Brit. J. vener. Dis. (1970) **46**, 145

Rifampicin (Rimactane) in the treatment of gonorrhoea

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THE prevalence of gonococci possessing partial resistance to penicillin and other antibiotics varies in both time and locality, but for the most part it has continued to increase over the years, and there are now some parts of the world in which the limits of 'single-session' penicillin therapy have been reached because of the unacceptable bulk of the injection (WHO, 1969). There is a pressing need for regular scrutiny of trends of antibiotic sensitivity and for examination of new antibiotics. Fortunately the rate of discovery of agents effective in the treatment of gonorrhoea is keeping pace with the deteriorating position, but there must be no complacent assumption that such will continue to be the case (Willcox, 1968). A new semi-synthetic antibiotic, rifampicin, is the subject of this report.

Rifampicin (Rimactane) is one of the group of rifamycins produced by *Streptomyces mediterranei* which has been shown to be active *in vivo* and *in vitro* against many Gram-positive and Gram-negative organisms and also, as was the case with the earlier discovered Rifamycin SV, against *Mycobacterium tuberculosis*.

Rifamycin acts by inhibiting bacterial RNA synthesis of the DNA templates, *i.e.* it stops the expression of genes (*Nature (Lond.)*, 1969). Such synthesis is achieved by the DNA-dependent enzyme RNA synthetase with which rifampicin interacts, but the antibiotic has no effect on human RNA synthetase and therefore on the synthesis of RNA in mammalian cells (Wehrli, Nüesch, Knüsel, and Staehelin, 1968; Umezawa, Mizuno, Yamazaki, and Nitta, 1968). Anti-bacterial effect has been demonstrated both *in vivo* (Frontali, Leoni, and Tecce, 1964) and *in vitro* (Hartmann, Honikel, Knüsel, and Nüesch, 1967). More recently the antibiotic has been shown *in vitro* to stop vaccinia virus from multiplying without killing the host cell (Heller, Argaman, Levy, and Goldblum, 1969).

Paper presented at the Meeting of the Medical Society for the Study of Venereal Diseases in Budapest, Hungary, June, 1969.

So far little has been published concerning the effect of rifampicin in gonorrhoea, but preliminary reports (Cobbold, Morrison, and Willcox, 1968; Fuga, 1968; Willcox, Morrison, and Cobbold, 1968) show the drug to be active and, apart from its property of making the urine orange-red, to be free of side-effects in the doses used. Moreover, preliminary findings suggest that, when the drug is used in cases of gonorrohoea, it has no prejudicial effect on the results of dark-field examinations in patients also infected with early syphilis (Fuga, 1968). Serum concentrations after a single oral dose of 900 mg. have been shown to be as high as 27·2 μg./ml. at 2 hrs, 15·44 at 8 hrs, and 8·33 at 12 hrs; even the level of 1·64 μg./ml. noted at 24 hrs is in excess of the minimum inhibitory concentration *in vitro* for the gonococcus (Le Petit Pharmaceuticals, 1968). The effect of a single dose of the drug was investigated first because single-session therapy has considerable administrative and epidemiological advantages.

Material and methods

103 male patients attending the Venereal Diseases Department of St. Mary's Hospital were investigated. Forty were born in the United Kingdom, 43 were Negroes, and twenty were other immigrants. The average age was 27·9 years. Nineteen were married.

Diagnosis was based on the detection of gonococci by Gram-stained urethral smears in all cases before treatment; cultures were also made in some patients.

All patients were given six 150 mg. capsules of rifampicin (90 mg.) orally under supervision and were then instructed to return within 1 to 3 days. It was planned that they should subsequently be examined at 1 and 2 weeks and then 1, 2, and 3 months from the day of treatment. At each post-treatment visit the urethra was examined for discharge and a smear was taken if any discharge was present; also the urine was examined for haze and threads. It was intended that the prostatic secretion should be examined at least once after treatment.

Follow-up and results

The rifampicin was well tolerated and no adverse side-effects were noted. Immediately after treatment

the urine was orange-red but this caused no undue concern.

By no means all patients attended at the times requested. The follow-up and results obtained are shown in Table I.

Thus, of 103 male patients treated, 89 were followed-up and there were ten suspected failures (11·2 per cent.) in patients who denied further exposure to risk of infection. The same figure was obtained if all recurrences noted in the first 2 weeks regardless of history were considered to be failures, but if only recurrences noted in the first week were counted—as has been suggested as reasonable on the basis of sensitivity findings before and after treatment in patients with gonorrohoea treated with penicillin (Curtis and Wilkinson, 1958)—the rate would have been 6·7 per cent.

Results in Negro and other patients

The results in Negro and other patients are shown in Table II. No significant differences were found.

Results related to time of last meal

The results in relation to the time of the last meal before administration of rifampicin in the 101 cases for which data are available are shown in Table III.

Comparison with single doses of other orally-administered antibiotics

In Table IV the results obtained with a single dose of 900 mg. rifampicin are compared with those yielded by single doses of limecycline, demethylchlortetracycline, ampicillin, and spiramycin, given under similar conditions.

