Oral ampicillin in gonorrhoea

Clinical evaluation

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THE standard treatment of uncomplicated gonorrhoea in Sweden is a mixture of 1 million units benzylpenicillin G and 1.2 million units benzylpenicillin procaine G. With this treatment, therapeutic failure has been very rare (Krook and Juhlin, 1965; Gip, Lodin, Molin, and Nyström, 1968).

On account of its simpler administration and smaller risk of fatal allergic reactions (Idsøe and Guthe, 1968), oral treatment, when it has produced similarly good therapeutic results, has replaced injections for many infectious diseases. Several oral penicillin derivatives have been tested in gonorrhoea, but when the desirability of treatment of short duration is taken into account, these agents have not given satisfactory results (Willcox, 1968), with the exception of ampicillin, which has been found effective in men (Willcox, 1963; 1964a, b, 1965, 1966; Alergant, 1963; Marmell, Sills, Brown, and Prigot, 1964; Heinemann and Vinikoff, 1965, 1968; Reyn and Bentzon, 1968; Ødegaard, 1962).

Evaluation of the results of treatment of gonorrhoea is partly vitiated by the default rate, and also by the problem of distinguishing re-infection from treatment failure.

In a recent survey of follow-up examinations in cases of gonorrhoea in our venereal diseases clinic, it was possible to establish that 96 per cent. of all the patients seen during the 5-year period 1963 to 1967 attended for the stipulated number of examinations (Groth, Hallqvist, and Brundin, 1969). This figure seems to be substantially higher than those hitherto reported. Moreover, in most of the cases of post-treatment gonorrhoea, analysis of the route of infection usually determined whether re-infection or treatment failure had occurred. Consequently, it appeared to us that the conditions were particularly favourable for making a comparative investigation between results in cases treated by the above-mentioned standard method and by the oral administration of ampicillin. This investigation includes women patients.

Material and methods

The first series included 53 male patients who were treated orally with ampicillin in a dose of 0.5 g. given twice in one day, at an interval of 5 hours; 26 patients were given both doses at the clinic, a second urethral sample being taken immediately before the second dose, and the remaining 27 patients took the second dose without supervision 5 hours after the first dose.

The second and principal series comprised 311 patients (208 men and 103 women) with uncomplicated gonorrhoea who have attended the clinic during the past 2 years (Table I). They were given 1 g. ampicillin orally twice in one day at an interval of 5 hours (total dose 2 g.).

TABLE I *Initial diagnosis of gonorrhoea in main series of 311 cases treated with two doses of 1 g. ampicillin in one day*

Sex	Total	Positive findings		
		Culture and smear	Culture only	Smear only
Male	208	180	15†	13
Female*	103	36	62†	5

*27 females showed positive rectal cultures.

†Includes cases in which smears were suspicious but treatment was postponed until results of culture were available.

For comparison we collected a series consisting of 250 men and 250 women with gonorrhoea, who, during the same period or shortly before, had received the uniform treatment with 1 million units benzylpenicillin G combined with 1.2 million units benzylpenicillin procaine G given intramuscularly in one injection.

Follow-up tests consisted of at least two sets of smears and cultures from the urethra in men and two from the urethra, cervix, and rectum in women. From a previous investigation we knew that with these methods the risk of failing to recognize a case of treatment failure was less than 0.5 per cent. (Groth and others, 1969). However, as is shown in Table II (overleaf), with regard to the main series treated with ampicillin, most of the patients underwent additional follow-up tests.

Cases in which the presence of gonorrhoea could again be established after treatment were divided into three groups, based on the following criteria:

TABLE II *Follow-up examinations in 301* of the 311 cases in the main series treated with two doses of 1 g. ampicillin on the same day*

Sex	No. of follow-up examinations						No. of cases
	0	1	2	3	4	5	
Male	6	6	59	119	11	1	202
Female	1	2	15	46	7	28	99 } 301

*The ten patients who became positive during the follow-up period are shown in Table VI

TREATMENT FAILURE

Patients with positive specimens in the first follow-up examination who denied having renewed sexual intercourse.

RE-INFECTION

Patients with one or more sets of negative test results before results became positive again and who admitted renewed intercourse.

