

ORAL AMPICILLIN IN UNCOMPLICATED GONORRHOEA

V. Comparison of Bacteriological and Clinical Results

Gunnel Eriksson and Gösta Wallmark

From the Departments of Dermatology and Clinical Bacteriology Södersjukhuset, Stockholm, Sweden

Abstract. This report is the fifth part of a comparative study of oral ampicillin and intramuscularly injected penicillin G in the treatment of uncomplicated gonorrhoea. The statistical evaluation of 4247 patients (2419 men and 1828 women) showed no significant difference between the following treatment groups: 2.2 MIU penicillin G (1.0 MIU Na salt + 1.2 MIU procaine salt) in a single intramuscular dose, 2 g of ampicillin together with 1 g of probenecid in a single oral dose and 2 g of ampicillin in a divided oral dose with a 5 hour interval (1 day treatment) when the results of treatment were compared at three different MIC values of the gonococcal strains ($< 0.1 \mu\text{g/ml}$, $0.1/0.12 \mu\text{g/ml}$ and $\geq 0.18 \mu\text{g/ml}$). However, there was a tendency for ampicillin in divided dose to offer the best alternative in patients harbouring gonococci with decreased in vitro sensitivity. An extended study of 1000 patients (included in the above 4247 patients) treated randomly with a single dose of ampicillin plus probenecid, or ampicillin in a divided dose, showed the same overall results as those of the previous course. No increase in the proportion of less sensitive strains was observed during this extended study. Comparison of the in vitro sensitivity with the effect of treatment within the different groups showed penicillin G to be significantly less effective in patients infected with less sensitive gonococci (MIC ≥ 0.06 or $> 0.06 \mu\text{g/ml}$). In the group treated with single dose ampicillin plus probenecid, the treatment was significantly less effective in males with less sensitive gonococci (MIC ≥ 0.1 or $\geq 0.2 \mu\text{g/ml}$), but not in females. No such difference was found in the group treated with the two ampicillin doses, which was thus demonstrated as the most favourable treatment alternative. Side effects were registered in 6 of the 2813 patients treated with ampicillin.

In earlier reports on gonorrhoea (4, 5) a comparison was made between the results of 1 year's treatment with single intramuscular injection of penicillin G and 1 year's treatment with ampicillin in three oral dosage forms. The statistical evaluation showed that treatment with oral ampicillin either as 2 g together with 1 g of probenecid

in a single dose, or as 2 g in a divided dose given with a 5 hour interval (1 day treatment) was equivalent to the routine treatment with one intramuscular injection of 2.2 MIU penicillin G. Two g of ampicillin in a single dose was an inferior alternative. A comparison of treatment results in women with and without positive rectal culture (6) showed that penicillin G was significantly less effective than ampicillin in cases with positive rectal culture. No such difference was seen with single dose ampicillin combined with probenecid, or with a divided dose of ampicillin (1 day treatment). A comparison between clinical results and blood levels of the antibiotics has also been reported (7).

In the papers mentioned the patients were divided into two groups according to the sensitivity of the gonococcal strains to penicillin G during the first year of the trial and to ampicillin during the second year, namely fully and less sensitive. Strains with MIC $\geq 0.1 \text{ IU}$ ($\geq 0.06 \mu\text{g}$) penicillin G and $\geq 0.1 \mu\text{g}$ ampicillin per ml were denoted as less sensitive.

The purpose of this paper is to give an analysis of the relation between treatment failure and in vitro susceptibility of the gonococcal strains in this 2-year gonorrhoea material, as well as to report the results of an extended study during another half-year with the two most effective ampicillin dosage forms.

MATERIAL AND METHODS

Patients

Altogether 4247 patients (2419 men and 1828 women) have been statistically evaluated, 3247 of whom are identical with those in the earlier reports (4, 5, 6).

Table I. Result of treatment in groups B and C (men and women) during the two periods studied

Satisfactory: at least 2 negative follow-up cultures
Treatment failure: positive culture at first follow-up within 14 days

Treatment group	Treatment period	Result of treatment (no. of patients)	
		Satisfactory	Treatment failure
B	1968/69	563	17
	1969/70	478	14
C	1968/69	604	12
	1969/70	499	9

Another 1 000 patients were studied during a half-year period following the first course.

