Treatment of gonorrhoea with sulphamethoxazole-trimethoprim

Lack of effect on concomitant syphilis

H. B. SVINDLAND

From the Bureau of Public Health, Department for Skin and Venereal Diseases, Trondheim, Norway

Penicillins, either alone or in combination with other drugs, have been the treatment of choice for gonorrhoea since 1945, but despite the effectiveness of this treatment the incidence of venereal disease continues to increase. Over the years, the tendency has been towards short intensive courses of treatment.

The problem of associated incubating syphilis has by no means been solved; the treatment of gonorrhoea with penicillin should be followed by a prolonged surveillance, but in most cases this is impracticable, and the best way to meet the difficulty is to use a more specific agent for the primary treatment of gonorrhoea. It is necessary to find a drug which will have no effect (in conventional dosage) on the treponeme but is highly effective against the gonococcus. The aim of the present study was to determine how far sulphamethoxazole-trimethoprim (S-T) satisfies these criteria. The investigation was divided into three parts:

- (1) To study the effect of S-T in patients presenting with gonorrhoea.
- (2) To determine the resistance of gonococcal strains to sulphonamides.
- (3) To examine the outcome of concomitant syphilis infection when S-T is used to treat gonorrhoea.

Material and methods

Trondheim, a university city with a population of some 130,000, occupies a strategic geographical position and being a port receives a large number of occasional visitors. Our department treats approximately 70 per cent. of all reported cases of gonorrhoea and almost all cases of syphilis. A series of 659 patients with various manifestations of gonorrhoea and 43 with acquired syphilis was seen between July, 1970, and April, 1972. Patients known to be pregnant and those with a history of allergy to sulphonamides were excluded. The investigation was divided into three consecutive series, each comprising over 200 cases of gonorrhoea.

Received for publication July 19, 1972

Each group was treated according to the following schedule in order to determine the optimal dosage:

GROUP A Two tablets* every 12 hrs for 5 days, a total of twenty tablets.

GROUP B Three tablets every 12 hrs for 3 days, and a final dose of 2 tablets, thus keeping to the same total of twenty tablets.

GROUP C Four tablets every 12 hrs for 2 days, a total of sixteen tablets.

Twelve failures from Group A received a further course of treatment with the same schedule, again without success. The remaining fourteen failures were all cured with pivampicillin 700 mg. twice daily for 3 days, except one who finally responded to tetracycline.

Diagnosis was first made by microscopic examination of Gram-stained urethral smears in men and of urethral and cervical smears in women, and confirmed by cultures (urethral in men, and urethral, cervical, and rectal in women). The swabs for the cultures were placed in Stuart's transport medium and delivered the same day to the Bacteriological Institute at the Central Hospital in Trondheim, where they were subjected to sensitivity testing for sulphonamides using sulpha-isodimidine discs 2.5 mg.

All patients had cultures taken at 1 and 2 weeks after treatment and were declared cured only after two consecutive negative tests. A random selection of sixty of these 'cured' patients from all three groups was called in for a third examination after 2 to 3 months and all were free from infection.

The thirty defaulters were mainly sailors or tourists.

Results

Table I shows the percentage cure rates for the three groups. The most effective dosage was four tablets every 12 hrs for 2 days (Group C); almost 99 per cent. of the patients, both male and female, were cured after one course of treatment. Included in the total of 603 cured are 43 cases of re-infection. The few side-effects were not of a serious nature.

*Each tablet contained 400 mg. sulphamethoxazole and 80 mg. trimethoprim.

TABLE I Results of treatment of gonorrhoea with sulphamethoxazole-trimethoprim*

Group	Dosage (tablets)	Total patients	No. returned for follow-up	Results		
				Failures	Cures	Per cent.
					No.	
A	2 twice daily for 5 days (Total 20)	Female 116	114	4	110	96.46
		Male 125	120	11	109	90.52
B	3 twice daily for 3 days plus final dose of 2 tablets (Total 20)	Female 92	85	4	81	95.30
		Male 118	112	5	107	95.55
C	4 twice daily for 2 days (Total 16)	Female 98	95	1	94	98.89
		Male 110	103	1	102	99.03
Total		659	629	26	603	95.87

*Bactrim (Roche)—each tablet contains: Sulphamethoxazole 400 mg.
Trimethoprim 80 mg.

