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ORAL AMPICILLIN IN UNCOMPLICATED GONORRHOEA

IV. *Comparison of Pharmacological and Clinical Results*

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Abstract. As part of a project designed to investigate the efficacy of oral ampicillin in uncomplicated gonorrhoea, the absorption and excretion of the clinically used dosage forms of oral ampicillin and penicillin G injection have been studied. Twenty-four healthy volunteers (12 of each sex) took part in the study carried out in a cross-over fashion. All conditions were as strictly standardized as possible with the subjects taking the preparations in a fasting state. The following dosage forms were used: 2 g of ampicillin in a single oral dose, the same dose with 1 g of probenecid, 2 g of ampicillin divided into 2 doses at an interval of 5 hours—always in 0.5 g tablets with 100 ml of water. Some of the volunteers were given 2 g of ampicillin with 250 ml of water or as 5% syrup. An intramuscular dose of 2.2 MIU of penicillin G was also tested. Antibiotic concentrations were determined by the cylinder plate method. Ampicillin plus probenecid gave approximately 2–3 times as high serum concentrations (21.2 μg/ml) as the divided dosage, and twice as high as the single oral dose. Increase in the water intake or the use of a syrup did not improve the serum concentrations significantly. The penicillin G injection gave serum concentrations lower than with ampicillin plus probenecid, but higher than with the other dosage forms. The duration of penicillinaemia was considerably longer than with the oral ampicillin dosages. The pharmacological findings are compared with the clinical results, and required serum levels as well as the minimum duration of therapeutical levels are discussed.

In a two-year clinical trial at Södersjukhuset, Stockholm, oral ampicillin in one dose (with or without probenecid) or in two doses has been compared with a single penicillin G injection in treatment of uncomplicated gonorrhoea in both men and women (6, 7). The dosage schemes used are shown in Table I. The clinical results indicate that the treatments differ in efficacy. Treatments B and C were as efficient therapeutically as the routine treatment with penicillin G. On a percentage basis treatment C showed the best result. It is particularly interesting that the model A treatment proved to be less effective than the other three. Since the four different dosage schemes employed could be expected to differ in absorption and excretion, an examination was carried out to study these variables and their relation to the clinical results.

For several reasons it was considered proper to perform these studies on healthy volunteers. For one thing it is difficult to pick out patients randomly from a clinical material and expect them to participate. For another it was considered difficult to establish the same conditions for the different dosages under such circumstances and a cross-over design would not be feasible (14). There is no reason to expect patients with uncomplicated gonorrhoea to deviate from healthy volunteers in respect to absorption, metabolism and excretion. Many conditions such as mobility, age, decreased renal or liver function probably affect pharmacological variables more than does gonorrhoea. Iacobaeus & Wikander (14) have found (for propicillin) a correlation between the age of the patient and the duration of the penicillinaemia. Brandberg & Iwarson (1) found considerably higher serum concentrations of ampicillin in febrile patients confined to bed than had been observed in healthy volunteers. Similar observations have been made by Wahlqvist & Lönell (27) on patients receiving intramuscular injections of ampicillin. They found more elevated (double) and sustained serum concentrations in patients confined to bed than in healthy volunteers, probably due to a slower renal excretion.

In addition to these standardized cross-over studies in healthy volunteers, blood samples are

Table I. *Patients treated for uncomplicated gonorrhoea during July 1967–October 1969 included in the statistical evaluation*

Satisfactory: at least 2 negative follow-up cultures. Treatment failure: positive culture at follow-up no. 1 within 14 days

Patient group	Treatment	Male		Female	
		No. of pat.	Treatment failure (%)	No. of pat.	Treatment failure (%)
G	2.2 MIU of penicillin G intramuscularly (1.0 MIU Na salt + 1.2 MIU procaine salt)	833	3.4	601	3.0
A	2 g of ampicillin orally	341	8.8	276	5.8
B	2 g of ampicillin + 1 g of probenecid orally	329	3.0	251	2.8
C	1 g + 1 g of ampicillin orally with 5 hour interval	343	1.7	273	2.2

now being drawn as a complement from patients receiving ampicillin. In one group, out-patients with uncomplicated gonorrhoea and in another, hospitalized patients with complications such as benign gonococcal septicaemia and monarthritis are included, as well as patients with repeated positive cultures but denying the possibility of reinfection and accordingly hospitalized. As pointed out already, these patients have to be selected non-randomly and may therefore give a somewhat biased picture of the actual clinical situation.

