Clinical uses and control of rifampicin and clindamycin

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At first sight, rifampicin and clindamycin may appear to have little in common: the former is best known as a potent antimycobacterial drug while the main use of the latter is in treating infections due to staphylococci and streptococci. However, they can with justification both be placed in the late Professor Mary Barber's group I of antibacterial agents that have activity against Gram-positive organisms and Gram-negative cocci (Barber, 1966). It is mainly with these aspects that the present paper is concerned, although the activity of rifampicin against Gram-negative bacilli will also be discussed.

Pharmacological Properties

RIFAMPICIN

Rifampicin is a semisynthetic derivative of rifamycin B, one of five rifamycins isolated from *Streptomyces mediterranei* (Sensi, 1969). These compounds have a unique structure among antibiotics, consisting of an aliphatic bridge spanning a chromophoric naphtho-hydroquinone group. Rifampicin acts by inhibiting DNA-dependent RNA polymerase, thus stopping the expression of bacterial genes (Hartmann, Honikel, Knüsel, and Nüesch, 1967; Furesz, 1969). This action is bactericidal.

Fig. 1 Serum levels of rifampicin after oral doses of 600 mg and 900 mg.

The pharmacological properties of rifampicin have been reviewed by Jouhar (1968) who gives many references to earlier Italian work. The antibiotic is well absorbed from the gut, but peak levels are diminished if the antibiotic is given after food. Figure 1 (modified from Furesz, Scotti, Pallanza, and Mapelli, 1967) shows mean serum levels produced after doses of 600 mg and 900 mg. There is considerable individual variation in peak levels (Verbist, 1969) but useful concentrations persist for more than 12 hours. On this basis a daily dose of about 10 mg per kilogram is recommended. In the case of tuberculosis, this is usually given as a single dose, but for acute infections it is probably best divided, and a dose of 300 mg to 450 mg twice daily would be suitable for most adults. Doses of up to 30 mg per kilogram have been given daily as a single dose without harm. It is a disadvantage that a parenteral preparation is not available for the treatment of seriously ill patients.

A microbiologically active desacetyl metabolic derivative is excreted in the bile along with the parent compound. The latter is reabsorbed from the gut resulting in an enterohepatic recirculation which maintains blood levels but desacetylrifampicin is largely not reabsorbed (Curci, Ninni, and Iodice, 1969). Excretion by the liver competes with bromsulphthalein, and falsely high BSP retention results if hepatic function is assessed by this method in patients receiving rifampicin.

Concentrations in bile reach levels above 1500 µg/ml and a plateau is attained with doses above about 300 mg, as is shown in Figure 2 (based on results of Acocella, Nicolis, and Lamarina, 1967). Bile levels are not nearly as high as those of rifamide which is rapidly and almost exclusively excreted by this route, producing concentrations of the order of 1,000 µg/ml. Unlike rifamide, rifampicin is excreted in the urine, in increasing amounts when the biliary route is saturated, that is, with doses in excess of about 300 mg (Figure 2). About 25% of a 600 mg dose is excreted in an active form in the urine in 24 hours, producing concentrations above 100 µg/ml for more than 12 hours.

Fig. 2 Rifampicin levels in serum, bile, and urine after a single oral dose of 450 mg.

Rifampicin is 85% bound to serum proteins but of the unbound fraction most is non-ionized and therefore free to diffuse more easily into the tissues (Curci *et al*, 1969). However, levels in cerebrospinal fluid are only 15% of serum levels even when the meninges are inflamed, as are levels in pleural exudate and ascitic fluid (Furesz *et al*, 1967). The drug crosses the placenta.

Both hepatocellular disease and biliary obstruction impede excretion: the half-life of rifampicin in the serum of patients with complete obstruction is about three to four times normal. Serum levels should be monitored if the drug is to be used in patients with these conditions. On the other hand renal failure has little effect on blood levels (Spring, 1968), but little is known of the fate of microbiologically inactive metabolites, and, although toxicity has not been observed, the drug should be used with caution in patients with renal failure. Rifampicin levels are not significantly affected by either peritoneal dialysis or haemodialysis (Spring, 1968).

