Treatment of gonorrhoea with amoxycillin

C. D. ALERGANT
Liverpool Royal Infirmary, Liverpool, L3 5PU

The synthesis of the penicillin nucleus 6-amino-penicillanic acid was first achieved by Sheehan (1958), but it was not until the following year that a team of workers at the Beecham Research Laboratories discovered a method of producing the compound on a large scale, and thus made possible for the first time the synthesis of innumerable penicillin compounds.

Until recently ampicillin, introduced in 1961, was the only semi-synthetic penicillin with an activity against the gonococcus comparable to that of penicillin G. Recently, however, workers in the same laboratories have produced a new compound, amoxycillin, for which similar or even greater activity has been claimed.

In chemical structure and spectrum of activity amoxycillin is closely related to ampicillin. Like ampicillin, it is stable to gastric juice and is very well absorbed by the oral route. Peak levels occur 2 hours after ingestion and are frequently double those produced by equivalent doses of ampicillin. Moreover, the presence of food in the stomach has only a slight effect on absorption. Protein binding is low compared with most penicillins and is similar to that of ampicillin (17 to 18 per cent.). After oral administration, 55 to 65 per cent. of the dose can be recovered from the urine after 6 hours as unchanged amoxycillin (Sutherland, Croydon, and Rolinson, 1972).

Preliminary studies in vitro suggested that amoxycillin was more active than penicillin G against so-called resistant gonococci, and only slightly less active against sensitive strains, and it was therefore decided that a clinical trial would be worth undertaking. The trial, which lasted nearly a year, extended from early April, 1971, to the end of March, 1972.

Patients and methods

The subjects of the trial were 414 patients (370 men and 44 women) suffering from uncomplicated gonorrhoea attending either the Liverpool Royal Infirmary or the Seamen’s Dispensary, Liverpool. No attempt at selection was made apart from the deliberate exclusion of those seafarers and other transients who were thought unlikely to remain in the district for at least 2 weeks. Similarly excluded were patients who were known or thought to be penicillin sensitive.

Diagnosis

In males diagnosis was by Gram-stained smear but cultures were taken in all cases. In females diagnosis was by smear or positive culture.

Follow-up

Male patients were asked to re-attend 7 days after treatment and again at the end of the second and fourth week; smears and cultures were taken when any discharge was found.

Female patients were asked to re-attend weekly for 3 weeks for further smears and cultures.

Criterion of cure

Men who lived locally and failed to attend for follow-up were presumed to be cured; this assumption seems to be justified, as my observations agree with those of Evans (1966) that most patients will return to the same clinic if symptoms recur soon after treatment. This assumption does not, however, apply to females.

In view of the difficulty of distinguishing between relapse and re-infection, those patients were regarded as failures in whom gonococci were demonstrated within 14 days of treatment, provided further sexual intercourse was denied.

Sensitivity of gonococcus

During the period of the trial gonococci with a wide range of penicillin sensitivities were encountered (Fig. 1). Positive cultures numbered 283, of which 68 (24.7 per cent.) were classed as ‘insensitive’, i.e. with MICs of 0.125 μg. or above, but, as will be seen subsequently, this percentage varied considerably at different periods during the trial.

Treatment and results

AMOXYCILLIN ALONE

The initial trial, which extended from April to August 1971, consisted of the administration of a single dose of 1 g. amoxycillin, four 250 mg. capsules being
Amoxycillin in gonorrhoea

 Failures

140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

FIG. 1 Penicillin sensitivities of 283 strains of gonococci

swallowed under supervision. The number of patients so treated totalled 158 (135 males and 23 females). 22 of the men and one of the women failed to attend for follow-up examination. There were seventeen failures, 10.8 per cent. of the total treated or 12.6 per cent. of those followed. This compares unfavourably with the 5 per cent. failure rate obtained with 1 g. ampicillin nearly 10 years ago (Alergant, 1963). Data relating to sensitivities were available in 102 cases and all but eleven (10.8 per cent.) fell within the range of so-called sensitive strains (Fig. 2). Of the seventeen failures, sensitivities were known in fourteen cases, and only five were in the insensitive range. Nevertheless, the failure rate was some four times greater among those with insensitive strains.

