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Evidence that rifampicin can be used safely for non-tuberculous diseases

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ABSTRACT The incidence of primary resistance to rifampicin in *Mycobacterium tuberculosis* has been analysed in countries where rifampicin is restricted to use for treating tuberculosis and in countries where its use is not restricted. There is no evidence that rifampicin-resistant *M tuberculosis* strains are more common where the use of the drug is unrestricted. Resistance to rifampicin is less common than is resistance to streptomycin or to isoniazid. We can thus see no danger of producing resistant strains of *M tuberculosis* if rifampicin therapy is used for short periods for non-tuberculous infections. The problem of resistant mutants arising in the non-tuberculous species being treated is overcome by combining rifampicin with trimethoprim.

Rifampicin has a uniquely wide spectrum of antimicrobial activity, which includes Gram-positive and Gram-negative organisms as well as *Mycobacterium tuberculosis*.[1] Because of this, in a relatively early phase of the clinical use of this antibiotic for non-tuberculous indications, rifampicin was employed alone in infections of the chest[2] and urinary tract.[3 4] However, the observation that in these circumstances resistant mutants were rapidly selected caused the use of monotherapy with rifampicin in non-tuberculous infections to fall into disrepute.

As a logical means of overcoming this problem, a combination of rifampicin and trimethoprim was envisaged, based on a "double blockade" type of approach. The basic assumptions were confirmed in a series of microbiological studies,[5 6] which indicated both the existence of synergism between the two compounds and the prevention of the selection of resistant mutants. The situation concerning fears for the development of resistance in *M tuberculosis*[7] as a result of rifampicin/trimethoprim being used was summarised in a provocative editorial.[8]

Since then, the pharmacokinetic properties of the combination[9 10] and its clinical effectiveness[11] have been evaluated, and confirmed the encouraging preclinical evidence. A further and most important part of the development of the combination has been, and continues to be, devoted to the evaluation of possible risks connected with the extra-tuberculous use of rifampicin.

We agree whole-heartedly with Simmons[12] who stated: "those who advocate that rifampicin should be used much more freely should surely be certain that the risk of development of widespread rifampicin-resistant *M tuberculosis* is not only small but virtually non-existent." We, therefore, decided to carry out a comparative study on primary resistance in *M tuberculosis* to rifampicin in countries where the use of the antibiotic is restricted to tuberculosis, and in those where it is freely available for the treatment of both tuberculous and non-tuberculous infections.[13] Our results indicated that *M tuberculosis* had remained uniformly sensitive to rifampicin after several years of use in both groups of countries. The incidence of primary resistance to rifampicin was extremely low. It was lower (although not significantly) than that observed to ethambutol and PAS (which are used only for tuberculosis), and significantly lower than that observed to streptomycin and isoniazid.

In view of the importance of this information we have decided to update and to extend the survey. The new and old data are reported in the present communication.

Method and sources

Primary resistance was defined, detected, and diagnosed as by Canetti *et al.*[14] Data were

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collected from countries and centres shown in tables 1 and 2, not only from the literature but also by personal communication with a number of acknowledged experts: Dr J Grosset (Paris), Dr FJ Guerra-Sanz and Dr Ortega-Calderon (Madrid), Dr M Tavares da Lima Filho (Sao Paulo), Dr GA Jaramillo (Bogota), Dr A Giobbi (Milan), and Dr M Lucchesi (Rome). In France, USA, and West Germany rifampicin is restricted for use in tuberculosis, while in the other countries in tables 1 and 2 it is freely available for the treatment of any infection.

Results

As is clear from table 1, the incidence of primary resistance to rifampicin is low and has not changed with time—hence, for practical purposes, it is a small clinical problem. From the data in table 2 it can be observed that much the same applies for the other major antitubercular drugs. Primary resistance has altered very little with time, and is relatively low in absolute terms.

Discussion

As in the previous survey, the level of sensitivity is similar in countries like France, where rifampicin is used only for tuberculosis, and Colombia, where the ratio of non-tubercular to tubercular use of the antibiotic is of the order of 9:1.