TABLE I *Follow-up and results*

Length of follow-up	*Cases followed*	*Results*			
		Satisfactory	*Non-gonococcal infection*	*Suspected re-infection*	*Suspected failure*
0	103	—	—	—	—
1–3 days	89	15	1	—	4
4–7 days	69	7	3	—	2
8–14 days	57	3	4	1	3
15–21 days	46	3	3	—	1
22–28 days	39	—	2	2	—
1–2 months	35	10	2	5	—
2–3 months	18	1	—	2	—
Over 3 months	15	5	5	5	—
Total	89	44	20	15	10

TABLE II *Result in Negro and other patients*

Race	*Total*	*No. followed-up*	*Results*				
			Satisfactory	*Non-gonococcal infection*	*Re-infection*	*Failure*	*Percentage failure of those followed*
Negro	43	36	23	4	6	4	11·1
Others	60	53	21	16	9	6	11·3
Total	103	89	44	20	15	10	11·2

TABLE III *Results related to time of last meal*

Hours since last meal	*No. treated*	*No. followed-up*	*Result*	
			Failure	*Percentage failure of those followed*
0–2	27	23	2	8·7
2–4	30	28	3	10·7
4 and over	44	36	5	13·8
Total	101	87	10	11·4

The results obtained with single oral doses of rifampicin thus compare favourably with those previously obtained with comparable doses of other orally-administered antibiotics.

Comparison with single doses of injectable antibiotics

The findings are compared in Table V with those obtained under like conditions with single injections of injectable antibiotics.

It is evident that the results obtained with single doses of 900 mg. rifampicin were comparable to those currently obtained with single injections of 1·2 mega units procaine penicillin.

Summary and conclusions

The need for the development of new antibiotics for the treatment of gonorrhoea is stressed and the use of a new rifamycin derivative, rifampicin (Rimactane), is described.

Of 103 male patients with acute uncomplicated gonorrhoea treated with single oral doses of 900 mg. of this antibiotic, 89 were followed. There were ten apparent failures (11·2 per cent. of those followed) in patients who denied further exposure to risk of infection. This rate is identical with that of all recurrences within the first 2 weeks after treatment regardless of the possibility of re-infection.

The drug was well tolerated and the results obtained were comparable with those currently being obtained with 1·2 mega units aqueous procaine penicillin. Rifampicin thus provides an alternative means of therapy retaining all the administrative and epidemiological advantages of single-session therapy.

Our thanks are due to Ciba Laboratories and Le Petit Laboratories for supplies of Rifampicin used in this study.

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TABLE IV *Results obtained with single doses of other antibiotics*

Antibiotic	*Author*	*Date*	*Single dose*	*No. treated*	*No. followed-up*	*Result*	
						Failure	*Percentage failure of those followed*
Limecycline	Willcox	1965	816 mg. 1·22 g.	25 50	23 43	5 8	21·7 18·6
Demethylchlortetracycline	Willcox	1967	900 mg. 1·2 g.	33 52	30 46	6 6	20·0 13·0
Ampicillin	Willcox	1964	0·5–1·0 g.	200	174	26	14·9
Spiramycin	Willcox	1956	2 g. 3·4 g.	24 30	22 25	6 —	27·2 —
Rifampicin	Cobbold and others	1968	900 mg.	103	89	10	11·2

TABLE V *Results compared with single doses of injectable antibiotics*

Antibiotic	*Author*	*Date*	*Dose*	*No. treated*	*No. followed-up*	*Result*	
						Failure	*Percentage failure of those followed*
Procaine penicillin (1968–1969)	Willcox	1970	1·2 mega units	307	253	36	14·2
Procaine penicillin (1966–1967)	Morrison, Cobbold, Bor, Spitzer, Foster, and Willcox	1968	1·2 mega units	238	200	17	8·5
Procaine penicillin (1963)	Willcox	1964	1·2 mega units	279	207	23	11·1
Streptomycin	Spitzer and Willcox	1968	1·0 g.	130	104	33	31·7
Spectinomycin	Willcox	1963	1·6 g.	151	134	23	9·7
Rifampicin by mouth			900 mg.	103	89	10	11·2

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La Rifampicine (Rimactane) dans le traitement de la gonococcie

SOMMAIRE ET CONCLUSIONS

Il est nécessaire de disposer de nouveaux antibiotiques pour le traitement de la gonococcie, et l'on expose les résultats obtenus par l'emploi d'un nouveau dérivé de la Rifamicine: la Rifampicine (Rimactane).

Parmi 103 malades atteints de gonococcie aigue non compliquée, et traités par une dose buccale unique de 900 mg., 89 furent suivis. Il y eut 10 échecs apparents (11,2 pour cent des cas suivis) chez des malades qui nièrent s'être exposés de nouveau à un risque d'infection. Ce taux est semblable à celui de l'ensemble des rechutes constatées, sans tenir compte des possibilités de réinfection, au cours des 2 premières semaines après le traitement.

Le médicament fut bien toléré, et ces résultats se comparent à ceux que l'on obtient normalement avec 1,2 méga-unités de pénicilline-procaine en suspension aqueuse. Ainsi, la Rifampicine fournit un moyen thérapeutique de rechange, qui conserve tous les avantages administratifs et épidémiologiques d'un traitement en une seule séance.