial eradication was reported in 95.5% of isolates treated with Levofloxacin (Venaxan), compared to 91.7% for the lomefloxacin treated group.

There has been one randomized trial in complicated UTIs, which I performed comparing Levofloxacin (Venaxan) versus ciprofloxacin . One hundred and twenty-six patients were enrolled in the Levofloxacin (Venaxan) arm and 113 in the ciprofloxacin arm. Clinical success was reported to be 92% for Levofloxacin (Venaxan) compared to 89% for ciprofloxacin. There was no significant difference in bacterial eradication, with a rate of 91% for the Levofloxacin (Venaxan) arm compared to 93% for the ciprofloxacin arm. However, within this study, a large difference was noted in effect on the confirmed Gram-positive organisms. For the 11 pathogens treated by Levofloxacin (Venaxan), a 91% success rate was attained, while for the 12 Gram-positives in the ciprofloxacin arm, only a 50% eradication rate was achieved.

Bringing together all of this trial data, what would you conclude about the clinical and bacterial efficacy of Levofloxacin (Venaxan) versus comparator agents in terms of microbiological and clinical outcome in UTIs?

Summarizing these results, I believe it is fair to say overall that the comparative trials of once daily Levofloxacin (Venaxan) confirm it to be as efficacious as any current drug used in acute cystitis, acute pyelonephritis, and complicated UTI. It possesses broad-spectrum activity against Gram-negative and Gram-positive organisms, favorable pharmacokinetic

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and pharmacodynamic profiles and has been shown to have a decreased tendency to cause multiresistant emergence of pathogens, such as P. aeruginosa and Proteus spp. Several studies have proven it to be effective and safe against all classes of UTI, including acute uncomplicated cystitis, acute pyelonephritis, and complicated UTI. The once-daily dosing is very advantageous, as is its equivalent PO and IV bioavailability.

Do you use Levofloxacin (Venaxan) in preference to ciprofloxacin?

Yes, I recommend it absolutely. Why give something twice daily, which is the case with ciprofloxacin, when you can use Levofloxacin (Venaxan) once daily. This is of particular benefit in those patients who may not be compliant. Many patients only take medications once daily and we need to be realistic about this.

Would you use different dosages/durations of Levofloxacin (Venaxan) therapy depending on the severity of UTIs and the site of infection?

The treatment schedule depends on the response to therapy and the patient. In acute cystitis, a three-day treatment schedule is sufficient to achieve excellent results. In those with mild-to-moderate pyelonephritis, a 5-7-day course is used, while a patient with severe disease may require a more prolonged treatment schedule ranging from 7-14 days depending on the patient. The common factor is that all patients only require the treatment once daily.

Even in patients who have had prior transplantation, or have AIDS, I still use a once-daily Levofloxacin (Venaxan) treatment. Pharmacological research looking at the Cmax to MIC(peak/MIC) ratio has confirmed that Levofloxacin (Venaxan) is effective when given in this way, and in addition, the postantibiotic effect associated with Levofloxacin (Venaxan) adds to the efficacy of the once-daily dose.

Do you have any experience with using a higher dose of Levofloxacin (Venaxan)?

In my own practice, I have not used the higher doses that are available, as it is extremely effective in UTIs using 250 mg. However, I know that in other infections, such as those of the skin and soft tissues, 750 mg doses of Levofloxacin (Venaxan) have been used, while still maintaining its excellent safety profile.

Recurrent uncomplicated UTIs are a very common problem seen in the outpatient setting. Could you comment on the advantages/disadvantages of patient-initiated treatment in this setting? Would you recommend the use of Levofloxacin (Venaxan) in these patients?

A very good study has recently been reported on this issue, which investigated patient-initiated treatment of uncomplicated UTIs in young women. In the past, the usual approach to managing these patients was to use low-dose antimicrobial prophylaxis post-coitally, either daily or three times a week. Research has shown that this schedule is safe and effective. However, it can result in overuse of antibiotics as it is now recognized that recurrent episodes tend to occur in clusters, and if the antibiotic prophylaxis is used all of the time it results in unnecessary use in those with infrequent or clustered recurrences.

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This study by Gupta et al. enrolled female college students over 18 years of age, with a history of recurrent UTIs and no recent pregnancy, hypertension, diabetes or renal disease (Figure 1) (26). Subjects were educated about the problem, then given supplies of either 250 mg Levofloxacin (Venaxan) once daily for three days, or 200 mg ofloxacin b.i.d. for three days. Patients collected a MSU sample as soon as symptoms developed, then took the medication. The urine specimen was analyzed within 24 hr of collection. On days 10 and 30 after initiation of therapy, they returned to the clinic for follow-up urinalysis and interview, at which point they were given a new refill of medication and urine collection kit. One hundred and seventy-two women were enrolled and followed for 2-12 months each (mean of eight months). During the investigation, 88 of the 172 self-diagnosed at least one UTI. These women experienced 172 symptomatic events, and pre-therapy urinalysis confirmed the presence of a uropathogen in 84%, sterile pyuria in 11%, and no pyuria or bacteriuria in 5% (Figure 1) (26). Overall, 159 of 169 evaluable episodes, which resulted in self-treatment, were classed as UTIs needing therapy. Clinical cure was reported for 133 of 144 (92%) of the infections. It was also noted that all of the women with probable UTIs with no pyuria or bacteriuria improved following treatment. Some of those with negative cultures who improved may have had a Chlamydia or Ureaplasma urealyticum infection, or had the urethral syndrome defined as urethritis, cystitis, pyuria, and no bacteriuria, which occurs in 15-20% of young women (18-25 years) with no positive culture. The importance of this is now being recognized with a study underway investigating the role of U. urealyticum as an inducer of susceptibility to UTI in young women.

