Pivampicillin hydrochloride in uncomplicated gonorrhoea

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Because of the inconvenience of injections and the serious anaphylactic reactions sometimes seen in connection with parenteral penicillin treatment, oral ampicillin has been proposed as an alternative in the treatment of gonorrhoea. Extensive studies have shown that the efficacy of ampicillin in a single dose of 2 g. combined with probenecid, or 2 g. divided into two doses with a 5-hour interval without probenecid is of the same order as 2·2 m.u. penicillin G (Eriksson 1970 a, b; 1971 a, b). A new broad-spectrum semi-synthetic penicillin, pivampicillin HCl*, which is absorbed more efficiently than ampicillin, into which it is rapidly hydrolysed in the organism (Figure), has given serum concentrations considerably higher than those obtained with a corresponding dose of ampicillin (von Daehne, Frederiksen, Gundersen, Lund, Mørch, Petersen, Roholt, Tybring, and Godtfredsen, 1970; von Daehne, Godtfredsen, Roholt, and Tybring, 1970; Foltz, West, Breslow, and Wallick, 1970; Frederiksen, Godtfredsen, Nielsen, and Roholt, 1971; Jordan, de Maine, and Kirby, 1970). It was therefore considered worthwhile to carry out a clinical trial of pivampicillin HCl in the treatment of uncomplicated gonorrhoea.

Material and methods

The series consisted of 193 males and 93 females with uncomplicated gonorrhoea, diagnosed and treated at the Out-Patients Department for Venereal Diseases, University Central Hospital, Helsinki. Specimens for direct microscopy and culture were taken from the urethra of males and from the urethra, cervix, and rectum of females when the patients first attended and at follow-up visits at weekly intervals. The criterion for diagnosis was a positive culture from at least one site. Sensitivity tests to penicillin G and ampicillin *in vitro* were carried out by the plate dilution method (Reyn, Korner, and Bentzon, 1958; Jokipii and Renkonen, 1970) on all strains isolated. The cultures and sensitivity tests were made at the

FIGURE Chemical structure of pivampicillin hydrochloride and ampicillin

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The patients were divided into subgroups according to the sensitivity of the gonococcal strains to penicillin G and ampicillin. Strains with minimal inhibitory concentrations (MIC) ≥ 0.2 μ g. ampicillin and ≥ 0.2 i.u. penicillin G per ml. were classified as less sensitive strains.

Patients with complicated gonorrhoea were excluded from the study, as were also 52 men and 21 women who did not return for at least one follow-up examination. Patients known to be allergic to penicillin were treated with doxycycline.

The trial was performed during the period May to October, 1971. The patients were divided into two random groups: 121 patients were given three capsules* of 350 mg. pivampicillin HCl (equimolar to 3×250 mg. ampicillin) in the out-patients clinic, and the same dose 5 to 6 hours later; the remaining 165 patients received 2.4 m.u. procaine penicillin intramuscularly as a single dose.

Most of the male patients attended for only one follow-up examination. Of the 93 females, sixty (64.5 per cent.) attended for at least two follow-up examinations.

Results

The overall results obtained with the two treatment regimens are given in Table I. The recurrence rate in the pivampicillin treated group was 3.3 per cent. and in the penicillin treated group 4.2 per cent. The difference is not statistically significant ($P > 0.05$).

In Table II re-infections and possible treatment failures are shown separately. We classed two cases as re-infections in which renewed sexual contact with an untreated infected partner was admitted. In one case treated with penicillin, re-infection was indicated by a rise in the MIC of the strains isolated before and after treatment from 0.03 to 1.0 i.u./ml. penicillin G. After re-infections had been excluded the possible failure rate was 2.5 per cent. in the

pivampicillin-treated group and 3 per cent. in the penicillin-treated group.

In both groups treatment failure was more common in females, but the numbers are too small for this difference to be significant.

