SINGLE DOSE ORAL AMOXYCILLIN AND CLAVULANIC ACID IN THE TREATMENT OF GONOCOCCAL URETHRITIS IN MALES

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SUMMARY

Forty-two previously untreated male patients with uncomplicated gonococcal urethritis were treated with a single dose oral regimen comprising 3 gm of amoxycillin and 125 mg of clavulanic acid. Thirty-five patients returned for follow-up and the cure rate among them was 89 percent. The cure rate for patients infected with penicillinase producing ***Neisseria gonorrhoeae*** *(PPNG) was 73 percent. Further work is required to establish the optimum dosage for this particular regimen.*

INTRODUCTION

Penicillin and other beta-lactam antibiotics are still the mainstay of anti-gonococcal therapy in most parts of the world. The Centre for Disease Control (CDC) of the United States recommends, as a first line treatment for uncomplicated gonorrhoea the use of either procaine penicillin (4.8 megaunits intramuscularly) as a single dose combined with 1 gm of probenecid orally; or ampicillin 3.5 gm (or amoxycillin 3.0 gm) with 1 gm of probenecid orally. [1] In Malaysia, single dose oral ampicillin has been shown previously to be unsatisfactory for the treatment of uncomplicated gonorrhoea in males. [2] This is due largely to the high incidence of beta-lactamase producing strains of *Neisseria gonorrhoeae* of PPNGs (penicillinase producing *Neisseria gonorrhoeae)* in this country. [3] Recently a new antibiotic formulation has been described which is a combination of amoxycillin and clavulanic acid, a beta-lactamase inhibitor. [4] This study is undertaken to assess the efficacy of this new antibiotic formulation, Augmentin, used as a single dose oral regimen in the treatment of uncomplicated gonorrhoea in males.

MATERIALS AND METHODS

This is a single blind prospective clinical trial of male patients attending the Sexually Transmitted Diseases (STD) clinic at the Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur. Between the months of June and December 1981 a total of 42 male patients were treated with a single dose oral regimen comprising 3.0 gm amoxycillin and 125 mg clavulanic acid. All patients had bacteriologically proven uncomplicated gonococcal urethritis, denied allergy to penicillin and were previously untreated. Treatment for all patients was given in the clinic itself under direct supervision. It consisted of giving each patient 5 x 500 mg capsule amoxycillin, 1 x 250 mg capsule

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amoxycillin and 1 tablet Augmentin (which comprises 250 mg amoxycillin and 125 mg clavulanic acid).

At the initial visit, an intraurethral specimen of urethral discharge was obtained using a sterile wire loop and plated immediately onto both chocolate and VCNT media. The plates were placed in a candle jar and sent to the bacteriology laboratory within two hours of initial plating. In addition a smear of the urethral discharge was stained by Gram's method and examined microscopically for intracellular Gram-negative diplococci. The examination of the plates and identification of *Neisseria gonorrhoeae* were as described previously. [3] All strains of *Neisseria gonorrhoeae* were tested for their ability to produce beta-lactamase using a commercial filter paper strip method based on an acidimetric principle. [5] Minimum inhibitory concentrations (MIC) for Augmentin, amoxycillin and penicillin were determined by a tube dilution method, using Mueller-Hinton broth (Oxoid) supplemented with 1% (v/v) CVA (Gibco). The Augmentin and amoxycillin powders were provided by Beecham Research Laboratories while the penicillin powder was obtained from the Sigma Chemical Company. The two-fold dilutions of antibiotics were inoculated with approximately 10^7 colony forming units. After incubation for 24 hours at 37°C in a 10% CO_2 atmosphere, the MIC was determined as the lowest concentration of antibiotic which exhibited no growth visually.

All patients were requested to return for reexamination after 2 - 4 days when a repeat smear and culture was performed. All patients were questioned about any side effects they may have suffered following the treatment. A treatment failure was defined as the inability to eradicate *Neisseria gonorrhoeae* from the urethra in the absence of any further sexual contact.

RESULTS

MICs for penicillin, amoxycillin and Augmentin against 37 out of the 42 strains of *Neisseria gonorrhoeae* were obtained. The strains comprised 17 PPNGs and 20 non-PPNGs. The MIC results are summarised in Tables I and II.

Of the 20 non-PPNGs, 14 had penicillin MICs of ≤ 0.015 mg/L while the other 6 strains had MICs of between 0.03 to 1.0 mg/L. The penicillin MICs of all 17 strains of PPNGs were greater than 4 mg/L. The MICs of amoxycillin against all 17 strains of PPNGs were greater than 4 mg/L (ranging from 8 mg/L to 128 mg/L). In the presence of clavulanic acid there was a marked reduction in the MICs of amoxycillin. The MICs of Augmentin against PPNGs ranged from 0.5 mg/L to 4 mg/L.