Grouping and dosage

During the first year of the trial the patients were treated with penicillin G (group G), 2.2 MIU penicillin G i.m. = 1.0 MIU Na salt + 1.2 MIU procaine salt (Gonocillin®, AB Leo, Sweden). The following year oral ampicillin was given in three dosage forms, namely group A with a single dose of 2 g ampicillin (Doktacillin®, Astra Läke-medel AB, Sweden), group B with 2 g ampicillin combined with 1 g probenecid (Probecid®, Astra) in a single dose, and group C 1 g ampicillin twice with a 5 hour interval. Being an inferior alternative, the group A treatment was discontinued in the extended study covering half a year, during which only treatment forms B and C were given.

Table II. Result of treatment in 4 247 statistically evaluated patients with uncomplicated gonorrhoea

Satisfactory (S): at least 2 negative follow-up cultures
Treatment failure (F): positive culture at first follow-up within 14 days

Treatment group	Sex	MIC ($\mu\text{g/ml}$)									
		<0.1		0.1/0.12 ^a		0.2/0.18 ^a		0.5/0.3 ^a		>0.5	
		S	F	S	F	S	F	S	F	S	F
G	♂	699	17	66	6	26	3	12	2	2	
	♀	541	13	25	2	11	1	5	1	1	1
A	♂	270	21	19	5	17	3	5	1		
	♀	236	10	11	3	11	2	2	1		
B	♂	490	9	65	4	21	4	5			
	♀	412	12	27	2	20		1			
C	♂	532	7	61	3	34	1	8	1		
	♀	413	7	34	1	16	1	5			

^a Ampicillin/penicillin G. In group G MIC means susceptibility to penicillin G, in groups A, B and C to ampicillin.

Acta Dermatovener (Stockholm) 52

Clinical methods

Great care was taken not to change any feature in the routine of diagnosis and follow-up. Samples for direct microscopy and culture were collected at all visits, in men from urethra, and in women from urethra, cervix and rectum.

In the clinical evaluation of the results of treatment, patients with at least two negative follow-up cultures were counted as satisfactory. Patients with positive cultures at first follow-up within 14 days were denoted as treatment failures. Only very probable reinfections (contact positive) were excluded. To be included in the statistical evaluation, the patients had to fulfil the criteria for follow-up.

During the periods of ampicillin administration, side-effects were questioned about and registered at follow-up.

Bacteriological methods

The samples were taken with a charcoaled swab which was transferred to a modified Stuart transport medium (11) and inoculated after 1-12 hours into chocolate medium with antibiotics added (12). The plates were read after incubation in CO₂-atmosphere at 37°C for about 18 hours and again after a further 24 hours in air. Verification tests included microscopy of a Gram-stained smear, oxidase-test and fermentation tests.

Sensitivity tests for antibiotics were performed with the quantitative disc method of Ericsson et al. (3). Gonococci of known sensitivity were currently included in the sensitivity tests as controls. A sensitivity test for ampicillin was done only during the period when the drug was clinically used.

The results of the sensitivity test were not taken into consideration when the treatment was given.

Statistical tests employed have been the χ^2 -test with Yates' correction and, for small groups, the exact test by Fischer.

RESULTS

In the extended study during the half-year period 1969/70 only treatment forms B and C were used, as A had proved to be an inferior treatment form. The overall results, compared with those obtained in 1968/69, (Table I) showed no significant differences, either between B and C or between the two periods.

In Table II, recording the total material, the results of treatment in the four different treatment groups are tabulated according to the in vitro susceptibility of the gonococcal strains. In group G, MIC means susceptibility to penicillin G; in groups A, B and C, to ampicillin. Out of 4 247 patients 468 harboured gonococci denoted as less sensitive to the given drug according to the definition, i.e. MIC \geq 0.12 μg penicillin G per ml

and $\geq 0.1 \mu\text{g}$ ampicillin per ml. The highest MIC of ampicillin observed was $0.5 \mu\text{g}$ per ml.