The aims of the absorption and excretion studies may be summarized as follows:

1. To establish if an elevation of the peak serum levels of ampicillin affects the therapeutic result.
2. To establish if a prolongation of the duration of ampicillin serum levels affects the therapeutic result.
3. To establish which relation between MIC and maximum serum concentration could be accepted with clinical effect maintained.
4. To establish if higher serum levels of ampicillin can be attained with ampicillin syrup or with increased water intake.

It can often be difficult to establish a correlation between attained serum levels and clinical results. In some instances one finds paradoxically that a preparation that is effective in clinical use, e.g. in sinusitis and otitis media, can be shown to reach only low concentrations at the actual site of infection (17), while on the other hand clinical effect is often not attained when it should be expected from in vivo studies showing therapeutic levels at the site of infection (2).

In this respect uncomplicated gonorrhoea seems to offer a good clinical model for the evaluation of the efficacy of different antibiotic treatments. It has been shown that the degree of resistance of the infecting gonococcus as well as the attained serum level of penicillin is correlated with the therapeutic result (8, 23).

MATERIAL AND METHODS

Twenty-four healthy volunteers, 12 of each sex, took part. They were selected to correspond to the age distribution of the patients treated for gonorrhoea during the 2 years of investigation. The men were betwen 19 and 40 years and the women between 17 and 35 years. The body weight varied for men between 54 and 87 kg, mean 71 kg, and for women between 51 and 62 kg, mean 56 kg.

The dose schedules were the same as in the earlier study (Table I) and the following preparations were used:

Table II. *Blood serum levels following oral administration of 2 g of ampicillin (dosage form A)*

No. of subjects and sex	Serum levels in μg/ml (Mean ± S.E.)				
	2 hr	3 hr	5 hr	8 hr	12 hr
12 men	8.85 ± 0.93	7.50 ± 0.81	2.42 ± 0.35	0.29 ± 0.049	0.050 ± 0.006
12 women	12.82 ± 1.83	10.02 ± 1.51	3.40 ± 0.65	0.52 ± 0.20	0.073 ± 0.018
Mean	10.84 ± 1.09	8.76 ± 0.88	2.91 ± 0.37	0.40 ± 0.10	0.062 ± 0.010

Table III. *Blood serum levels following oral administration of 2 g of ampicillin and 1 g of probenecid (dosage form B)*

No. of subjects and sex	Serum levels in μg/ml (Mean ± S.E.)				
	2 hr	3 hr	5 hr	8 hr	12 hr
12 men	16.25 ± 1.23	18.29 ± 1.39	9.20 ± 1.04	1.87 ± 0.23	0.36 ± 0.062
12 women	23.96 ± 1.82	24.07 ± 2.04	11.91 ± 1.67	2.48 ± 0.46	0.48 ± 0.11
Mean	20.11 ± 1.34	21.18 ± 1.35	10.54 ± 1.00	2.18 ± 0.26	0.42 ± 0.062

ampicillin: Doktacillin® (Astra Läkemedel AB, Sweden) 0.5 g tablets, operations SL 41 and F 7.

probenecid: Probecid® (Astra Läkemedel AB, Sweden) 0.5 g tablets op. TF 81,

penicillin G: Gonocillin® (AB Leo, Sweden) 2.2 MIU (1.0 MIU sodium pc G + 1.2 MIU procaine pc G) op. T 49585.

The ampicillin tablets were taken with 100 ml of water. Twelve of the volunteers also received 2 g of ampicillin with 250 ml of water and 10 of these volunteers were also given 2 g of ampicillin as a syrup (Doktacillin® Syrup 5%, op. 17).

Before taking the dose the subjects had been fasting overnight and were not allowed to take any food or drink until the three-hour blood sample had been drawn. With the divided dose, food or drink was not allowed 1.5 hours before and 2 hours after the second dose.