Table III relates the recurrence of gonorrhoea to the penicillin sensitivity of the gonococcal strain in the two treatment groups. The incidence of gonococcal strains with reduced sensitivity to penicillin was 27.3 and 17.6 per cent. in the pivampicillin and penicillin groups respectively. The overall proportion of less sensitive strains for penicillin G was 22.8 per cent. in the males and 19.4 per cent. in the females. Failure of treatment occurred predominantly among patients infected with strains less sensitive to penicillin G. Among cases infected with less sensitive strains, the failure rates were 6.1 and 17.2 per cent. for pivampicillin and penicillin respectively. For infections caused by gonococcal strains fully sensitive to penicillin G, the failure rate was extremely low, regardless of the type of treatment. Treatment failure occurred in only two females, and in one of them this was possibly due to vomiting soon after swallowing the capsules.

The overall incidence of gonococcal strains less sensitive to ampicillin was of the same order as that of strains less sensitive to penicillin (21 and 21.7 per cent. respectively). Of the strains less sensitive to penicillin, 79 per cent. were also less sensitive to ampicillin; of the strains less sensitive to ampicillin, 82 per cent. were also less sensitive to penicillin.

*The capsules were taken with about 100 ml. of water.

TABLE I Overall results of treatment with pivampicillin hydrochloride compared with procaine penicillin

Treatment	Result	Males	Females	Total	
				No.	Per cent.
Pivampicillin	Cure	86	31	117	96.7
	Recurrence	2	2	4	3.3
	Total	88	33	121	100.0
Procaine penicillin	Cure	102	56	158	95.8
	Recurrence	3	4	7	4.2
	Total	105	60	165	100.0

TABLE II Proportion of re-infections and possible treatment failures after treatment with pivampicillin hydrochloride and procaine penicillin

Treatment	No. of patients		No. of re-infections	No. of possible treatment failures	
	Males	Females		Males	Females
Pivampicillin	88	33	1	1	2
Procaine penicillin	105	60	2	2	3
Total	193	93	3	3	5

TABLE III *Recurrence of gonorrhoea related to penicillin sensitivity of the gonococcal strain and type of treatment*

Treatment	Sex	Strains sensitive to penicillin G			Strains less sensitive to penicillin G		
		Total	Possible treatment failure	Re-infection	Total	Possible treatment failure	Re-infection
Pivampicillin	Male	62	—	1	26	1	—
	Female	26	1 ^a	—	7	1	—
	Total	88	1	1	33	2	—
Procaine penicillin	Male	87	—	1	18	2	—
	Female	49	—	—	11	3	1
	Total	136	—	1	29	5	1
Whole series	Male	149	—	2	44	3	—
	Female	75	1	—	18	4	1
	Total	224	1	2	62	7	1

^aThe capsules caused vomiting

In Table IV the results of the two treatment regimens have been correlated with the ampicillin sensitivity of the gonococcal strains isolated before treatment. Regardless of the type of treatment given, treatment failures occurred only in infections caused by strains less sensitive to ampicillin.

Of the 93 females, 22 had positive cultures from rectal specimens before treatment. In one of these patients the organism was isolated from the rectum only. Of the 22 patients with rectal gonorrhoea, eight were treated with pivampicillin and fourteen with procaine penicillin; there were no treatment failures.

SIDE-EFFECTS

In one patient the pivampicillin capsules caused vomiting although they were given with water. No case of drug eruption or anaphylactic reaction was seen.

Discussion

The study shows that the treatment of uncomplicated gonorrhoea with six capsules of 350 mg. pivampicillin HCl divided into two equal doses with a 5 to 6 hour interval is a useful oral alternative to parenterally administered procaine penicillin. It is at least as effective as 2.4 m.u. procaine penicillin. In infections caused by strains of gonococci less sensitive to penicillin G or ampicillin, the pivampicillin gave a somewhat lower failure rate than procaine penicillin. No trial with pivampicillin in a single dose combined with probenecid has yet been carried out.