TABLE I
ANTIBIOTIC SUSCEPTIBILITY OF 20 STRAINS OF NON-BETALACTAMASE PRODUCING STRAINS OF *NEISSERIA GONORRHOEAE* (NON-PPNGs)

	No. of strains with minimum inhibitory concentrations (mg/L) of						
Antibiotic	≤ 0.015	0.03	0.06	0.12	0.25	0.5	1
Penicillin	14		3	1	1		1
Amoxycillin		7	6	1	3		3
Augmentin*		8	2	3	3	3	1

(* In the ratio of amoxycillin : clavulanic acid = 2 : 1)

TABLE II
ANTIBIOTIC SUSCEPTIBILITY OF 17 STRAINS OF BETA-LACTAMASE PRODUCING STRAINS OF *NEISSERIA GONORRHOEAE* (PPNG)

	No. of strains with minimum inhibitory concentrations (mg/L) of						
Antibiotic	0.25	0.5	1	2	4	8	≥16
Penicillin						2	15
Amoxycillin						1	16
Augmentin*		2	10	3	2		

(* In the ratio of amoxycillin : clavulanic acid = 2 : 1)

Only 35 cases were evaluable as 7 patients did not return for reexamination. Of these 35 cases, 20 were infected with non-PPNGs and 15 with PPNGs. A cure was achieved in all 20 patients with non-PPNGs. Of the 15 patients infected with PPNGs a cure was recorded in 11 patients giving a cure rate of 73 percent (11/15). All 4 patients who failed to respond to treatment denied any subsequent sexual contact following the initial treatment. In 3 of them the urethral discharge persisted unabated while in one the discharge disappeared for about 24 hours but recurred. The cure rate in this trial was 89 percent (31/35). The results of treatment are summarised in Table III.

TABLE III
TREATMENT RESULTS FOLLOWING SINGLE DOSE AMOXYCILLIN/CLAVULANIC ACID REGIMEN

Response	Number of patients		
	PPNG *	non-PPNG@	Total
Cure	11	20	31
Failure	4	0	4
Total	15	20	35

* penicillinase producing *Neisseria gonorrhoeae*
@ non-penicillinase producing *Neisseria gonorrhoeae*

Only 4 patients reported minor side-effects following therapy. One patient complained of nausea while the other three complained of mild transient giddiness. No treatment was required for these side-effects.

DISCUSSION

Augmentin is a formulation comprising amoxycillin and clavulanic acid, a beta-lactamase inhibitor. [4] Many bacteria, including certain strains of *Neisseria gonorrhoeae* are resistant to beta-lactam antibiotics by virtue of the production of beta-lactamases. Beta-lactamases are a family of enzymes that split the beta-lactam ring of these antibiotics thus inactivating them. There are two main ways of overcoming this problem. The first is to manufacture antibiotics which are resistant to attack by beta-lactamases. The other is to try to inhibit the action of beta-lactamase itself. Clavulanic acid, a beta-lactam compound itself, is isolated from *Streptomyces clavuligerus* and is a potent inhibitor of beta-lactamase. [6] Clavulanic acid in combination with penicillin and amoxycillin has been shown to be active against many strains of bacteria including PPNGs. [7] Augmentin, which can be given orally therefore appears to be a potentially useful antibiotic formulation for use in a single dose oral regimen in the treatment of uncomplicated gonococcal urethritis in males. This is especially so in a region with a high incidence of PPNGs.

The MICs for penicillin, amoxycillin and Augmentin obtained in this study are similar to those which have been reported elsewhere. [8,9,10] With penicillin a trimodal distribution is seen. There is a sensitive group (MIC $\leq$ 0.015 mg/L), a relatively resistant group (0.03 - 1.0 mg/L) and the beta-lactamase producing group (>4mg/L). Clavulanic acid markedly increases the activity of amoxycillin against PPNGs. The increase in amoxycillin activity was as high as two-hundred-fold in one strain (MIC 128 mg/L reduced to 0.6 mg/L).

The cure rate in this trial was 89 percent which is higher than that previously obtained with a single dose oral penicillin regimen (58.5 percent). [2] This is not unexpected as ampicillin has no activity against PPNGs. There were 4 failures in this small trial. All 4 patients were infected with PPNGs. The exact reason for these failures is not known. The MICs of Augmentin against the 4 strains of PPNGs in these patients were 1,1,2 and 4 mg/L respectively. These strains were therefore not resistant to Augmentin in vitro. It is felt that individual variation in the pharmacokinetics of clavulanic acid in the body may have contributed to the treatment failures. It has been shown that a critical minimum concentration of clavulanic acid is necessary in order to inhibit the beta-lactamase of various bacterial species. [11] It is postulated therefore that in these 4 patients, the levels of clavulanic acid were insufficient to inhibit the beta-lactamase of the PPNG. This treatment regimen should perhaps be modified and the dose of clavulanic acid increased. Further trials are necessary to establish this.

It has been shown in this small trial that a combination of amoxycillin and clavulanic acid used in a single dose oral regimen may be effective in the treatment of uncomplicated gonococcal urethritis in males in a region where the incidence of PPNGs is high. However further work is necessary in order to establish the optimum dosage for this regimen.

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