In a recent editorial that considers over 100 reports of the clinical use of rifampicin, the *Lancet* (1969) concludes that it is 'remarkably free from

toxicity'. In a very few patients, most of them receiving other drugs in addition for the treatment of tuberculosis, serious but reversible liver damage has resulted, with raised alkaline phosphatase and transaminase levels. Many of these patients probably had preexisting liver disease. A solitary, transient rise in serum bilirubin is commoner but of less sinister significance, and probably results from competition for excretion. Because rifampicin has been shown to be teratogenic in rats and mice given the equivalent of 10 times the human dose, it should be used during pregnancy only when absolutely necessary.

Among more minor side effects reported have been reversible leucopenia, eosinophilia, rashes, and diarrhoea. Patients should be warned that rifampicin may colour urine, sputum, and tears various shades of orange.

CLINDAMYCIN

There is still confusion in the nomenclature of this drug. The British Medical Association's recently published booklet 'Today's Drugs' (1970) follows earlier American usage and refers to the drug as clindamycin. Unfortunately, a recent brand of oxytetracycline has

the proprietary name Clinimycin. The approved name, in Britain, of the drug to be discussed is clindamycin.

Clindamycin is 7-chloro-7-deoxylincomycin, a semi-synthetic derivative of lincomycin which is isolated from *Streptomyces lincolnensis*. It was one of a number of derivatives investigated for better absorption, higher activity, and a broader spectrum than lincomycin itself (Magerlein, Birkenmeyer, and Kagan, 1966). The lincomycins, like erythromycin, bind to the 50S ribosomal subunit, inhibit the binding of aminoacyl transfer RNA to nascent polypeptides, and therefore stop protein synthesis (Weisblum and Davies, 1968). This action is bacterostatic at low concentrations but bactericidal at slightly higher ones.

Figure 3, based on the results of McGehee, Smith, Wilcox, and Finland (1968), which are similar to those of Wagner, Novak, Patel, Chidester, and Lummis (1968), shows serum levels reached after oral doses of 500 mg of lincomycin and 500 mg clindamycin taken before and after food. Levels of clindamycin are considerably higher and are not significantly affected by food. Doses of 150 mg to

Fig. 3 Serum levels of clindamycin and lincomycin after oral doses of 500 mg of the two drugs before and after a meal.

450 mg clindamycin four times daily are recommended, the exact dose depending on the severity of the disease. Again, no parenteral preparation is available and lincomycin has to be substituted if injections are required.

An active demethyl derivative has been detected in serum (Brodasky, Argoudelis, and Eble, 1968) but the major metabolic pathways in man are not established. Using radioactive labelling some 60% of the drug and its metabolites can be recovered from faeces in animals (Sun, 1970). There is evidence of moderate concentration in bile, and about one eighth of the activity appears in the urine in 24 hours, considerably more than with lincomycin.

The degree of protein binding of clindamycin varies with the method of determination, but is probably low. Like the parent compound it is known to give high levels in bone and to cross into the cerebrospinal fluid in meningitis but not in the normal subject.

Cimino and Tierno (1969) have reported that anuria prolongs the half-life of clindamycin only moderately, and that only minor modification of dosage is needed in renal failure. Levels are not affected by haemodialysis. In an anephric patient whom we investigated recently, with a dose of 150 mg four times daily used to treat pneumococcal pneumonia and bacteraemia, peak levels varied between 3 $\mu\text{g/ml}$ and 3.8 $\mu\text{g/ml}$ —not much above normal—but five hours after a dose levels varied between 1.8 $\mu\text{g/ml}$ and 2.5 $\mu\text{g/ml}$. Information on the effect of biliary obstruction and liver disease is lacking, but as the major excretion route is probably via the liver, clindamycin should be used with caution in these conditions.

