Treatment of gonorrhoea with single oral doses *Results obtained with doxycycline or rifampicin compared with intramuscular penicillin*

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Since the introduction of antibiotics in the treatment of gonorrhoea, efforts have been made to reduce the entire therapy to a single dose – the so-called 'one-shot' therapy, but no generally accepted satisfactory dosage has so far been established. Once it was found that oral administration could produce an adequate concentration of antibiotic in the serum, many physicians abandoned the syringe in favour of tablets or capsules. This oral form of medication using various antibiotics in various schemes of administration, usually required one or several doses to be given on one or several days, but it always involved multiple doses. The very variable results thus obtained were ascribed in part (especially if disappointing) to uncertainty whether the scheme of administration had been followed completely, partly, or not at all; and in many cases the doubt was justifiable. The *traitement minute* (single-session therapy) which Siboulet devised with spiramycin (Siboulet and Egger, 1967), was based on the assumption that one could be certain about the medication only if the dosage prescribed were ingested at one session in the presence of a physician or nurse. Siboulet's results were very good, but because of his reports of nausea and other side-effects, we decided to look for antibiotics which could give at least comparable results without these disadvantages.

Present investigation

With the possibility that doxycycline hyclate (Vibramycin, Pfizer) and rifampicin (Rimactane, Ciba) possessed suitable properties, the following comparative study was made:

- (1) 50 patients treated with penicillin (six intramuscular injections each of 100,000 u. aqueous penicillin G at 3-hrly intervals);
- (2) 32 patients treated with doxycycline (two capsules each of 100 mg. Vibramycin in a single dose);
- (3) 50 patients treated with rifampicin (six capsules each of 150 mg. Rimactane in a single dose).

Methods

The gonococcus was demonstrated in all cases, both microscopically in a smear from the urethra and on culture, chocolate agar, after 24 hrs' incubation at 37°C. The cultures were carried out in the bacteriological laboratory of the hospital (Dr. J. J. van Gogh, Bacteriologist).

In all cultures, special attention was paid to mixed infections, and tests for sensitivity to antibiotics (penicillin, tetracycline, rifampicin, sulpha-drugs, cloxacillin, ampicillin, streptomycin, and erythromycin) were applied to both the cultured gonococcus and, separately, to such mixed bacilli as had been found. The special attention given to the mixed flora was based on the consideration that these organisms might be insensitive to the antibiotic given against the gonococcus, and that this might influence the therapeutic result, regardless of the sensitivity of the gonococcus.

All patients were military personnel in the age group 19 to 35 years. They spent one night in hospital for treatment. This was unavoidable for the first series, and was also adopted for the cases of single-session oral therapy, so that a first follow-up could be made after 24 hrs. We regarded the admission to hospital for one night as an advantage because it ensured that no alcohol was taken within the first 24 hrs, and that no fatigue occurred. These two factors are regarded by many investigators as influencing the therapeutic result (although no objective evidence to this effect is available).

The second antibiotic chosen, doxycycline hyclate (α -6-deoxy-5-oxytetracycline) was first used because one dose of 200 mg. rapidly gives a serum concentration of about 2 g./ml. which lasts about 15 hrs (Sylvestre and Gallai, 1968). The treponemicidal action of tetracyclines was considered to be a disadvantage.

The rifampicin which was used subsequently also rapidly produces a high serum concentration (27–8 g./ml.) which lasts about 12 hrs (Keberle, Schmid, and Meyer-Brunot, 1968). Investigations by Fuga and Gentili (1968) showed no effect on *T. pallidum*.

Results

In all cases, bacteriological and clinical examinations were made after 24 hrs, 1 week, and 2 weeks. A few cases were found to be positive between the second

and third examination; only those who admitted intercourse were considered to have been re-infected. Positive findings within the first week were always regarded as due to relapse even if the patient admitted further exposure to risk of infection (Table I).

Table II shows the admixture of other bacilli in the cultures. In one case there was growth of a Gram-negative rod which could not be identified exactly; in all other cases the additional organisms were coagulase-positive *Staph. aureus*.

The data in Table III indicate that an admixture or overgrowth is unlikely to be responsible for a relapse.

Determination of the sensitivity of the micro-organisms cultured was performed by the use of discs, the bacterial suspension being evenly distributed over a chocolate agar plate on which a 'multi-disc' platelet had been laid (Oxoid Limited London, Code SI). After 24 hrs' incubation at 37°C., the sensitivity was read on the basis of the presence or absence of bacteria-free zones around the discs. This method gives only a qualitative determination. The sensitivity distribution is shown in Tables IV and V.

