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The Reliability of Self-administration of Dapsone by Leprosy Patients in Burma

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A study of urinary dapsone/creatinine (D/C) concentration ratios has been performed on 852 leprosy patients in the Rangoon and Mandalay regions of Burma. The results show that, by comparison with in-patients who are assumed to be compliant with their therapy, hospital out-patients and urban and rural clinic patients had overall compliance rates of only 74% and 24% respectively. In each group, substantial numbers of patients were identified who had taken no dapsone (DDS) tablets whatsoever.

The findings are in line with similar studies performed in other countries and they indicate an urgent need to reassess the existing programme of treatment supervision particularly in the urban and rural clinic environments.

Introduction

Compliance with DDS therapy may be monitored by a quantitative test in which DDS and its diazotizable metabolites, and creatinine concentrations, are determined on single urine samples (Ellard *et al.*, 1974*a*). The DDS/creatinine (D/C) concentration ratios measured on urine samples from patients receiving

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supervised administration of DDS are compared with the urinary D/C concentration ratios determined from patients who are relied upon to self-administer their DDS. An estimation may then be made of the percentage of prescribed DDS therapy taken by the unsupervised patients (Ellard *et al.*, 1974*b*).

Compliance with DDS therapy has been studied in populations of leprosy patients in Africa, (Ellard *et al.*, 1974*b*; Low and Pearson, 1974; Huikeshoven *et al.*, 1976) and India (Balakrishnan, 1977; Naik and Ganapati, 1977). The results show disappointingly low levels of compliance among out-patients.

This paper assesses, in a similar manner to previous authors, compliance with DDS therapy by leprosy patients in two regions of Burma—Mandalay and Rangoon. The degree of supervision with therapy varies between groups of patients in these areas. A small proportion of patients who are resident in leprosy hospitals receive full supervision of their medication, while other patients regularly attend out-patient clinics but are relied upon to administer their own medication. The majority of the Burmese patients studied live in rural areas and receive treatment through a system of drug distribution by leprosy health workers. The successful mass treatment of leprosy is therefore largely dependent on the regularity of patients to self-administer their medication and on the system of drug distribution. Some of the present findings have been the subject of a previous report (Kin Ma Gyi *et al.*, 1978) and are reassessed together with further findings obtained in different parts of Burma, which are published for the first time.

Methods

PATIENTS

All leprosy patients were on a 6 days/week regimen of either 12.5 mg, 25 mg, 50 mg, 75 mg or 100 mg DDS with the exception of one patient taking 200 mg. Urine samples were collected from a total of 852 patients in Mandalay and Rangoon. The patients consisted of the following groups:

(a) Leprosy hospital patients: in Mandalay residents receiving either 100 mg or 50 mg DDS, and in Htauk Kyant, Rangoon, residents receiving 50 mg DDS, each provided a urine sample 24 h after ingestion of DDS therapy. Hereinafter these patients are referred to as IN-PATIENTS.

(b) Hospital out-patients: urine samples were collected from patients at their weekly visit to the Special Skin Clinic at Mandalay General Hospital and these patients were prescribed either 12.5 mg, 25 mg, 50 mg or 100 mg DDS. Urine samples were provided also by patients attending their weekly visit to the Htauk-Kyant out-patient clinic in Rangoon and those patients attending Rangoon General Hospital out-patient clinic. The Rangoon out-patients were prescribed 50 mg DDS. Hereinafter these patients are referred to as OUT-PATIENTS.

(c) Urban and rural clinic patients: in Mandalay, urine samples were provided by patients prescribed either 25 mg, 50 mg, 75 mg or 100 mg DDS. These patients live in the townships of Madaya, Patheingyi and Amarapura and Maymyo Town. In Rangoon, urine samples were provided by patients from

Htauk Kyant village, prescribed 50 mg DDS, and patients from Taik Kyi village and the Hmawbi and Hlegu areas, all prescribed 100 mg DDS. Leprosy workers collected urine samples from the urban and rural clinic patients at surprise visits by the worker to each village or town. Hereinafter these patients are referred to as URBAN AND RURAL CLINIC PATIENTS.

Areas from which patient urine samples were obtained are identified by map references, indicated in Fig. 1.

All urine samples from the Rangoon patients were collected and preserved in 0.5 volumes of 2N HCl. Urine samples from the Mandalay patients were not acidified but were refrigerated until determinations could be carried out. Ten volunteers from the staff of the Htauk Kyant Leprosarium, Rangoon, provided urine samples for control determinations.

CREATININE AND DDS DETERMINATIONS

Creatinine was determined by the alkaline picrate method (Ellard *et al.*, 1974*a*). DDS, as total diazotizable compounds, was determined by modifications of the Bratton and Marshall (1939) procedure. In Rangoon, the modification carried out was as described by Ellard *et al.* (1974*a*); in Mandalay, as recently described by Hagan and Smith (1979).