Like lincomycin, clindamycin has few toxic effects. Impaired bilirubin excretion has been reported, particularly among those with liver disease, as have transient rises in SGPT in apparently normal individuals. Mild diarrhoea is not uncommon, but is said to be much less troublesome than that following lincomycin. Skin rashes are relatively common according to one report (Geddes, Bridgwater, Williams, Oon, and Grimshaw, 1970) and eosinophilia has occasionally been seen.

Microbiological Assay

RIFAMPICIN

Procedures are described for the filter-paper disc method and the cup-plate or well method, using *Sarcina lutea* ATCC 9341 (*Staphylococcus lactis*, NCTC 8340) as the assay organism. We have found *Sarcina* to be more suitable than *Bacillus subtilis* which appears to be not sufficiently sensitive. The recommended assay medium is Difco Penassay seed

agar (Bacto-Antibiotic medium 1) with 3 ml $M.KH_2PO_4$ (pH 4.2) added to each 100 ml. Rifampicin standard solutions, which are stable for several weeks at 4°C, can be made by dissolving 1,000 µg/ml rifampicin in 20% methanol in pH 7 phosphate buffer, or if higher concentrations are needed, 10,000 µg/ml rifampicin in dimethyl-formamide. Serial dilutions of this stock solution over the required range should be made in serum, if serum levels are to be assayed, or in pH 7 buffer for urine. It appears that the linear portion of the standard curve lies below 10 µg/ml in the well method. Sera and other fluids will often need to be diluted for assay for this reason.

CLINDAMYCIN

Again procedures are described for the filter-paper disc and well methods using *Sarcina lutea* ATCC 9341 (*Staphylococcus lactis*, NCTC 8340) as the

assay organism and Difco Penassay seed agar (Bacto-Antibiotic medium 1). Clindamycin stock solutions, stable at 4°C for at least two weeks, are made by dissolving powder of known potency in distilled water or 0.1M phosphate buffer pH 8, to a concentration of 1,000 µg/ml. This solution is diluted in serum to give a series of standards over a range from about 10 to 0.2 µg/ml. Serum can usually be assayed undiluted.

Sensitivity Testing *in vitro*

RIFAMPICIN

It has been suggested that there is poor correlation between zone sizes around antibiotic-containing discs and minimal inhibitory concentrations (MICs) determined in liquid or on solid media (McCabe and Lorian, 1968). However, as a rough screen, disc testing is probably worthwhile: in our laboratory,