In the present study treatment failure was more frequent in females than in males, regardless of the type of treatment, but the number of cases was small. This difference between the sexes did not depend on the presence of rectal infection, because all patients with rectal gonorrhoea responded. Nor did it depend on a higher frequency of less sensitive

TABLE IV *Recurrence of gonorrhoea related to ampicillin sensitivity of the gonococcal strain and type of treatment*

Treatment	Sex	Strains sensitive to ampicillin			Strains less sensitive to ampicillin		
		Total	Possible treatment failure	Re-infection	Total	Possible treatment failure	Re-infection
Pivampicillin	Male	66	—	1	22	1	—
	Female	24	—	—	9	2	—
	Total	90	—	1	31	3	—
Procaine penicillin	Male	88	—	1	17	2	—
	Female	48	—	—	12	3	1
	Total	136	—	1	29	5	1
Whole series	Male	154	—	2	39	3	—
	Female	72	—	—	21	5	1
	Total	226	—	2	60	8	1

strains in females. The somewhat higher failure rate in females may be due in part to the fact that the females attended for follow-up examinations for a considerably longer period than the males, so that the chance of re-infection was greater. However, it has also been shown that, in infections caused by gonococci less sensitive to penicillin, the results may be poorer in females than in males (Putkonen, Kiistala, and Lassus, 1969).

Summary

Pivampicillin HCl, which in the organism is rapidly hydrolysed into ampicillin, achieves serum concentrations after oral administration considerably higher than those obtained with a corresponding dose of ampicillin. A clinical trial of pivampicillin in the treatment of uncomplicated gonorrhoea was carried out on 88 males and 33 females. The dose given was six capsules of 350 mg. divided into two equal doses with a 5 to 6 hour interval. After exclusion of patients with re-infections, the incidence of possible treatment failure was 2.5 per cent. In a control group of 105 males and sixty females, treated during the same period with 2.4 m.u. procaine penicillin intramuscularly, the rate was 3 per cent. The difference is not statistically significant. In both groups failures were somewhat more common in females than in males. The overall incidence of gonococcal strains less sensitive to ampicillin was of the same order as that to penicillin G, amounting to about 21 per cent. Treatment failures occurred only in patients infected with strains less sensitive to ampicillin. The failure rate in cases with gonococcal strains less sensitive to ampicillin was three out of 31 in the pivampicillin group and 5 out of 29 in the procaine penicillin group.

The pivampicillin capsules caused vomiting in one case. No other side-effects were seen.

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Le chlorhydrate de pivampicilline dans la gonococcie non compliquée

SOMMAIRE

Le chlorhydrate de pivampicilline, que est rapidement hydrolysé dans l'organisme en ampicilline, permet d'atteindre des concentrations sériques, après administration buccale, considérablement plus élevées que celles que l'on obtient avec une dose correspondante d'ampicilline. Un essai clinique de la pivampicilline a été effectué dans la gonococcie non compliquée chez 88 hommes et 33 femmes. La posologie a été de six capsules de 350 mg données en deux doses égales, à un intervalle de 5 à 6 heures. En éliminant les malades qui se sont réinfectés, le taux possible d'échec thérapeutique fut de 2,5 pour cent. Dans un groupe témoin de 105 hommes et de 60 femmes, traités pendant la même période avec 2,4 m.u. de pénicilline-procaïne par voie intra-musculaire, ce taux fut de 3 pour cent. La différence n'est pas statistiquement significative. Dans les deux groupes, les échecs furent plus volontiers observés chez la femme que chez l'homme. L'incidence totale de souches de gonocoques moins sensibles à l'ampicilline fut du même ordre que pour la pénicilline G, se chiffrant autour de 21 pour cent. Les échecs s'observèrent seulement chez les malades infectés par des souches moins sensibles à l'ampicilline. Le taux d'échec dans les cas infectés par des souches de gonocoques moins sensibles à l'ampicilline fut de 3 sur 31 dans le groupe pivampicilline et de 5 sur 29 dans le groupe pénicilline-procaïne.

Les capsules de pivampicilline ont entraîné des vomissements dans un cas. Il n'y eut pas d'autre effet secondaire.