PAPERS AND ORIGINALS

Adverse Reactions to Daily and Intermittent Rifampicin Regimens for Pulmonary Tuberculosis in Hong Kong*

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British Medical Journal, 1972, 1, 765-771

Summary

This paper reports the nature, incidence, and severity of adverse reactions to regimens of rifampicin and ethambutol given once weekly, twice weekly, or daily and to a standard reserve regimen in a total of 330 Chinese failure patients who completed at least six months' chemotherapy in a therapeutic comparison in Hong Kong.

The adverse reactions which occurred on the regimens of intermittent rifampicin were termed cutaneous, abdominal, "flu", and respiratory; in addition, purpura and abnormal liver function tests were encountered. There was an association of adverse reactions with the interval between doses and with the dose size of rifampicin, the highest incidence occurring with once-weekly rifampicin

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in high dosage. A procedure was developed for managing adverse reactions to intermittent rifampicin. Of 202 patients treated with intermittent rifampicin 60 developed adverse reactions, but in only 7 (3%) was it necessary to terminate the drug, though a further 10 (5%) were changed to daily rifampicin. On daily rifampicin, generalized hypersensitivity, cutaneous reactions, (one with purpura), and impaired liver function were encountered. Adverse reactions on the standard ethionamide, pyrazinamide, and cycloserine regimen were frequent and some were serious.

Introduction

There is a large body of evidence that rifampicin in combination with other suitable drugs in daily regimens (Decroix *et al.*, 1969, 1971; Newman *et al.*, 1971; Pines, 1971), or even when given alone (Nitti, 1969; Lucchesi and Mancini, 1970), is a potent antituberculosis agent. In-vivo and in-vitro experiments have suggested that it may be even more effective than isoniazid (Canetti *et al.*, 1968). A number of workers have reported on the efficacy of intermittent rifampicin in animal disease (Grumbach and Rist, 1967; Grumbach *et al.*, 1969, 1970; Verbist, 1969; Batten, 1969, 1970; Verbist *et al.*, 1971), and Dickinson and Mitchison (1970), in experimental tuberculosis of the guinea-pig, found that to retain equivalent suppression of lesions and reduction of viable counts in the spleen it was not necessary to increase the dose size proportionately as the interval between doses was increased from one to eight days. Suggestions that the increased efficacy with increasing interval between doses can be completely accounted for by the more than proportionate rise in serum concentration which occurs with increasing dose size (Furesz *et al.*, 1967; Constans *et al.*, 1969; Dickinson and Mitchison, 1970) are not supported by the recent work of Dickinson *et al.* (1972). Although the mechanisms of action are not yet fully understood, there is now considerable laboratory evidence that rifampicin is a drug which is particularly valuable in fully intermittent regimens.

Rifampicin, when given in conventional daily dosage in man, although highly effective (Decroix *et al.*, 1971), is very expensive, costing well over £200 for a year's chemotherapy. This makes its use in daily regimens for newly diagnosed cases unrealistic

in most developing countries and indeed in many of those that are technically advanced (Fox, 1969). If an intermittent regimen containing a smaller total weekly dosage which was both therapeutically effective and of low toxicity could be found, the applicability of this valuable drug would be much increased. Furthermore, the level of success achieved with standard reserve regimens in the treatment of failure patients is often disappointingly low (British Tuberculosis Association, 1963; International Union Against Tuberculosis, 1968). One of the reasons for this is that patients fail to take regularly, for many months, unpleasant daily regimens which can only exceptionally be fully supervised. There is, therefore, an urgent need for reserve regimens which are highly effective, which can be fully supervised on an outpatient basis, which are relatively non-toxic, and which are cheap. All these criteria may be met by intermittent regimens (Fox, 1969, 1971).

For these reasons it was decided to explore in Hong Kong the role of rifampicin in combination with ethambutol in reserve regimen chemotherapy, studying the combination when given daily, twice weekly, and once weekly, the dosages of rifampicin (and ethambutol as well) being increased moderately as the interval between doses increased. Because of the evidence that an initial intensive phase may improve the efficacy of intermittent regimens of other antituberculosis drugs (Tuberculosis Chemotherapy Centre, Madras, 1970), it was decided to include in the study a regimen in which the once-weekly administration of rifampicin and ethambutol was preceded by a two-month period of daily treatment with these drugs. In order fully to evaluate these four regimens, in terms of both therapeutic efficacy and toxicity, the standard failure regimen of ethionamide, pyrazinamide, and cycloserine used in Hong Kong was also included as an essential control.