Organism	Antibiotic ¹	No. of Strains	Percentage Strains with MIC (µg/ml)														
			0.003	0.007	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32	>32
<i>Staph. aureus</i>	R	243	6	60	27	6	—	—	—	—	—	—	—	0.5	—	—	0.5
	C		—	—	—	3	90	6	—	—	—	—	—	—	—	1	
	L		—	—	—	—	—	2	11	39	43	4	—	—	—	—	1
	E		—	—	—	—	—	3	26	14	1	—	—	—	—	—	56
						↑ S											↑ R
Beta-haemolytic streptococci	R	43	—	—	18	18	22	30	10	2	—	—	—	—	—	—	—
	C		—	—	—	—	47	49	4	—	—	—	—	—	—	—	—
	E		—	—	—	—	—	47	44	9	—	—	—	—	—	—	—
	L		—	—	—	—	—	1	55	40	2	2	—	—	—	—	—
<i>Str. viridans</i> and <i>Str. pneumoniae</i>	C	52	—	—	40	42	18	—	—	—	—	—	—	—	—	—	—
	E	52	—	—	—	79	11.5	7.5	2	—	—	—	—	—	—	—	—
	R	25	—	4	24	24	44	4	—	—	—	—	—	—	—	—	—
	L	52	—	—	—	—	—	25	46	21	8	—	—	—	—	—	—
<i>Str. faecalis</i>	R	10	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
	E	12	—	—	—	—	—	—	—	—	30	20	10	10	30	—	—
	C	12	—	—	—	—	—	—	—	8	17	23	25	17	—	—	—
	L	12	—	—	—	—	—	—	—	—	—	8	—	—	—	—	92
											↑						100
<i>Cl. welchii</i>	R	14	—	—	—	71	—	—	—	14.5	14.5	—	—	—	—	—	—
	C		—	—	—	—	—	—	71	—	—	—	29	—	—	—	—
	L		—	—	—	—	—	—	—	7	86	7	—	—	—	—	—
	E		43	57	—	—	—	—	—	—	—	—	—	—	—	—	—
								↑									
<i>Neisseria gonorrhoeae</i>	E	82	—	—	—	24	40	20	9	3	2	2	—	—	—	—	—
	R	105	—	6	2	3	30	40	15	4	—	—	—	—	—	—	—
	C	82	—	—	—	2	2	—	5	21	18	29	23	—	—	—	—
	L	82	—	—	—	—	—	—	—	2	—	3	4	4	32	31	24
					↑ S				↑ R								
<i>Haemophilus influenzae</i>	R	36	—	—	—	—	—	28	60	9	3	—	—	—	—	—	—
	E		—	—	—	—	3	—	—	—	9	44	44	—	—	—	—
	C		—	—	—	—	3	—	—	3	—	—	19	42	11	11	11
	L		—	—	—	—	—	—	—	—	—	3	—	11	44	33	9
								↑ S			↑ R						

Table I Sensitivity to rifampicin, clindamycin, lincomycin, and erythromycin of strains of common pathogenic bacteria recently isolated from clinical samples

¹C = clindamycin, E = erythromycin, L = lincomycin, R = rifampicin, arranged in order of diminishing sensitivity *in vitro* for each organism.

↑ usual MIC of penicillin G. ↑ S MIC of penicillin for sensitive strains. ↑ R MIC of penicillin G for more resistant strains (from Garrod and O'Grady, 1968).

using a 2 μ g disc, highly sensitive *Clostridium welchii* had zones of 30 to 44 mm diameter, sensitive beta-haemolytic streptococci zones of 22 to 32 mm diameter, relatively less sensitive *Haemophilus influenzae* had zones of 0 to 14 mm diameter, and similarly less sensitive *Streptococcus faecalis* had zones of 0 to 12 mm diameter. All staphylococci had moderate zones with the exception of the only two resistant strains which had no zones. Table I shows the range of MICs for all these strains.

CLINDAMYCIN

There is good correlation between results of disc sensitivity testing and MICs. In our laboratory, beta-haemolytic streptococci, with MICs of 0.006 to 0.12 μ g/ml, had zones around a 2 μ g disc of 17 to 28 mm, with 32 out of 37 tests falling in the range 19 to 23 mm. Sensitive *Str. viridans* and *Str. pneumoniae* had similar zone sizes. *Cl. welchii* with MICs of less than 0.03 μ g/ml had zones of 30 to 35 mm, while those with MICs of 0.5 or 1 μ g/ml had zones of 21 to 29 mm. Many strains of *H. influenzae*, with MICs mostly above 4 μ g/ml, had no zones of inhibition, although nine out of 45 strains had zones of 8 to 13 mm in diameter. No strains of *Str. faecalis*, most of which had MICs above 32 μ g/ml, had zones. Sensitive *Staph. aureus* with MICs around 0.06 μ g/ml had zones ranging from 19 to 27 mm, while three resistant strains with MICs greater than 32 μ g/ml had no zones.