These results are statistically evaluated in Table III, comparing treatment failures in the different treatment groups in relation to in vitro sensitivity. In patients treated with penicillin G in a large single dose (group G) there was a highly significant difference in effect between sensitive and less sensitive strains, when gonococci with $\text{MIC} \geq 0.06 \mu\text{g/ml}$ ($\geq 0.1 \text{ IU/ml}$) or $\geq 0.12 \mu\text{g/ml}$ penicillin G were denoted as less sensitive. A significant difference was also found within group A when strains with $\text{MIC} \geq 0.1 \mu\text{g/ml}$ ampicillin were denoted as less sensitive. In group B such a difference occurred in men but not in women with the boundary for decreased sensitivity at $\text{MIC} \geq 0.1$ or $\geq 0.2 \mu\text{g/ml}$ ampicillin. In group C, no such differences were found, either in men or in women.

Fig. 1 shows the percentage of treatment failures at three different MIC levels for the penicillins used in the clinically acceptable treatment groups G, B and C (men + women). The diagram shows a tendency towards group C as being the best choice of treatment, although statistically there is no significant difference between any of the three groups at any single one of the points tested.

The comparison of the in vitro level of resistance to ampicillin and penicillin G is shown in Fig. 2. Strains within the less sensitive group are, in the main, more sensitive to ampicillin than to penicillin G. Fifty-six strains were less sensitive to ampicillin and fully sensitive to penicillin G while 85 strains were fully sensitive to ampicillin and less sensitive to penicillin G. Altogether 391 strains were less sensitive to penicillin G and/or ampicillin.

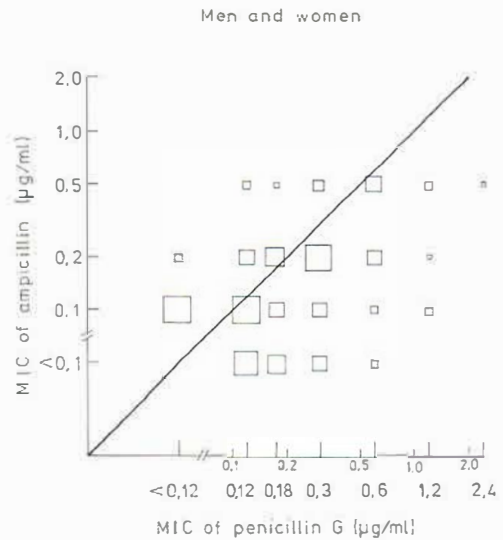


Fig. 2. Comparison of in vitro sensitivity to ampicillin and penicillin G in 391 strains of gonococci with decreased sensitivity for ampicillin and/or penicillin G.

Only one female patient of the 1 000 patients given ampicillin during the extended period of the present study reported that she had vomited after taking the tablets. No other side-effects were registered.

DISCUSSION

The frequency of gonococcal strains with a decreased sensitivity to penicillin differs widely in different parts of the world. Such strains are particularly common in South-East Asia where a single session treatment is gradually becoming impossible (13). From some parts of Scandinavia, on the other hand, a decreasing number of less sensitive strains has been reported (2). Therefore, it seems important to evaluate continuously the treatment forms of gonorrhoea in the area where they are intended to be used. This study deals with single-session or one-day treatment within the Stockholm area.

In previous papers of this series it was shown that oral ampicillin administered either as a single 2 g dose combined with 1 g of probenecid (group

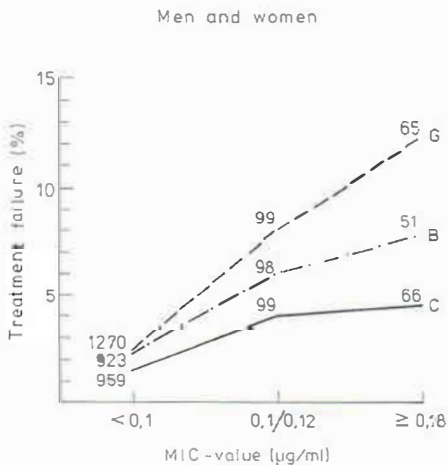


Fig. 1. Result of treatment in groups G, B and C correlated to in vitro sensitivity.