Although some workers have encountered no serious toxicity when giving rifampicin plus isoniazid intermittently (Decroix *et al.*, 1971; Verbist *et al.*, 1971), Poole *et al.* (1971), giving the same combination, reported a high incidence of unusual and sometimes serious adverse reactions. Adverse reactions have also been reported with intermittent rifampicin plus ethambutol (Zierski, 1971; Eule, 1971), and they have also been encountered in the current Hong Kong study. Relatively few patients have yet completed a year of treatment, so the observations reported here are interim ones. The full findings, including the crucial therapeutic results, will be published when all patients have completed their full course of chemotherapy. It is the aim of the present paper to describe the syndromes attributable to intermittent rifampicin which are occurring in the study and to compare the frequency and severity of adverse reactions on the three intermittent rifampicin regimens, on the daily rifampicin regimen, and on the standard reserve regimen. Finally, the ways in which adverse reactions to intermittent rifampicin are now being managed in clinical practice in Hong Kong are described.

Plan and Conduct of the Study

PATIENTS ADMITTED TO THE STUDY

For the main intake patients with active pulmonary tuberculosis from the six main Government tuberculosis clinics and the four hospitals co-operating were eligible for admission to the study if they were aged 15 years or over, had had at least six months' treatment with standard chemotherapy, including isoniazid plus streptomycin and/or PAS, but had had no treatment with any of the second-line drugs used in the study, had a positive sputum on direct smear examination, and were known to be infected with strains resistant to isoniazid. Patients with non-tuberculous disease which might have been exacerbated by any of the drugs under study were excluded. After a few months a subsidiary group of patients previously treated with ethionamide or pyrazinamide or cycloserine were admitted but were allocated only to the four rifampicin-containing regimens.

REGIMENS

In the main intake the patients were allocated at random to one of the following five regimens:

EtZC—the standard reserve regimen for Hong Kong—namely, ethionamide (0.75 or 0.5 g) plus pyrazinamide (2.0 or 1.5 g) plus cycloserine (0.5 g) daily for six months, followed by ethionamide plus pyrazinamide daily, given together in one dose a day.

ER₇—ethambutol plus rifampicin daily.

ER₂—ethambutol plus rifampicin twice a week.

ER₁—ethambutol plus rifampicin once a week.

ER₇ER₁—ethambutol plus rifampicin daily for two months and then once a week.

The rifampicin dosages, which were given as a single dose, were 450 mg in the daily regimen and in the intermittent regimens, 900 mg for patients weighing less than 90 lb (40.9 kg), 1,050 mg for patients weighing 90–109 lb (40.9–49.5 kg), and 1,200 mg for patients weighing 110 lb (49.9 kg) or more. The dosages of once-weekly rifampicin in the ER₁ and ER₇ER₁ regimens were originally higher (1,200, 1,500, and 1,800 mg for the three weight classes) but were reduced to the lower schedule seven months after the intake had begun because of the occurrence of adverse reactions. The results for the patients who started once-weekly treatment with the higher dosage schedules, termed the ER₇ER₁ (high) and ER₁ (high) groups, have been presented separately from the ER₇ER₁ and ER₁ groups who received the same dosage schedule as the ER₂ patients.

The ethambutol dosages, given as a single dose, were 25 mg/kg body weight for two months and then 15 mg/kg in the daily regimen, 45 mg/kg per dose in the twice-weekly regimen, and 90 mg/kg per dose in the once-weekly regimen.

Because of the reduction in rifampicin dosage which was made in the once-weekly regimens, the findings for the individual regimens presented in this report are not strictly concurrent.

RECORDING OF ADVERSE REACTIONS

Monthly reports on each patient were sent from Hong Kong to London, giving details of the chemotherapy received during the month, the serum alanine aminotransferase (SGPT) results, and the severity (mild, moderate, or severe) and management of any adverse reactions which had occurred during the month. For the rifampicin-containing regimens special care was taken to clarify any doubts about the nature of symptoms, the frequency or severity of reactions, or their management. Other liver function tests were performed if SGPT levels rose above normal.

MANAGEMENT OF ADVERSE REACTIONS

How the episodes were managed in actual practice is described in the results section. As the study progressed a general procedure for managing adverse reactions on intermittent regimen was evolved. This is described in the discussion.

Results

PATIENTS IN THE ANALYSIS

This interim analysis was restricted to 330 patients who had completed six months in the study—namely, 74 ER₇ patients, 69 ER₂, 33 ER₁, 48 ER₇ER₁, 34 ER₁ (high), 18 ER₇ER₁ (high), and 54 EtZC.