Determination of Bacteriostatic and Bactericidal Activity

McCabe and Lorian (1968), Kunin, Brandt, and Wood (1969), Atlas and Turck (1968), and Arioli, Pallanza, Furesz, and Carniti (1967) have recently discussed the activity *in vitro* of rifampicin. Garrison, DeHaan, and Lawson (1968) and Phillips, Fernandes, and Warren (1970) have similarly reported studies on clindamycin.

MINIMUM INHIBITORY CONCENTRATIONS

For both antibiotics, MIC determinations are uncomplicated. With rifampicin, results are little affected by the addition of protein, pH makes little difference over a range pH 6-8, and changes of inoculum size up to about 10^6 organisms have little effect (McCabe and Lorian, 1968; Arioli *et al*, 1967). Clindamycin sensitivity is similarly little affected by these factors.

Table I shows our determinations of MICs of rifampicin, clindamycin, lincomycin, and erythromycin for a series of common pathogens isolated recently in the Department of Clinical Microbiology, St. Thomas's Hospital. Average expected penicillin

MICs are also indicated, although they were not actually determined for these particular strains. Important organisms not included, but tested by others, and differences between our results and those of others are commented on below.

Staph. aureus

We examined 243 selected strains, 34 sensitive to all antibiotics, 43 resistant to penicillin only, 29 resistant to penicillin, streptomycin, and tetracycline, and 137 resistant to erythromycin (that is all the erythromycin-resistant staphylococci isolated in this laboratory in the past five years). Among the more resistant strains, 25 were also resistant to methicillin. Rifampicin is the most active drug: all strains are inhibited by 0.03 μ g/ml or less, except two resistant strains with MICs of 8 μ g/ml and 32 μ g/ml. Rifampicin was not used in St. Thomas's Hospital when these organisms were collected. As expected, clindamycin is more active than lincomycin, and is also more active than erythromycin. Among the 137 erythromycin-resistant strains, only three were resistant to clindamycin and lincomycin. Neither lincomycin nor clindamycin was much used when these strains were collected and therefore we have no information on the emergence of resistance noted by Geddes *et al* (1970). Many of the erythromycin-resistant strains were isolated at a time when that antibiotic was fairly widely used, usually in combination with novobiocin (Ridley, 1966). On a weight-for-weight basis rifampicin is as active as penicillin G (against sensitive strains) and clindamycin is as active as cloxacillin.

Staph. albus

Published reports indicate that coagulase-negative staphylococci are generally as sensitive as *Staph. aureus* to both rifampicin and clindamycin.

Beta-haemolytic streptococci

The 43 strains examined included 18 group A, 2 group B, 16 group C, and 7 group G. None of the antibiotics are as active as penicillin G but all are highly effective in the order rifampicin, clindamycin, erythromycin, lincomycin. We did not encounter either erythromycin- or lincomycin/clindamycin-resistant strains, although both have been reported, especially from burns units (Lowbury and Hurst, 1959; Kohn, Hewitt, and Fraser, 1968; Kohn and Evans, 1970).

Str. viridans and *Str. pneumoniae*

We tested 25 strains of *Str. viridans* and 27 pneumococci (only about half of each with rifampicin). Clindamycin, erythromycin, and rifampicin are all about as effective as penicillin. We did not see

Antibiotic	<i>Str. viridans</i> from Blood before Treatment	<i>Str. viridans</i> from Teeth after Penicillin	<i>Str. faecalis</i> from Blood before Treatment
Penicillin	0.001	0.3	2.5
Cephaloridine	0.005	0.3	2.5
Vancomycin	0.6	1.2	5.0
Erythromycin	0.03	0.03	—
Clindamycin	0.03	0.03	10.0
Rifampicin	0.03	0.03	—
Streptomycin	25.0	12.5	>100
Gentamicin	10.0	5.0	10.0
Kanamycin	50.0	25.0	25.0

Table II Minimum inhibitory concentrations of nine antibiotics for streptococci isolated from blood and teeth in cases of subacute bacterial endocarditis

resistant pneumococci although they have been reported, almost always after treatment with either lincomycin (Dixon, 1967) or rifampicin (Citron and May, 1969).

