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PIVAMPICILLIN COMBINED WITH PROBENECID IN THE TREATMENT OF ACUTE UNCOMPLICATED GONORRHOEA

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Abstract. Pivampicillin (1.4 g) combined with probenecid (1 g) in a single oral dose was given to 535 patients of both sexes with acute gonorrhoea. Less than 1% of true recurrences were observed, and few side effects, none of a severe nature. The effect was as good in cases with decreased sensitivity to benzyl penicillin and ampicillin as in female cases with rectal gonorrhoea. As a comparison, oral treatment with pivampicillin or ampicillin in two doses, and parenteral treatment with penicillin G gives 3–4% probable true recurrences.

Ampicillin given in two doses with a 5 hour interval, or in a single oral dose together with probenecid has been reported to be highly effective in the treatment of acute gonorrhoea. The efficacy is comparable to that of penicillin G in high intramuscular doses (1, 3, 4, 15). Ampicillin, however, is far from completely absorbed when administered orally (12). The pivaloyloxymethyl ester of ampicillin (pivampicillin chloride), on the other hand, is almost completely absorbed after oral administration and promptly converted into free ampicillin after absorption (8).

Recently the effect of pivampicillin has been compared to that of ampicillin and penicillin G in the treatment of uncomplicated acute gonorrhoea in both men and women (9, 14). In these studies pivampicillin and ampicillin were given in two oral doses with a 5 hour interval. There are, however, some disadvantages in using divided doses. If the patient does not take the second dose, or takes it too late or too early, the treatment may be inadequate. The aim of the present study thus was to investigate the effect of pivampicillin in one single oral dose combined with probenecid in the treatment of acute uncomplicated gonorrhoea in men and women. Special regard was given to its effect in cases with gonococcal strains of decreased sensitivity to benzyl penicillin and ampicillin and in female cases with rectal gonorrhoea. The intention was also to compare the results of this therapy with the results of oral treatment with pivampicillin and ampicillin in divided doses and single-dose parenteral therapy with penicillin G as earlier presented (14).

MATERIAL AND METHODS

During the period December 1971 to January 1973 every male and female out-patient attending the Department of Dermatology, Karolinska sjukhuset, Stockholm, and suffering from an uncomplicated acute gonorrhoea, was studied. The material comprises 535 cases, 347 males and 188 females. The age and sex distribution is given in Table I.

In every case the diagnosis was verified by a bacteriological culture according to standard methods. The sensitivity of the isolated gonococcal strains to benzyl penicillin and to ampicillin was determined by the quantitative disc diffusion method (7).

All cases were treated with 1.4 g of pivampicillin (4 capsules containing 350 mg each) plus 1 g of probenecid (2 tablets containing 500 mg each) in one single oral dose taken with 100–150 ml of water.

The efficacy of the treatment was checked at two or three weekly examinations. At each examination, both before treatment and at follow-up, specimens for culture were taken from the urethra of males and from the urethra, cervix and rectum of females.

In 32 consecutive cases the plasma concentration of ampicillin was measured 1 hour after ingestion of the drugs. The cases studied comprised both males and females in the age range 18 to 32 years. The plasma concentration was determined by an agar diffusion method using paper discs as diffusion centres (11).

If the initial treatment failed, a probable true recurrence in these cases was assumed if a sexual contact during the follow-up period was denied by the patient at interview both with the doctor and with the social officer.

Only those patients who completed the follow-up ex-

Table I. *Age and sex distribution*

Age (years)	♂	♀	Total
≤24	16	49	65
20–24	157	79	236
≥25	174	60	234
Total	347	188	535

aminations were included in the material studied. The number of defaulters in the follow-up was small, however (3–6%).

All patients were asked about side-effects of the therapy at follow-up by a general question such as: Did the ingestion of the medicine cause you any discomfort?

RESULTS

As illustrated in Table II, only 2 cases of probable true recurrence of gonorrhoea occurred among the 535 cases treated, i.e. a frequency of less than 1%.