Fourteen other patients were excluded. One (ER₂) who had had no adverse reactions, absconded in the fourth month. Three ER₇ER₁ patients received over five months' treatment on the daily regimen in error—one had no adverse reactions, the second had a transient rise in SGPT in the third month so that the therapy was temporarily interrupted, and the third (encountered

early in the study) had a severe cutaneous episode in the first month, including a purpuric rash for one day. The regimen was resumed uneventfully after a temporary interruption. Seven patients (1 ER₁, 2 ER₂, 3 ER₁, and 1 EtZC) died of or with active pulmonary tuberculosis or from non-tuberculous diseases before they had received six months' treatment; none had had any adverse reactions. Finally, three patients were withdrawn from the study—one (ER₁) because of previous treatment with ethambutol, the second (ER₂) because of bone marrow depression, detected in the third week but thought to be unassociated with the regimen, and the third (ER₂) because of an unassociated cardiac arrhythmia.

SYMPTOMATOLOGY OF ADVERSE REACTIONS TO RIFAMPICIN

Intermittent Rifampicin Regimens.—Five symptom complexes have occurred: (1) the cutaneous syndrome, consisting of flushing and/or itching, with or without a rash, involving particularly the face and scalp, and often including redness and watering of the eyes; (2) the abdominal syndrome, consisting of attacks of abdominal pain and nausea, sometimes associated with vomiting or, less commonly, with diarrhoea; (3) the "flu" syndrome, consisting of attacks of fever, chills, headache, malaise, and bone pains, the last mentioned sometimes being severe; (4) the respiratory syndrome, consisting of attacks of dyspnoea, with or without wheezing and sometimes accompanied by shock; and (5) purpura. The first four syndromes typically began two to three hours after the single, morning dose

of rifampicin and were gone by the evening of the same day. Transient rises in SGPT levels occasionally occurred, and levels above 80 units were taken, for the the purposes of analysis, to indicate liver dysfunction.

Daily Rifampicin.—Three types of episode have occurred during treatment with daily rifampicin plus ethambutol; it was not always possible to be certain that the rifampicin was responsible. (1) Cutaneous reactions, consisting of itching with or without a rash. (2) Liver dysfunction—that is, raised SGPT levels—sometimes accompanied by symptoms or by jaundice. (3) Generalized hypersensitivity reactions.

INCIDENCE AND TIME OF ONSET OF EPISODES

The cumulative numbers of patients having adverse reactions are given in Table I. On all the regimens adverse reactions occurred even during the first month. By the end of the sixth month the cumulative incidence was similar and low on the ER₁, ER₂, and ER₁ER₂ regimens, but substantially higher on the ER₁ regimen and the two high-dosage regimens. Thus there was evidence of an association of adverse reactions with the interval between doses and with the dose size of rifampicin, the highest incidence occurring with the once-weekly rifampicin in high dosage.

Table II shows the month of onset of the more common syndromes. The onset of most of the cutaneous episodes was during the first month, except in the two high-dosage regimens in which nearly all the episodes started in the first three months.

TABLE I—Cumulative Totals of Patients Having One or more Episodes of Adverse Reactions of Any Type during the First Six Months of Chemotherapy (All Regimens)

Regimen	No. of Patients	No. of Patients with Episodes of Any Type by End of Month:						6	
		1	2	3	4	5		No.	%
ER ₁	74	5	7	7	8	9		9	12
ER ₂	69	3	4	7	9	12		12	17
ER ₁	33	5	7	7	9	13		14	42
ER ₁ ER ₂ ..	48	1	1	4	4	5		7	15
ER ₁ (high) ..	34	8	10	13	17	17		19	56
ER ₁ ER ₁ (high) ..	18	1	2	6	7	8		8	44*
EtZC	54	16	21	24	26	28		28	52

*Percentage based on fewer than 25 observations.