A number of strains of streptococci isolated from patients with bacterial endocarditis have been examined in more detail. As an example of our results Table II shows MICs of a wide range of antibiotics for three streptococci, two of them *Str. viridans* isolated from the blood before treatment and from the teeth of the same patient after penicillin, and the third, *Str. faecalis*-like, isolated from the blood of another patient before treatment. When the first two strains are compared, it will be seen that the expected increase in penicillin resistance has occurred, and this has been accompanied by a very similar increase in cephaloridine resistance. However, MICs of clindamycin, rifampicin, erythromycin, and vancomycin, as well as gentamicin, kanamycin, and streptomycin, have remained unchanged. It is often suggested that these organisms are *Str. faecalis*-like in antibiotic sensitivity, but this is clearly untrue from these results, which are representative of a number that we have examined.

Str. faecalis

Neither lincomycin nor clindamycin has useful activity against *Str. faecalis* with MICs usually greater than 32 µg/ml. Erythromycin is a little better than rifampicin, but neither drug has much to offer in the treatment of infections with this difficult organism.

Cl. welchii

We examined only 14 strains, all of which were sensitive to all three agents. Rifampicin is best and is as active as penicillin. Both clindamycin and lincomycin are generally more effective than erythromycin, but it is interesting that strains fell into two groups, one highly sensitive and the other somewhat less sensitive. Willis (personal communication) has found all of 161 strains of *Cl. welchii* sensitive to clindamycin in disc sensitivity tests.

Other Gram-positive bacilli

Willis (personal communication) found all of 71 strains of *Cl. tetani* sensitive to clindamycin, but among other Clostridia some were sensitive and some resistant. *Bacillus anthracis* and *Corynebacterium diphtheriae* are usually sensitive to both clindamycin and rifampicin (Garrison *et al*, 1968). Clindamycin is active against *Actinomyces* (Lerner, 1969) but neither clindamycin nor rifampicin seems active against *Nocardia*.

Neisseria gonorrhoeae

Both erythromycin and rifampicin are about as active as penicillin against 82 strains examined. Clindamycin, like lincomycin, is much less active.

Neisseria meningitidis

It has been reported that *N. meningitidis* is, like *N. gonorrhoeae*, sensitive to rifampicin (Deal and Sanders, 1969) and resistant to the lincomycins (McGehee *et al*, 1968).

Haemophilus influenzae

It is generally agreed that rifampicin is moderately active, erythromycin is less so, and lincomycin only weakly active but there is disagreement on the range of sensitivity of *H. influenzae* to clindamycin. Garrison *et al* (1968), McGehee *et al* (1968), and Pelzl (1969) report MICs in the range found by us, but Oppenheimer and Turck (1968), Meyers, Kaplan, and Weinstein (1969), Geddes *et al* (1970), and Zinnemann and Fraser (1970) have found them considerably more sensitive. Until strains are exchanged and methods compared directly, the controversy will continue.

Bacteroides

Ingham, Selkon, Codd, and Hale (1970) have found *Bacteroides fragilis* sensitive to clindamycin, with MICs in the range 0.07 to 0.6 µg/ml and sensitive to rifampicin B (and thus, presumably, to rifampicin). Willis (personal communication) found five strains of *Bacteroides melaninogenicus* and 13 of 15 other

Bacteroides species sensitive to clindamycin, using 2 µg discs.

Other Gram-negative bacilli

Rifampicin was highly active against two strains of *Pasteurella multocida* tested by Arioli *et al* (1967). It also has considerable activity *in vitro*, unlike clindamycin, against a large number of other Gram-negative bacilli. Minimum inhibitory concentrations in the range 1-15 µg/ml are reported for *Pseudomonas aeruginosa*, *Escherichia coli*, *Klebsiella-Enterobacter*, *Proteus*, *Salmonella*, *Shigella*, and *Brucella* (Arioli *et al*, 1967; Atlas and Turck, 1968; McCabe and Lorian, 1968; Kunin *et al*, 1969). On this basis it is rather more active than ampicillin or cephaloridine.