Blood samples were drawn from the cubital vein at 2, 3, 5, 8 and 12 hours after the administration of ampicillin. When the divided dose was given a sample was drawn also at 7 hours, i.e. 2 hours after the second dose. From half the group receiving probenecid a blood sample was taken after 24 hours. When ampicillin was given as a syrup, the first blood sample was drawn after 1.5 hours. Following intramuscular administration of penicillin G, blood samples were drawn at 20 and 40 min, 1, 2, 3, 5, 8, 12 and 24 hours. The serum was separated by centrifugation.

Urine samples were collected from all the subjects. They were told to void their urine at 2, 5, 8 and 12 hours after dosing. When ampicillin was given with probenecid or in a divided dose and when penicillin G was given, the urine voided between 12 and 24 hours after dosing was also collected.

All the serum and urine specimens were, if not analysed immediately, stored in a freezer at −20°C.

Antibiotic concentrations were determined by the cylinder plate method with Sarcina lutea ATCC 9341 as test organism (11). The solutions of ampicillin and penicillin G were prepared in pooled human serum, using the concentrations 1–0.03 μg/ml (in a two-fold serial dilution) of the standard curve. The serum samples to be assayed were diluted in pooled human serum to give a concentration within the range of this standard curve. However, if the concentrations in the serum samples were so high that a dilution of 20 times or more was required, the dilution was performed in Sörensen's phosphate buffer, pH 7.0, and compared against a standard in the same diluent. At these high dilutions the serum binding of the penicillins to albumin is negligible. The urine specimens were diluted and assayed against a standard in Sörensen's phosphate buffer, pH 7.0.

RESULTS

The absorptions of ampicillin following oral administration according to the dose schedules used in the clinical trial is shown in Tables II–IV and Figs. 1–2. As can be seen from the figures, the corresponding concentration curves for men and women are almost parallel. Men have throughout lower values than women, 29% lower on average with the single dose of 2 g and 15% lower with the divided dose. The simultaneous medication with probenecid increases the serum levels giving 12-hour values of about the same level as the 7–8 hour values without probenecid (0.4 μg/ml). The divided dose also gives a 12-hour value of the same magnitude.

Table IV. *Blood serum levels following oral administration of 2 g of ampicillin in a divided dose with an interval of 5 hours (dosage form C)*

No. of subjects and sex	Serum levels in μg/ml (Mean ± S.E.)					
	2 hr	3 hr	5 hr	7 hr	8 hr	12 hr
12 men	6.12 ± 0.86	5.39 ± 0.74	2.39 ± 0.44	7.32 ± 0.88	5.06 ± 0.60	0.33 ± 0.056
12 women	7.24 ± 0.78	6.26 ± 0.72	2.27 ± 0.35	9.24 ± 1.23	5.97 ± 0.69	0.43 ± 0.068
Mean	6.68 ± 0.58	5.82 ± 0.51	2.33 ± 0.28	8.28 ± 0.77	5.51 ± 0.46	0.38 ± 0.042

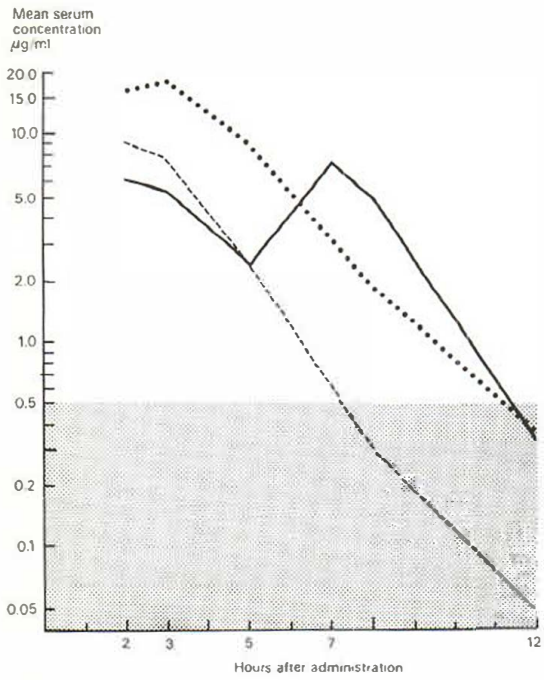

Fig. 1. Mean blood serum levels in 12 men following administration of 2 g of ampicillin orally. – – –, 2 g ampicillin (A); · · ·, 2 g ampicillin + 1 g probenecid (B); —, 1 g + 1 g ampicillin (C).

