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Cefixime for the prophylaxis of urinary tract infections in children with malformative uropathies: an open study

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Abstract. – **Urinary tract infections are often associated with urinary anomalies. An appropriate pharmacologic treatment may prevent, or may at least limit, any kidney damage due to pyelonephritis.**

The antibiotic prophylaxis plays a role as significant as early surgical therapy, taking into consideration also the present limitative trend for a softer therapeutic regimen. In the past few years a greater bacterial resistance has emerged against some commonly administered antibiotics. Cefixime (3rd generation cephalosporin) has been used on a wide series of patients suffering from urinary infections associated with urinary tract anomalies. A few significative results emerge from the present study.

In conclusion, cefixime's effectiveness long-term prophylaxis of urinary infections associated with anomalies.

Key Words:

Cefixime, Urinary tract infections, Urinary tract anomalies, Long-term prophylaxis of urinary infections.

Introduction

Urinary tract infections (UTIs) are the most common bacterial diseases affecting pediatric subjects[1]. They are often associated with urinary tract anomalies, with special reference to vesicoureteral reflux (VUR).

Available data in the literature indicate that in the western world only one fetal ultrasonography out of 500 (0.2%) either reveals the presence of or suggests the suspicion for an anomaly[2]. Obviously, these figures are lower than the actual incidence of congenital uropathies. In fact, the current incidence of such conditions has been conventionally set between 1% and 2% of the general population[3]. Therefore, it appears to be demonstrated what had been theoretically suggested by virtually all the authors: approximately one half of congenital anomalies remain undetected by prenatal diagnostic screening. Another portion is not diagnosed since no ultrasound (US) examinations are performed; an additional portion consists of originally non "dilative" forms (at an early stage).

We are going to leave out any discussion on the natural history of the individual malformative uropathies (MUs); however, it should be pointed out that 75% of the carriers of "silent" anomalies, which have not been discovered during the prenatal period as "dilative" conditions, are being documented at the time of diagnosis as UTIs (with varying degrees of renal damages).

A few UTIs only involve the kidney parenchyma; moreover, hematological and

clinical studies do not clearly establish the site of infection. This is especially true in children under 1 year old. UTIs are most common in this age group. In view of the fact that only the infections producing renal involvement are able to cause long-term difficulties, it appears necessary to know any prospective association between UTIs and renal damage in order to devise those strategies which can counteract any recurrence as well as delay or avoid any future complication.

An appropriate and well-timed pharmacologic treatment may prevent, or may at least limit, any kidney damage due to pyelonephritis. In the past few years, however, in certain types of urinary tract malformations, such as VUR, a clear cut switching towards a softer regimen of treatment has occurred, in other words a less dramatic attitude towards the prevention at any rate (always and in every way). More recently, for instance, some attention has been directed towards the genetic deregulation of the nephrogenic program, as being the direct responsible for reflux or reflux-associated nephropathy[4]. In fact, it has been definitely disproved the idea of a fundamental role exerted by infection as the only causative agent directly responsible for inducing a pyelonephritic renal damage in patients with VUR[4]. However, it is certainly "helpful" (essential condition to be looked for) to be capable of maintaining urinary sterility in instances of MUs, thus allowing a "less aggressive" attitude in the management of such patients. Therefore, the antibiotic prophylaxis plays a role as significant as early surgical therapy, taking into consideration also the present limitative trend – as compared with the past – for a softer therapeutic regimen.

The drugs to be used for preventive purposes must possess a few basic features, such as effectiveness against the pathogenic strains most commonly encountered, good tolerability together with lack of unwanted adverse reactions[5].

In the past few years a greater bacterial resistance has emerged against some commonly administered antibiotics, such as amoxycillin. The administration of co-trimoxazole during the earliest moths of life, instead, has been discouraged.

For the treatment and prophylaxis of UTIs, the use of oral cephalosporins appears to be a useful decision to take.

When a pediatrician prescribes a drug, he or she is supposed to be acquainted fully with active principle, dosage, therapeutic effects and adverse reactions of such a drug. We have chosen to assess both effectiveness and tolerability of cefixime for the prophylactic treatment of UTIs in children with VUR or other uropathies.

Cefixime is classified as a 3rd generation cephalosporin as far as activity against gram-negative (G-) micro-organisms is concerned, and as a 2nd generation cephalosporin as far as activity against gram-positive (G+) micro-organisms is concerned.