TABLE II—Month of Onset of the More Common Episodes* Arising during the First Six Months of Chemotherapy (All Regimens)

Group	Episode	Regimen	No. of Patients	No. of Patients with Episodes arising for the First Time in Month:						No. of Patients with Episodes during the 6 Months	
				1	2	3	4	5	6	No.	%
Rifampicin	Cutaneous	ER ₁	74	4†	1	—	1	—	—	6	8
		ER ₂	69	3	—	—	—	—	—	3	4
		ER ₁	33	3	—	—	—	1	—	4	12
		ER ₁ ER ₂	48	1	—	—	—	—	—	1	2
		ER ₁ (high)	34	3	2	1	—	1	—	7	21
		ER ₁ ER ₁ (high)	18	1‡	1	3	—	—	—	5	28§
	Abdominal	ER ₁	74	—	—	—	—	—	—	0	0
		ER ₂	69	—	1	2	1	—	—	4	6
		ER ₁	33	3	2	1	—	2	1	9	27
		ER ₁ ER ₂	48	—	—	1	—	1	1	3	6
		ER ₁ (high)	34	4	—	2	4	—	2	12	35
		ER ₁ ER ₁ (high)	18	—	—	3	—	—	—	3	17§
	"Flu"	ER ₁	74	—	—	—	—	—	—	0	0
		ER ₂	69	—	—	2	2	2	—	6	9
		ER ₁	33	1	2	—	3	4	2	12	36
		ER ₁ ER ₂	48	—	—	1	—	1	2	4	8
		ER ₁ (high)	34	1	1	4	6	2	1	15	44
		ER ₁ ER ₁ (high)	18	—	—	1	1	1	—	3	17§
Control	Cutaneous Abdominal Neuropsychiatric Arthralgia	EtZC	54	5	1	—	—	—	—	6	11
				4	4	1	1	1	—	11	20
				6	4	2	1	2	—	15	28
				2	1	1	—	1	—	5	9

*Less common episodes are described in the text.

†One of these patients had a rash as part of a generalized hypersensitivity reaction.

‡This patient had a rash as part of a generalized hypersensitivity reaction.

§Percentages based on fewer than 25 observations.

The onset of abdominal episodes, which were confined to the intermittent regimens, was spread over the six months, 12 out of 31 episodes occurring in the second three months. The "flu" syndrome, also confined to the intermittent regimens, began predominantly in the third, fourth, and fifth months of treatment when 30 of the 40 episodes started. All three main syndromes were commonest on the ER₁, ER₂, ER₁ (high), and ER₁ (high) regimens.

SYNDROME COMBINATIONS ON INTERMITTENT REGIMENS

Many patients had more than one syndrome in the six months—namely, 3 out of 12 ER₂ patients, 9 out of 14 ER₁, 2 out of 7 ER₂, ER₁, 14 out of 19 ER₁ (high), and 4 out of 8 ER₂, ER₁ (high) patients. It is noteworthy that all nine patients who had three or four syndromes were on once-weekly regimens. Multiple syndromes usually occurred simultaneously, but sometimes in sequence.

MAXIMUM SEVERITY OF EPISODES ON INTERMITTENT REGIMENS

The maximum severity of syndromes which were present on their own tended to be recorded as less than that of those occurring simultaneously with others. For example, of six patients on intermittent rifampicin who had the cutaneous syndrome on its own, five had only mild attacks and only one ever had a severe episode. Of the eight patients who had the abdominal syndrome on its own, the maximum severity recorded was mild in six and moderate in two. Of 14 patients who had the "flu" syndrome on its own, the maximum severity recorded was mild in eight and moderate in six. In contrast, of 26 patients who had the "flu" syndrome simultaneously with one or more other syndromes, the maximum severity recorded was mild in only 7, moderate in 10, and severe in 9.

Of the four patients who had the respiratory syndrome, the maximum severity recorded was moderate in two and severe in two.

MANAGEMENT OF ADVERSE REACTIONS

Adverse reactions, in general, proved comparatively easy to manage. Table III (first part) summarizes the changes in chemotherapy which were made to manage episodes of all types.

Of the 60 patients who developed adverse reactions on the intermittent rifampicin regimens, 29 (48%) required no modification of their regimen, 3 (5%) who were among the earliest to develop symptoms responded to a temporary interruption in treatment, 11 (18%) responded to a reduction in rifampicin

dosage, and of the remaining 17, 10 (17%) were able to continue on standard dosage daily rifampicin. In only 7 (12%) was treatment with rifampicin terminated. Of the nine patients who developed adverse reactions among the 74 on the ER₂ regimen, four required no change in chemotherapy, four responded to a temporary interruption, and only in one was rifampicin terminated.

The second part of Table III summarizes the action taken to treat the more common syndromes.

The cutaneous syndrome was usually self-limiting and rarely required anything more than symptomatic treatment. In only one patient, with hypersensitivity to ethambutol as well as to rifampicin during the daily phase of the ER₂, ER₁ regimen, was it necessary to change the regimen; this patient had a generalized hypersensitivity reaction with fever, rash, jaundice, enlarged liver, and lymphadenopathy during the second week of treatment.