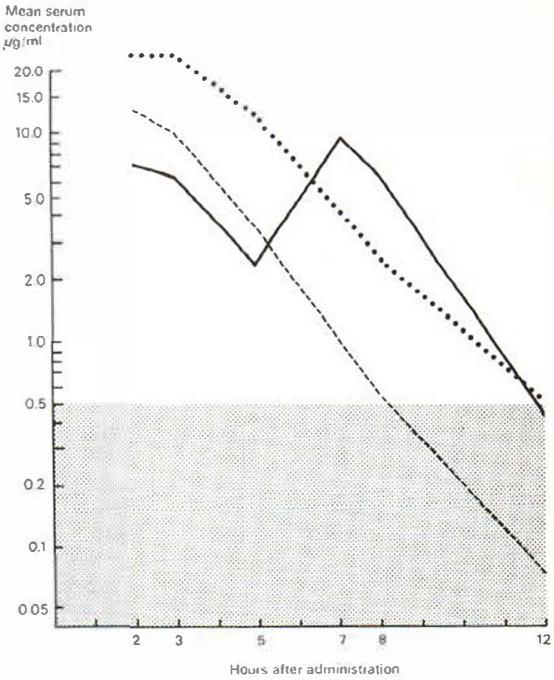

Fig. 2. Mean blood serum levels in 12 women following administration of 2 g of ampicillin orally. – – –, 2 g ampicillin (A); · · ·, 2 g ampicillin + 1 g probenecid (B); —, 1 g + 1 g ampicillin (C).

The relative difference between men and women in the amount of ampicillin excreted in urine during the first 12 hours after administration is less pronounced: 6.2% lower for men with the single doses of 2 g and 10.0% less with the divided dose. The results in the subjects receiving the 2 g of ampicillin with an increased water intake (250 ml) and as syrup are given in Table V.

These alternatives do not give any better absorption. The small differences observed are not statistically significant ($P > 0.05$). The cumulative percentage of urinary excretion is shown in Table VII and in Fig. 3. The amount of penicillin found in urine after the administration of 2 g of ampicillin as syrup or as tablets with 250 ml of water does not differ significantly from the amount found when 2 g of ampicillin is given as tablets with 100 ml of water.

Individual and mean serum levels in subjects receiving penicillin G are shown in Table VI. Lower serum concentrations were reached in women than in men. In Fig. 4 the serum levels of penicillin G are compared with the levels of ampicillin in the same 7 subjects. The ampicillin

Table V. *Blood serum levels following oral administration of 2 g of ampicillin: (a) tablets with 100 ml of water, (b) tablets with 250 ml of water, and (c) as a syrup*

No. of subjects (♂+♀)	Time in hours after administration (Mean ± S.E.)					
	1.5 hr	2 hr	3 hr	5 hr	8 hr	12 hr
(*a*) 6+6	—	11.26 ± 1.98	7.80 ± 1.22	2.40 ± 0.40	0.30 ± 0.056	0.051 ± 0.009
(*b*) 6+6	—	13.81 ± 1.65	9.63 ± 1.42	2.72 ± 0.72	0.30 ± 0.060	0.066 ± 0.015
(*c*) 5+5	10.83 ± 1.15	9.81 ± 0.85	6.93 ± 0.83	1.80 ± 0.31	0.28 ± 0.048	0.048 ± 0.008

Table VI. *Blood serum levels in μg/ml following intramuscular administration of 0.6 g (1.0 MIU) sodium and 1.2 g (1.2 MIU) procaine penicillin G (dosage form G)*