Table III. Comparison of result of treatment in patients with sensitive and less sensitive gonococci

MIC-values for penicillin G in group G, for ampicillin in groups A, B and C. Satisfactory: at least 2 negative follow-up cultures. Treatment failure: positive culture at first follow-up within 14 days

Treatment group	Sex	Sensitive strains		Less sensitive strains		χ^2	P
		MIC ($\mu\text{g/ml}$)	Treatment failure (%)	MIC ($\mu\text{g/ml}$)	Treatment failure (%)		
G	♂	< 0.06	2.1	≥ 0.06	7.5	11.82	+++
		≤ 0.06	2.4	≥ 0.12	9.4	13.20	+++
	♀	< 0.06	1.9	≥ 0.06	9.5	11.83	+++
		≤ 0.06	2.3	≥ 0.12	10.6	7.60	++
A	♂	< 0.1	7.2	≥ 0.1	18.0	4.91	+
		≤ 0.1	8.3	≥ 0.2	15.4	0.76	N.S.
	♀	< 0.1	4.1	≥ 0.1	20.0	9.69	++
		≤ 0.1	5.0	≥ 0.2	18.8	3.00	N.S.
B	♂	< 0.1	1.8	≥ 0.1	8.1	9.62	++
		≤ 0.1	2.3	≥ 0.2	13.8	9.39	++
	♀	< 0.1	2.8	≥ 0.1	4.0	0.00	N.S.
		≤ 0.1	2.7	≥ 0.2	7.1	0.60	N.S.
C	♂	< 0.1	1.3	≥ 0.1	4.6	3.81	N.S.
		≤ 0.1	1.7	≥ 0.2	4.3	0.54	N.S.
	♀	< 0.1	1.7	≥ 0.1	3.5	0.19	N.S.
		≤ 0.1	1.8	≥ 0.2	3.1	0.02	N.S.

B) or as 1 g twice with a 5 hour interval (group C) was at least as effective in uncomplicated gonorrhoea as a single dose of 2.2 MIU penicillin G intramuscularly (group G), whereas a single dose of ampicillin without probenecid was significantly less effective (4, 5, 6). There was, however, a tendency for ampicillin in divided dose to be the best alternative in patients with less sensitive gonococci.

No significant difference was revealed in another 1 000 patients given treatment forms B and C randomly (Table I). But still the number of patients infected with less sensitive gonococci is not large.

The percentage of strains denoted as less sensitive in vitro to ampicillin (MIC $\geq 0.1 \mu\text{g/ml}$) during the two periods was also the same, namely 16%.

Because of a shift of the borderline of in vitro susceptibility for gonococci to be denoted as less sensitive to penicillin G in Sweden since the earlier reports in this series, this change has been taken into consideration in the present paper. Thus, comparisons have been made both when strains with MIC $\geq 0.06 \mu\text{g/ml}$ ($\geq 0.1 \text{ IU/ml}$) and with the new boundary of MIC $> 0.06 \mu\text{g/ml}$ penicillin G have been denoted as less sensitive.

In this study, penicillin G had a significantly weaker effect in patients with gonococci denoted as less sensitive, regardless of which boundary was chosen (Table III). Within the groups treated with ampicillin there was no such difference in treatment group B (females) or group C (males and females), either when decreased sensitivity was denoted as MIC ≥ 0.1 or as $\geq 0.2 \mu\text{g/ml}$ ampicillin. This may to some extent be explained by the more narrow range of MIC-values for ampicillin found in this study. Halverson et al. (8) also found the distribution of MIC-values to be broader for penicillin G than for ampicillin. The better effect of ampicillin than penicillin G in patients infected with gonococci of decreased sensitivity is in agreement with the in vitro susceptibility of gonococci to the two penicillins found by Reyn & Bentzon (10) and Ödegaard (14).

Besides the clinical studies referred to in earlier papers (4, 7), Malmberg et al. (9) have reported a rate of probable true recurrence of 3% with 2 g of ampicillin in divided dose with 5 hour interval when all isolated gonococcal strains except one were highly sensitive to ampicillin. Bro-Jørgensen & Jensen (1) had a failure rate of 3.2% with 2 g of ampicillin plus probenecid in a single oral dose. About 30% of their cases were

caused by gonococci of reduced sensitivity to penicillin G ($IC_{50} \geq 0.053 \mu\text{g/ml}$) but no test for ampicillin sensitivity was reported.