DOUBTFUL

The remaining patients whose results had become positive after treatment.

This terminology has been used in all the series.

Besides this schematic classification, all the cases still positive after treatment with ampicillin were further analysed to elucidate possible routes of infection. This investigation was greatly helped by the fact that our patients came from a settled population and were co-operative.

The age distribution of patients in the penicillin-treated series and in the ampicillin-treated series were in good agreement, showing the now usual predominance of persons under 25 years of age.

Diagnosis

For the men, specimens were taken from the urethra, and for the women, from the urethra, cervix, and rectum. Diagnosis was established by smears, culture, or both. The smears were stained with Löffler's methylene blue.

For culture, Stuart's transport medium was used, and within at most 16 hours the swabs were streaked on plates containing McLeod's medium with the addition of polymyxin and spontin. Oxidase-positive cultures were Gram-stained, and fermentation tests, with phenol red as the indicator, were carried out on plates with glucose, laevulose, maltose, and saccharose.

Sensitivity tests of the gonococci were routinely carried out by the disc method (Ericsson, 1960). All strains showed sensitivity to benzylpenicillin up to 0.1 I.U. per ml. serum.

Results

In the first series, consisting of 53 male patients who were treated twice with 0.5 g. ampicillin with a 5-hour interval (total dose 1 g.), there were two definite treatment failures (Table III). Like the three cases of re-infection from the original source, the patient designated as 'doubtful' could, after careful investigation be classified as a definite rebound infection, whereas the fourth re-infected case derived the infection from some other source (Table IV, opposite).

Of the samples taken 5 hours after the first dose of 0.5 g. ampicillin had been administered to 26 of the patients, in nearly half gonococci were present in the smears, and in about one-third culture was positive (Table V).

TABLE V *Smears and cultures for gonococci in first series of 53 men 5 hours after oral treatment with 0.5 g. ampicillin*

Results	No. of cases	
Negative smears and cultures	12	} 26
Positive smears	6	
Positive cultures	2	} 8
Positive smears and cultures	6	

TABLE III *Results of treatment with oral ampicillin compared with intramuscular penicillin, by sex*

Sex	Treatment	No. of cases		Cases positive during follow-up period					
		Treated	Followed	Re-infected		Doubtful		Failure	
				No.	Per cent.	No.	Per cent.	No.	Per cent.
Male	Ampicillin 0.5 g. × 2	53	53	4	7.5	1	1.9	2	3.8
	1 g. × 2	208	196	5	2.6	1	0.5	0	0
	Benzyl penicillin G 1 m.u. + benzyl procaine penicillin G 1.2 m.u.		250	10	4.0	7	2.8	3	1.2
Female	Ampicillin 1 g. × 2	103	100	3	3.0	1	1.0	0	0
	Benzyl penicillin G 1 m.u. + benzyl procaine penicillin G 1 - 1.2 m.u.		250	13	5.2	10	4.0	1	0.4

TABLE IV Seven cases in which gonococci were demonstrated during the follow-up period in the series of 53 male patients treated with two oral doses of 0.5 g. ampicillin in one day

Case no.	Day after treatment									Source of infection (retrospective analysis)
	1	3	5	7	9	11	13	21	25	
8	+									Treatment failure
45		+								Treatment failure
43					C				+	Usual, still untreated partner
11		—	C	+						Infected, but still untreated female partner
14		—C		+						Usual, still untreated partner
23		—		C		+				Usual, still untreated partner
53		—			—	C		+		Usual, still untreated partner

C = intercourse, + = positive sample, — = negative sample (smear and culture)

In the main series, comprising 311 cases treated with 1 g. ampicillin twice at an interval of 5 hours (total dose 2 g.), twelve men and three women (4.8 per cent.) did not return for the required number of follow-up tests (Table II). In the case of six of the remaining 196 men and in four of the 100 women, genital tests for the gonococcus became positive again after treatment (Table III). All these patients admitted renewed coitus; two of them must be described as 'doubtful' according to our criteria whereas eight could be accepted as re-infections.