AMOXYCILLIN PLUS PROBENECID

As with other oral penicillins, it has been shown that

the simultaneous administration of probenecid with amoxycillin produces higher peak and more prolonged serum levels. From mid-August to the end of December, 1971, 145 males and sixteen females were treated with a single dose of 1 g. amoxycillin combined with 1 g. probenecid. Twenty men and three women did not attend for follow-up. There were only eight failures, 5 per cent. of the total, or 5.8 per cent. of those followed, about half the rate obtained when amoxycillin was used alone. Data relating to sensitivities were available in 110 cases, but in contrast to the earlier part of the year insensitive strains numbered 33 (30 per cent.) of the total (Fig. 3). Sensitivities were known for seven of the eight

FIG. 2 Penicillin sensitivities in group treated with 1 g. amoxycillin alone

FIG. 3 Penicillin sensitivities in group treated with amoxycillin plus probenecid

FIG. 4 Penicillin sensitivities in group treated with amoxycillin plus procaine penicillin
failed cases. Only two of the failures occurred with
strains in the sensitive range, the remaining five being
in the insensitive range.

AMOXICILLIN PLUS PROCAINE PENICILLIN
For some years we have used a combination of 1·2
m.u. procaine penicillin intramuscularly plus 1 g.
amoxicillin orally, each given at the same time as a
single dose for uncomplicated gonorrhoea in both
sexes. A few years ago, in a series of 593 male patients
treated with this regime, a failure rate of 3·5 per cent
was reported (Alergant, 1969). The substitution of
amoxicillin for ampicillin in this combination was
an obvious step, and during the first 3 months of 1972 a
combination of 1·2 m.u. procaine penicillin with 1 g.
amoxicillin was given to 95 patients (90 men and 5
women); there were sixteen defaulters, all men, and
only one failure. Data concerning sensitivities were
available in 71 cases (Fig. 4). No less than 33·8 per
cent. were classed as insensitive strains.

SIDE-EFFECTS
One patient developed a transient urticarial eruption,
apart from which no untoward side-effects were
reported.

Summary
Three groups of patients were treated with single
doses of 1 g. amoxicillin, alone, combined with
probenecid, or combined with procaine penicillin.
When the drug was used alone in 158 cases, the
result were disappointing (12·6 per cent. failure rate
among those followed) and compared unfavourably
with those obtained nearly 10 years ago in the same
clinic using 1 g. ampicillin. In 161 cases given
1 g. probenecid also, the results were substantially im-
proved (5·8 per cent. failure rate among those
followed). The best results were obtained in 95 cases
given amoxicillin combined with 1·2 m.u. procaine
penicillin (only 1 failure). This latter combination
therefore clearly deserves further trial.

I wish to thank Dr. E. C. Armstrong of the Public Health
Laboratory Service, Liverpool, for the sensitivity deter-
minations.

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Traitement de la gonococcie par l’amoxicilline

SOMMAIRE
Trois groupes de malades furent traités par doses uniques
de 1 g. d’amoxicilline, soit seule, soit combinée avec le
probénécide soit avec la pénicilline procain. Dans les
158 cas où le médicament fut utilisé seul, les résultats
furent décevants (12,6 pour cent d’échec parmi les cas suivis)
et se comparèrent défavorablement avec ceux qui avaient
été obtenus il y a presque 10 ans, dans la même clinique,
avec 1 g. d’ampicilline. Dans les 161 cas recevant en outre
du probénécide, les résultats furent sensiblement amé-
liorés (5,8 pour cent d’échec parmi les cas suivis). Les
meilleurs résultats furent obtenus dans 95 cas recevant
l’amoxicilline associée à la pénicilline-procain (1
échec seulement). Cette dernière association mérite donc
nettement un essai plus élargi.
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C D Alergant

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