The abdominal syndrome, when it occurred alone, required only symptomatic treatment. When it occurred simultaneously with other syndromes the records suggest that it was invariably the other syndrome which led to any change in the rifampicin schedule.

The "flu" syndrome occurred on one or more occasions in 40 patients. The episodes stopped spontaneously in 15, in one case they stopped after a temporary interruption of treatment, in 10 cases they ended when the rifampicin dose size had been reduced, in five of these by only one capsule (150 mg), and all except four of the remaining 14 were able to continue on daily rifampicin in conventional dosage.

Of the 14 patients with the "flu" syndrome occurring on its own, 8 (57%) required no adjustment of chemotherapy, 3 (21%) had a reduction in dosage, 2 (14%) a change to daily rifampicin, and in 1 the rifampicin was terminated. Of the 26 patients with the "flu" syndrome occurring in combination with other syndromes 7 (27%) required no adjustment of chemotherapy, 1 had a temporary interruption in rifampicin treatment, 7 (27%) had a reduction in dosage, 8 (31%) had a change to daily rifampicin, and in 3 (12%) the rifampicin was terminated. There was thus a suggestion that when the "flu" syndrome occurred simultaneously with other syndromes more adjustments of the rifampicin regimen were required than when it occurred on its own.

LESS COMMON EPISODES AND THEIR MANAGEMENT

Respiratory Syndrome.—This occurred in four patients. In one (ER₁ (high)) its onset in the second month was followed two weeks later by the "flu" syndrome but symptoms stopped spontaneously. In the second (ER₁) it started in the fifth month, one month after the onset of the "flu" and abdominal syn-

TABLE III—Changes in Allocated Chemotherapy Made to Manage Adverse Reactions

Management of Episodes	All Patients with Adverse Reactions of any Type							Common Episodes*						
								Rifampicin Regimens			EtZC regimen			
								All		Intermittent	Cutaneous	Abdominal	Neuro-psychiatric	Arthralgia
								All	Intermittent	"Flu"				
No change ..	4	7	2	3	13	4	18	22	31	15	4	8	10	1
Temporary interruption ..	4	1	0	0	0	2	0	3	0	1	2	2	0	0
Size of dose reduced† ..	0	0	6	2	2	1	0	0	0	10	0	0	0	0
Changed to daily rifampicin ..	—	2	4	2	2	0	—	0	0	10	—	—	—	—
Offending drug(s) terminated ..	1	2	2	0	2	1	10	1	0	4	0	1	5	4
Patients with episodes ..	9	12	14	7	19	8	28	26	31	40	6	11	15	5
Total patients at risk ..	74	69	33	48	34	18	54	276	202				54	

*Some of these episodes occurred simultaneously. When they did so, the action taken refers only to the predominant episode.

†Four of these patients had temporary interruptions of rifampicin treatment before the dose size was reduced and in one the reduction of dosage was only temporary.

dromes, and was managed successfully by reducing the rifampicin dosage. In the third (ER₇ER₁) it started in the fifth month, at the same time as the "flu" and abdominal syndromes, accompanied by a raised SGPT, and was managed by a change to daily rifampicin. In the fourth (ER₂) it started in the fifth month, at the same time as the "flu" syndrome. Although the respiratory syndrome stopped when the dose size of rifampicin was reduced, the "flu" syndrome continued and daily rifampicin was therefore introduced. In the first two patients, both with a past history of asthma, it was accompanied by rhonchi and wheezing and was relieved with intravenous aminophylline; in the third it was associated with a fall in blood pressure on five occasions, once, when the patient became shocked, to a systolic pressure of 70 mm Hg. The fourth patient became acutely dyspnoeic and shocked during an attack of the "flu" syndrome, but there was no wheezing.

Liver Dysfunction.—Ten patients developed liver dysfunction, six (4% of 140) while on daily rifampicin, whether on the ER₇ or the daily phase of the ER₇ER₁ regimen, and four (2% of 202) while on intermittent rifampicin. Of the six patients on daily rifampicin, two developed jaundice, one (ER₇), with a history of having once been a heavy drinker, during the fifth month and the other (ER₇ER₁ (high)) during a generalized hypersensitivity reaction with rash, fever, palpable liver, and lymphadenopathy in the first month. In both patients the rifampicin regimen was terminated and liver function tests returned to normal within 10 days. The other four (all ER₇) patients developed raised SGPT alone. In the first three the SGPT returned to normal after interruption of rifampicin of from five to six weeks, and in the fourth the regimen was continued and the SGPT returned to normal in three weeks. Of the four patients who developed raised SGPT on intermittent rifampicin none developed jaundice. One (ER₁) responded to a temporary reduction in rifampicin dosage, in the second (ER₁ (high)) the rifampicin dosage was reduced because of simultaneous "flu" and abdominal syndromes, in the third (ER₇ER₁ (high)) rifampicin was resumed at full dosage after a six-week interruption, while in the fourth (ER₇ER₁) rifampicin was resumed after a two-week interruption, but because of simultaneous "flu," abdominal, and respiratory syndromes, it was given daily.