A more detailed analysis of the ten cases in the main series which were positive after treatment (Table VI) showed that one of the two considered to be doubtful had since had intercourse with his

untreated consort. The other patient admitted coitus with two unknown men and possibly also with her usual partner between treatment and the first follow-up investigation 12 days later. Of the eight remaining positive cases, three were established as rebound infections, and the other five admitted renewed coitus. Four of their partners were strongly suspected of infection, and the fifth patient had intercourse with a new partner after two negative tests.

Six of the patients with positive findings at follow-up tests were treated again with the same dose, 1 g. ampicillin given twice at an interval of 5 hours, and were then cured. The remaining two men and two women received a different kind of treatment.

TABLE VI Ten cases in which gonococci were demonstrated during the follow-up period in the main series of 311 patients (208 males and 103 females) treated with two oral doses of 1 g. ampicillin in one day, by sex

Sex	Case no.	Day after treatment								Source of infection (retrospective analyses)
		5	10	15	20	25	30		55	
Male	44	—			C	+				Usual, still untreated partner
	56	—		C		+				Probably repeated contacts with usual partner (slept in same bed)
	89	—	—C			+				Unknown partner
	92	C—	C	+						Untreated female, already regarded as infection source
	103	—	C	+						Infected, but still untreated female
	130	C	+							Usual, still untreated partner
Female	12	—		—	C			—	+	South American waiter in Spain
	29	—	C			+				Usual partner, infected but still untreated
	34		—				C		+	Infected, but still untreated male
	35	C	C	+						Two unknown males, possibly usual ordinary partner also

C = intercourse, — = neg. test (smear and culture), + = pos. test (culture and in 7 cases, smear also).

No treatment failure was found among the 27 women in whom gonococci were demonstrated in the rectum.

For comparison, the results of treatment with the standard intramuscular penicillin dosage are presented in Table III. Among 250 males followed there were three instances of treatment failure (1.5 per cent.) ten of re-infection (4 per cent.), and seven 'doubtful' (2.8 per cent.). Corresponding figures for the 250 female cases were one (0.4 per cent.), thirteen (5.2 per cent.), and ten (4 per cent.).

Discussion

A necessary condition for obtaining good therapeutic effects in gonorrhoea appears to be that the preparation or combination of preparations used should give, in the first place, a high concentration of penicillin in the serum (Krook and Juhlin, 1965). The duration seems to be of less importance. Slow elimination of penicillin, with a subtherapeutic serum concentration persisting for several weeks, may contribute to an increased frequency of resistant strains of gonococci (Bøggild, 1965; Olsen and Lomholt, 1968).

Ampicillin, which is acid-stable and undergoes relatively less protein-binding in plasma compared with other penicillins, gives a high blood concentration, greatest within 1 to 3 hours after a single oral dose, and decreases to an immeasurably small quantity after 6 to 8 hours (Stewart, 1965). A high urinary concentration is also obtained during the same period (Knudsen, Rolinson, and Stevens, 1961).

The maximum serum concentration obtained with 1 g. ampicillin corresponds approximately to that obtained with the standard treatment of 1 million units benzylpenicillin G and 1.2 million units benzylpenicillin procaine G. With the two doses of 1 g. ampicillin administered in this investigation, two such peaks were obtained, but not the longer duration of therapeutic concentration in the serum that was achieved with the standard treatment (Krook and Juhlin, 1965). Of the authors who tested one dose of 1 g. ampicillin, Alergant (1963) reported only 5 per cent. treatment failures in a group of 200 patients, but did not state how many of the patients were followed-up. In other investigations in which single doses of 1 g. ampicillin were given, treatment failure was reported to vary between 7 and 16 per cent., but it should be pointed out that the variations are partly due to the fact that different criteria for re-infection or treatment failure were used. In a series comprising 153 patients treated with 2 g. ampicillin in two doses (each of 1 g.), the failure rate was stated to be between 4.5 and 11.8 per cent.

(Willcox, 1965); these figures agree with those for the control cases in which a single injection of 1 to 2 mega units procaine penicillin had been given.