The risk of side-effects seems to be very small with the oral ampicillin treatment. Earlier, 5 cases of side-effects, 3 men and 2 women have been reported (4, 5). Thus only 0.2% (6/2813) patients treated with ampicillin showed some kind of side-effect. No side-effects were reported by Bro-Jørgensen & Jensen in their study with oral ampicillin (1).

The Swedish Board of Social Welfare recommends at present that patients harbouring gonococci with decreased sensitivity should be checked four times compared with twice in fully sensitive cases. The definition of decreased sensitivity thus has several implications. At present, strains with MIC of $> 0.06 \mu\text{g/ml}$ ampicillin and penicillin G are denoted as less sensitive. The results obtained in this study indicate that this boundary might be too low for ampicillin.

To be able to evaluate further the MIC-values for gonococcal strains to be denoted as less sensitive to ampicillin it seems necessary to follow continuously the results of treatment with ampicillin and the *in vitro* susceptibility of the gonococci.

REFERENCES

1. Bro-Jørgensen, A. & Jensen, T.: Single dose oral treatment of gonorrhoea in men and women, using ampicillin alone and combined with probenecid. *Brit J Vener Dis* 47: 443, 1971.
2. Danielsson, D.: Gonokockernas känslighet för olika antibiotika. *Läkartidningen* 68: 4273, 1971.
3. Ericsson, H., Högman, C. & Wickman, K.: A paper disc method for determination of bacterial sensitivity to chemotherapeutic and antibiotic agents. *Scand J Clin Lab Invest* 6: Suppl. 11, 1954.
4. Eriksson, G.: Oral ampicillin in uncomplicated gonorrhoea. I. Treatment of gonococcal urethritis in men. *Acta Dermatovener (Stockholm)* 50: 451, 1970.
5. — Oral ampicillin in uncomplicated gonorrhoea. II. Results of treatment in women. *Acta Dermatovener (Stockholm)* 50: 461, 1970.
6. — Oral ampicillin in uncomplicated gonorrhoea. III. Results of treatment in women with positive rectal culture. *Acta Dermatovener (Stockholm)* 51: 305, 1971.
7. — Oral ampicillin in uncomplicated gonorrhoea. IV. Comparison of pharmacological and clinical results. *Acta Dermatovener (Stockholm)* 51: 467, 1971.
8. Halverson, C. W., Keys, T. F. & Clarke, E. J.: *In vitro* susceptibility of *Neisseria gonorrhoeae* to different antibiotics. *Milit Med* 134: 1427, 1969.
9. Malmberg, A. S., Molin, L. & Nyström, B.: Comparative evaluation of ampicillin, pivampicillin chloride and penicillin G in the treatment of acute uncomplicated gonorrhoea. To be published.
10. Reyn, A. & Bentzon, M. W.: A study of relationships between the sensitivities of *Neisseria gonorrhoeae* to sodium penicillin G, four semi-synthetic penicillins, spiramycin and fusidic acid. *Brit J Vener Dis* 44: 140, 1968.
11. Ringertz, O.: A modified Stuart medium for the transport of gonococcal specimens. *Acta Path Microbiol Scand* 48: 105, 1960.
12. Thayer, J. D. & Martin, J. E.: A selective medium for the cultivation of *N. gonorrhoeae* and *N. meningitidis*. *Public Health Rep* 79: 49, 1964.
13. Willcox, R. R.: A survey of problems in antibiotic treatment of gonorrhoea with special reference to South-East Asia. *Brit J Vener Dis* 46: 218, 1970.
14. Ödegaard, K.: Følsamhet *in vitro* hos gonokokker over for tre penicilliner. *T Norsk Laegeforen* 2: 55, 1962.

Received March 23, 1972

Gunnel Eriksson, M.D.
Department of Dermatology
Södersjukhuset
S-100 64 Stockholm 38
Sweden