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ORAL AMPICILLIN IN UNCOMPLICATED GONORRHOEA

II. *Results of Treatment in Women*

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Abstract. This study on women is the second in a series relating to the treatment of uncomplicated gonorrhoea. One year's treatment of 856 patients with an intramuscular injection of 2.2 MIU penicillin G is compared with a 1 year oral ampicillin treatment of 953 patients divided into three groups, viz. 2 g ampicillin in a single dose; 2 g ampicillin combined with 1 g probenecid in a single dose; 2 g ampicillin in a divided dose with a 5 hour interval. A comparison has also been made of the results of treatment in the three ampicillin groups. The statistical analysis showed no significant difference between any of the ampicillin groups and the penicillin G group. Nor did any difference appear on comparison between the individual ampicillin groups. On a percentage basis a high single dose of ampicillin showed throughout the poorest result, and ampicillin in divided dose the best. Among patients with less sensitive gonococcal strains there were percentually fewer treatment failures within the ampicillin-in-divided-dose and ampicillin-combined-with-probenecid groups than in the ampicillin-in-single-dose and penicillin-G-injection groups. Side-effects of ampicillin have been observed in 2 patients. The sensitivity of the gonococcal strains to penicillin and age distribution have been taken into consideration during the 2 years of examination.

The preceding paper reports the results of oral ampicillin treatment of men with gonococcal urethritis (2). A preliminary assessment was made after the trial had been proceeding for 1 month. As the results of this treatment proved to be promising in comparison with the intramuscular penicillin G treatment in the preceding year, the same type of investigation was started on the female patients with uncomplicated gonorrhoea.

The present paper thus presents a comparison of a 1 year treatment of uncomplicated gonorrhoea in women with intramuscular single injection of penicillin G with a 1 year treatment with oral ampicillin. During the ampicillin year the patients were randomly distributed into three treatment groups which, as in the male material, were: a high single dose of ampicillin, a high dose of ampicillin combined with probenecid in single dose, and 1 day treatment with ampicillin, i.e. ampicillin in divided dose with a 5 hour interval. A comparison has also been made between the results of the various ampicillin groups. The object was to discover whether any one or more of these forms of treatment was equal or possibly superior to the present routine treatment of female gonorrhoeal patients in Sweden with a single injection of penicillin G. A further comparison was made between the results in the various treatment groups and the corresponding results in male patients. For further details of method, discussion and literatur, reference is made to the preceding paper (2).

MATERIAL AND METHODS

A diagnosis of uncomplicated gonorrhoea was made on 856 female patients during the 1 year period 1967–68 (Table I) and on 953 in the 1 year period 1968–69 (Table II). Methods of examination and analysis were the same as in the preceding male study (2) with the following exceptions.

Samples for direct microscopy and culture were taken from the urethra, cervix and rectum. Patients with positive rectal culture are included in this material and will be reported in detail in a subsequent paper (3). For the result to be denoted as *satisfactory,* 2–4 negative follow-up cultures were required. In this study no statistical analysis has been made of the groups in which the first and first or second follow-up cultures, respectively, were positive and where the interval between treatment and the positive culture is allowed to be longer than 21 days.

Patients who had a positive culture at first follow-up within 14 days and those with a positive first or second follow-up culture within 21 days were counted as *treatment failures.* Only very probable reinfections (contact

Table I. *Female patients treated for uncomplicated gonorrhoea during July 1967–June 1968*

Treatment	No. of patients
Penicillin G	
(positive culture; sensitivity test)	652
(positive culture; no sensitivity test)	12
(positive smear; negative culture)	10
Tetracycline, erythromycin, sulpha, ampicillin	136
Treated, not followed	22
No treatment	24
Total	856

Table II. *Female patients treated for uncomplicated gonorrhoea during November 1968–October 1969*

Treatment	No. of patients
Ampicillin	
(positive culture; sensitivity test)	856
(positive culture; no sensitivity test)	10
(positive smear; negative culture)	17
Tetracycline	33
Treated, not followed	18
No treatment	19
Total	953

positive) have been excluded. *Grouping and dosage* will be seen from Table III. The preparations used were Doktacillin® (ampicillin), Probecid® (probenecid), Astra Läkemedel AB, Sweden and Gonocillin® (combination of sodium and procaine—penicillin G), AB Leo, Sweden.