In our investigation, one oral dose of 0.5 g. ampicillin did not prove satisfactory; even when the dose of 0.5 g. was repeated after 5 hours the result was unsatisfactory. In the main series, consisting of 311 male and female patients treated with 1 g. ampicillin in two doses (total 2g.) at an interval of 5 hours, the results were very good in both sexes. There was no definite case of treatment failure; and in the two cases designated as doubtful, reinfection was probable. The doubtful cases and the treatment failures in our control series of cases treated with intramuscular penicillin do not necessarily mean that this form of treatment is therapeutically inferior; some of the cases were studied before the ampicillin investigation, and it is probable that some of the presumed failures might have been shown to be re-infections if a more detailed analysis had been made. We emphasize that, in both the ampicillin series and the penicillin control series, all gonococcal strains encountered were sensitive to penicillin, as shown by the disc method, which is that mainly used in Sweden (Ericsson, 1960).

If certain criteria used by previous authors (including Willcox, 1965) are applied to our cases treated with 1 g. ampicillin in two doses the following results are obtained:

- (a) Recurrences in patients followed who denied intercourse: 0 per cent.
- (b) Recurrences in first week in patients followed: males 0.5 per cent. and females 1.0 per cent.
- (c) Recurrences in first week in patients treated: males 0.5 per cent. and females 1.0 per cent.

When the corresponding criteria are applied to cases in our control series, slightly higher percentages are obtained.

To evaluate the therapy of gonorrhoea adequate follow-up is essential. The difficulty of persuading patients to undergo sufficient examinations is a serious problem in most investigations. Even in the virtually 'enclosed' group investigated in Greenland by Olsen and Lomholt, 7 per cent. of the patients did not return for even one follow-up examination. Reports of the default of patients treated with ampicillin have varied between 8 per cent. (Willcox) and just over 50 per cent. (Marmell and others, 1964). In the present series, more than 95 per cent. of the patients were examined after treatment by means of at least two sets of smears and cultures.

It would be an advantage if only one dose of ampicillin could be given and that under supervision; investigations with this aim in view are in progress. For this, a combination of ampicillin and oral

probenecid is being used; but a disadvantage is that the risk of side-effects is increased when two different preparations are used. Moreover, our experience indicates that there is no difficulty in persuading the patients themselves to take the second ampicillin dose. With men this is probably explained by the fact that the subjective symptoms have rarely ceased by the end of 5 hours when the second dose is due.

The purpose of this investigation was to evaluate oral ampicillin treatment in gonorrhoea because of its ease of administration and the smaller risk of side-effects as compared with parenteral penicillin treatment as at present recommended. Special efforts were made to analyse the cases of post-treatment gonorrhoea so as to determine the true frequency of treatment failure, and it was found that supposed treatment failures were more often re-infections. The amount of promiscuity within an infected population during the follow-up period was notable.

On the basis of our results of treatment with ampicillin in two doses of 1 g. given at an interval of 5 hours, and taking into account the advantages of oral therapy, we find this schedule to be the treatment of choice in cases of uncomplicated gonorrhoea, but we emphasize that our experience is limited to cases due to gonococci sensitive to penicillin.

Summary

311 male and female patients suffering from uncomplicated gonorrhoea were treated with ampicillin, administered orally in two doses of 1 g. given at an interval of 5 hours. 95 per cent. of patients were followed after treatment and underwent at least two examinations by smears and cultures. Gonococci were still present in six of the 208 male cases and in four of the 103 female cases. A detailed analysis revealed that these ten patients had probably all become re-infected. The therapeutic success rate, using different methods to determine failure, was 99–100 per cent.

In a control series of 250 men and 250 women, it was also found that recurrences were largely due to re-infection. Patients in this series received the standard treatment for uncomplicated gonorrhoea recommended in Sweden, namely, one intramuscular injection of a mixture of 1 million units of benzylpenicillin G and 1·2 million units of benzylpenicillin procaine G. Maximum failure rates, based on the sum of cases of proven failure and 'doubtful' cases were 4 per cent. among men and 4·4 per cent. among women, but less stringent efforts to elucidate the 'doubtful' cases had been made in some instances.

We now prefer ampicillin in two doses of 1 g. to the above-mentioned standard treatment of uncomplicated gonorrhoea, but we emphasize that

our experience is limited to infections with gonococci sensitive to penicillin by the *in vitro* test.

The Ampicillin (Doctacillin ®) used in this trial was supplied by Astra.