The sensitivity *in vivo* does not always correspond with that *in vitro*; this is implied by the fact that in the penicillin group the four patients who relapsed

TABLE I *Results of therapy in three series of cases*

Group	Therapy	No. of cases	Result		
			Cure	Relapse	(Re-infection)
1	Intramuscular penicillin	50	46	4	(2)
2	Doxycycline	32	28	4	0
3	Rifampicin	50	46	4	(1)

TABLE II *Incidence of additional organisms*

Group	Therapy	No. of cultures	Culture obtained			
			Pure gonococci	Some admixture	Nearly overgrown	Failure
1	Penicillin	50	19	22	9	0
2	Doxycycline	32	11	16	4	1
3	Rifampicin	50	15	33	2	0

TABLE III *Relationship of relapses to presence of additional organisms*

Group	Therapy	No. of relapses	Cultures obtained		
			Pure culture of gonococci	Some admixture	Gonococci virtually overgrown
1	Penicillin	4	2	0	2
2	Doxycycline	4	0	2	2
3	Rifampicin	4	0	4	0

TABLE IV *Antibiotic sensitivity of gonococci*

Group	Therapy	No. of cases	No. insensitive to:				
			Sulpha	Penicillin	Doxycycline	Rifampicin	More than one
1	Penicillin	50	23	2	1	—	2
2	Doxycycline	32	8	1	—	—	1
3	Rifampicin	50	21	3	5	—	5

TABLE V *Antibiotic sensitivity of mixed flora (Staphylococci)*

Group	Therapy	No. of cases	No. insensitive to:				
			Sulpha	Penicillin	Doxycycline	Rifampicin	More than one
1	Penicillin	31	26	4	4	—	5
2	Doxycycline	20	8	1	—	—	1
3	Rifampicin	35	23	4	5	1	6

had all been found to be infected with gonococci sensitive to penicillin *in vivo*, whereas two infected by organisms insensitive to penicillin *in vitro* responded well to penicillin therapy: it must, however, be noted that the method of sensitivity testing does not distinguish degrees of partial insensitivity.

In the doxycycline group, no tetracycline-insensitive micro-organisms were discovered; organisms from the four cases of relapse were all sensitive to tetracycline. The same applies to the rifampicin group: there were no rifampicin-insensitive micro-organisms, but nevertheless there were four relapses.

No correlation was established between sensitivity *in vivo* and *in vitro* in the cases of mixed staphylococcal infection.

Because no quantitative determinations were made of resistance these facts warrant no definite conclusion.

Apart from a temporary reddish-orange discoloration of the urine, rifampicin produced no side-effects in any of the patients studied; penicillin and doxycycline caused no side-effects whatsoever.

Discussion

The results obtained with somewhat higher dosages (250 to 300 mg.) of doxycycline, as described by Sylvestre and Gallai (1968) and Domescik, McLone, Scotti, and Mackey (1969), while comparable with our results, are distinctly better (cure rate 94 to 95 per cent. compared to 88 per cent.). The disadvantage of treponemicidal action remains, however, as with penicillin and other antibiotics. The results reported by Morrison and Cobbold (1968) and Willcox, Morrison, and Cobbold (1970) with the same dosage of rifampicin are similar to ours.

Summary

In an attempt to evaluate 'single-session' therapy, 132 male patients with gonorrhoea admitted to a military hospital for diagnosis, therapy, and initial tests for cure, underwent treatment as follows: rifampicin 900 mg. orally - 50 cases; doxycycline hyclate 200 mg. orally - 32 cases. A control group of

50 cases received six injections each of crystalline penicillin G 100,000 u. at 3-hrly intervals. There were four cases of relapse in each group. It was concluded that rifampicin administered in this manner is a useful alternative to penicillin in the treatment of gonorrhoea with the added advantage that it is not treponemicidal.

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Traitement de la gonococcie avec des doses orales uniques. Résultats obtenus par la doxycycline ou la rifampicine et comparaison avec la pénicilline intramusculaire

SOMMAIRE

Dans l'idée d'évaluer le traitement en une séance, 132 gonococciques masculins, admis dans un hôpital militaire pour le diagnostic, le traitement et les premières épreuves de guérison, furent traités selon les schémas suivants: rifampicine 900 mg. oralement—50 cas; doxycycline HCl 200 mg. oralement—32 cas. Un groupe témoin de 50 cas reçut de la pénicilline G cristallisée, 6 injections de 100.000 U, à 3 heures d'intervalle. Il y eut 4 rechutes dans chaque groupe. On conclut que la rifampicine administrée de cette sorte peut remplacer utilement la pénicilline dans le traitement de la gonococcie, avec l'avantage supplémentaire qu'elle n'est pas tréponémicide.