Comparison of susceptibility of *Neisseria meningitidis* to sodium sulphadiazine and sodium fusidate *in vitro*

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SUMMARY Out of 100 strains of meningococci examined 62 were resistant to 1 mg/l or more of sodium sulphadiazine, including 82% of group W135 strains and 69% of group B strains. All strains were sensitive *in vitro* to 0.5 mg/l of sodium fusidate. Sodium fusidate should be considered as a chemoprophylactic agent for those who may be at risk of meningococcal disease.

When prevalence of meningococcal disease is increased contacts of cases may require chemoprophylaxis, and sodium sulphadiazine is the drug of choice. However, increasing numbers of meningococci are resistant to sulphonamides (Fallon, 1975, 1977) and many alternative chemoprophylactic agents are ineffectual. Sodium fusidate is active against a few strains of meningococci *in vitro* (Barber and Waterworth, 1962; Godtfredsen *et al.*, 1962). We report an *in-vitro* study of the susceptibility of 100 strains of *Neisseria meningitidis* to sodium fusidate and sodium sulphadiazine.

Material and methods

STRAINS OF MENINGOCOCCI

One hundred strains of meningococci were examined. Eighty-seven of them had been isolated from throat swabs of patients attending the Department for Sexually Transmitted Diseases, The Royal Infirmary of Edinburgh; one had been isolated from the cerebrospinal fluid of a young male patient; and 12 were from laboratory stock cultures. All strains from patients were isolated on Columbia agar base enriched with 10% heated human blood. 80% of the concentrations of vancomycin, colistin, and nystatin recommended by Thayer and Martin (1966) were incorporated in the agar. All strains were identified by a rapid carbohydrate utilisation test (Young *et al.*, 1976). All strains were serologically typed by Dr R. J. Fallon, Meningococcal Reference Laboratory (Scotland), Ruchill Hospital, Glasgow.

SENSITIVITY TESTING

Sensitivity to sulphonamide was tested on Mueller-

Hinton agar (Oxoid) by the method of Feldman (1967). Sodium sulphadiazine was added to the agar in varying amounts from 0.1 to 100 mg/l. Sensitivity to sodium fusidate (Leo Laboratories Ltd) was tested by a similar method with antibiotic added to the agar in varying amounts from 0.015 to 1 mg/l. All cultures were incubated at 37°C in an atmosphere containing 10% carbon dioxide.

Results

SEROTYPING

The serotypes of the strains are shown in Table 1. Group W135 strains were common and group B strains predominated, although a large proportion (24%) of strains were non-groupable. One of the group A strains was isolated from cerebrospinal fluid.

SULPHONAMIDE SENSITIVITY

The results of testing 100 strains are shown in Table 1. Fourteen strains, including seven group W135 and all three group A strains, were resistant to 10 mg/l or more of sulphadiazine. They were called fully resistant (Feldman, 1967). Forty-eight strains, including 25 group B, six group W135, and four group C were resistant to 1 mg/l sulphadiazine but were sensitive to 10 mg/l. They were called partially resistant (Feldman, 1967). Thirty-eight strains were fully sensitive to sulphadiazine and were inhibited by 1.0 mg/l. In all, 62 strains were either partially or fully resistant to sulphadiazine, and this total included 13 (76%) of group W135 strains and 27 (72%) of group B strains.

SODIUM FUSIDATE SENSITIVITY

The results of testing 100 strains are shown in

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Table 1 Sensitivity of 100 strains of meningococci to sodium sulphadiazine

Group	No. of strains inhibited by sodium sulphadiazine (mg/l)							Total
	0.1	1.0	5.0	10	50	100	> 100	
A					1	1	1	3
B		10	15	10	2			37
C		3	1	3			1	8
W135		4	4	2	7			17
X			1					1
Y		4	2					6
Z ¹ /29E		2	2					4
NT		15	3	5	1			24
Total		38	28	20	11	1	2	100

NT = not typed.

Table 2 Sensitivity of 100 strains of meningococci to sodium fusidate

Group	No. of strains inhibited by sodium fusidate (mg/l)							Total
	0.015	0.03	0.06	0.12	0.25	0.5	1.0	
A				1	2			3
B	11	15	7	2	1	1		37
C		4	3		1			8
W135	3	6	6	2				17
X	1							1
Y		3	3					6
Z ¹ /29E			3	1				4
NT	4	8	8	3		1		24
Total	19	36	30	9	4	2		100

NT = not typed.

Table 2. Ninety-four strains were inhibited by 0.12 mg/l and all strains were sensitive to 0.5 mg/l sodium fusidate.