EXCLUSION OF DATA

D/C concentration ratios of 53 patients were excluded from this study, leaving 799 out of the original 852 results. The reason for such exclusion was that these samples had unusually high D/C concentration ratios. Some had creatinine levels of zero, suggesting that the samples were not urine at all. Others, with measurable creatinine concentrations, had grossly high DDS concentrations, indicating either that the samples were contaminated or that the patients were taking sulphonamides or other drugs which yield the same colour in the analysis. The upper limits for acceptable D/C concentration ratios, 150 μg/mg for patients on DDS 100 mg/day, 120 μg/mg for those on DDS 50 mg/day, were set slightly higher than the upper limits observed by Low and Pearson (1974) in a study of fully compliant patients.

A further 76 results were not included in the calculation of group compliance rates (Tables 1, 2 and 3) either because the numbers were too small for valid estimates to be made or because no appropriate supervised group of patients was available for comparison. The excluded data consisted of 14 results from Mandalay General Hospital and 22, 18, 14 and 8 from Madaya, Patheingui, Amarapura and Maymyo townships, respectively.

CALCULATION AND STATISTICAL EVALUATION

Estimates of the proportions of DDS doses taken by different groups of patients (compliance rates) were derived as described by Ellard *et al.* (1974*a*). Individual urine samples found to have D/C concentration ratios of < 6.8 μg/mg, the highest figure obtained in control urine samples from volunteers not taking DDS, were classified as negative. Patients providing such samples were judged to be totally non-compliant.

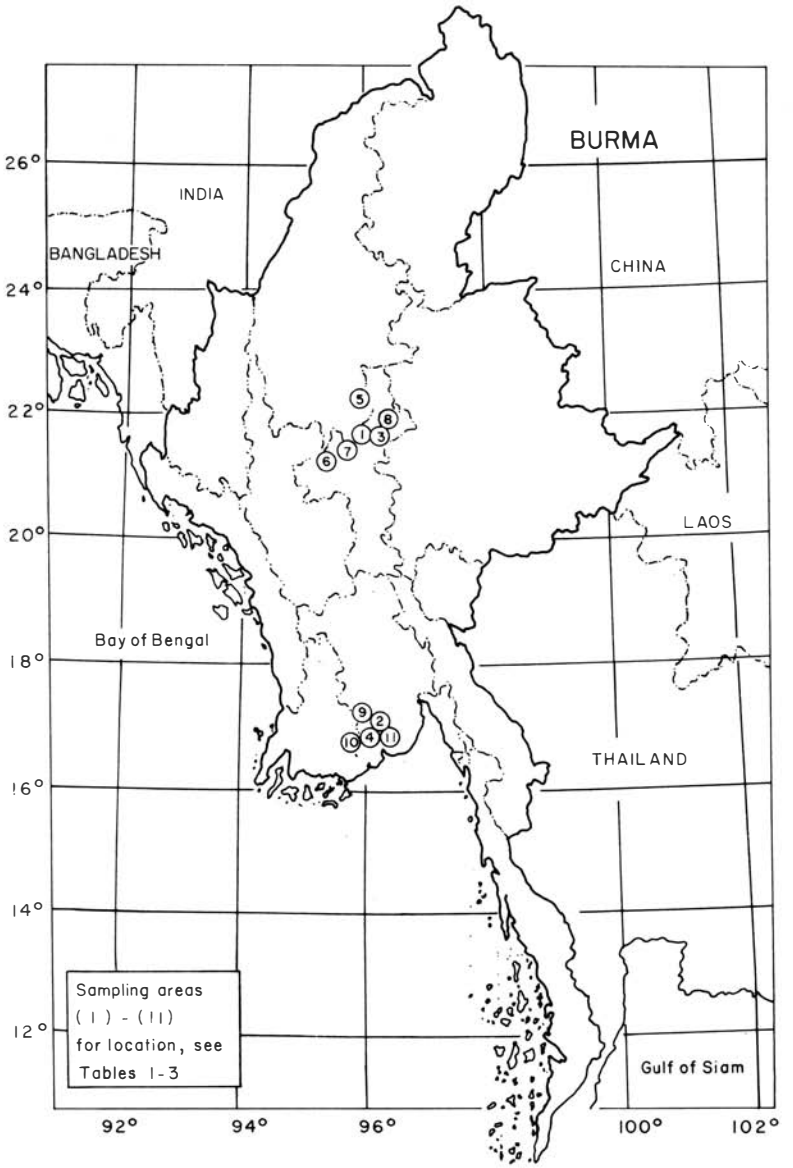

Fig. 1.

Comparisons between compliance and total non-compliance rates were effected by analysis of variance using a standard technique of nested data classification (Snedecor and Cochran, 1967).