Purpura.—One patient (ER₂) developed purpura during the fifth month within an hour of a dose of rifampicin and the platelet count was 112,000/mm³ at three hours. The purpura faded within three days, without any other evidence of abnormal bleeding, and the platelet count rose to 341,000/mm³. The rifampicin was terminated.

ADVERSE REACTIONS ON CONTROL REGIMEN

Information about the control regimen was taken from the monthly reports and has not been systematically amplified by

special correspondence as was that of patients on the rifampicin-containing regimens. Although it may underestimate the incidence of minor side effects, details of the management of episodes were always obtained. The overall incidence (Table I) of side effects (52%) was high and of the same order as that of the high-dosage rifampicin regimens. More than half the episodes started during the first month. Abdominal and neuropsychiatric symptoms were more common than cutaneous symptoms or arthralgia (Table II). One patient developed depression (in the fifth month), a second an acute paranoid reaction in the third month, and a third an acute psychosis in the fifth month. The six patients with cutaneous reactions all developed generalized itching but only one developed a rash. Of three patients with liver dysfunction one became jaundiced in the fourth month. There was no history of previous liver disease.

Of 28 patients who had adverse reactions (Table III, first part) 18 (64%) required no change in chemotherapy, and though 10 (36%) had either one drug stopped prematurely or one drug replaced by another, the planned period of triple chemotherapy (six months) was longer than is often prescribed. However, four patients, referred to above, had serious adverse reactions—psychiatric episodes in three and jaundice in one—and all four had the offending drug terminated, as did two others on account of troublesome insomnia in one and paraesthesiae in the other.

ADVERSE REACTIONS STARTING LATER THAN SIX MONTHS

The results given above concern only those episodes which started during the first six months of chemotherapy. Comparisons of the cumulative numbers of episodes at six and at nine months were made for patients who had completed nine months in the study, and at six, nine, and 12 months for those who had completed a year (Table IV). Most patients who had adverse reactions developed them during the first six months of treatment, though on the intermittent rifampicin regimens the cumulative incidence showed some increase between six and nine months, largely due to episodes of the "flu" syndrome arising for the first time. So far, 118 patients have completed a year of chemotherapy, but there is no evidence in this relatively small number of any appreciable increase in the overall cumulative incidence of adverse reactions between 9 and 12 months.

Three major episodes arose after six months in the 198 patients followed for nine or more months. Two further patients (ER₁ and ER₇ER₁ (high)) developed purpura in the seventh and ninth months respectively and the rifampicin was terminated. A third (ER₇) patient developed jaundice in the eleventh month, necessitating the termination of the rifampicin. There were no more episodes of the respiratory syndrome.

Only three patients on the EtZC regimen developed adverse reactions after six months.

TABLE IV—Episodes Arising after Six Months in Patients on the Rifampicin-containing Regimens Who had Completed 9 or 12 Months Chemotherapy

Months of Treatment Completed	Regimen	No. of Patients	Patients with One or More Episodes by:					
			6 months		9 months		12 months	
			No.	%	No.	%	No.	%
9	ER ₇	56	7	12	7	12		
	ER ₂	47	11	23	14	30		
	ER ₁	17	6	35*	8	47*		
	ER ₇ ER ₁	30	4	13	9	30		
	ER ₁ (high)	31	18	58	20	65		
	ER ₇ ER ₁ (high)	17	8	47*	9	53*		
12	ER ₇	30	4	13	4	13	5	17
	ER ₂	29	7	24	9	31	10	34
	ER ₁	2	1	50*	2	100*	2	100*
	ER ₇ ER ₁	15	1	7*	5	33*	5	33*
	ER ₁ (high)	29	18	62	20	69	20	69
	ER ₇ ER ₁ (high)	13	5	38*	6	46*	6	46*

*Percentages based on fewer than 25 observations.