As compared with the other oral cephalosporins, cefixime shows the following features:

- Increased activity against some Enterobacteriaceae
- Overlapping activity against Haemophilus influenzae even if it produces b-lactamase
- Reduced activity against some gram-negative micro-organisms, with special reference to Streptococcus pneumoniae

Cefixime's tolerability profile is overlapping both Cefaclor's and Amoxycillin + clavulanic acid's profiles

Cefixime
Trade name
Cefixoral®
Suprax®
Unixime

Cefixime has been used on a wide series of patients suffering from lower urinary tract infection (UTI), in which a short-lasting antibacterial therapy at high doses has been found helpful. It is the drug of choice in switch therapy. Minimal Bactericidal Concentration/Minimal Inhibitory Concentration (MBC/ MIC) ratio for cefixime is close to 1.

Materials and Methods

A total of 52 children, 25 m and 27 f, aged from 1 month to 9 years (mean age: 7 months), suffering from an UTI superimposed to a malformative uropathy (MU), were enrolled in the study. The morbid conditions under study were documented and assessed by means of renal and vesical US, voiding cystourethrography (VCU), and scintigraphy plus urodynamic investigation.

The diagnosed MUs under study included primary hydronephrosis (15), primary megaloureter (8), ureterocele (2), VUR (11), vesical diverticula (2), posterior urethral valve (PUV, 2), and hypospadias complex (12). With the term primary hydronephrosis we indicated any dilatation of renal pelvis and calyces due to a congenital anomaly located at the pyeloureteral junction (PUJ).

PUJ anomaly was found to be permanent in 8 cases (42%); all these patients were complaining of UTI symptoms.

In severe calycopyelic dilatations (2 cases, 25%), a marked dilatation was associated with parenchymal thinning. In these cases an early surgical reconstruction procedure at the PUJ was performed in view of the fact that a functional asymmetry greater than 8% to 10% was demonstrated. Such procedure was carried out within a short time period, following a VCU plus a renal scintigraphy using 2,3-dimercaptosuccinic acid (DMSA) [rather than diethylenetriaminopentacetic acid (DTPA), thus assessing separately the rate of bilateral renal function (RF) while renouncing the determination of pyeloureteral emptying]. In those cases in which the parenchymal thickness was considered to be satisfactory, we chose to proceed with an ongoing "ultrasound surveillance". No aggravation enough severe as to require a surgical correction was ever recorded in any of these patients.

We treated 4 cases (50%) of primary megaloureter; all had a left sided anomaly; 1 case had an associated homolateral PUJ obstruction. All these patients came to our observation on account of an UTI.

Two cases of ureterocele involved a single pyeloureteral system with a ureterocelic cyst entirely contained inside the bladder. In both cases the ureterocele led to stasis and dilatation, even rather marked, of proximal urinary passages. In one of them a vesical diverticulum was associated with the ureterocelic cyst.

All the patients were administered the antibiotic prophylaxis with cefixime. Those scheduled for surgery received the drug under study both in the preoperatory and in the postoperatory period. Cefixime was administered in the evening as a single daily dose of 8 mg/kg of body weight. Mean treatment duration was set at 6 months (varying from 3 months to 1 year). During the treatment period the patients were monitored by urinalysis and urine culture at monthly intervals – in order to evidence the onset of bacterial resistance, if any, or a potential recurrence of the infection. Extreme care was taken in all patients in order to elicit symptoms and signs associated with documented recurrences of infection. During the treatment period, laboratory tests, with special reference to ematopoietic, hepatic and renal functions, were performed for the purpose of assessing adverse reactions, if any. In addition, the diseased children's parents were instructed to record the onset of any manifestation involving the gastrointestinal tract, the skin (rashes) or any other sign that could be ascribable, to any extent, to the administration of the drug under study.

Results

A few significative results emerge from the present study:

1. Cefixime showed to be very effective in preventing UTIs associated with MU (28% of the patients enrolled in our study had a "primary hydronephrosis" and 42% out of them had a permanent anomaly of the PUJ). In fact, only 2 patients (3.8% of the entire study population) had a recurrence of the UTI. In both cases, the recurrence developed a few months after the start of the treatment (after 6 and 10 months, respectively, of antibiotic therapy) and in concomitance with a higher grade of VUR (grade 3 and 4, respectively). On the

other hand, in both cases the UTIs were due to strains of Proteus (vulgaris) and Pseudomonas aeruginosa belonging to species intrinsically resistant to cefixime as well as to other 2nd generation cephalosporins (Cefaclor, Cefpodoxime).