Sex	20 min	40 min	1 hr	2 hr	3 hr	5 hr	8 hr	12 hr	24 hr
Female	8.19	9.12	8.11	4.76	3.19	1.68	0.90	0.75	0.55
Female	9.04	14.14	11.64	4.81	2.66	1.05	0.46	0.44	0.40
Female	7.38	10.76	10.34	5.25	2.55	0.88	0.44	0.29	0.43
Male	18.57	12.59	9.43	4.95	5.10	2.92	2.01	0.80	0.035
Male	17.42	15.77	12.89	8.50	4.61	3.46	2.10	0.63	0.11
Male	14.60	10.70	7.77	3.65	3.65	3.12	1.49	0.53	0.033
Male	19.60	14.79	10.48	6.78	4.03	2.56	0.99	0.71	0.20
Mean ± S.E.	13.54 ±1.98	12.55 ±0.93	10.09 ±0.69	5.53 ±0.61	3.68 ±0.36	2.24 ±0.39	1.20 ±0.26	0.59 ±0.069	0.25 ±0.079

curves following therapy with probenecid or divided dose intersect the penicillin G curve at 11–12 hours. The level of penicillin G in serum at 24 hours is 0.25 μg/ml. Out of twelve 24-hour samples of ampicillin in connection with probenecid only one gave a measurable concentration, of 0.038 μg/ml. The rest were below 0.025 μg/ml. The cumulative percentage of urinary excretion of penicillin G is given in Table VII. As expected, the penicillin G excretion is higher than that of ampicillin, even if it is slower.

DISCUSSION

For several years the penicillin treatment of gonorrhoea was carried out with preparations that give a prolonged serum level, e.g. procaine penicillin G, (but a lower peak concentration) as compared with the sodium salt of penicillin G, which had to be given in repeated doses. With the increasing emergence of less sensitive gonococcal strains interest was focused on achieving higher peak serum levels. One method has been to combine procaine penicillin G with sodium penicillin G (16). The result of this is an increase in the serum-peak and a considerably higher penicillinaemia for more than 3 hours.

Knudsen et al. (22) have shown a linear dose–response relation for the 2 hour serum levels of ampicillin doses from 250 mg to 1 000 mg. It has not been possible to show such a linear relationship between 1 and 2 g doses in this study. A tentative explanation of this phenomenon is some kind of absorption threshold. This is supported by the fact that the comparatively low peak levels correspond to a low urinary excretion, 29% in 12 hours with 2 g of ampicillin and 36% during the same time with the divided dose. It is a well-known fact that the urinary excretion is smaller when probenecid is added (21).

The higher serum levels in women than in men receiving oral ampicillin may partly be due to the lower body weight of women, whose mean weight is 21% less than that of men. On the

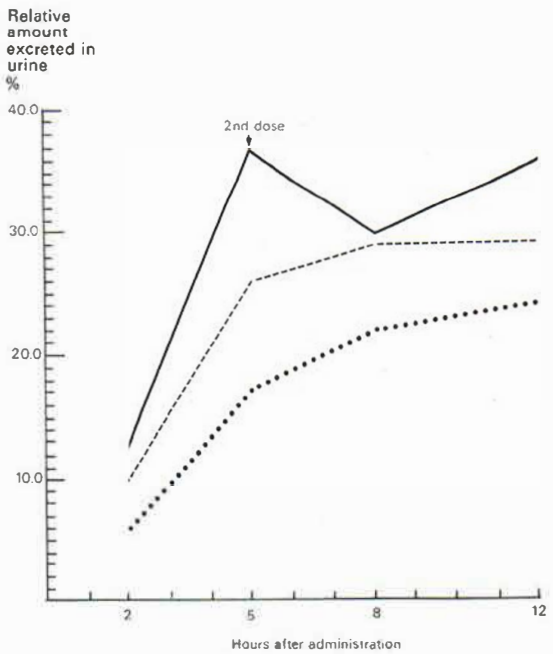

Fig. 3. Mean cumulative percentage of urinary excretion in 24 volunteers following administration of 2 g of ampicillin orally. – – –, 2 g ampicillin (A); · · ·, 2 g ampicillin + 1 g probenecid (B); —, 1 g + 1 g ampicillin (C).

