The African Journal of Medicine and Medical Sciences

Volume 14
1985

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Boston Palo Alto Melbourne

Afr. J. Med. med. Sci. (1985) **14**, 169–173.

Single dose treatment of gonococcal urethritis with augmentin in Ibadan

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Summary

Augmentin, a new orally absorbed broadspectrum antibacterial agent comprising of amoxycillin trihydrate and potassium clavulanate, was investigated in the treatment of gonococcal urethritis in Ibadan, Nigeria, where penicillinase producing *Neisseria gonorrhoeae* (PPNG) constitute about 80% of the circulating strains of gonococci. Two different formulations of the agent were employed in the study. The first formulation consisting of 3.0 g amoxycillin and 125 mg clavulanic acid, achieved a cure rate of 75% (i.e. eighteen out of twenty-four patients) among PPNG infections, but 100% cure rate among nine patients with non-PPNG infections. The second formulation consisting of 3.0 g amoxycillin and 250 mg clavulanic acid, had a cure rate of 86% (i.e. fifty-seven out of sixty-six patients) among PPNG infections, and 91% (i.e. ten out of eleven patients) among non-PPNG infections. Clavulanic acid appears to potentiate and enhance the activity of amoxycillin against the β-lactamase produced by the gonococci. Augmentin seems to be a good and acceptable agent for the treatment of gonococcal infections, in this environment and further studies on its efficacy are therefore justified, such as the simultaneous administration of probenecid.

Résumé

Laugmentin est un agent antimicrobien à large sspectre absorbe' per voie orale. Il est compose' de trihydrate d'amoxycilline et de la clavulanate de potasse. Son efficacité, dans le traitement de l'urétrite gonococcique a été essaié' a Ibadan, Nigeria, la ou les souches productrices de la penicillinase (NGPP) constituent d'environ 80% des isolements courants. Deux formulations ont été emplyées: L'une contenant 3.0 g d'amoxycilline et 125 mg de l'acide clavulanique a achevé une cure de 75%. (c.a.d. dix-huit sur vingt-quatre) parmi les souches productrices de la penicillinase tandisque 100% de cure a été achevée avec les non-productrices de cet enzyme (neuf cas). La deuxieme formulation constituee de 3.0 g d'amoxycilline et 250 mg de l'acide clavulanique a achevé parmi les NGPP une cure de 86% (c.a.d. cinquante-sept sur soixante-six cas) alors qu'elle a achevé 91% (c.a.d. dix sur onze cas) avec les non-productrices de l'enzyme. L'acide clavulanique parait avoir potentié et augmenté l'activité de l'amoxycilline contre l'enzyme (β-lactamase) produit par le gonocoque. L'augmentin semble d'être efficace' et acceptable dans le traitement des infections gonococciques au Nigeria, et il est justifiable d'élargir les études sur l'efficacité de ce produit, comme par exemple, sur l'administration simultanée de probenecide.

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Introduction

The epidemiology of gonococcal urethritis due to penicillinase producing *Neisseria gonorrhoae* (PPNG) has been extensively studied and discussed in recent literature (Perine *et al.*, 1979; Arya *et al.*, 1978; Siegel *et al.*, 1978; Piot, 1977; Robins-Browne, Gaillard & Koornhof, 1977; Osoba *et al.*, 1981; Osoba *et al.*, 1984; Osoba & Ogunbanjo, 1983). Within a decade of its first identification in West Africa penicillinase

producing gonococci have spread across to at least twenty-five countries in Africa, thus constituting a major health problem in many of the countries affected.

The result of continued search for a therapeutic agent which will satisfy the criteria of efficacy, safety, availability and cheapness in the treatment of these infections, is the emergence of new agents or those new formulations based on modification of the structure of old drugs which were hitherto efficacious in the treatment of non-PPNG infections. One such of the latter is augmentin.

Augmentin is a new orally absorbed broad-spectrum antibacterial agent comprising amoxycillin trihydrate and potassium clavulanate. Amoxycillin is a well-known broadspectrum semi-synthetic penicillin, sensitive however to destruction by penicillinase (β-lactamase). Clavulanic acid is a fused beta-lactam microbial metabolite produced by fermentation of streptomyces clavuligerus (Reading & Cole, 1977). At low concentrations it is an extremely potent, progressive and irreversible inhibitor of a wide range of β-lactamase enzymes mediated by bacterial chromosomes or by transmissible plasmides, (Fischer, Charnas & Knowles, 1978; Charnas, Fischer & Knowles, 1978; Labia & Peduzzi, 1978). It is a particularly efficient inhibitor of TEM-type β-lactamases, which are the ones most frequently found in *Escherichia coli, Haemophilus influenzae* and *Neisseria gonorrhoeae* (Reading & Cole, 1977). Clavulanic acid is able to protect β-lactam antibiotics from the destructive action of β-lactamase enzymes and various studies have shown that it protects amoxycillin from inactivation by many β-lactamase producing organisms, thus allowing the activity of amoxycillin against the infecting organism to be manifested (Hunter, Reading & Witting, 1977; Wise, 1977).

