Treatment of gonorrhoea using a combination of intramuscular and oral ampicillin

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Recent studies have proved that the treatment of uncomplicated gonorrhoea with oral ampicillin, administered either in a single dose of 2 g. plus 1 g. probenecid or 2 g. divided into two doses at an interval of 5 hrs, is an effective alternative to conventional treatment with a single intramuscular injection of 1.2 m.u. procaine penicillin plus 1 m.u. sodium penicillin G (Gundersen, Ødegaard, and Gjessing, 1969; Eriksson, 1970 a,b, 1971). Other regimens of ampicillin treatment are reviewed by Willcox, Woodcock, Latto, John, Redmond, Parker, Rees and Cobbold (1973).

Ampicillin given by intramuscular injection is less frequently used in the treatment of gonorrhoea. Kercull (1968) reported a primary cure rate of 95 per cent. in acute gonorrhoea in military patients in Vietnam, using 1 g. ampicillin daily for two or three days. In the Far East, Keys, Halverson, and Clarke (1969) reported a failure rate of only 1 per cent. with an intramuscular dose of 2 g. ampicillin together with 1 g. probenecid orally.

In this study we have tested the efficacy of 1 g. ampicillin intramuscularly in combination with an oral dose of 2 g. ampicillin taken 4 hrs later.

In order to find out if there was a correlation between therapeutic failures and the minimum inhibitory concentrations (MICs) for ampicillin of the strains of *N. gonorrhoeae* isolated, the MICs for ampicillin were estimated before and, in the cases of therapeutic failure, also after treatment. In addition, ampicillin serum levels were measured in six male patients.

Patients and methods

The study included 619 outpatients with uncomplicated urogenital or rectal gonorrhoea; 289 were male civilians, 204 were female civilians, and 126 were sailors.

Six of these patients were excluded. One developed an urticarial rash and two had a drop in blood pressure (but not real shock) after the ampicillin injection. These three patients were not given oral ampicillin. Three other patients admitted that they forgot to take the oral ampicil-

lin. Of the remaining 613 patients, 286 were male civilians, 202 were female civilians, and 125 were sailors; they all received 1 g. ampicillin intramuscularly and took 2 g. ampicillin by mouth 4 hrs later.

Diagnosis was based on the results of Gram-stained smears and cultures from the urethra in males and from the cervix and urethra in females. Culture was performed on material from the rectum in all females and in eight homosexual males. Specimens were cultured on a selective medium (Thayer and Martin, 1966). Sensitivity tests for ampicillin using the agar-dilution method (Ericsson and Sherris, 1971) were performed on all positive cultures. Strains with MICs of ampicillin ≥ 0.16 $\mu\text{g./ml.}$ were denoted as relatively resistant.

Female patients were asked to return after 1, 2, 6, and 12 weeks, and male patients after 1 and 2 weeks. Smears and cultures were taken at each visit. The criterion for a satisfactory result was two consecutive negative examinations in the first 2 weeks after treatment.

Any patient with a recurrence within 2 weeks who admitted re-exposure to risk of infection, was considered to have been re-infected. Any patient with a recurrence after 2 weeks was also considered to have been re-infected.

In six male volunteers, all with gonococcal urethritis, specimens of serum were assayed by means of the cylinder plate method using *Sarcina lutea* NCTC 8340 as test organism. (Michel, van Waardhuizen, and Kerrebijn, 1973).

The volunteers satisfied the following conditions: Age between 20 and 40 years, weight between 75 and 80 kg., height between 170 and 190 cm., serum creatinine within the normal range and no history of renal or gastrointestinal disease.

Specimens of serum were taken just before ampicillin treatment started and 15 min., 30 min., and 1, 2, and 4 hrs after the injection. After the oral treatment further samples were taken after 30 min., and 1, 2, 4, and 6 hrs.

Results

The follow-up achieved is presented in Table I.

Of the 613 patients treated, 142 (23.2 per cent.) did not return for follow-up within 2 weeks, whereas 54 (8.8 per cent.) returned after a longer interval than 2 weeks, but within 3 months. Sailors who did not return for any follow-up within 2 weeks (56 per cent.) were not considered to be genuine defaulters. In most cases their ships had to leave Rotterdam and so

TABLE I Follow-up of ampicillin-treated patients

Follow-up	Male civilians		Female civilians		Sailors		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Within 2 wks	192	67.1	172	85.1	53	42.4	417	68.0
Later than 2 wks but within 3 mths	35	12.2	17	8.4	2	1.6	54	8.8
No follow-up	59	20.6	13	6.4	70	56.0	142	23.2
Total	286	99.9	202	99.9	125	100.0	613	100.0

it was impossible for them to return. The percentage of patients who returned within 2 weeks for follow-up was highest among female civilians (85.1 per cent.) and lowest among sailors (42.2 per cent.); however, a considerable disparity was observed between female and male civilian patients also (85.1 per cent. and 67.1 per cent. respectively).

