ANKEM Derg 2 (No 4): 272-277 (1988).

AMOXYCILLIN-CLAVULANIC ACID IN URINARY TRACT INFECTIONS

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ÖZET

Üriner infeksiyonlarda amoksisilin-klavulanik asit.

Bakteriyolojik olarak ispatlanmış üriner infeksiyonu olan 54 olguda yeni oral antibakteriyel ajanlardan Augmentin kullanıldı. Hastalarda 500 mg amoksisilin trihidrat ve 125 mg potasyum klavulanat kombinasyonu sekiz saat arayla olmak üzere 10 gün süreyle verildi. İkinci haftanın sonunda kontrol kültürleri alınarak, tedaviye cevap vermeyenlere ikinci bir 10 günlük tedavi verildi.

Dördüncü haftanın sonunda değerlendirmeye alınan 50 hastanın 35'inde (% 70) bakteriyolojik başarı saptandı. Basit infeksiyonlarda % 83 ve komplike infeksiyonlarda % 58'lik bir başarı oranı sağlandı.

Olguların üçünde bakteriyel persistans görülürken 12 olguda da tedaviye yanıt alınamadı. Bir hasta ilacın yan etkileri nedeniyle çalışma dışında bırakıldı.

SUMMARY

A new oral antibacterial agent, Augmentin, comprising amoxycillin and clavulanic acid was used to treat 54 patients with documented urinary tract infection. The patients were treated with 500 mg of amoxycillin trihydrate plus 125 mg of potassium clavulanate three times daily for 10 days. The control cultures were obtained on the 14th day. The non-responders received a treatment for a second period of 10 days.

At the end of four weeks there was a bacteriological cure in 35 of 50 (70 %) assessable patients while a cure rate of 83 % was achieved in uncomplicated UTI and 58% in complicated UTI.

There were three bacterial persistence and unresolved bacteriuria occured in 12 patients. One patient discontinued treatment due to side-effects.

INTRODUCTION

In recent years beta-lactamase producing strains of both Gram positive and Gram negative species significantly increased so that beta-lactamase mediated antibiotic resistance limits the physician's choice of effective antibiotics. Besides beta-lactamase stable penicillin derivatives and third genaration cephalosporins, beta-lactamase inhibiting compounds began to be used in various infections (8).

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Amoxycillin is a broad spectrum semi-synthetic penicillin frequently prescribed for the treatment of lower and upper urinary tract infections (UTI). It is a beta-lactam antibiotic and its administration rapidly gives high bactericidal urinary concentrations. Its disadvantage is being sensitive to destruction by beta-lactamase enzymes. Clavulanic acid which is derived from *Streptomyces clavuligerus*, is an irreversible inhibitor of a wide range of those enzymes. It prevents beta-lactam antibiotics such as amoxicillin from hydrolysis by beta-lactamase enzymes (13). So their combination is effective against bacteria producing beta-lactamase. Also minimum inhibitory concentrations for amoxycillin are reduced by its accompanience (5). In man both drugs are well absorbed orally and their serum and urine levels are high.

The purpose of the clinical trial reported here was to evaluate the bacteriological effectiveness of Augmentin (amoxycillin trihydrate and potassium salt of clavulanic acid) in the treatment of UTI.

MATERIALS AND METHODS

Our study lasted seven months from March 1987 to October 1987. 54 out-patients with UTI confirmed by a positive urine culture ($\geq 10^5$ colony forming units per mililiter) entered the trial. Three of the patients were lost and one patient discontinued the treatment due to side-effects. A total of 50 patients were assessed, with 25 males and 25 females aged between 17-89 years (mean 62). None of them were allergic to penicillin and pregnant.

Samples for cultures were collected from mid-stream urine of uretheral catheters after disinfection by 10 % povidone-iodine solution. The sensitivity testing were performed by discs of 20 micrograms amoxycillin plus 10 micrograms clavulanic acid. Patient with UTI caused by an organism sensitive to amoxycillin-clavulanic acid combination were treated orally with 625 mg of combination (500 mg amoxycillin and 125 mg of clavulanic acid) at eight hour intervals for 10 days. 48-72 hours after treatment control urine cultures were collected from all of the patients. According to bacteriological assessment of the cultures and sensitivity testing, the non-responders who were still sensitive to the combination received a second treatment for 10 days. After 48-72 hours from this period which means the end of fourth week, second control cultures were collected from all of the 50 patients.

The patients included in this study consisted of uncomplicated and complicated UTI cases. The differential diagnosis were done upon history, physical examination, routine urine analysis, white blood count, radiographic and ultrasonographic procedures. The complicated cases were defined as patients having underlying urinary tract diseases (Table 1).

Cure was defined as the bacteriological eradication of the original infecting organism. If eradication of the original organisms was followed by the appearance of the same one in the second culture, the result was cathegorized as bacterial persistence (14). Unresolved bacteriuria was defined as the insistance of the pathogen after second treatment period (14). Reinfection was the appearance of an organism different from the original one.

