J. Hyg., Camb. (1986), **96**, 419–423
Printed in Great Britain

In vitro and *in vivo* study of fosfomycin in methicillin-resistant *Staphylococcus aureus* septicaemia

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(*Received 15 October 1985; accepted 12 December 1985*)

SUMMARY

Five hundred strains of methicillin-resistant *Staphylococcus aureus* were tested against various anti-staphylococcal agents. Vancomycin, fusidic acid and fosfomycin were found to be the most effective. Only 1 strain out of 500 was resistant to fosfomycin. Three patients with methicillin-resistant *Staphylococcus aureus* septicaemia were successfully treated by fosfomycin. We conclude that fosfomycin could be the drug of choice for methicillin-resistant *Staphylococcus aureus* infection.

INTRODUCTION

Outbreaks of methicillin-resistant *Staphylococcus aureus* (MRSA) infection are causing increasing problems in centres all over the world (Thompson & Wenzel, 1982; Editorial, 1983). There has been a gradual increase in the incidence of MRSA in our hospital in Hong Kong from 317 in 1982 (18·7 % of all *S. aureus* isolated) to 511 in 1983 (32·7 %) and 833 in 1984 (34·9 %). *In vitro*, resistance of MRSA is often demonstrated to many anti-staphylococcal agents including the penicillins, first-generation cephalosporins, aminoglycosides, erythromycin, clindamycin and chloramphenicol (Peacock *et al.* 1981). Second- and third-generation cephalosporins also have poor activity *in vitro* (Thompson, Fisher & Wenzel, 1982) though many MRSA strains have been found to be susceptible to rifampicin, trimethoprim-sulphamethoxazole and fusidic acid (Watanakunakorn, 1983).

However, clinical experience of treating serious staphylococcal infection with rifampicin and trimethoprim-sulphamethoxazole is limited (Guenther & Wenzel, 1984) and fully resistant organisms may emerge rapidly after exposure to fusidic acid *in vitro* and *in vivo* (Watanakunakorn, 1983). As vancomycin shows good activity *in vitro* and *in vivo* it has been regarded as the drug of choice (Myers & Linneman, 1982; Thompson & Wenzel, 1982; Watanakunakorn, 1982, 1983). Unfortunately, vancomycin is more toxic than the penicillinase-resistant penicillins (Wenzel, 1982), and despite removal of impurities thought to be responsible for toxicity, in a recent report of a series of a hundred courses of vancomycin therapy 5 % of patients developed nephrotoxicity and 1–2 % marked neutropenia (Farber & Mollering, 1982). Because of the side-effects of vancomycin and because tolerance to vancomycin has been reported amongst strains of MRSA (Sabath *et al.* 1978; Watanakunakorn & Guerriero, 1981; Levine *et al.* 1982; Watanakunakorn, 1983), other drugs found to be effective *in vitro* and known to be free from side-effects

https://doi.org/10.1017/S0022172400066183 Published online by Cambridge University Press

should be considered for clinical trial. In the present study, fosfomycin satisfied those requirements.

MATERIALS AND METHODS

From January to June 1984, 500 strains of MRSA were isolated from various infected foci from 500 patients in Queen Mary Hospital, Hong Kong. The foci included blood cultures, wounds, abscesses, sputum, drain fluids, intravenous catheters and urine.

Standard disk susceptibility tests were used to determine the *in vitro* susceptibilty of these 500 strains to various anti-staphylococcal agents. The minimal inhibition concentration (MIC) of fosfomycin was determined by the method recommended by the International Collaborative Study (ICS) (Andrews *et al.* 1983). Mueller-Hinton agar with glucose-6-phosphate (25 mg/l) and a bacterial inoculum of approximately 10^5 colony-forming units were used. The MIC was defined as the lowest antibiotic concentration which inhibited visible growth after 24 h of incubation at 37 °C. *S. aureus* ATCC 25923 was used as control.

Antibiotic concentration in the serum was determined by the bioassay method based on ICS (Andrews *et al.* 1983). The medium used was DST, pH 7, supplemented with glucose-6-phosphate (25 mg/l). The indicator organism was *Escherichia coli* NCTC 10418.

Encouraged by the results obtained from *in vitro* sensitivity tests, three patients with MRSA septicaemia were treated with fosfomycin. The criteria for septicaemia were elevated body temperature over 38·5 °C for at least 2 days, with two or more blood cultures positive for *S. aureus*. None of these patients had responded to cloxacillin or cefazolin used before the identification of the MRSA strains. Fosfomycin was given as a continuous infusion, 4 g over 4 h, immediately the sensitivity test results were known. The treatment was continued daily for 4 weeks. No patient was suspected of having endocarditis clinically. Serum levels of fosfomycin were determined after 1 and 2 h of infusion. Blood cultures were repeated and further samples were taken from the wound, intravenous cannulae, body fluid, nares, nasopharynx and urine for the detection of portal of entry. A patient was considered cured only if repeated blood cultures were negative and there was a good clinical response without any residual infective foci or development of endocarditis.