Discussion

A number of reports from various countries of adverse reactions to intermittent rifampicin, whether given with isoniazid or ethambutol, have been published (Blajchman *et al.*, 1970; Poole *et al.*, 1971; Sepúlveda *et al.*, 1971; Zierski, 1971) or presented at committee meetings (Farga, 1970a, 1970b; Eule, 1971). Most reports have described small numbers of patients and various dosage schedules and rhythms have been studied. The adverse reactions have also been managed in a variety of ways. Poole *et al.* (1971) not only terminated the rifampicin regimen in patients having reactions but also discontinued it in the rest of the patients under study. Other workers have attempted desensitization for reactions and reduction in dosage (Zierski, 1972), have continued the same dosage under steroid cover (Zierski, 1972), or have changed to daily treatment (Eule, 1971; V. Farga, personal communication, 1971).

This paper presents the interim findings for 330 Chinese patients who have so far completed at least six months' chemotherapy in a large-scale controlled study of reserve regimens in Hong Kong. Adverse reactions on once-weekly and on twice-weekly rifampicin regimens observed in 202 patients in a six-month period are compared not only with those in 74 patients on a daily rifampicin regimen but also with those in 54 patients treated with the standard reserve regimen of ethionamide, pyrazinamide, and cycloserine normally used for failure patients in Hong Kong. Analyses on smaller populations at nine months (198 patients on rifampicin) and at 12 months (118 patients on rifampicin) suggest that in Hong Kong most side effects, though not all the major ones, arise within the first six months.

MANAGEMENT OF ADVERSE REACTIONS

Adverse reactions were most frequent on the once-weekly rifampicin regimens, not only when the rifampicin dosage was high (1,800, 1,500, or 1,200 mg according to body weight) but also when lower (1,200, 1,050, or 900 mg). At these lower dosage levels the incidence was still higher than in the twice-weekly regimen, even though the *individual* dose size in the latter was the same. Thus both the dose size and the interval between doses are factors that influence the frequency of side effects to intermittent rifampicin. In the event, the reactions were either self-limiting or could almost always be managed either by reducing the dose size or by reducing the interval between doses by changing to daily rifampicin. A procedure for the management of adverse reactions on intermittent rifampicin regimens, evolved during the study, is as follows:

If purpura occurs rifampicin is stopped immediately and is not given again, not even as a small test dose. For the other syndromes the following steps are taken: (1) if an episode severe enough to require more than just simple symptomatic treatment occurs, lowering the dose of rifampicin, usually by one capsule (150 mg) at a time, to a minimum of 600 mg a dose, is tried; and (2) if troublesome symptoms persist an attempt to induce tolerance to rifampicin is made by giving daily doses, usually starting with 150 mg, a dose size which rarely produces symptoms, and increasing by 150 mg a day so that in three days a dose of 450 mg is reached, and this is then continued daily (with daily ethambutol in conventional dosage).

Only in the uncommon event of these procedures failing either to terminate episodes or to make them so trivial or infrequent as to be of no concern to the patient is rifampicin discontinued.

ADVERSE REACTIONS IN PRESENT STUDY

In the present investigation, for 32 of the 60 patients with episodes on intermittent rifampicin, no change in the rifampicin dosage was necessary. In 11 more all that was required was a reduction in the rifampicin dosage and a further 10 were

changed to daily rifampicin, which was then continued uneventfully. In fact, in only seven patients (3% of the 202 patients on the intermittent regimens who completed six months of observation) was it necessary to terminate the rifampicin.

Experience so far suggests that this way of handling adverse reactions to intermittent rifampicin is practical and safe, acceptable to both clinicians and their patients, and it is in keeping with long-established practice of the management of patients with adverse reactions to other antituberculosis drugs. It is with purpura and the respiratory syndrome that particular caution is necessary.

Adverse reactions to daily rifampicin in the present study have consisted of generalized hypersensitivity reactions, cutaneous reactions (one of which was accompanied by transient purpura), abnormal liver function test results, and one instance of jaundice. Although it is possible that ethambutol may sometimes also have been involved, daily rifampicin regimens are clearly not free from side effects, some of which are potentially serious. At least one other case of purpura attributed to daily rifampicin has been reported in the literature (Ferguson, 1971). Some workers have reported a high incidence of liver dysfunction, including jaundice (Lees *et al.*, 1971), especially in patients with known liver disease (Lesobre *et al.*, 1969), while a much lower incidence was reported in a general review of the literature (Bergamini *et al.*, 1971).