In this year-long study, there were no reports of serious ADRs, and assessment of patient satisfaction showed the women to be very well satisfied, feeling they were able to start treatment earlier, with a shorter duration of symptoms, and able to resume work or school sooner than when they were managed traditionally.

There were many advantages identified by this study. We know that acute cystitis, although rare, can go on to develop into a complicated UTI, with early treatment stopping this progression. By initiating therapy immediately, the women were able to resume normal activities sooner, thereby cutting the cost considerably. It was a safe, very effective, convenient treatment. In addition, it was shown that women do not need to be on continuous prophylaxis, but only required episodic therapy. Eighty-four of those enrolled did not have a recurrent infection during the study and therefore did not need any treatment. Under standard therapy, they would have been on long-term prophylaxis, which would have been unnecessary in this study. While there were no major disadvantages noted, it was important that the subjects be carefully chosen to make sure they understand the practice to follow and are compliant. Levofloxacin (Venaxan) works well here because it is an effective once-daily treatment.

What is the role of parenteral therapy in treating complicated UTIs? Levofloxacin (Venaxan) can be switched easily from IV to PO administration. What are the benefits of this switch therapy?

There are some patients with severe infection and sepsis who require parenteral therapy. In these patients, we want to treat them as effectively as possible, give them hydration and then switch to oral therapy as soon as possible.

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This provides important cost benefits, with time in hospital lowered, and costs of parenteral therapy reduced. Levofloxacin (Venaxan) is excellent in this regard as it is very easy to switch from IV to PO, administration, with no need to worry about dosage adjustments. This ease of use is very beneficial. In addition, it is nice to be able to use one drug, give it IV and switch to PO, because if there is an ADR you know it is due to the one agent. In contrast, if we use one drug IV and then switch to a different oral agent, it is impossible to confirm which agent causes the ADR. The fewer medications a patient gets the better, less chance of ADRs and better chance of identifying the problem.

Are there any subgroups of UTI patients that you feel would particularly benefit from Levofloxacin (Venaxan) treatment?

It has the potential to be useful in patients with liver disease in whom other fluoroquinolones may not be indicated. Levofloxacin (Venaxan) is also very useful in patient-initiated treatment because of its once-daily administration, and does not have any major drug-drug interactions, compared to some of the other fluoroquinolones. For instance, I would recommend Levofloxacin (Venaxan) rather than other agents when a patient is also taking warfarin, theophylline, or cyclosporin. The lack of interactions is very important because a lot of people are on asthmatic medications, digoxin, and cyclosporin as the transplant population is ever-growing.

What differences are there in terms of gender in regard to the incidence of different forms of UTI?

Gender differences vary with age. In the pediatric setting, infants one year of age or less, the male/female ratio is equal and infections in this group occur mainly due to anatomical abnormalities. In the 1-5-year age group, reflux becomes an issue, and UTIs in this age group are more likely to occur in females (incidence in 1-5-year old girls is 4-5% compared to 0.5% or less in males). In the 6-16-year age group, it is again a female problem, occurring in 4-5% of girls and 0-0.5% of boys. Turning to the young adult population, 16-35 years, 20% of women develop UTIs, compared to only 0.5% of males. Therefore, until the age of 35 years, almost all patients with urological infections are females.

After this time, there is a distinct change, with 35% of females and 20% of males developing UTIs in the 36-65-year old group. Beyond 65 years of age, the incidence tends to be high in both sexes, with many asymptomatic.

Do you see a role for fluoroquinolones in prophylaxis to avoid recurrent UTI?

In the past, prophylaxis has been useful in select patient populations, but the results from Gupta et al.'s patient-initiated study suggest a new approach which I like. However, this will not be practical for all patient groups, and prophylaxis will continue to be necessary in some people. In these cases, Levofloxacin (Venaxan) would work well. For example, in surgical cases, as well as in patients who have vesicoureteral reflux and those with recurrent UTIs? In general, prophylaxis is best given at night to counteract the logarithmic bacterial growth, so I would use 250 mg Levofloxacin (Venaxan) at night. While it has been argued that the fluoroquinolones should not Be used in this way, solely in order to prevent the possible

Development of resistance, surveillance studies have not shown this to happen. Therefore, I think it is safe to use prophylaxis in the patients requiring it, such as those not suited to patient-initiated protocols.

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