Two regimens of sultamicillin in treating uncomplicated gonorrhoea

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SUMMARY Sultamicillin is a covalent union of ampicillin and the β lactamase inhibitor, sulbactam (CP-45,899). Two studies were conducted to assess its efficacy in treating uncomplicated gonorrhoea. In the first study treatment comprised sultamicillin 1.5 g and probenecid 1 g; 124 (89.2%) of 139 patients responded including seven of 11 patients harbouring β lactamase (penicillinase) producing strains of *Neisseria gonorrhoeae* (PPNG). In the second study sultamicillin 2.25 g and probenecid 1 g were given; 122 (93.8%) of 130 patients responded. Only two of seven pharyngeal infections resolved, and if pharyngeal infections are excluded the overall cure rate rose to 95.3%. Thirteen of 14 patients infected with PPNG strains were cured by the larger dose. Side effects were mild and transitory. It may be concluded that sultamicillin 2.25 g plus probenecid 1 g is an effective regimen to treat uncomplicated rectal and genital gonorrhoea and is useful for treating infections with PPNG strains. Most β lactamase resistant antimicrobials must be given parenterally; sultamicillin is given by mouth.

Introduction

Sultamicillin is a covalent union of two antimicrobials, the semisynthetic penicillin, ampicillin, and the β lactamase inhibitor, sulbactam (CP-45,899). We conducted two studies to see if a single dose of this new drug would be effective in treating gonorrhoea due to β lactamase (penicillinase) producing strains of *Neisseria gonorrhoeae* (PPNG) and non-PPNG, and to see if it was an acceptable alternative to spectinomycin and the new cephalosporins in treating infection with PPNG strains.

Patients and methods

We studied all patients with uncomplicated gonorrhoea attending the department of genitourinary medicine at this hospital during the study periods 1 November 1982 to 5 January 1983 and 9 March to 1 June 1983 except those hypersensitive to penicillin, travellers unable to attend for follow up, patients in whom syphilis was suspected, women not using oral contraception or an intrauterine device (IUD), and patients who declined to take a new drug.

Presumptive diagnoses were made by microscopical identification of typical Gram negative intracellular diplococci in smears taken from the urethra and, when indicated, from the rectum of men, from the urethra and cervix of all women, and from the rectum of sexual contacts. Specimens from the same sites, and the pharynx when indicated, were also cultured on selective medium¹ for *N gonorrhoeae*; cases not confirmed by culture were excluded.

Minimum inhibitory concentrations (MICs) of ampicillin alone and ampicillin and sulbactam in a 1:1 ratio were measured for all but 20 of the isolates in the first trial and all except nine in the second. All organisms with MICs of ampicillin of 0.25 mg/l or more were assessed for production of β lactamase as already described.²

All patients were observed while swallowing the appropriate number of 375 mg sultamicillin tablets and two 500 mg tablets of probenecid. They were then asked to return after 1, 7, and 14 days. At each visit they were examined, and smears for Gram staining and cultures were taken as above. Patients in whom culture positive gonorrhoea was found during the follow up period and who admitted to having had sexual intercourse were excluded.

Results

In the first trial 168 patients with gonorrhoea were treated with 1.5 g sultamicillin and 1 g probenecid;

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TABLE I Patients treated with 1.5 g or 2.5 g sultamicillin and 1 g probenecid in two trials and those excluded from analysis

Dose of sultamicillin	No treated	No excluded from analysis:			No included in analysis
		Culture negative	Not attending follow up	Culture positive. Sexual intercourse during follow up	
1.5 g (trial 1)	168	7	14	8	139
2.25 g (trial 2)	169	11	22	6	130

TABLE II Follow up visits of successfully treated patients

	No of patients attending:				Total
	3 Visits	2 Visits	1 visit >1 day after treatment	1 visit only 1 day after treatment	
Trial 1 (1.5 g sultamicillin)	51	44	14	15	124
Trial 2 (2.25 g sultamicillin)	50	41	16	15	122

their mean age was 26.2 (range 15-66) years, 66% (111) were born in Britain, 20% (33) in Jamaica, and 14% (24) elsewhere. In the second trial 169 patients were treated with 2.25 g sultamicillin and 1 g probenecid; their mean age was 26 (range 15-63) years, 72% (121) were born in Britain, 14% (24) in Jamaica, and 14% elsewhere. Taking the two trials together only six patients were born in Nigeria and three in Ghana. As detailed in table I, several patients in each trial were excluded because they failed to attend for follow up, because they were reinfected, or because the laboratory was unable to confirm the diagnosis with a positive culture result. Table II details the number of follow up visits made by patients accepted in each trial who responded to treatment.

Table III shows that in the first trial 124 (89.2%) of 139 patients responded to treatment. Treatment failed at 17 (9.8%) of 173 sites. The 17 documented

treatment failure sites occurred in 15 patients, one woman showing positive cervical, urethral, and throat swabs at follow up. MICs were available for 14 of these organisms, of which all but two had MICs in the upper range of ampicillin and ampicillin-sulbactam (0.25-1.0 mg/l). Of the two sensitive strains (MIC 0.03 mg/l) one was from a man with urethritis and the other from a man with pharyngitis. Four of the organisms from patients who failed to respond were PPNG strains, two occurring in men with urethritis and the other two in women with pharyngitis.