TABLE II Sensitivity of gonococcal strains to sulphonamides in patients treated for gonorrhoea with sulphamethoxazole-trimethoprim

		Results					
Group	Sensitivity	Cures		Failures		Defaulters	Total
		Female	Male	Female	Male		
A	0	4	1	0	0	0	5
	+	5	3	0	2	0	10
	++	23	28	1	3	3	58
	+++	57	61	3	6	4	131
	No. of strains	89	93	4	11	7	204
B	0	2	2	0	0	0	4
	+	0	0	0	0	1	1
	++	7	4	1	1	2	15
	+++	56	86	3	4	9	158
	No. of strains	65	92	4	5	12	178
C	0	1	1	0	0	0	2
	+	2	0	0	0	1	3
	++	11	8	1	0	0	20
	+++	69	71	0	1	9	150
	No. of strains	83	80	1	1	10	175

0—totally resistant + } —moderately sensitive ++ } —sensitive
+ + }

Table II shows the occurrence of resistant strains. Five resistant and 68 relatively resistant strains were demonstrated in Group A, four resistant and sixteen relatively resistant in Group B, and two resistant and 23 with reduced susceptibility in Group C. There were no resistant strains amongst the failures. It should be noted that the total of both resistant and relatively resistant strains tended to diminish over the 2-year period and that all these resistant strains appeared in successfully treated patients.

Table III (overleaf) shows that, of 43 patients with acquired syphilis, thirteen had received treatment with either antibiotics or S-T before the diagnosis of

syphilis was confirmed. The three patients previously treated with S-T had all received it for gonorrhoea. Two of them later developed a primary chancre, 4 and 6 weeks respectively after S-T treatment. The third, a young female drug-addict, had also received penicillin 4 months before the S-T treatment. At the time of the first consultation weakly positive serological tests for syphilis were observed, and these became more strongly positive during the follow-up period for gonorrhoea; no primary lesion was observed but she developed a secondary eruption on the face.

Of the ten patients who had previously received antibiotics, seven had received this treatment for

TABLE III *Patients with acquired syphilis treated during the investigation period (July, 1970 to April, 1972)*

Syphilis	Not previously treated		Previously treated with				Total
			Penicillin or tetracycline		Sulphamethoxazole-trimethoprim		
	Female	Male	Female	Male	Female	Male	
Primary	3	18	0	1	1	1	24
Secondary	6	2	4	2	1	0	15
Latent	0	1	1	2	0	0	4
Total	9	21	5	5	2	1	43

gonorrhoea (five with penicillin and two with tetracycline). Five of the seven patients presented with secondary rashes, one with primary syphilis, and one with positive serological tests. The patient with primary syphilis presented 8 weeks after treatment for gonorrhoea; of the five cases of secondary syphilis, three presented 5 months, one 6 months, and one 7 months after treatment for gonorrhoea. Common to these cases of secondary syphilis was an apparent masking of the primary symptoms and the appearance of secondary symptoms much later after the presumed date of infection than one would normally expect. The other three patients had been given penicillin for a sore on the penis without consulting a doctor; two of these developed latent syphilis, and the third presented with secondary syphilis 3 months later.

Discussion

A cure rate of 99 per cent. for gonorrhoea treated with S-T, four tablets every 12 hrs for 2 days, compares favourably with the best results obtained by other workers with this combination. Arya, Pearson, Rao, and Blowers (1970) obtained a 96 per cent. cure rate with three or four doses, each of four tablets, every 12 hours. Carroll and Nicol (1970) administered a dose of four tablets once a day for 5 days and obtained cure rates of 95.5 per cent. for men and 93 per cent. for women. Csonka (1969) obtained the best results in males (95.6 per cent. cure rate) with three tablets, twice daily for 4 days. Schofield, Masterton, Moffett, and McGill (1969) treated female patients with two tablets twice daily for 5 days and obtained a cure rate of 98.5 per cent. Csonka (1969) noted a cure rate of only 83.5 per cent. in women who were given three tablets twice daily for 4 days; in these cases failure was sometimes not seen until many weeks after treatment; this was not so in the present study. It may be important for patients to adhere strictly to a 12-hour interval as S-T has an approximate half-life of 11 to 12 hours. Schofield and others (1969) suggested that, despite the present apparent low resistance of *N. gonorrhoeae* to sulphonamides, we should monitor sensitivity to this new drug to ensure