Strains of *N. gonorrhoeae* could not be tested for sensitivity in all patients. In some cases the culture was negative and the Gram-stained smear positive. In other cases cultures were positive, but sensitivity testing could not be carried out because the strains did not survive.

In 388 (93.0 per cent.) of the 417 patients who returned within 2 weeks, the strains of *N. gonorrhoeae* had been isolated before treatment and could be tested for sensitivity. The percentages for male civilians, female civilians, and sailors were 91.1, 95.3, and 92.5 per cent. respectively.

MICs of ampicillin for all strains of *N. gonorrhoeae* tested were in the range of 0.005 to 0.64 µg./ml.

Table II shows the numbers and percentages of

strains relatively resistant (RR) to ampicillin (MIC ≥ 0.16 µg./ml.) among strains of *N. gonorrhoeae* isolated in the three patient groups.

The percentage of strains relatively resistant to ampicillin was lowest among those isolated from patients who returned within 2 weeks and, with the exception of the male civilians, highest among those isolated from patients who did not return for follow-up. The greatest difference was found between strains isolated from sailors who returned within 2 weeks (53.1 per cent. RR to ampicillin) and strains isolated from sailors who did not return at all (74.1 per cent. RR to ampicillin). No satisfactory explanation could be found for this difference. A higher percentage of strains relatively resistant to ampicillin was found in sailors than in male and female civilians. This finding has been noted in previous studies (Stolz, Zwart, and Michel, 1974; Wols-van der Wielen, 1971).

In Table III, relapses and re-infections in patients who returned for follow-up within two weeks after treatment are recorded.

TABLE II Strains relatively resistant (RR) to ampicillin (MIC ≥ 0.16 µg./ml.) among strains of *N. gonorrhoeae* isolated in the three patient groups

Follow-up	MC ^a strains RR to ampicillin		FC ^b strains RR to ampicillin		S ^c strains RR to ampicillin		Total strains RR to ampicillin	
	No.	Per cent. of all MC strains	No.	Per cent. of all FC strains	No.	Per cent. of all S strains	No.	Per cent. of all strains
Within 2 wks	62	35.5	53	32.3	26	53.1	141	36.4
later than 2 wks but within 3 mths	16	50.0	6	35.2	1	50.0	23	45.1
No follow-up	21	42.0	5	38.5	51	74.1	77	58.4
Total	99	38.5	64	32.9	78	65.0	241	42.3

^aMC = male civilian

^bFC = female civilian

^cS = sailor

TABLE III Relapses and re-infections among patients who returned for follow-up with 2 weeks

Result	Male civilians		Female civilians		Sailors		Total	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Relapses	4	2.1	—	—	—	—	4	1.0
Re-infections	5	2.6	4	2.3	1	1.9	10	2.4
Relapses and re-infections	9	4.7	4	2.3	1	1.9	14	3.4
Total number of patients examined within 2 wks	192	100.0	172	100.0	53	100.0	417	100.0

Relapses were found in only four male civilians. The relapse rate was 2.1 per cent. in male civilians and 1.0 per cent. in all patients. Thus the cure rate was 97.9 per cent. in male civilians and 99.0 per cent. in all patients. Re-infections were found in five male civilians, four female civilians, and one sailor. Re-infection rates in male civilians, female civilians, sailors, and in all patients were 2.6, 2.3, 1.9, and 2.4 per cent. respectively. The total recurrence rate within 2 weeks (relapse rate + re-infection rate) was therefore 4.7 per cent. in male civilians, 2.3 per cent. in female civilians, 1.9 per cent. in sailors, and 3.4 per cent. in all patients.

In all four patients with relapses, strains relatively resistant to ampicillin ($\text{MIC} > 0.16 \mu\text{g./ml.}$) were isolated. In three the MIC was $0.64 \mu\text{g./ml.}$ and in one it was $0.16 \mu\text{g./ml.}$ Of the ten patients with re-infections, eight had sensitive strains and two relatively resistant strains (MIC of $0.64 \mu\text{g./ml.}$ in both). In the latter two patients the strains isolated after treatment were highly sensitive to ampicillin. In all other patients with relapses and re-infections the sensitivities to ampicillin of the strains isolated before and after treatment did not differ by more than one dilution.