Results

Group means (± S.E.M.) and ranges of individual D/C concentration ratios for in-patients, out-patients and urban and rural clinic patients are presented in Tables 1, 2 and 3 respectively. These tables also provide group estimates of percentages of DDS doses taken, together with sub-totals (by daily dosage) and weighted estimates of percentages of DDS doses taken (compliance rates) by each patient source (in-patients, out-patients, urban and rural clinic patients).

The results indicate that by comparison with in-patients (assumed compliance rates 100%), out-patients and urban and rural clinic patients showed 74% and 24% compliance respectively. This difference was statistically highly significant ($P < 0.001$), but no significant difference was found in compliance rates between regions (Rangoon v. Mandalay) nor between dosages (25, 50 or 100 mg/day) [Table 5(a)].

Estimates of the percentage of urine samples negative for DDS are given in Table 4. Seven per cent of in-patients, 24% of out-patients and 56% of urban and rural clinic patients had negative urines. The differences were statistically highly significant [Table 5(b)].

Group estimates of the percentage of DDS doses not taken (calculated from Tables 2 and 3) and the percentage of urines negative for DDS (calculated from Table 4), are illustrated in Fig. 2.

Discussion

This study has assessed the compliance with a 6 days/week DDS regimen in Burmese out-patients, by comparing the mean D/C concentration ratios of patients fully compliant with DDS therapy with the values obtained from the out-patients. Fifty-three D/C concentration ratios (6.2%) were excluded from the assessment because these ratios were unusually high. Several factors may have contributed to these high ratios:

(i) Simultaneous ingestion of sulphonamide therapy which may or may not have been officially prescribed. A similar problem was encountered by Ellard *et al.* (1974*a*), who were able to test suspect urine samples for interfering sulphonamides. Other drugs, notably the diuretics frusemide, hydrochlorothiazide, bendrofluazide and also diazepam and its metabolite desmethyldiazepam have also been found to interfere with the DDS assay in our laboratory. No interference was shown by rifampicin and its metabolites, clofazimine, erythromycin, indomethacin, clindamycin and its metabolite N-demethylclindamycin, or pyrazinamide, when tested in the assay procedure.

(ii) Patients ingesting more than the prescribed dose of DDS. It is conceivable that patient compliance was directly affected by the knowledge that they were to attend clinics (and temporary excess tablet consumption could result from this). The objective of this investigation was, however, kept hidden from patients, so the compliance study *per se* was unlikely to have influenced the results.

This study has shown substantial failure to comply with medication among some patients, most obviously those managed in urban and rural clinics. The

TABLE 1

Mean D/C concentration ratios and estimates of percentage of prescribed DDS doses taken by each population: IN-PATIENTS AND CONTROLS

Origin of samples (map ref.)	No. of subjects	Prescribed DDS dosage (mg/day)	D/C concentration ratio* Mean ± S.E.M.	Range	Estimated % of doses taken
Leprosy Hospital, Mandalay (1)	67	100	47.0 ± 4.5	5.0–150.5	100
Leprosy Hospital, Mandalay	15	50	38.3 ± 7.5	7.5–111.1	
Htauk Kyant hospital (2)	56	50	29.1 ± 2.8	4.0– 89.5	
(sub-total	71	50	31.2 ± 2.8		100)
(estimated	—	25	25.1		100)
ALL PATIENTS	138	25–100			100
VOLUNTEERS, no medication	10	0	3.6 ± 0.4	2.0– 6.8	

* µg DDS/mg creatinine.

TABLE 2

Mean D/C concentration ratios and estimates of percentage of prescribed DDS doses taken by each population: OUT-PATIENTS

Origin of samples (map ref.)	No. of subjects	Prescribed DDS dosage (mg/day)	D/C concentration ratio* Mean ± S.E.M.	Range	Estimated % of doses taken
Special skin clinic, Mandalay General Hospital (3)	22	100	26.2 ± 5.4	0 –120.0	52
Mandalay General Hospital	24	25	17.3 ± 3.5	0 – 69.0	64
Mandalay General Hospital	28	50	20.7 ± 4.0	0 – 66.7	62
Outpatient clinic Rangoon General Hospital (4)	45	50	31.6 ± 4.3	2.7–116.3	100
Htauk Kyant hospital (2)	44	50	23.1 ± 2.9	0.7– 66.9	71
(sub-total	117	50	25.8 ± 2.2		80
ALL PATIENTS	163	25–100			74

* µg DDS/mg creatinine.