that resistance does not develop. Our investigation over a 2-year period shows a reduction in both resistant and relatively resistant strains towards sulphonamides. This finding is strengthened by the fact that our patients came from a relatively restricted area of some 130,000 inhabitants, where one might expect the development of resistant strains amongst the local promiscuous female pool. Our results also show that primary resistance of gonococcal strains to sulphonamides does not necessarily affect successful treatment with S-T, because trimethoprim acts by potentiating the effect of sulphonamides.

Hallinger (1968) treated eight patients with primary syphilis with 1 g. probenecid and 5 m.u. sodium penicillin, which was the usual treatment for gonorrhoea. The patients were observed weekly and seven developed a clinical or serological relapse 5 to 11 weeks after treatment. The author concluded that syphilis might be masked for long periods by this treatment and suggested serological tests both 3 and 6 months after treatment for gonorrhoea. These findings fit in with my own clinical observations in which the delay in diagnosis was even greater. It would therefore seem necessary to follow up patients treated for gonorrhoea with treponemicidal drugs for 6 months, but in practice this is unrealistic. It would be better to treat gonorrhoea with a preparation such as S-T which has no effect on *Treponema pallidum* (Csonka, 1969). If penicillin is prescribed in the treatment of gonorrhoea the dosage should be spread over several days (Svindland, 1968) as this will cure a concomitant developing syphilis infection.

Summary

Three schedules of sulphamethoxazole-trimethoprim were used in the treatment of gonorrhoea. A dose of four tablets every 12 hours for 2 days gave the best cure rate (almost 99 per cent.). Treatment during the last 2 years does not appear to have produced sulphonamide-resistant gonococcal strains. The results were not affected by the primary resistance of gonococci to sulphonamides.

This treatment is preferable to that with treponemocidal antibiotics as it does not mask the classical symptoms of an accompanying syphilis infection.

This is of special importance in the treatment of occasional visitors such as seamen where there is often a lack of continuity of treatment and where masking of a concomitant syphilis infection can more easily occur.

References

- ARYA, O. P., PEARSON, C. H., RAO, S. K., and BLOWERS, R. (1970) *Brit. J. vener. Dis.*, **46**, 214
 CARROLL, B. R. T., and NICOL, C. S. (1970) *Ibid.*, **46**, 31
 CSONKA, G. W. (1969) *Postgrad. med. J.*, **45**, Suppl. (Nov.), p. 77
 HALLINGER, L. (1968) *Acta derm.-venereol. (Stockh.)*, **48**, 260
 SCHOFIELD, C. B. S., MASTERTON, G., MOFFETT, M., and MCGILL, M. I. (1969) *Postgrad. med. J.*, **45**, Suppl. (Nov.), p. 81
 SVINDLAND, H. B. (1968) *T. norsk. Laegeforen*, **88**, 2252

Traitement de la gonococcie par le sulfaméthazole-triméthoprim

SOMMAIRE

Trois schémas de traitement avec le sulfaméthazole-triméthoprim ont été employés dans le traitement de la gonococcie. Quatre comprimés chaque 12 heures pendant 2 jours ont donné le meilleur taux de guérison (presque 99 pour cent). Au cours des deux dernières années, le traitement ne semble pas avoir entraîné une sulfamido-résistance des souches de gonocoques. Le résultat ne fut pas influencé par la résistance primaire des gonocoques aux sulfamides.

Ce traitement est préférable aux antibiotiques tréponémocides car il ne masque pas les symptômes classiques d'une infection syphilitique concomitante.

Ceci est d'une importance particulière pour le traitement de consultants occasionnels, tels que les marins, chez lesquels on peut souvent craindre un défaut dans la continuité du traitement et où le masquage d'une syphilis concomitante peut plus facilement survenir.