Table II also gives a comparison with the results of treatment with pivampicillin in an oral dose of 0.7 g plus 0.7 g given 5 hours later, with ampicillin given orally in a dose of 1 g plus 1 g given 5 hours later, and with penicillin G in a single intramuscular injection of 1.0 MU of aqueous benzyl penicillin plus 1.5 MU of procaine penicillin. These results have been reported in greater detail earlier (14).

In the same table the results from all the mentioned investigations are related to the sensitivity of the isolated gonococcal strains to benzyl penicillin. A decreased sensitivity (MIC ≥0.1 μg/ml) was found in 19% of the strains.

Table II. *Sensitivity to penicillin G of the isolated gonococci strains before treatment*

The number of probable true recurrences is given within parentheses

Treatment	MIC μg penicillin G/ml serum			
	<0.1	0.1–0.5	≥0.5	Total
Pivampicillin + probenecid	432 (1)	74 (0)	29 (1)	535 (2)
Pivampicillin, two doses	156 (4)	41 (4)	3 (0)	200 (8)
Ampicillin, two doses	168 (2)	31 (4)	1 (0)	200 (6)
Penicillin G	170 (0)	27 (6)	3 (1)	200 (7)

Table III. *Sensitivity to penicillin G of the isolated gonococci strains before treatment, in females with rectal gonorrhoea*

The number of probable true recurrences is given within parentheses

Treatment	MIC μg penicillin G/ml serum			
	<0.1	0.1–0.5	≥0.5	Total
Pivampicillin + probenecid	61 (1)	11 (0)	4 (0)	76 (1)
Pivampicillin, two doses	27 (2)	8 (0)	0 (0)	35 (2)
Ampicillin, two doses	32 (0)	8 (0)	0 (0)	40 (0)
Penicillin G	42 (0)	4 (1)	1 (0)	47 (1)

In the 188 females treated with pivampicillin + probenecid, the rectal culture was positive in 76 patients, 41%. Probable true recurrence was found in 1 case (Table III). The frequency of true recurrence in females with rectal gonorrhoea did not differ from that in the other patients in this treatment group. No case of clinical proctitis was seen.

A decreased sensitivity to ampicillin (MIC ≥0.25 μg/ml) was found in 9% of the isolated gonococcal strains. In 4 of these cases a MIC value of ≥3 μg/ml was found. The frequency of probable true recurrence was not higher in cases with a decreased ampicillin sensitivity than in the other patients (Table IV). None of the 4 cases with a gonococcal strain of MIC value for ampicillin ≥3 μg/ml relapsed.

One hour after ingestion of pivampicillin plus probenecid the plasma concentration of ampicillin was 13.9±3.9 μg/ml (mean±standard deviation) in the 32 cases thus studied (Fig. 1).

Table IV. *Sensitivity to ampicillin of the isolated gonococci strains before treatment*

The number of probable true recurrences is given within parentheses

Treatment	MIC μg ampicillin/ml serum			
	<0.25	0.25–1.0	≥1.0	Total
Pivampicillin + probenecid				
Total group	488 (1)	31 (1)	16 (0)	535 (2)
Females with rectal gonorrhoea	69 (1)	6 (0)	1 (0)	76 (1)

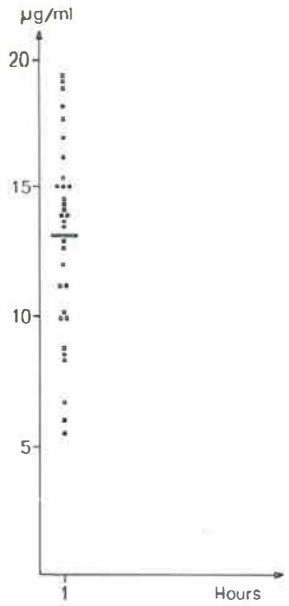

Fig. 1. Ampicillin concentration in plasma 1 hour after oral ingestion of pivampicillin 1.4 g + probenecid 1 g. — = mean value.