All four patients with relapses were successfully treated with tetracycline HCl, 2 g. daily for 5 days:

In the follow-up period after 2 weeks and within 3 months, 65 patients returned with gonococcal infections. In fifty of these 65 patients, the recognition of the gonococcal infection was preceded by one or more negative examinations. In only fifteen patients (eleven male civilians and four female civilians) had no previous examination taken place. All 65 patients admitted re-exposure to risk of infection. Together with the ten re-infections seen within the first 2 weeks, there was thus a total of 75 patients with re-infections (33 male civilians, 37 female civilians, and 5 sailors). The total re-infection rate within 3 months after treatment amounted to 14.6 per cent. in male civilians, 19.6 per cent. in female civilians, 9.1 per cent. in sailors, and 15.9 per cent. in all patients. All 75 patients with re-infections were re-treated with our standard ampicillin treatment; 39 returned at least once within 2 weeks of re-treatment and cultures were negative in all.

During the 3 months after treatment, 42 male civilians (18.5 per cent. of all male civilians) and eight sailors (14.5 per cent. of all sailors) were treated for a post-gonococcal urethritis with tetracycline HCl 2 g. daily for 5 days.

Ampicillin serum levels in six male patients (A, B, C, D, E, and F) treated with 1 g. ampicillin intramuscularly, followed by 2 g. ampicillin 4 hrs later are presented in Figs 1 and 2. Three patients

(A, B, and C) had fasted overnight before the start of treatment and were not allowed to take any food or drink until 10 hrs after the start of treatment. Their ampicillin serum levels are presented in Fig. 1.

FIG. 1 Ampicillin serum levels in three patients (A, B, and C), who had fasted overnight before the start of treatment and who were not allowed to take any food or drink until 10 hrs after the start of treatment. Treatment consisted of 1 g. ampicillin intramuscularly followed by 2 g. ampicillin orally 4 hrs later

The other three patients (D, E, and F) had also fasted overnight before the start of treatment, but were allowed to take a light breakfast 15 min. before the oral dose. Their ampicillin serum levels are presented in Fig. 2.

Wide variations in ampicillin serum values were found. Two patients (A and E) showed very high levels after the injection of 1 g. ampicillin. Peak levels after injection were noticed after 1 hr in patients A, B, C, E, and F and after 2 hrs in patient D. Peak

FIG. 2 Ampicillin serum levels in three patients (D, E, and F) who had fasted overnight before the start of treatment and who were allowed a light breakfast 15 min. before the oral dose of ampicillin. Treatment consisted of 1 g. ampicillin intramuscularly followed by 2 g. ampicillin orally 4 hrs later

levels after the oral dose of 2 g. given 4 hrs after the injection were noticed after 1 hr in patient B, after 2 hrs in patients A, C, D, and F, and after 4 hrs in patient E. Patient E absorbed the orally administered ampicillin very slowly. The light breakfast did not seem to have any significant effect on the serum levels achieved (Fig. 2).

The MICs of ampicillin for the strains of *N. gonorrhoeae* isolated in the six patients A, B, C, D, E, and F were respectively: 0.64, 0.16, 0.005, 0.64, 0.01 and 0.01 µg./ml. All these patients were cured.

Discussion

A high defaulter rate for male civilians (20.6 per cent. compared with 6.4 per cent. for female civilians)

was found in the civilian population in the Rotterdam outpatient department. The higher percentage of defaulters in males can partially be explained by the fact that males without symptoms after treatment often assume that they are cured and no further examination is necessary, while females, frequently symptomless before treatment, are anxious to know whether they are cured or not. High re-infection rates within 3 months (14.6 per cent. in male civilians and 19.6 per cent. in female civilians) are, like high defaulter rates, a common characteristic of large venereal diseases clinics. In patients treated for gonorrhoea, Willcox (1963) reported a re-infection rate within 3 months of 11 per cent. (St. Mary's Hospital, London). In our study the majority of patients with re-infections were re-infected by their regular consorts. Some of these consorts were not named by the patients in the first interview and others refused to visit a physician. These findings imply that, in the Rotterdam outpatient department, intensified contact tracing is of the utmost importance to reduce the re-infection rate.