2. Tolerability towards cefixime showed to be very good. In fact, only 2 children developed an episode of skin rash; both patients had a positive history of intolerance against other drugs (subjects generically affected by atopy). From the stand-point of gastrointestinal side effects, it should be pointed out that even in the youngest infant – only 1 month old – intolerance manifestations were not observed; moreover, the drug under study showed a high gustatory acceptance (so that the dosage schedule could be adhered to without any difficulty).

Discussion

Cefixime is the forerunner of the 3rd generation of cephalosporins showing a wide spectrum of antibacterial action. Cefixime is an oral cephalosporin possessing a wide spectrum and stability of action. It shows a marked activity, especially against the most important pathogens responsible for UTIs, including β-lactamase producing strains and amoxycillin- cefaclor- and cefpodoxime-resistant strains. The drug under study is excreted mainly through the urinary passages and appears to be effective for the treatment of non-specific UTIs, either uncomplicated or complicated by MU, mostly due to E. coli, Klebsiella, and several strains of Proteus and Staphylococcus; the recovery rate is ≥ 85% while bacteriological eradication is ≥ 89%[6].

Cefixime is clinically effective as cefaclor and amoxycillin (Cox CE et al.) in patients suffering from uncomplicated UTIs or from surgical MUs due to E. coli, K. pneumoniae, P. mirabilis, and S. saprophiticus, at a preoperatory stage. UTIs are due to the presence and multiplication, within the urinary system, of pathogenic bacteria, usually γ- micro-organisms of fecal origin. The infection becomes manifest when bacterial virulence predominates over host's defences.

Bacteria reproduce by binary division, with total cell number doubling at regular intervals. Therefore, bacterial growth is "exponential" or "logarithmic". If we follow in vitro the time pattern of bacteriat growth, we will be able to draw a variable curve depending on bacterial species and culture media (Figure 1).

The generic terminology of UTIs may be better characterized by site of infection (i.e., upper and lower urinary passages), potential presence of predisposing factors (organic and functional), type of isolated micro-organisms (i.e., bacteria, mycetes), subjective symptoms, clinical course of the disease, and response to therapy. An early return of infection is defined as recurrence when sustained by the same bacterial agent, as reinfection when produced by a different micro-organism, and as superinfection when two or more bacterial agents are concomitanly inducing the infection.

Among the factors that may favor both colonization and multiplication of bacteria, the slowing down of urinary efflux plays a widely recognized role of primary significance. Such a slowing down is secondary to organic and/or functional changes, such as those observed in instances of MU, most often revealed by a dilatation in the urinary passages developing during the prenatal or neonatal period.

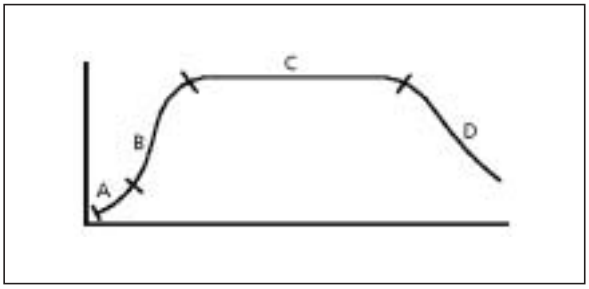

Figure 1. A = latent phase in which growth is close to zero. This phase may even be absent. B = expanding phase in which growth reaches its maximum and steady value. Bacteria are highly sensitive to antibiotic action in this phase. C = steady phase in which growth is zero. D = declining phase: following a time period of permanence in the steady phase, the mortality rate increases and reaches a steady level.

Such a dilatation may be due to a variety of causes:

1. An obstruction of urine efflux localized at different urinary tract levels:
   - pyeloureteral junction (potential hydronephrosis);
   - vesicoureteral junction (potential hydroureteronephrosis);
   - urethra, where the most common cause in males is the urethral valve (potential bilateral hydroureteronephrosis);
2. Previous obstructions spontaneously subsided
3. Hypotonia of urinary passages without obstruction that may either involve the entire urinary tract (megaloureter) or be limited to the renal pelvis (pyelic hypotonia) or to the calyces (congenital megalocalycectasis)
4. High grade vesicoureteral reflux
5. Uncomplying or neurologic bladder.

The possible presence of an obstructive pathology must be taken into consideration when a dilatation of the urinary tract is detected in a patient by means of US esaminations or other investigations.

The concept of obstruction must be interpreted in a functional fashion, that is, any impingement to urine flow that leads, if left untreated, to a progressive kidney damage[7].