Table VII. *Cumulative percentage of urinary excretion at different times after administration*

In group G 3 women and 4 men. In each of groups A, B and C 12 women and 12 men

Treatment group	Sex group mean	Hours after administration (Mean ± S.E.)				
		2	5	8	12	24
G	Mean	37.2 ± 4.7	50.5 ± 5.4	58.1 ± 7.3	63.5 ± 8.1	69.0 ± 7.8
A	♀	11.9 ± 1.3	24.6 ± 2.6	28.7 ± 2.8	28.1 ± 2.6	—
	♂	8.9 ± 1.1	27.2 ± 4.1	29.2 ± 4.2	30.3 ± 4.6	—
	Mean	10.5 ± 0.9	25.8 ± 2.3	28.9 ± 2.4	29.1 ± 2.5	—
B	♀	5.8 ± 0.7	20.2 ± 1.2	24.6 ± 1.5	26.7 ± 1.7	27.2 ± 1.7
	♂	5.0 ± 0.9	14.2 ± 2.2	19.3 ± 2.5	21.3 ± 2.7	22.4 ± 3.0
	Mean	5.4 ± 0.6	17.2 ± 1.4	21.9 ± 1.5	23.9 ± 1.7	24.8 ± 1.8
C	♀	12.6 ± 1.8	37.3 ± 3.9	—	37.8 ± 2.9	—
	♂	11.8 ± 2.2	35.3 ± 4.5	—	34.0 ± 4.0	—
	Mean	12.2 ± 1.4	36.3 ± 2.9	—	35.8 ± 2.5	—

other hand the lower serum levels of penicillin G in women may be due to different fat depositions in the gluteal region in men and women (16).

The number of volunteers presented in Fig. 4 may seem small. A comparison of Figs. 1, 2 and 4 shows that the serum levels of these 7 persons are representative for all 24 volunteers taking part in this study in respect of ampicillin absorption. On the other hand it can be seen from Table VII that the dispersion of the penicillin G values is small. The serum levels of the penicillin G preparation in this study are comparable, on average, to data published earlier (16).