Discussion

The first known epidemic of meningitis due to sulphonamide-resistant meningococci occurred at a naval training centre in San Diego in 1963 (Millar *et al.*, 1963). Since then interest in the clinical aspects of sulphonamide-resistant meningococci has increased. In the United Kingdom the incidence of meningococcal infection increased about threefold between 1967 and 1974 (*British Medical Journal*, 1976). Although laboratory notifications of isolations of *N. meningitidis* were lower in 1976 than in previous years they remained at a higher level than before 1974 (Fallon, 1977). Fallon (1975) reported an increasing number of strains of meningococci that showed partial resistance to sulphonamides in the laboratory, and many of these strains show more than a marginal partial resistance (Fallon, 1977).

Our results of sulphonamide sensitivity testing were similar to those of Fallon (1977). Eighty-seven of our strains were isolated from persons free from meningococcal disease and 51 (58%) of these

organisms were resistant to 1.0 mg/l of sulphadiazine. A total of 62 strains was resistant to 1.0 mg/l of sulphadiazine including a high percentage of group W135 and group B strains. This is important because in field prophylaxis trials meningococci resistant to 1.0 mg/l of sulphadiazine were not eliminated from the nasopharynx by recommended doses of sulphadiazine (Brown and Condit, 1965).

Asymptomatic carriage of *N. meningitidis* is common and between 5% and 20% of the general population may harbour the organism in the nasopharynx. In confined populations the carrier rate may rise to over 70%, but an increasing carrier rate does not always mean that meningococcal disease will occur (Fraser *et al.*, 1973) although during an epidemic of meningococcal disease Kaiser *et al.* (1974) isolated *N. meningitidis* from pharyngeal cultures of 35% of close contacts compared with 1% of controls. In the presence of clinical cases of meningococcal infection some groups of individuals seem to be at increased risk of disease and may require chemoprophylaxis. These persons include those in the household under 5 years of age together with other close household contacts and infant contacts in a day nursery. Groups who may also be at increased risk are military recruits among whose

ranks meningococcal disease has developed and ship crews who are to spend time at sea and who have been exposed to cases of meningococcal disease. Other individuals, including casual contacts and medical personnel (excluding those who have had intimate contact such as in mouth-to-mouth resuscitation), seem to be at little or no increased risk of disease after case contact and do not require chemoprophylaxis (Kaiser *et al.*, 1974).

When the strain of *N. meningitidis* is susceptible to sulphonamides sulphadiazine in full dosage for 24 hours is the best prophylaxis available (Lancet, 1974). When the meningococcus is resistant to sulphonamides many antibacterial agents have been used as prophylactics and have been shown to be ineffective in eliminating meningococci from asymptomatic persons. There is evidence that benzylpenicillin does not work in prophylaxis (Artenstein *et al.*, 1967), although it is essential in treatment, and ampicillin, oxytetracycline, and erythromycin were tried by Dowd *et al.* (1966) with little success. Rifampicin and minocycline have been recommended for prophylaxis. While rifampicin is moderately effective in eliminating the meningococcal carrier state (Deal and Sanders, 1969; Devine *et al.*, 1970) it has caused the rapid selection of rifampicin-resistant strains in treated populations (Beam *et al.*, 1971).

Minocycline reduces meningococcal carriage but has the serious disadvantage that it may cause toxic vestibular effects (Williams *et al.*, 1974; Devine *et al.*, 1971), although Masterton and Schofield (1975) claim that when it is given for gonorrhoea the incidence of vestibular side effects is low. Furthermore, minocycline, like other tetracyclines, may cause discoloration of permanent teeth when given to children under 6 years of age and to women in the third trimester of pregnancy (Demers *et al.*, 1968), although this effect may be related to total dose (Grossman *et al.*, 1971). A combination of minocycline and rifampicin eradicates meningococcal carriage but when used sequentially does not prevent the appearance of rifampicin-resistant strains (Devine *et al.*, 1973). Minocycline and rifampicin given at the same time might avoid this problem, but Munford *et al.* (1974) report a high incidence of unpleasant side effects due to minocycline.

There is as yet no totally acceptable agent suitable for chemoprophylaxis when the strain of *N. meningitidis* is resistant to sulphonamides. In our study 100 strains of meningococci were sensitive *in vitro* to 0.5 mg/l of sodium fusidate. We suggest that this antibiotic, which is well absorbed after oral administration, producing high serum levels with good distribution and penetration (Williamson *et al.*, 1970), and is well tolerated with few side effects, is worthy of

clinical trial in those persons who may be at increased risk of meningococcal disease.

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