The causes of obstruction include:

1. Kidney stones (most common in adults, quite often subsiding spontaneously)
2. Congenital derangements
3. Inflammations
4. Neoplasms
5. Blood clots

– Experimental evidence, substantiated by clinical observation, has pointed out that an acute obstruction involving upper urinary passages leads to a sudden rise in pressure with dilatation of the urinary system proximally as well as to an increase in peristaltic activity with loss of peristaltic coordination. At the beginning the pressure in the renal pelvis, ranging between 4 and 10 cm H_2O under normal conditions, may rise up to 50 or 60 cm H_2O. Such a pressure increase modifies the pressure gradient all along the renal tubules, with consequent early increment in blood flow through a reflex mechanism and a prostaglandin E_2 release. Subsequently, renal perfusion decreases and after approximately 24 hours drops down to 40-70% of normal values, because of a vasoconstriction involving pre- and post-glomerular capillaries. This, in turn, leads to a drop in glomerular filtration rate (GFR). Such a mechanism produces a pressure reduction down to normal values in the tubules. As a consequence, tubular function is maintained virtually at a normal level, thus protecting glomeruli from hypertension-induced damage. Experimental models have allowed to disclose how a concomitant clinical picture of "upper" UTI may be able to counteract the realization of such a mechanism of pathofisiologic compensation, with a subsequent progressive trend to damaging the kidney parenchyma.

– Parenchymal damage induced by the obstruction associated with UTI appears to be variable; a complete obstruction may produce in adults a permanent reduction in function as early as a week, whereas a satisfactory functional recovery is possible in children, even though obstruction has persisted for months, provided an adequate antibiotic therapy has been administered. Under such circumstances, chronic obstruction produces an early, gradual reduction in kidney function, followed by an equally gradual and progressive recovery – in 80-90% of the cases – in those patients who received an adequate therapy (responsive treatment).

– Usually, in 75% of obstructive MUs, the obstruction is partial, with hydronephrosis of varying degree and urinary efflux occurring only when the pressure in the territory proximal to the site of obstruction exceeds a certain pressure gradient.

In most patients, hydronephrosis developing in adults is due to an obstruction (i.e., lithiasis, neoplastic spread, adhesive bands) and it requires a surgical correction if does not resolve within a short time period. The situation differs in children; in this age group hydronephrosis is more commonly found (in 1-1.5% of the cases), on account of the diffusion and improvement achieved by prenatal and neonatal US screening. A high

proportion (perhaps above 50%) of patients with hydronephrosis detected in the pediatric age group does not require any surgical correction, since the situation becomes stabilized or improves spontaneously without any loss of kidney function, when treated by an "adequate" antibiotic therapy.

– Intravenous pyelogram (IVP) investigates the morphology of urinary excretory passages in detail and can detect an obstruction as well as its site. Presently, its use in pediatric age group is limited.

– Ultrasonography is the routine modality for neonatal screening; it is the first study to be performed in adults with suspected urinary obstruction. It shows the presence of hydronephrosis and provides important morphologic information, such as dilated structures and malformations, if any; however, it cannot generally evidence whether any obstruction is actually present.

– CT and MRI play a marginal role in the diagnosis of obstruction; they may be useful when kidney function is markedly reduced and there is consequently a low concentration of urographic contrast material.

– All the above mentioned modalities may play a role in the etiologic diagnosis of obstruction; however, they cannot provide any objective functional information. On the contrary, sequential renal ultrasonography, although usually poorly capable of assessing the etiology, may provide significant functional data, useful for the appropriate evaluation of patients with hydronephrosis.

– Scintigraphy plays an essential role in the assessment of hydronephrosis in pediatric patients; first because it allows to observe the dynamics of urine efflux, thus differentiating the obstructive forms from the dilative forms, and second because it provides an appraisal of the dilated kidney function. Scintigraphic controls associated with US studies allow to evaluate with time the trend of the hydronephrotic kidney function, the degree of dilatation and its natural evolution, thus facilitating the selection, after due consideration, between a conservative treatment and a surgical approach.

In 50% of the cases, UTIs are associated with anatomical anomalies of the urinary tract, such as obstructive uropathies and VUR.

Imaging techniques (i.e., US, cystography, scintigraphy, CT, urinary MRI) are the second diagnostic level. These modalities must be used both when UTIs are recurrent and when a malformative uropathy is being suspected.

Primary end-points of treatment are the following:

1. Eradication of pathogenic agent
2. Prevention of both systemic complications and long-term sequelae.

Such objectives should be pursued by means of a cost-effective policy and with an incidence of adverse reactions as low as possible, even when there is not any potentially resistant bacterial flora.

With this in mind, the appropriate diagnostic profile and the identification of the predisposing factors, if any, are items of utmost significance.