Bacteriological method. Determination of the in vitro sensitivity of the gonococci to penicillin G, chloramphenicol and tetracycline was routinely made by the diffusion method reported by Eriksson et al. (1). Furthermore, tests were carried out on streptomycin during the first and on ampicillin during the second year of the trial. As in the male material, the patients were divided into two groups according to the sensitivity of the gonococci to penicillin G or ampicillin namely fully and less sensitive. Strains with MIC $\geq$ 0.1 IU penicillin G and MIC $\geq$ 0.1 μg ampicillin per ml have been denoted as less sensitive strains.

Statistical analysis was performed in collaboration with the Statistical Research Group at the University of Stockholm. The χ^2 test was used.

The significance limits for χ^2 values are:

$\chi^2 < 3.841$ for $P > 0.05$
$3.841 < \chi^2 < 6.635$ for $0.01 < P < 0.05$
$6.635 < \chi^2 < 10.827$ for $0.001 < P < 0.01$
$\chi^2 > 10.827$ for $P < 0.001$

Yates' correction has been used, and for small groups Fisher-Yates' test.

RESULTS

The number of female patients in the evaluation (Tables III and IV) totals 1 508, 652 of whom were treated with penicillin G (group G) and 856 with ampicillin. Three hundred patients were treated with a high single dose of ampicillin (group A), 262 with a high dose of ampicillin combined with probenecid in single dose (group B) and 294 by a 1 day treatment with ampicillin, i.e. the same quantity of ampicillin as in group A but in a divided dose with a 5 hour interval (group C). The age distribution will be seen from Fig. 1 and is closely similar in the four groups. The incidence of all gonococcal strains with reduced sensitivity to penicillin G isolated at the Bacteriological Laboratory at Södersjukhuset in 1967–68 was 23.3 % and in 1968–69 26.5 %. The frequency of strains with reduced sensitivity to penicillin G in the statistically evaluated material in this paper was in 1967–68 approx. 14.0 % and in 1968–69 approx. 22.5 %.

Fig. 2 shows the result of treatment in the four groups for all patients possible to evaluate, treatment failure being counted as positive culture at

Table III. *Modes of treatment and number of female patients in each group*

Patient group	Treatment	No. of patients
G	2.2 MIU penicillin G intramuscularly (1 MIU Na salt + 1.2 MIU procaine salt)	652
A	2 g ampicillin orally	300
B	2 g ampicillin + 1 g probenecid orally	262
C	1 g + 1 g ampicillin orally with 5 hour interval	294

Table IV. *Findings at follow-up in all evaluated cases*

Treatment group	Number of negative cultures		Positive culture at follow-up number		
	1	2, 3 or 4	I	I or II	III
G	17	583	30	45	7
A	13	260	21	25	2
B	2	244	11	14	2
C	6	267	9	14	7

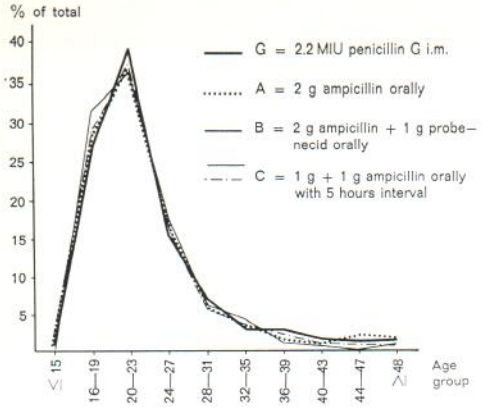

Fig. 1. Age distribution in the different treatment groups.

first follow-up within 14 days after treatment. No statistical difference appears between the four groups. But the difference between A and C is close to the significance limit, $P < 0.05$, and between G and A, fairly close to the limit.

Nor does the same comparison, though regarding only patients harbouring sensitive gonococci (Fig. 3), show any significant differences.

In the patients with bacteria with reduced sensitivity to the respective penicillins (Fig. 4), on the other hand, there is some difference between groups A and B ($0.01 < P < 0.05$) and between A and C ($0.01 < P < 0.05$). Counting as treatment failure a positive culture at follow-up I or II within 21 days, there are no significant differences in any test, whether one compares the various groups in respect of all patients (Fig. 5) or patients with sensitive gonococcal strains (Fig. 6) or patients with less sensitive gonococcal strains (Fig. 7).