In view of the above, a therapeutic trial of augmentin was carried out in this unit with the main objective of assessing the efficacy of the agent in the treatment of acute gonococcal infection in Nigeria especially those due to β-lactamase producing gonococci.

Materials and methods

One hundred and forty consecutive patients presenting at our Special Treatment Clinic with acute gonococcal urethritis were included in the trial. The criteria for inclusion include:

(i) recent sexual exposure with obvious purulent urethral discharge;
(ii) no history of antibiotic therapy since appearance of signs and symptoms;
(iii) demonstration of intracellular gram negative diplococci in the urethral smear. The microscopical findings were confirmed by culture of the smear on Thayer-Martin medium for gonococcus and incubation at 37°C in a candle extinction jar for 24–48 h; positive oxidase test and typical carbohydrate utilization reactions.

Sensitivity tests by the disc diffusion method were carried out against penicillin G, ampicillin, tetracycline, chloramphenicol, cotrimoxazole, amoxycillin and augmentin. Beta-lactamase production was tested for the chromogenic cephalosporin test.

Concomitant infection due to *Trichomonas vaginalis, Candida albicans, Schistosoma* ova, or *Gardnerella vaginalis* were excluded by examining a wet preparation of the urethral exudate. Serological tests of syphilis (VDRL, TPHA) were carried out on the first day to rule out a concomitant syphilitic infection.

Two regimens, 3 g amoxycillin plus 125 mg clavulanic acid (regime 1) and 3 g amoxycillin with 250 mg clavulanic acid (regimen 2) as a single oral dose were given respectively to alternate entrants into the trial initially; but after the first ninety patients had entered the trial, all subsequent patients were treated with regime 2. Informed consent was obtained from all the patients. The patients were advised to abstain from sex, alcohol or any other antibiotic during follow-up. The patients were reviewed on the third, eighth, fourteenth and twenty-first days after the treatment. At each follow-up visit, after taking the history and performing a physical examination, a microscopical examination and culture of the urethral swab were carried out. The two-glass urine test was done and a centrifuged deposit of the first glass urine was examined microscopically for pus cells, and pathogens.

The criteria for cure included disappearance of signs and symptoms and reversion of the culture from positive to negative between the third and fourteenth days. A patient who had a

positive culture between the third and fourteenth days was regarded as a failure, provided there had not been a sexual exposure between the time of treatment and the fourteenth day. Such patients were treated with an alternative antibiotic. Direct questioning on follow-up visits was used in assessing tolerability and any side effects.

Results

One hundred and forty patients who satisfied the required criteria were entered into the trial. However only 110 were available for assessment. The others were not assessible either because they failed to complete their follow-up or because their microscopical diagnosis was not confirmed by culture.

Of the assessible entrants thirty-three had regime 1 (3.0 g amoxycillin plus 125 mg clavulanic acid) while seventy-seven had regime 2 (3.0 g amoxycillin plus 250 mg clavulanic acid) (Tables 1 and 2). Twenty-seven of those treated with regime 1 were cured representing 81.8%; eighteen were PPNG infections while nine were non-PPNG infections. In regime 2, sixty-seven of the seventy-seven entered were cured (i.e. a cure rate of 87.0%). Fifty-seven of these were PPNG infections while ten were non-PPNG infections (Table 2). All the sixteen patients (14.5%), except one who failed the trial, had PPNG infections (Table 3). They were given alternative antibiotics and routinely followed up to assess cure. The overall cure rate was 85.5% (i.e. ninety-four out of 110). Seventy-five of those cured had PPNG infections while nineteen were non-PPNG infections (Table 3).