The administration of antibiotic therapy must be regulated by clinical pharmacology principles and must take into consideration both the site and the severity of infection. It is appropriate to use drugs that reach an adequate urinary concentration so that it will be unnecessary to increase blood levels of the drug.

The development of resistant pathogenic bacteria – often induced by the indiscriminate administration of antibiotics – has brought about with time some changes in the selection of the antibiotic molecule to be used from time to time.

At any rate, the natural resistance (i.e., the situation in which all the cells of a microbial population are insensitive to an antibiotic) must be differentiated from those types of resistance that are acquired as a result of the presence of specific genes in the cell genome. Genes controlling bacterial resistance may be located on either the chromosome or the extrachromosomal genetic elements called plasmids. The following processes are responsible for the presence of such genes within the bacterial cell: (a) mutation, (b) transformation, (c) transduction, and (d) conjugation. The first three mechanisms lead to the development of resistance mostly in G+ bacteria, whereas all 4 mechanisms may be responsible for the onset of resistance in G- bacteria. The antibiotic often counteracts an enzyme and in most instances interacts with its active site. Resistance de-

velops as the result of a chromosomic gene mutation and this, in turn, generates an enzyme no longer sensitive to the drug. Currently, approximately 30% of bacteria responsible for uncomplicated UTIs appear to be resistant to amoxycillin and sulfa drugs, from 15% to 20% to nitrofurantoin, and from 5% to 15% to co-trimoxazole.

A variable proportion from 20% to 30% of bacteria responsible for pyelonephritis, either concomitant with or predisposing to MUs, are resistant to amoxycillin and 1st generation cephalosporins. An even lower sensitivity has been reported in instances of polymicrobism in complicated UTIs and in UTIs combined with MUs.

Interesting advances in the pharmacologic field have been reported more recently; these studies have allowed to widen the spectrum of antibacterial action and to counteract the reduction in effectiveness of the conventional therapy.

The antibiotic selected for this purpose must possess

1. Effectiveness
2. Tolerability
3. Gustatory acceptance and lack of side effects
4. Excretion through the urinary tract.

A low dosage antibiotic prophylaxis is indicated in subjects with urinary tract anomalies in order to minimize the risk of UTI.

In conclusions a variety of new antibiotics have become available in the past few years (and many more are currently under investigation at different stages of development) in the attempt to overcome bacterial resistance. In addition, the use of novel molecules is warranted by the search for a decrement in toxicity, the reduction in number of daily doses, and the need for controlling the cost-effectiveness of the therapy.

Cefixime is the first oral cephalosporin of the 3rd generation that has become available (Figure 2).

The drug under study possesses a higher activity on g- micro-organisms, including most of Proteus and Serratia strains.

Unlike other oral cephalosporins whose half-life lasts 1 hour only, cefixime's half-life shows about 3 to 4 hours duration; therefore, the drug under study may be administered once daily.

Its clinic and bacteriologic effectiveness against UTIs in the pediatric age group has been widely documented by non-comparative and comparative trials[8]. It is interesting to point out that the drug under study has shown to be active in patients who had not responded to previous therapies with cefaclor or amoxycillin plus clavulonic acid (switch therapy). Bacteriologic eradication rate was found to be higher than 79% against some micro-organisms, such as S. aureus, S. pneumoniae, S. pyogenes, H. influenzae[9].

To conclude, the present study substantiates cefixime's effectiveness – due to its antibacterial activity and pharmacokinetic properties- and tolerability in the medium – and long-term prophylaxis of UTIs associated with MUs. We would like to emphasize the usefulness of the drug under study administered to patients under 2-year old, belonging to an age group in which the administration of other drugs is rather difficult on account of the poor patient compliance, the lower tolerability, and the higher risk of adverse reactions.

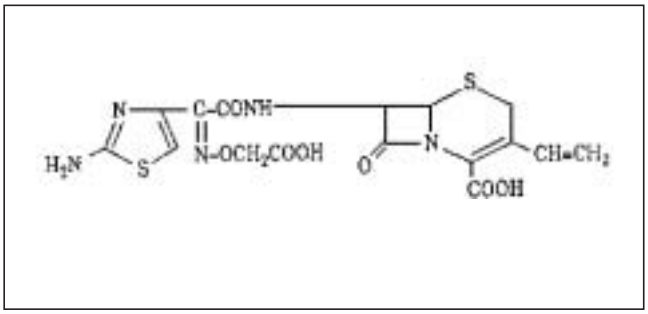

Figure 2. Chemical formula of cefixime.

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