Mycoplasmata

Clindamycin is active, though less so than erythromycin, against *M. pneumoniae*, but unlike erythromycin it is active against *M. hominis* (Harwick and Fekety, 1969). Rifampicin has a very weak action on *M. hominis* (Harwick and Fekety, 1969).

BACTERICIDAL PROPERTIES

Rifampicin

If bactericidal concentrations (MBCs) of rifampicin are determined in liquid medium with a light inoculum, MBCs and MICs appear to be very close. If, however, heavier inocula are used, 'skip' tubes become common even in MIC determinations, that is, in a series of increasing concentrations of antibiotic, no growth occurs in some but *does* occur in occasional tubes containing more antibiotic. This is due to the presence of resistant mutants, found in a proportion of $1:10^{6-7}$ in many strains of *Staph. aureus*, for example (McCabe and Lorian, 1968), a rate similar to that of resistance to fusidic acid, erythromycin, and streptomycin. However, the very low MBCs obtained with small inocula are also often false, as Baudens and Chabbert (1969) have demonstrated that rifampicin remains attached to cells on subculture and can only be removed by several washes in antibiotic-free medium. They have also shown that such antibiotic-free cells do not begin to multiply immediately but remain quiescent for several hours and then multiply at a normal rate—a phenomenon that they call 'bacteriopause'.

Clindamycin

There appear to be no problems in determining bactericidal levels of clindamycin, and MBCs are usually about 10 times the MICs.

The Clinical Uses of Rifampicin and Clindamycin

The review of antibacterial activity *in vitro* of these two antibiotics suggests that both deserve serious consideration for use against most Barber group 1 organisms, and that rifampicin should also be considered in the treatment of infections due to a wide range of Gram-negative organisms. However, despite these encouraging results *in vitro*, the use of these drugs should be restricted for two reasons. First, penicillin is almost always as active or more active *in vitro*, and we know the good clinical potential of penicillin. Therefore when penicillin is known to be highly effective and not to be clinically contraindicated, for example by hypersensitivity, it should be preferred. The second reason is the emergence of resistance during treatment, almost unknown with penicillin, but seen with clindamycin relatively uncommonly and with rifampicin so often as to make the antibiotic alone virtually useless. Unfortunately, clindamycin resistance seems to emerge more rapidly in erythromycin-resistant staphylococci *in vitro* (McGehee, Barrett, and Finland, 1969).

Clindamycin has actually been used in a variety of infections due to sensitive organisms and has given, on the whole, very good results. Against *Staph. aureus* infections it has been at least as good as the penicillins for cellulitis, abscesses, and wound infections, as well as in more severe infections such as osteomyelitis, pneumonia, and septicaemia (Daschner and Marget, 1969; Pelzl, 1969; Schlegel and Hieber, 1969; Kanee, 1969; Geddes *et al*, 1970). It appears to give results as good as lincomycin, and possibly better than the penicillins, in staphylococcal infections of bones and joints (Geddes *et al*, 1970). Clindamycin has also given results as good as penicillin or erythromycin in the treatment of respiratory tract infections due to *Str. pyogenes*, and in streptococcal cellulitis and pyoderma (Berman and Levine, 1969; Kanee, 1969; Lattanzi, Krosnick, Hurwitz, Goldstein, and Krassner, 1969). It has been used successfully in a variety of pneumococcal infections (Geddes *et al*, 1970). In the absence of a clinical trial, its usefulness in the treatment of chronic bronchitis is difficult to assess, in spite of suggestions that both serum and sputum levels are adequate (Mitchell, 1970).