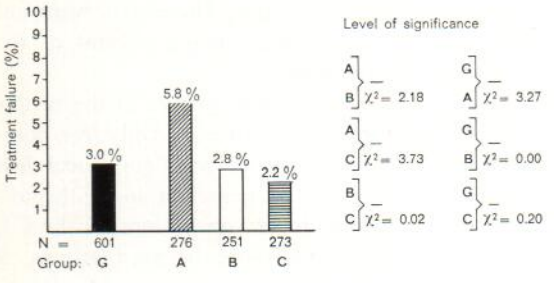

Fig. 2. Result of treatment (all patients). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failures: positive culture at follow-up I within 14 days.

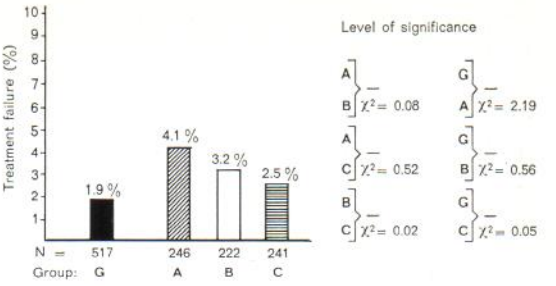

Fig. 3. Result of treatment in patients harbouring sensitive strains (MIC < 0.1 IU penicillin G/ml and < 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

Side-effects

As in the male material, the number and types of side-effects during the penicillin G year were not satisfactorily recorded. During the ampicillin year, on the other hand, the patients were questioned at follow-up concerning side-effects of the treatment. Two of 883 patients reported side-effects.

Case 1. One week after a single dose of ampicillin (group A) widespread exanthema with itch. The patient does not know whether she had earlier received penicillin.

Case 2. One week after a single dose of ampicillin combined with probenecid (group B) general exanthema with itch. The patient does not know whether she had earlier received penicillin.

DISCUSSION

The methods of examination and treatment in respect of penicillin G and of ampicillin treat-

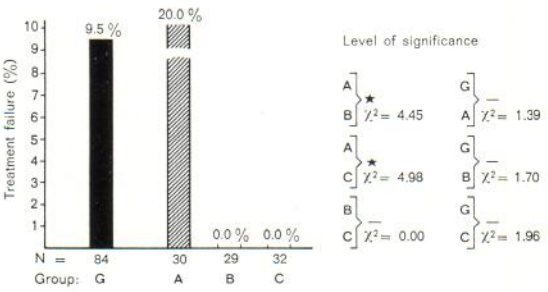

Fig. 4. Result of treatment in patients harbouring less sensitive strains (MIC ≥ 0.1 IU penicillin G/ml and ≥ 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I within 14 days.

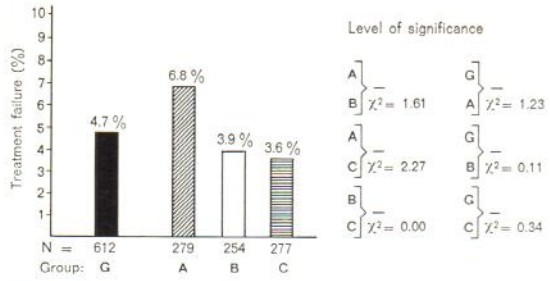

Fig. 5. Result of treatment (all patients). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

ment of uncomplicated gonorrhoea in the female material were the same as in the male study (2). There are, of course, certain obvious differences. When a female presents for suspected gonorrhoea, the diagnosis is made less often by direct microscopy than when dealing with male gonorrhoeal patients. In female patients, therefore, sensitive determination can be used to a greater extent for the choice of antibiotic and dosage. In this material, however, the patients were randomly assigned to treatment groups A, B or C irrespective of the results of the sensitivity determination. All patients with gonococcal strains with reduced sensitivity to ampicillin are therefore included. The frequency of strains with *reduced* sensitivity has not diminished but, percentually, has increased somewhat during the second year of the investigation. If this change of resistance has any significance for the result of treatment, it would have discriminated rather against the ampicillin groups. A detailed comparison between clinical results and bacteriology will be presented in a subsequent paper (5).