Table 1. Pathologies underlying complicated UTI.

Pathology	No. of cases
Renal stone	7
Urethral catheter	6
Benign prostatic hyperplasia	5
Bladder tumor	4
Vesico-ureteral reflux	1
Uretero-pelvic juntion stenosis	1
Prostatic carcinoma	1
Urethral stricture	1
Total	26

All of the patients were questioned by a physician for the side-effects during the treatment.

RESULTS

Twenty-six of 50 patients had complicated UTI and the remaining 24 had uncomplicated UTI. In complicated cases, a total of 58 % cure rate was achieved. Uncomplicated UTI, as expected, had a cure rate that of 83 % (Table 2).

Table 2. Cure rates.

	No. of cases	Cure rate
Complicated UTI	26	58 %
Uncomplicated UTI	24	83 %
Total	50	70 %

After the first treatment period of 10 days 18 of 26 patients with complicated UTI and 14 of 24 with uncomplicated UTI were cured. The non-responders, eight in the complicated group and ten in the uncomplicated group had a second amoxycillin-clavulanic acid treatment of 10 days. On the control cultures and sensitivity testing, all of these 18 non-responders were still sensitive to this combination (3 of 10 in the uncomplicated group being moderately sensitive) (Table 3). At the end of the fourth week there were three bacterial persistence in complicated group while none occured in uncomplicated UTI. In the complicated group no cure was achieved whereas six of ten patients were cured during the second course of treatment (Table 3). Thus, 35 patients (15 from the complicated and 20 from the uncomplicated group) out of 50 were cured, achieving 70 % overall success rate. There was no reinfection in either group.

Table 3. Treatment results according to periods.

	No. of cases	
	Complicated	Uncomplicated
Cure[1]	18	14
Non-responder[1]	8	10
Cure[2]	0	6
Bacterial persistence[2]	3	0
Cure[3]	15	20
Unresolved bacteriuria[3]	8	4
Bacterial persistence[3]	3	0

1. First treatment period (At the end of second week)
2. Second treatment period (At the end of fourth week)
3. Overall results

Significant side-effects were seen in three patients (6 %). One of them had to be withdrawn from the trial because of diarrhoea. Remining two, one having rashes and the other with some nausea could be able to complete the therapy.

DISCUSSION

The importance of UTI lies both in its being the most common bacterial infection and an ideal model for the evaluation of new forms of antimicrobial therapy. Among the wide range of drugs for the treatment of UTI, amoxycillin-clavulanic acid combination is reported to be active in vivo and in vitro against a broad range of amoxycillin sensitive and resistant bacteria (1, 8).

The relatively low rate of cure in complicated UTI (58 %) than in uncomplicated UTI (83 %) was probably due to the second and possibly the main pathology. It is obvious that an infection can hardly be eradicated unless the underlying cause is subsided. The difference between curability of complicated and uncomplicated UTI is best seen in the number of bacterial persistence and cure during the second treatment period. All of the bacterial persistences occured in the complicated group whereas none was recorded in the other. Most of the non-responding cases having uncomplicated UTI were treated eventually after the second treatment period, but no cures were achieved in the complicated group although all of the bacteria isolated from patients were sensitive to combination.

Our results are compatible with most of the somewhat similar studies seen in table 4 (2-4, 6, 7, 9-11, 15). A comparison with unlike results shows that the difference lies in the mode of interpretation. In the treatment of complicated UTI Ohkawa and Kuroda

(11) achieved a success rate of 75 % which seems to be higher than we found. Their evaluation was done in accordance with criteria proposed by UTI Commitee of Japan (12) so that it is not the pure rate of bacteriological eradication but clinical effectiveness. Also in the trial performed by Nishiura (10) the rate of 70.5 % for complicated and 98.8% for uncomplicated UTI reflect again the clinical efficacy of this combination. However, Karachalios (7) reported a cure rate of 95 % in uncomplicated UTI but if the recurrences are taken into account, this rate would be lower.

Table 4. Some studies and their results with amoxycillin-clavulanic acid.

Study	Dose (mg)	Success rate (%)		
		Complicated	Uncomplicated	Overall
Ohkawa, Kuroda (11)	250+125	75		
Nishiura (10)	250+125	70.5	98.8	88.1
Karachalios (7)	250+125		95	
Derluyn (3)	500+125		83.3	
Umbach et al (15)	500+125		85	
Leng (9)	500+125	58.1		72.5
	1000+250		79.2	
Bell et al (2)	500+250	62		
Iravani, Richard (6)	250+125		78	
Gallacher et al (4)	250+125		87.5	
This study	500+125	58	83	70

As to side-effects, the treatment was well tolerated and they were no more frequent than might be expected.

The data from our study support that the formulation of amoxycillin and clavulanic acid is particularly effective in oral treatment of uncomplicated UTI. In conclusion, amoxycillin-clavulanic acid seeming to be reasonably safe, appears to be a valuable addition to the choice of antibacterial agents used for uncomplicated UTI but it should be combined with other antibiotics in the treatment of complicated UTI.

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