In agreement with the previous observations, the very few cases of acquired resistance to rifampicin were found to be associated with the improper use of the drug in tuberculous patients, including cases of monotherapy. The latter observation is important, since it is well known that cases of bacteriological failure observed during combined antituberculosis regimens can occur with strains which are still sensitive to rifampicin.[30]

It can, therefore, be concluded that treatment of non-tuberculous infections with rifampicin for short periods does not carry a risk of selecting rifampicin-resistant strains of *M tuberculosis*. Thus, the proposed use of the combination rifampicin-trimethoprim for periods of one week in non-tuberculous indications should in no way jeopardise the antituberculous efficacy of rifampicin.

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Table 1 *Percentage of strains of M tuberculosis found primarily resistant to rifampicin in the years 1969-78 in numerous different geographical locations*

Country	*Centre* (*)	*Reference* (**)	*Percentage primary resistance of M tuberculosis to rifampicin in indicated years (no of strains tested in parentheses)* 1969	1970	1971	1972	1973	1974	1975	1976	1977	1978
Italy	MI	15 (1978)			1·05(379)	0·87(689)	0·48(617)	0·62(484)	0·00(486)	0·83(479)	0·00(443)	0·00(429)
	CE	15			←	0·00(433)	→					
	VR	16				←	0·58(173)	→				
	RO	17 (1977)			0·90(119)	1·06(283)		0·40(248)	0·90(331)	0·91(328)	0·76(261)	
	SS	17 (1974)	←		0·00(70)	→						
	NA	18 (1976)	←		0·0(726)	→		←	0·4(464)	→		
	TO	19				←	0·58(171)	→				
Argentina	NAT	20	←		0·00 (3110)	→						
Brazil	VAR	21				←	→		0·00(1268)	→		
Colombia	NAT	†			←	→		0·0(653)	→			
Spain	VA	22 (1978)		←		0·0(1216)	→		0·35(564)	0·2(675)	0·2(938)	
	VA	23							1·40(136)			0·00(179)
	SA	23							0·00(110)			
France	VAR	24								←	0·00(1907)	→
	LY	25			←	0·2(483)	→	←	0·0(369)	→		
Tunisia	SF	26					←	0·28(713)	→			
West Germany	NAT	27				←	0·1(1036)	→				
USA	MAIN	28						←	0·3(3146)	→		
USA	HW	29				←		0·0(313)	→			

(*) MI = Milan; GE = Genoa; VR = Verona; RO = Rome; SS = Sassari; NA = Naples; TO = Turin; NAT = National; VAR = Various VA = Valencia; MA = Madrid; SA = Salamanca; LY = Lyon; SF = Sfax; MAIN = Mainland; HW = Hawaii.
(**) Year quoted in parentheses indicates year of last updating completed (generally unpublished).
† Personal Communication, Jaramillo 1979.

Table 2 *Comparative data on percentage of primary resistance of M tuberculosis to some of the major antituberculous drugs in different countries*

Percentage primary resistance of M tuberculosis at the indicated years and countries

Antitubercular agents	*Italy*	*Argentina*			*Brazil*		*Spain*			*France*	*Tunisia*	*West Germany*	*Mainland USA*		*Hawaii*	*Bolivia, Colombia Mexico*
	1975–77	*1969*	*1972*	*1969–74*	*1975*	*1978*	*1970*	*1975*	*1977*	*1978*	*1978*	*1973–75*	*1972–75*	*1961–66*	*1975–77*	*1972–77*	*1974–77*
Streptomycin	6·9	6·7	5·7	6·1	10·5	1·68	6·6	10·4	9·16	7·8	5·8	6·31	2·9	2·3	5·1	1·0	2·6
Isoniazid	3·17	3·7	3·2	3·8	9·7	5·04	8·8	7·2	6·60	5·5	2·4	7·99	3·4	1·8	4·4	0·3	4·5
p-Aminosalicylic acid	0·84	0·2	0·2	0·2	2·2		0·0	0·17	0·53	0·5	—	1·14	1·9	0·7	1·3	0·3	1·6
Ethambutol	0·84	0·0	0·0	0·0	0·0		0·0	0·17	0·21	0·5	0·05	—	0·2	—	0·7	0·0	0·6
Kanamycin	0·31	0·0	0·07	—	1·3		—	—	—	—	—	—	—	—	0·1	—	—
Rifampicin	0·74	0·0	0·0	0·0	0·0	0·0	0·0	0·35	0·21	0·0	0·0	0·28	0·1	—	0·3	0·0	0·0

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