The addition of probenecid either to the earlier

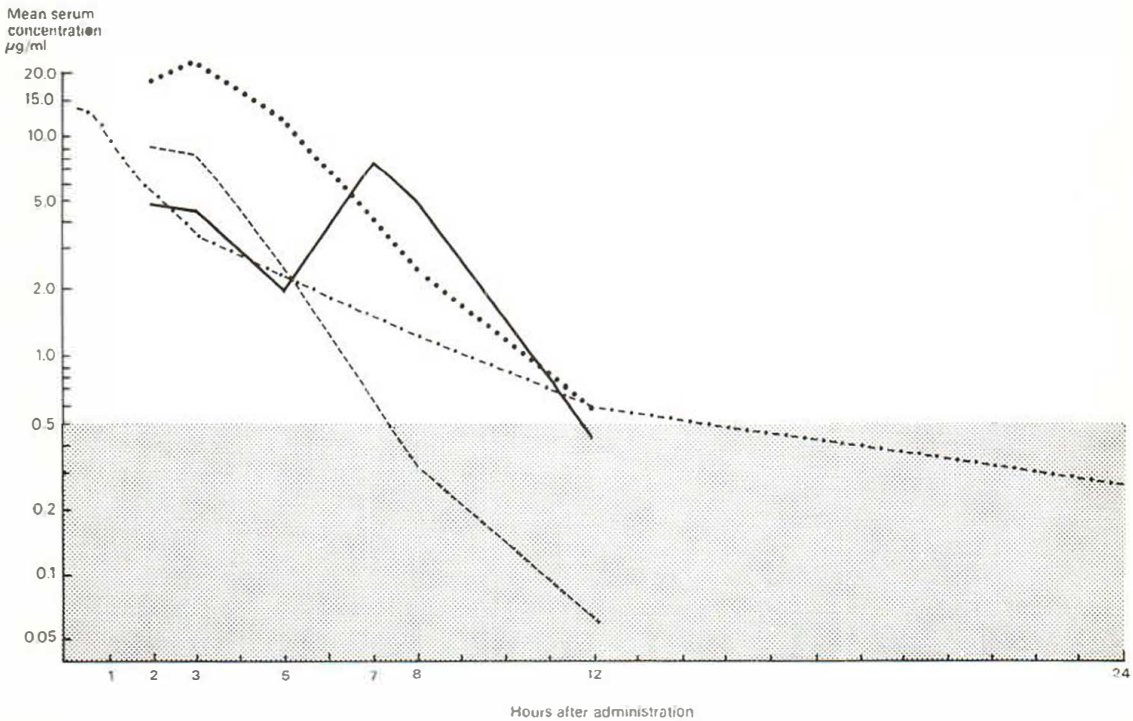

Fig. 4. Mean blood serum levels in 7 volunteers following administration of 2.2 MIU penicillin G intramuscularly and 2 g of ampicillin orally with or without probenecid. -·-, 2.2 MIU sodium- and procaine-penicillin (G); – – –, 2 g ampicillin (A); ···, 2 g ampicillin + 1 g probenecid (B); —, 1 g + 1 g ampicillin (C).

used procaine penicillin G salt, to the sodium salt or to a combination of the type mentioned above has gained increasing interest (3, 7, 13, 15, 18, 26). This addition gives a higher and more sustained penicillinaemia. Cobbold et al. (3) have achieved significantly better results with the addition of 1 g probenecid to 1.2 MIU of procaine penicillin G. Olsen & Lomholt (25) have had excellent results with intramuscular injection of 5 MIU of sodium penicillin G plus 1 g of probenecid orally in Greenland, where as much as 54% of the gonococci were less sensitive to penicillin G. Similarly good results were achieved by Johnson et al. (15) in the Philippines. As these large volumes are unattractive and as the injection therapy has other disadvantages (6), oral ampicillin regimens have been investigated as alternatives (6, 7, 10, 12, 15, 28).

As compared with oral penicillin V and G the blood levels of ampicillin rise more slowly (20), reaching a peak at 2 or 3 hours rather than at $^1/_2$ to 1 hour, and thereafter show a much slower decrease. Ampicillin seems to have an inherent property of slow absorption from the intestinal tract. Kirby (19) suggests that the very good results with oral ampicillin in the treatment of gonorrhoea may be associated with the more prolonged blood-levels achieved with ampicillin as compared with other oral penicillin.

Adequate dosage with penicillin depends on at least two factors. One is the concentration attained at the site of infection and the other is the total time for which that concentration is provided.

According to Eagle (4) the rate at which bacteria die under the impact of penicillin *in vitro* is independent of its absolute concentration, provided only that the latter is in excess of the level which, in vitro, kills the particular organism at the maximal rate. Large doses of penicillin in vivo are more effective than smaller doses primarily because of the longer time during which they provide that effective concentration (4). Widely disparate but equi-effective curative doses have in common the fact that in a given infection they provide the effective concentration of penicillin for essentially the same total period of time (4). It is therefore essential to take into consideration both the minimum efficient concentration, MEC; and the minimum efficient duration, MEDu, of penicillin in serum or any other pertinent body fluid or tissue.

Importance of maximum serum levels

Eagle (5) showed that the penicillin G concentration which killed staphylococci and pneumococci at a maximal rate was 2 to 20 times the MIC and that paradoxically a further increase of the concentration could reduce the rate at which the organisms died.

For the treatment of gonorrhoea, penicillin serum levels of the magnitude of 2, 3 or 5 times the MIC have been advocated (9) and there seems to be substantial support for this (23).

From Fig. 4 it can be seen that the mean serum concentrations are high in comparison with the MIC-values reported for most gonococcal strains isolated in Europe (MIC < 0.1 μg ampicillin/ml or IU penicillin G/ml; one IU penicillin G $\approx$ 0.6 μg).

In Fig. 4, the area under the highest MIC for ampicillin observed in the therapeutic trial (0.5 μg/ml) is indicated. Only 4 patients out of 1 434 treated with penicillin G harboured gonococcal strains with an MIC above this value; therefore in the discussion this value can be accepted as a suitable upper limit of resistance even for penicillin G in the clinical material.

The observed differences in maximum serum levels between the different dosage forms do not seem to be correlated with the clinical efficacy since treatment A, which is the least effective of the four treatments therapeutically, gives higher levels than treatment C, which seems to be the most effective one. In view of the clinical results it seems that the maximum levels in the patients have been well above what is needed with the resistance pattern encountered in this therapeutic study.