Table IV shows that in the second trial 122 (93.8%) of 130 patients (146 out of 154 sites) responded to treatment. The eight treatment failures concerned eight different patients.

In the first trial 62.6% and in the second 54% of available isolates had MICs of ampicillin $\leq$ 0.12 mg/l. There was close correlation between MICs of

TABLE III Results of trial 1 (1.5 g sultamicillin)

			PPNG strains	
Sites of infection	No infected	No (%) responding to treatment	No infected	No (%) responding to treatment
Men				
Urethritis	91	81 (89·0)	8	6 (75·0)
Proctitis	9	8 (88·9)	0	
Pharyngitis	3	2 (66·7)	0	
Women:				
Cervicitis	35	34 (97·1)	2	2 (100·0)
Urethritis	26	25 (96·1)	2	2 (100·0)
Proctitis	4	4 (100·0)	0	
Pharyngitis	5	2 (40·0)	2	0 (0)
Total sites	173	156 (90·2)	14	10 (71·4)
Total patients	139	124 (89·2)	11	7 (63·6)

PPNG = Penicillinase (β lactamase) producing strains of *Neisseria gonorrhoeae*.

TABLE IV Results of trial 2 (2.25 g sultamicillin)

Sites of infection	No infected	No (%) responding to treatment	PPNG strains	
			No infected	No (%) responding to treatment
Men				
Urethritis	91	88 (96.7)	4	4 (100.0)
Proctitis	11	11 (100.0)	0	
Pharyngitis	4	1 (25.0)	0	
Women:				
Cervicitis	23	23 (100.0)	1	1 (100.0)
Urethritis	19	19 (100.0)	1	1 (100.0)
Proctitis	3	3 (100.0)	0	
Pharyngitis	3	1 (33.3)	0	
Total sites	154	146 (94.8)	6	6 (100.0)
Total patients	130	122 (93.8)	5	5 (100.0)

PPNG = Penicillinase (β lactamase) producing strains of *Neisseria gonorrhoeae*.

ampicillin and ampicillin-sulbactam. Table V shows in greater detail the in vitro sensitivities of all isolates tested.

Of the 337 patients treated in the two trials, three complained of nausea, four of nausea and abdominal pain, 13 of diarrhoea, and two developed a rash. All of these side effects were transitory and mild, and none precipitated admission to hospital. Ten patients treated with the lower dose and nine treated with the higher dose complained of these symptoms.

In addition to patients treated in these trials, 11 harbouring PPNG strains were treated with 2.25 g sultamicillin plus 1 g probenecid, of whom 10 responded satisfactorily. The total number of patients infected with these strains treated with the higher dose of sultamicillin was 16, of whom 15 responded satisfactorily.

Discussion

The emergence of total resistance to penicillin in *N gonorrhoeae* due to β lactamase production now poses a considerable problem over treatment. In Britain the prevalence of PPNG strains in gonococcal isolates is still only about 5%,³ but in parts of South East Asia it is nearly 50%.⁴ West Africa is the source

of many of our PPNG strains.⁵ The prevalence in this series was lower than previously reported.

In Britain oral ampicillin is probably the antimicrobial most commonly used in treating gonorrhoea,⁶ although dosage varies. In the United States the recommended dose for uncomplicated gonorrhoea is ampicillin 3.5 g plus probenecid 1 g by mouth.⁷ This treatment is ineffective against PPNG strains and would be poor first line treatment in South East Asia. For PPNG strains usual treatments are either spectinomycin, resistance to which has been reported,⁸ or a new cephalosporin such as cefotaxime.⁵ Such medications are expensive and, as most of them must be given intramuscularly, syringes and needles further increase the cost. Injections also take more time for nurses to administer and are less well tolerated by patients.

Clearly a single dose oral treatment for gonorrhoea that would cover all strains would be more acceptable. Sultamicillin with probenecid may provide such an alternative. The findings with the 1.5 g regimen were unsatisfactory. The results with the 2.25 g dosage resembled those with sultamicillin 2 g plus probenecid 1 g reported by Atia *et al*,⁹ and show sultamicillin to be well tolerated and effective against PPNG and non-PPNG strains. Among

TABLE V In vitro sensitivity of 558 strains of gonococci isolated during two trials in 1982 and 1983

Antibiotic	Type of strain	No of isolates	% isolates inhibited by MICs (mg/l) of:								
			<0.01	0.03	0.06	0.12	0.25	0.5	1	2	≥4
Ampicillin	Non-PPNG	528	3	23	12.5	14	36	10.5	1	(0.2)	
	PPNG	30									100
Sulbactam	Non-PPNG	528			(0.4)	10	23	9	14.5	27.5	16
	PPNG	30							20	63	17
Sulbactam and ampicillin (1:1)	Non-PPNG	528	5	27.5	6	20	33	7.5	1		
	PPNG	30					10	70	20		

PPNG = Penicillinase (β lactamase) producing strains of *Neisseria gonorrhoeae*. Figures in parentheses represent <1% of isolates.

patients with anogenital gonorrhoea the response in the first trial was 128 (92.1%) out of 139 and in the second 127 (97.7%) out of 130. A 95% response is generally regarded as acceptable in Britain for first line treatment for anogenital gonorrhoea, but lower cure rates are unsatisfactory for uncomplicated infection. As treatment with single dose ampicillin gives poor results in gonococcal pharyngitis, a course of antimicrobial treatment is apparently necessary to cure this condition.

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