A high cure rate of 99 per cent. was found in all patients (97.9 per cent. in male civilians, 100 per cent. in female civilians and sailors) who returned within 2 weeks. These results are comparable with those of other ampicillin treatment schedules reported by Keys and others (1969), Gundersen and others, (1969), and Eriksson (1971).

All four patients with relapses harboured strains of *N. gonorrhoeae* relatively resistant to ampicillin. The majority (8 out of 10) of strains isolated in patients with re-infections within 2 weeks were, on the contrary, sensitive to ampicillin. Of 388 strains from patients who returned within 2 weeks, 247 strains (63.6 per cent.) were sensitive and 141 strains (36.4 per cent.) were relatively resistant to ampicillin. For 175 strains from male civilians, the corresponding numbers were 113 strains (64.5 per cent.) sensitive and 62 strains (35.5 per cent.) relatively resistant to ampicillin (Table II).

According to these findings, male civilian patients with strains of *N. gonorrhoeae* relatively resistant to ampicillin are more prone to relapses than male civilian patients with strains sensitive to ampicillin ($\chi^2 = 4.85$; $P < 0.05$). Eriksson and Wallmark (1972), on the contrary, observed therapeutic failures with oral ampicillin treatment both when the strains were sensitive and when they were relatively resistant to the antibiotic.

Eickhoff, Kislak, and Finland (1965) and Klein and Finland (1963) ascertained ampicillin serum levels by the agar diffusion method using *Sarcina lutea* (described by Grove and Randall, 1955) after a single intramuscular injection of 1 g. ampicillin in ten

normal young men. Average ampicillin serum levels in blood samples drawn $\frac{1}{2}$, 1, 2, and 4 hrs after injection were 9.27, 10.10, 7.28, and 2.52 $\mu\text{g./ml.}$ respectively (Eickhoff and others, 1965). These values are considerably lower than those obtained in our six patients.

The difference might be explained by the fact that our six patients were confined to bed during the trial. Eriksson (1971) recorded a personal communication of Wahlqvist and Lönnell that serum concentrations twice as high and more sustained were found in patients confined to bed than in healthy volunteers. Eriksson (1971) ascertained blood serum levels, using the method described by Grove and Randall (1955), after the oral administration of 2 g. ampicillin in one dose in twelve healthy male volunteers. Average mean ampicillin serum levels and standard errors after 2, 3, 5, and 8 hrs were 8.85 ± 0.93 , 7.50 ± 0.71 , 2.42 ± 0.35 , and 0.29 ± 0.049 $\mu\text{g./ml.}$ respectively. In our patients, oral treatment was given 4 hrs after injection and therefore the results are not comparable. We found wide variations in ampicillin serum values (Figs 1 and 2). Eriksson (1973) also stressed the fact that these variations can be found with both oral and intramuscular treatment. However, with the exception of patient E, ampicillin serum levels were high over a period of 8 hrs in comparison with the MICs of ampicillin for the strains of *N. gonorrhoeae* in our patients ($0.005 \mu\text{g./ml.} \leq \text{MIC} \leq 0.64 \mu\text{g./ml.}$). Eriksson (1971) estimated that a minimum effective duration of 5 to 12 hrs, and most likely 7 to 8 hrs, and a minimum ratio between maximum serum concentration and MIC of two to five times, was required for successful ampicillin therapy. The treatment described in this paper satisfied both conditions.

Summary

In a series of 417 patients (245 men and 172 women) followed-up after treatment for gonorrhoea, a cure rate of 99 per cent. was obtained using 1 g. ampicillin intramuscularly followed by an oral dose of 2 g. ampicillin 4 hrs later. In the four patients with relapses, strains of *N. gonorrhoeae* relatively resistant to ampicillin ($\text{MIC} \geq 0.16 \mu\text{g./ml.}$) were isolated. Ampicillin serum levels were measured in six of the male patients.

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Emploi d'une association d'ampicilline intramusculaire et buccale dans le traitement de la gonococcie

SOMMAIRE

Sur une série de 417 gonococciques (245 hommes et 172 femmes) suivis après traitement, on obtint un taux de guérison de 99 pour cent par l'emploi de 1 g d'ampicilline intra-musculaire suivi, quatre heures après, d'une dose buccale de 2 g d'ampicilline.

Chez les 4 malades ayant rechuté, on isola des souches de *N. gonorrhoeae* relativement résistantes à l'ampicilline ($\text{CMI} \geq 0,16 \mu\text{g/ml}$). Le taux sanguin de l'ampicilline fut mesuré pour six des malades hommes.