Though the therapeutic margin with the ampicillin treatments B and C is unknown it seems to be better than that with the penicillin G treatment judging from the therapeutic efficacy in patients harbouring less sensitive gonococci (8). It would be interesting to test the same doses and larger in patients harbouring strains even more resistant to penicillin.

In cases with strains of N. gonorrhoeae which fail to respond to penicillin treatment, serum levels may not be the only important factor controlling the eradication of infection. Concentrations in tissues, urine and prostatic fluid (among other factors) may also be of importance (24).

Duration of therapeutic concentrations in serum

From Fig. 4 it can be seen that the mean serum concentration—in the standardized absorption study—is well above the limit of 5 times the MIC for fully sensitive gonococci for treatments G, B and C even after (9–)12 hours, whereas the duration for treatment A is considerably shorter at these levels. This could clearly be correlated with the clinical results, showing treatment A to be significantly less effective than the others in infections with fully sensitive gonococcal strains.

It seems that the time span between 5 and 12 hours is of crucial significance since the less effective treatment A cannot be said to give lower serum levels than treatments G or C before this time and after 12 hours the concentrations taper off rather quickly with treatments B and C, whereas the procaine salt of the penicillin G gives a slowly decreasing curve extending beyond 24 hours.

Clinically, the less sensitive strains of gonococci were killed to a lesser extent by the penicillin G treatment than by treatments B and C, though this was statistically significant only for C (8). This difference cannot be explained entirely by the marginal difference in MIC values of these strains of gonococci for the two penicillins (8). As can be seen from Fig. 4, treatments B and C give higher serum levels than treatment G between 5 and 11 hours. This also indicates that the MEDu of penicillinaemia lies somewhere between 5 and 12 hours. Fig. 4 also shows that there is a differentiation between the three acceptable treatments (with regard to serum levels), this being most obvious at 7–8 hours.

This differentiation is in accordance with the tendency in the clinical material and points to the MEDu being 7–8 hours. After 7–8 hours the serum levels with treatment A falls below the critical value of 5 times the MIC for some of the fully sensitive gonococcal strains. The clinical part of this investigation shows that adequate in vivo concentrations of ampicillin can be reached with treatments B and C. The "clinical" concentrations and MEDu may have been overestimated to some extent in the standardized absorption studies. This may be particularly true of patients with generally disturbed gastrointestinal absorption and also of patients who have eaten shortly before or after they take their ampicillin dose. On the other hand, Klein & Finland (21) did not notice any significant difference in serum concentrations with the same dose given during fasting or immediately after breakfast even if the levels were higher in most subjects 2 hours after the fasting dose.

The results from the absorption studies in non-fasting patients with uncomplicated gonorrhoea obtained up to now seem to confirm that the "clinical" concentrations are somewhat lower than the concentrations attained in this standardized trial, but at the same time seem to support the theoretical considerations concerning the MEDu postulated in this paper.

CONCLUSIONS

The answers to the questions put forward in the introduction may be summarized as follows:

1. It has been established that treatment B gives approximately 2–3 times as high ampicillin serum concentrations as treatment C without being therapeutically more effective. This indicates that the latter treatment has given satisfying ampicillin concentrations and any further increase of the absolute concentration does not seem to improve the result in patients harbouring gonococci sensitive to $\leqslant 0.5$ μg ampicillin/ml.

2. A considerable prolongation of the duration of ampicillin serum levels is achieved by the addition of probenecid to a single oral ampicillin dose or when this dose is divided into two with a 5-hour interval. This prolongation has been shown to be of therapeutic importance and the overall results point to a MEDu (minimum effective duration) of 5–12 and most probably 7–8 hours.

3. From these investigations it is not possible to establish any theoretical minimum ratio between MIC and maximum serum concentration. Nevertheless, the given data, together with preliminary data from absorption studies in patients, seem to support the validity of the earlier postulated ratio of 2–5 times the MIC.

4. A water intake of 100 ml seems to be satisfactory for the administration of ampicillin in tablet form. A further increase of the water intake or an administration in syrup form does not seem to give any further clinical advantage.

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