The usual adverse reactions on the standard reserve regimen were also frequent, occurring in about half of the patients. Indeed, over a quarter of the patients had adverse reactions even in the first month. Of the 54 patients on this regimen four had major episodes—namely, three major psychiatric disorders and one case of jaundice.

OTHER ANTITUBERCULOSIS DRUGS

All antituberculosis drugs carry a greater or lesser risk of adverse reactions. The risk is usually greatest when the drug is recently introduced—that is, before experience has shown how reactions can be prevented, recognized early, or, when they occur, best managed. A good example is ethambutol in which the incidence of ocular toxicity was found to be high and dose-associated (Leibold, 1966). Experience has shown, however, that a lower dosage, although still therapeutically effective, is associated with scarcely any ocular toxicity (Bobrowitz and Robins, 1967). Further, provided that the ethambutol is stopped as soon as impaired vision is detected, the prospects of full recovery are excellent, whereas if the ethambutol is continued, rapid deterioration may occur. With streptomycin the risks of deafness or disabling giddiness are now much smaller because experience has shown what dosage schedules are therapeutically appropriate and because the risk of toxicity in the elderly and in patients with impaired renal function is fully appreciated.

PAS remains a major standard drug despite the high incidence of adverse reactions requiring a reduction in dosage, a change to a different preparation, desensitization, or indeed its termination. Cycloserine retains a place as a reserve drug in spite of the occurrence of acute psychosis, depression, anxiety states, and even suicide. When new regimens, such as the current rifampicin regimens, are under investigation, the aim must be to evaluate them in terms of efficacy, safety, convenience, cost, and applicability, in comparison with the alternative regimens available for the treatment of the same type of disease in the same population. For an evaluation to be meaningful it must be made in such comparative terms, and not in isolation.

Poole *et al.* (1971), who studied 1,200 mg of rifampicin given twice a week, reported a highly significant correlation between the presence of rifampicin-dependent antibodies and the occurrence of adverse reactions. They encountered three cases of thrombocytopenia, one of them with purpura, among the 49 patients treated. However, the risk of purpura cannot now be completely discounted even with daily rifampicin. The occur-

rence of circulating antibodies may be one of the reasons for adverse reactions to rifampicin, but it is probable that, in due course, other mechanisms will be shown to be involved. In the Hong Kong study a large programme of immunological and haematological investigations is in progress, among the aims being to identify patients likely to develop adverse reactions and to find ways of preventing such reactions. Clinically, in Hong Kong the problems presented by adverse reactions, as now managed, on intermittent rifampicin regimens are so far not substantially greater than those encountered on the standard reserve regimen, although purpura and the respiratory syndrome require special caution. Even the daily rifampicin regimen cannot be regarded as free from hazard.

In the final analysis a vital issue in the choice of the best failure regimen among those under study will be the relative therapeutic efficacy of the different regimens balanced against the incidence of adverse reactions during the whole period of treatment, and this will be reported on later. In the meantime, reports from other workers on their experience of managing adverse reactions in patients on intermittent rifampicin-containing regimens will be awaited with interest.

We are grateful to the Director of Medical and Health Services, Hong Kong (Dr. G. H. Choa) for permission to report these findings.

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Total Body Potassium in Non-Dialysed and Dialysed Patients with Chronic Renal Failure

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British Medical Journal, 1972, 1, 771-775

Summary

Total body potassium was studied in 33 patients with chronic renal failure, 18 of whom had been receiving regular dialysis therapy for 1 to 48 months. In non-dialysed patients body potassium was not significantly different from normal in the group as a whole, but was significantly greater than normal in three patients, and significantly less than normal in two patients. In 14 of the dialysed patients, both as individuals and as a group,

body potassium was not significantly different from normal but in the remaining four it was less than normal.

Potassium transfer during dialysis was studied in two patients. Uptake by these two patients of ^{42}K added to the dialysate (1 mEq K/litre) was measured by whole-body monitoring. Transfer of administered ^{42}K from the patients to the dialysate was measured by whole-body monitoring and by radioactive and chemical assay of the dialysate. A negative balance due to twice-weekly dialysis of 178 and 244 mEq K/week was found, which with weekly faecal and urine losses of 20-30 mEq K approximately equals the dietary intake of 210-315 mEq K.

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Introduction

In non-dialysed patients with chronic renal failure, the 24-hour exchangeable body potassium was significantly lower than in control subjects (Moore *et al.*, 1954). In seven out of eight patients with chronic renal failure, who were being treated with a Kiil dialyser using the same potassium concentration in the dialysate as in the present study (1 mEq/litre), the 24-hour