DISCUSSION

On a weight basis, 1.4 g of pivampicillin is equimolar to 1 g of ampicillin. It has recently been shown that the effect of pivampicillin in the treatment of gonorrhoea is as high as that obtained with a double equimolar dose of ampicillin (14). The present study shows that the effect of pivampicillin given in one single oral dose together with probenecid is better than the effect of the same total dose of pivampicillin divided into two oral doses with a 5 hour interval. This difference is statistically significant ($p < 0.001$).

It may well be that the effect of the single dose pivampicillin + probenecid treatment is better still than reported here. Both the cases reported here as probable true recurrences, one male and one female, had repeated gonorrhoeal infections during the preceding year and had had several sexual partners. Their statement denying sexual contact during the follow-up period must be regarded as doubtful and reinfections as most probable.

The result of the present study is in agreement with that of a current study of pivampicillin plus probenecid in Malmö (10).

A comparison with the results of treatment with oral pivampicillin and ampicillin in divided doses and of parenteral penicillin G treatment as earlier reported (14) was considered to be of interest and relevant. During recent years, gonorrhoea patients at the outpatient department have been examined and controlled in the same way. The bacteriological routine has not changed. No seasonal variations in cure rates or in the penicillin sensitivity of gonococci have been observed. Thus the lapse of some months up to 1 year between the pivampicillin plus probenecid treatment and the pivampicillin, ampicillin and penicillin G treatments earlier studied (14) has been considered to be without significance and the four treatment groups to be comparable.

The effect of pivampicillin plus probenecid treatment was better than the effect of 1 g oral ampicillin plus 1 g 5 hours later ($0.01 > p > 0.001$), and also better than penicillin G in a single intramuscular injection of 1.0 MU of aqueous benzyl penicillin plus 1.5 MU of procaine penicillin ($0.01 > p > 0.001$).

The present study shows that there is no higher failure rate in cases with a gonococcal strain of decreased benzyl penicillin sensitivity. Similarly, the effect of the treatment is as good in cases with a gonococcal strain of decreased ampicillin sensitivity. This holds true in the present epidemiological situation with 19% of the strains having a decreased penicillin sensitivity and 9% a decreased ampicillin sensitivity, few strains having very high MIC values. It should, however, be of importance for the limitation of a further increase in gonococcal strains of decreased ampicillin sensitivity selected because of the increased use of ampicillin and pivampicillin.

Female patients with a positive rectal culture are a problem in the treatment of gonorrhoea with some drugs occasionally used (13, 16). With the pivampicillin and probenecid treatment used in this study as well as with pivampicillin or ampicillin in divided oral doses or penicillin G in single dose injection (5, 14), the results are equally good whether the patient has rectal gonorrhoea or not (Table III).

In 32 cases the plasma concentration of ampicillin was determined 1 hour after oral administration of pivampicillin plus probenecid. There was no difference in the ampicillin concentration between males and females. The plasma concentration in all cases was found to exceed 5 µg/

ml (mean value 13.9 μg/ml). It has recently been shown that a high peak concentration and a duration of 8 to 10 hours of a plasma concentration higher than the MIC value are both necessary for effective therapy (6).

Only 4 of the cases in the whole material treated had gonococcal strains with a MIC value ≥ 3 μg ampicillin/ml, and 91 % of the strains isolated had MIC values <0.25 μg ampicillin/ml. In this study it was unfortunately not possible to determine the plasma concentrations of ampicillin later than 1 hour after drug ingestation, as the patients were treated ambulatory and could not be kept waiting for repeated blood sampling. Studies on healthy volunteers have shown, however, that the plasma concentration of ampicillin 8 hours after the intake of pivampicillin and probenecid in the dosage used in this study is in the order of 2 μg/ml (2).

The side-effects of the treatment were very few. No serious symptoms such as shock, rashes or vomiting were recorded. In some cases a slight transitory nausea was mentioned. Three patients were not able to take the pivampicillin capsules due to their size and were excluded from the study.

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