RESULTS

The *in vitro* susceptibility of the 500 strains of MRSA to various anti-staphylococcal agents using the standard disk susceptibility tests is shown in Table 1. Vancomycin, fusidic acid and fosfomycin were found to be most effective. The incidence of gentamicin-resistant strains in this group of MRSA was very high (97·6%).

The MIC of fosfomycin for MRSA strains is shown in Table 2. Only one strain had an MIC of over 64 mg/l (0·2%) while 97·6% of MRSA had an MIC below or equal to 16 mg/l. A serum level of about 100 mg/l could be achieved with the dosage of fosfomycin used (Table 3).

The clinical response to fosfomycin was good and all patients survived.

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Table 1. *Susceptibility of 500 strains of methicillin-resistant* Staphylococcus aureus *to various antibiotics using standard disk susceptibility tests*

Antibiotics	Disk content	Susceptible	
		n	%
Penicillin G	10 units	0	0
Gentamicin	10 μg	12	2·4
Tetracycline	30 μg	16	3·2
Erythromycin	15 μg	248	49·6
Fosfomycin	50 μg	499	99·8
Fusidic acid	10 μg	500	100
Vancomycin	30 μg	500	100
Sulphamethoxazole Trimethoprim	23·75 μg 1·25 μg	451	90·2

Table 2. *Minimum inhibition concentration of fosfomycin for 500 strains of methicillin-resistant* Staphylococcus aureus

	Fosfomycin (mg/l)							
	1	2	4	8	16	32	64	128
No. of susceptible strains	3	11	206	136	132	6	5	1
Cumulative % susceptible	0·6	2·8	44·0	71·2	97·6	98·8	99·8	100

Recommendations from the ICS: MIC ⩽ 64 mg/l indicates susceptiblity; MIC ⩾ 128 mg/l indicates resistance.

Table 3. *Patients with MRSA septicaemia*

Patient...	LY	CCH	WCY
Sex/age	M/43	F/32	F/50
Underlying disease	Pancreatic abscess with intestinal fistula	50 % burn	Intestinal fistula on total parenteral nutrition
Portal of entry	Pancreatic abscess	Wound infection	Intravenous catheter
Serum fosfomycin level (mg/l)			
1 h after end of infusion	95·8	105·1	103·2
2 h after end of infusion	91·2	73·5	66·1
MIC of MRSA isolated (mg/l)	< 16	< 8	< 4
Clinical response	Good	Good	Good

DISCUSSION

Fosfomycin is a low-molecular-weight antibiotic with little or no reported toxicity and low binding to serum protein (Allona *et al.* 1977; Kestle & Kirby, 1969; Dai *et al.* 1981). It acts by blocking acetylmuramic acid synthesis and has a broad spectrum of activity against gram-positive and gram-negative organisms. No cross-resistance with other antimicrobial agents has been reported (Guenther & Wenzel, 1984). It has a serum half-life of 2 h (Hutzler *et al.* 1977).

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Fosfomycin has proved to be very active *in vivo* and *in vitro* (Gudin *et al.* 1983; Rodriguez, Olay & Vicente, 1983). It has good efficacy in serious infections including staphylococcal septicaemia (Gudin *et al.* 1983; Rodriguez, Olay & Vicente, 1983). It is synergistic with aminoglycosides and β-lactam antibiotics (Rodriguez, Olay & Vicente, 1980). Moreover, it has recently been demonstrated both clinically and experimentally to have a protective effect on the nephrotoxicity of aminoglycosides (Neuman, 1984).

Outbreaks of MRSA infection are causing problems in many centres all over the world (Thompson *et al.* 1982; Editorial, 1983). Vancomycin has been regarded as the antibiotic of choice for patients with MRSA septicaemia or endocarditis, but tolerance to vancomycin amongst MRSA strains has been reported (Sabath *et al.* 1978; Watanakunakorn & Guerriero, 1981; Levine *et al.* 1982; Watanakunakorn, 1983). Vancomycin has toxic side effects (Farber & Mollering, 1982) and it is expensive. A search has been in progress for alternative anti-staphylococcal agents and in our experience we have found fosfomycin to be effective both *in vitro* and *in vivo*. We suggest that fosfomycin could be the drug of choice in MRSA infection, having the advantages over vancomycin that it is less expensive and less toxic. Further clinical studies to evaluate its effectiveness are in progress.

We thank Mrs Sylvia Hulse for the secretarial assistance.

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