There remains a variety of infections for which clindamycin deserves to be assessed, as, for example, diphtheria, and *Bacteroides* infections, and in the prophylaxis of bacterial endocarditis, tetanus, and gas gangrene.

In whatever situation it is used, one should be prepared for the emergence of resistance during treatment—already reported with *Staph. aureus*,

pneumococci, and beta-haemolytic streptococci. The more regular use of other antibiotics in combination might prevent this. It should replace lincomycin completely, except when injections are needed.

Rifampicin is more difficult to assess from the few reports of clinical uses. The strikingly successful use is in tuberculosis, for which it is possibly the most active available drug, always used in combination with other drugs. We must ensure that this position is not jeopardized by its indiscriminate use in other conditions.

When rifampicin is used, it should almost always be used in combination with at least one other drug such as erythromycin, clindamycin, fusidic acid, or an aminoglycoside (Bals and Filipescu, 1969). In a small reported series Jensen (1967 and 1968) describes good clinical results in severe staphylococcal disease, but rifampicin resistance emerged in a number of cases in spite of the addition of fusidic acid or novobiocin. The point should not be missed, however, that clinical effects were good in infections with organisms resistant to most of the usual antistaphylococcal drugs. In addition to Jensen's report, there are brief reported series of cases of less serious staphylococcal disease and of respiratory tract infection that appear to have responded favourably (Brickner, 1969).

Gonorrhoea has also been treated with rifampicin, with a 10% failure rate in one series of patients given a single oral dose of 900 mg. Increased doses might cut down failure rate but better results can be obtained at the moment with several drugs. The emergence of resistance was not considered in this report (Willcox, Morrison, and Cobbold, 1970).

The worst clinical results are reported when rifampicin has been used to treat infections due to Gram-negative organisms—mostly of the respiratory and urinary tracts. For example, Citron and May (1969) treated five chronic bronchitics with rifampicin alone: all failed to respond and rifampicin-resistant *H. influenzae* and pneumococci were isolated after, but not before, treatment. Using rifampicin for the treatment of urinary tract infection, Murdoch, Speirs, Wright, and Wallace (1969) report clinical failures in 11 of 19 patients given 900 mg daily in divided doses, and relapse in the remaining eight, and Atlas and Turck (1968) report 23 failures out of 27 patients treated with 300 mg three times daily with large increases of antibiotic resistance in surviving organisms. Brickner (1969) also reports many failures. On the other hand, Trafton and Lind (1970) have recently reported a strikingly different situation. They treated 57 patients with genito-urinary infection, both acute and chronic, who had failed to respond to a variety of other antibiotics, using a dose of 300 mg three

times daily. Immediate results, both clinical and bacteriological, were on the whole good, but details on follow up are not included.

In one situation, tuberculosis apart, rifampicin seems to be a better drug than any, and this is in the clearing of meningococcal throat carriers. Deal and Sanders (1969) have reported from Florida that a dose of 600 mg per day for four days results in a permanent reduction of carriage rate by 93.3% and that no resistant organisms have emerged. Rifampicin is almost as good as was sulphadiazine when meningococci are fully sensitive, and is much more effective than any other agent. The results of more widespread use are awaited with interest.

Conclusion

Rifampicin and clindamycin are two non-toxic, orally administered antibiotics that have in common an antibacterial spectrum covering Gram-positive organisms. Both can be considered as alternatives to penicillin which should be used whenever possible. In addition rifampicin has high antimycobacterial activity, particular activity against *Neisseria meningitidis*, and unstable activity on many Gram-negative bacilli. Because of the likelihood of the emergence of resistance both rifampicin and clindamycin should probably always be used in combination with other antibiotics. Clindamycin already has a well assured clinical place in the treatment of infection due to Gram-positive organisms, but rifampicin should at the moment be reserved for the treatment of tuberculosis, for the treatment of meningococcal carriers, and for serious sepsis, particularly staphylococcal, due to organisms resistant to conventional drugs.

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