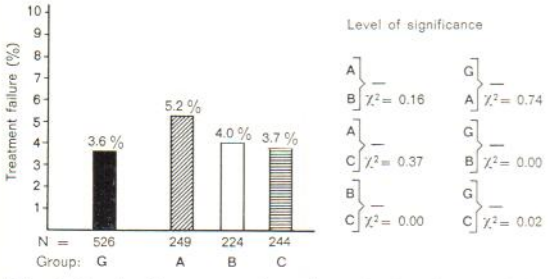

Fig. 6. Result of treatment in patients harbouring sensitive strains (MIC < 0.1 IU penicillin G/ml and < 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

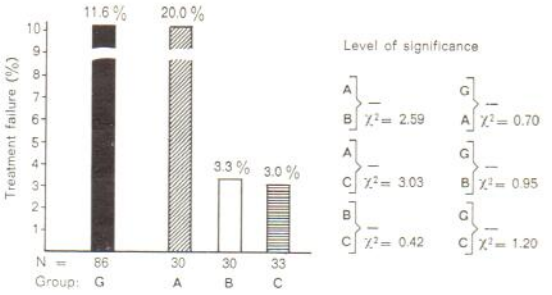

Fig. 7. Result of treatment in patients harbouring less sensitive strains (MIC ≥ 0.1 IU penicillin G/ml and ≥ 0.1 μg ampicillin/ml). Satisfactory: 2, 3 or 4 negative follow-up cultures. Treatment failure: positive culture at follow-up I or II within 21 days.

The *satisfactory* group comprises patients with two to four negative follow-up cultures. The requirement has been that culture tests from all sites—urethra, cervix and rectum—should be negative.

As *treatment failure* were counted patients with positive culture test from one or more sites irrespective of whether the site was the same as in the diagnostic test.

As regards women positive at the first follow-up, the period varies within the penicillin G group between 5 and 125 days after treatment, and in the ampicillin group between 5 and 69 days. This long interval between treatment and first follow-up probably resulted in an increased number of reinfections. In the male material, tests were made also for differences in results between the various types of treatment in respect of whether the first or the first or second follow-up culture was positive regardless of the time of "reinfection". These tests did not differ from those in which the time limit was put at 14 and 21 days, respectively, and consideration was paid to highly probable reinfections. These tests were not made on the female material on account of the mentioned results in men.

No significant difference appears in the results from the four forms of treatment. Only in a comparison as regards patients with gonococci less sensitive to the respective penicillin and with positive culture at first follow-up within 14 days is there a significant difference between groups A and B ($0.01 < P < 0.05$) and between A and C ($0.01 < P < 0.05$). Throughout, however, as in the male material, A is percentually least favourable

and C best. Exceptions are the two groups relating to patients with sensitive strains in which the failure rate is rather lower for group G than for C (Figs. 3, 6). Larger percentual differences, on the other hand, are found in respect of patients with gonococci less sensitive to penicillin, the failure rate here being higher for groups G and A than for B and C (Figs. 4, 7). Of special interest is the result of treatment in patients with positive rectal culture. This material is reported in a separate paper (3), as is also the comparison between clinical results and pharmacology (4).

The differences between certain groups are less pronounced in the female than in the male material. The tendency is, however, the same in the two, namely that A is the poorest type of treatment while C appears to the best. The results also show that, with the doses used in the two materials, both ampicillin in divided dose (1 day treatment) and ampicillin combined with probenecid in single dose are equivalent to a single injection of penicillin G for the treatment of uncomplicated gonorrhoea.

In women it appears to be even more important to continue the investigation of treatment types B and C, as ampicillin shows a tendency to be more effective than penicillin G in patients harbouring gonococci less sensitive to penicillin. It would also be of value to see whether any difference in effect exists between B and C. In group B an additional allergenic substance, probenecid, is administered. Should B prove to be better than C, one must weigh the better result of treatment against a possibly greater risk of side-effects. Hitherto the frequency of side-effects of ampicillin has been low, and have been found only in two women. Only 5 cases of side-effects with ampicillin have been observed in 2 033 men and women treated, so that no conclusions can be drawn concerning differences in side-effect frequency between the different ampicillin groups.

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