References

- ALERGANT, C. D. (1963). *Brit. J. vener. Dis.*, **39**, 225.
 BØGGILD, J. (1965). *Ugeskr. Laeg.*, **127**, 483.
 ERICSSON, H. (1960). *Scand. J. clin. Lab. Invest.*, **12**, Suppl. 50.
 GIP, L., LODIN, A., MOLIN, L., and NYSTRÖM, B. (1968). *Svensk. Läkartidn.*, **65**, 1226.
 GROTH, O., HALLQVIST, L., and BRUNDIN, G. (1969). *Ibid.*, **66**, 912.
 HEINEMANN, S., and VINIKOFF, M. R. (1965). *Med. Tms (N.Y.)*, **93**, 290.
 IDSØE, O., and GUTHE, T. (1968). In 'Antibiotic Treatment of Venereal Diseases', ed. A. Luger, p. 168. ('Current Problems in Dermatology', vol. 2). Karger, Basel.
 KNUDSEN, E. T., ROLINSON, G. N., and STEVENS, S. (1961). *Brit. med. J.*, **2**, 198.
 KROOK, G., and JUHLIN, I. (1965). *Acta dermat.-venereol. (Stockh.)*, **45**, 242.
 MARMELL, M., SILLS, J. R., BROWN, C. D., and PRIGOT, A. (1964). *N. Y. St. J. Med.*, **64**, 985.
 McLONE, D. G., BILLINGS, T. E., HARDEGREE, W. E., and HACKNEY, J. F. (1968). *Sth. med. J. (Bgham, Ala.)*, **61**, 287.
 ØDEGAARD, K. (1962). *Brit. med. J.*, **1**, 645.
 OLSEN, G. A., and LOMHOLT, G. (1968). *Ugeskr. Laeg.*, **130**, 1465.
 REYN, A., and BENTZON, M. W. (1968). *Brit. J. vener. Dis.*, **44**, 140.
 STEWART, G. T. (1965). 'The Penicillin Group of Drugs'. Elsevier, London.
 Willcox, R. R. (1963). *Brit. J. vener. Dis.*, **39**, 164.
 — (1964a). *Ibid.*, **40**, 261.
 — (1964b). *Postgrad. med. J.*, Suppl. **40**, p. 202.
 — (1965). *Brit. J. clin. Pract.*, **19**, 689.
 — (1966). *Clin. Med.*, **73**, no. 6, p. 80.
 — (1968). *Curr. Probl. Derm.*, **2**, 101.

Ampicilline buccale dans la gonococcie masculine et féminine. Evaluation clinique

SOMMAIRE

311 malades, hommes et femmes, atteints de gonococcie non compliquée, furent traités par l'ampicilline par voie buccale: deux doses de 1 g. données avec un intervalle de 5 heures. 95 pour cent des malades furent suivis après le traitement et eurent au moins deux examens, par colorations et cultures. Les gonocoques restèrent présents chez six des 208 hommes et chez 4 des 103 femmes. Une analyse détaillée montra que ces dix malades avaient probablement été réinfectés. Le taux de succès, selon différentes méthodes de calcul pour apprécier les échecs, fut de 99–100 pour cent.

Dans une série-témoin de 250 hommes et de 250 femmes, il fut également constaté que les rechutes étaient dues en grande partie à des réinfections. Les malades de cette série reçurent le traitement standard recommandé en Suède pour la gonococcie non compliquée, c'est-à-dire une injection intra-musculaire de 1 million d'unités de benzyl-pénicilline G et de 1,2 millions d'unités de benzyl-pénicilline G-procaïne. Le taux maximal des échecs, additionnant les cas certains d'échec et les cas "douteux", fut de 4 pour cent chez les

hommes et de 4,4 pour cent chez les femmes, mais, dans quelques cas, les efforts pour trouver l'explication des échecs furent moins rigoureux que pour les cas "douteux".

Maintenant, pour le traitement de la gonococcie non compliquée, nous préférons l'ampicilline à la dose de deux fois 1 g. au traitement standard indiqué mais nous soulignons que notre expérience se limite aux infections dues à des souches de gonocoques sensibles *in vitro* à la pénicilline.