Discussion

In an earlier study on the efficacy of amoxycillin with or without probenecid in the treatment of gonococcal infections due to PPNG and non-PPNG strains; the cure rate among PPNG infections was 15.8% (three out of nineteen) and 94.3% (thirty-three out of thirty-five) among non-PPNG infections (Osoba & Ogunbanjo, 1983). The result of the present study

Table 1. Result of treatment with regime 1 (3.0 g amoxycillin + 125 mg clavulanic acid)

No of patients	PPNG infections	Non-PPNG infections	Total
Cured	18	9	27
Failed	6	—	6
Total	24	9	33
% Cured	75	100	81.8

Table 2. Result of treatment with regime 2 (3.0 g amoxycillin + 250 mg clavulanic acid)

No of patients	PPNG infections	Non-PPNG infections	Total
Cured	57	10	67
Failed	9	1	10
Total	66	11	77
% Cured	86.4	90.9	87.0

Table 3. Combined result of treatment with regimes 1 and 2

No. of patients	Augmentin formulation: Regime 1 3.0 g amoxycillin + 125 mg clavulanic acid	Augmentin formulation: Regime 2 3.0 g amoxycillin + 250 mg clavulanic acid	Types of infection: PPNG infections	Types of infection: Non-PPNG infections	Total
Cases	33	77	90	20	110
Cured	27	67	75	19	94
Failed	6	10	15	1	16
% Cured	81.8	87.1	83.3	95.0	85.5

with augmentin showed a cure rate of 75% with regime 1 (3.0 g amoxycillin with 125 mg clavulanic acid) while with regime 2 a cure rate of 86% was achieved among PPNG infections. The impressive higher efficacy of augmentin has obviously been due to the clavulanic acid in the formulation. In all the cases cured by either formulation the urethral smear was negative for gonococcus on the third day post-treatment assessment. All the failures in both formulations (except one) had PPNG infections. These failures probably resulted from inadequate β-lactamase inhibition by the clavulanic acid. Since the only one non-PPNG infection among the failures was encountered under regime 2, this must have been due to a strain with an exceptionally high chromosomal resistance, and is probably due to failure of the drug to reach therapeutic blood levels in this particular patient.

Since the special formulations prepared in sachets were used in this study, dosage was not regulated on the weight of each patient. Future studies may therefore have to take the weight of patients into consideration. This assumption is supported by the fact that the *in vitro* susceptibility tests showed that this strain was resistant to penicillin, but sensitive to ampicillin, tetracycline, cotrimoxazole, spectinomycin and augmentin.

The tolerance of the patients with augmentin was good. There was no report of any gastrointestinal symptoms; e.g. nausea, vomiting and diarrhoea despite the high dosage of 250 mg of clavulanic acid in regime 2. Except for one patient who reported dizziness after taking the drug, no intolerance or significant adverse reactions were noted in any of the patients. This good tolerance with both formulations could be attributed to the single dosage employed.

One patient with gonococcal urethritis complicated by epididymo-orchitis was treated with a course of augmentin of regime 1 daily for 8 days. At the first post-treatment check-up (third day) gonococci had been erradicated from the urethral smear and by the eighth day post-treatment check the lesion was well-resolved and less painful, but a residual nodule was palpable in the upper pole of the epididymis. It appears, therefore that augmentin may be useful in the treatment of complicated infections due to PPNG strains such as salpingitis and disseminated gonococcal infections etc., and therefore further studies are justified.

The last 5 years have witnessed a dramatic increase in the incidence of PPNG strains in many parts of Africa, and in some cases they have become endemic infections. This has posed as a great threat to the usefullness of penicillin and ampicillin as the drugs of choice in gonococcal therapy, due to the production of β-lactamase by the PPNG strains. The drugs with proven efficacy against these PPNG infections, e.g. spectinomycin, cefuroxime, cefotaxime are beyond the financial resources of most patients and even governments in many developing countries, and furthermore they have to be given parenterally. The introduction

of augmentin with its relative cheapness, single dosage, oral administration and good tolerance by the patient is a significant and welcome advance in gonococcal therapy. Clavulanic acid appears definitely to potentiate the action of amoxycillin against the β-lactamase produced by the gonococcus.

Since increasing the clavulanic acid above 250 mg in the augmentin formulation may lead to gastrointestinal symptoms, it might be worth evaluating a formulation with increased amoxycillin e.g. 3.5 or 4.0 g amoxycillin with 250 mg clavulanic acid in an effort towards improving on the efficacy of the drug in the treatment of gonococcal infection especially those due to PPNG strains. Alternatively, simultaneous administration of probenecid to regime 2 may considerably increase the cure rate of the antibiotic but needs to be studied. The advantages of a single oral dose with 100% cured rate in gonococcal infections are well-known and it is the ideal form of therapy in Africa, where laboratory facilities to distinguish between PPNG and non-PPNG infections are not readily available in many areas. Augmentin appears to be a good and acceptable agent and further studies on its efficacy are therefore justified.

Acknowledgment

We are grateful to Beecham Pharmaceuticals (U.K.) for supporting the study and providing the augmentin sachets used in the study.

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(*Received* 4 *December* 1984; *accepted* 10 *December* 1984)