TABLE 3

Mean D/C concentration ratios and estimates of percentage of prescribed DDS doses taken by each population: URBAN & RURAL CLINICS

Origin of samples (map ref.)	No. of subjects	Prescribed DDS dosage (mg/day)	D/C concentration ratio*		Estimated % of doses taken
			Mean ± S.E.M.	Range	
Htauk Kyant village (2)	33	50	14.7 ± 2.4	2.1 – 59.7	40
Madaya township, Mandalay (5)	58	50	14.7 ± 2.7	0.7 – 100.0	40
Patheingyi township, Mandalay (6)	56	50	5.2 ± 0.9	0 – 37.0	6
Amarapura township, Mandalay (7)	61	50	7.7 ± 1.1	0.4 – 44.0	15
Maymyo town, Mandalay (8)	22	50	5.8 ± 0.5	0.9 – 16.6	8
(sub-total	230	50	9.7 ± 0.3		22)
Madaya township, Mandalay (5)	38	100	6.8 ± 1.5	0.2 – 53.1	7
Taik Kyi area, Rangoon (9)	59	100	21.9 ± 3.3	0 – 120.5	42
Hlegu area, Rangoon (10)	47	100	14.7 ± 2.6	0 – 60.6	26
Hmawbi area, Rangoon (11)	48	100	13.2 ± 1.7	0 – 56.8	22
(sub-total	192	100	15.0 ± 1.3		26)
ALL PATIENTS	422	50–100	12.1 ± 0.5		24

* μg DDS/mg creatinine.

TABLE 4
Estimate of urine samples negative for DDS (urine D/C concentration ratios > 6.8)

Origin of samples (map ref.)	No. of subjects	No. negative	%
IN-PATIENTS			
Leprosy Hospital, Mandalay (1)	82	4	5
Htauk Kyant hospital (2)	56	5	9
ALL	138	9	7
OUT-PATIENTS			
Mandalay General Hospital (3)	88	25	28
Rangoon General Hospital (4)	45	8	18
Htauk Kyant (2)	44	9	20
ALL	177	42	24
URBAN AND RURAL CLINICS			
Madaya township (5)	118	62	53
Patheingyi township (6)	74	58	78
Amarapura township (7)	75	53	71
Maymyo township (8)	30	20	67
Hlegu area (10)	47	26	55
Hmawbi area (11)	48	19	40
Taik Kyi area (9)	59	22	37
Htauk Kyant village (2)	33	9	27
ALL	484	269	56

TABLE 5
Analyses of variance

Source of variation	Sum of squares	Degrees of freedom	Mean square	*F*	*P*
(a) % DOSES TAKEN					
Between regions	1162.88	1	1162.88	0.31	N.S.
Between sources within regions	7397.36	2	3698.68	61.21	< 0.001
Between dosage within sources	241.72	4	60.43	0.26	N.S.
Within dosage	1379.25	6	229.87		
TOTAL	10,181.21	13			
(b) % URINES NEGATIVES FOR DDS					
Between regions	1411.87	1	1411.87	1.19	N.S.
Between sources within regions	4759.55	4	1189.89	11.29	< 0.01
Within sources	737.50	7	105.36		
TOTAL	6908.92	12			

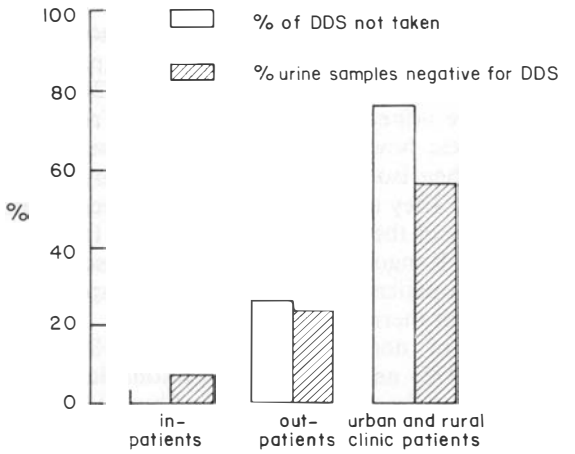

Fig. 2. Percentage estimates of non-compliance among different groups of leprosy patients.

results must, however, be interpreted with care. Leprosy patients attending out-patient departments in Mandalay and Rangoon weekly do not receive direct supervision of medication. Attendance at weekly intervals does, however, ensure continued motivation for compliance and continued supply of DDS tablets. The findings of an overall compliance rate of 74% and a totally non-compliant rate of 24% could be taken to indicate that a proportion of such patients are irregular attenders rather than poor tablet takers. This conclusion is supported by the observation that those urine samples which were positive for DDS contained on average as much drug as did the samples obtained from in-patients. By comparison, urban and rural clinic patients are not directly supervised at all. The estimates obtained in this group of 24% overall compliance and 56% total non-compliance are therefore likely to indicate more directly failure to adhere to the treatment regimen as such. In this case, for example, it is apparent that those patients who did comply took only half their tablets. In either instance, however, the findings show that there is substantial failure to take the drug in the absence of supervision. Such a conclusion warrants further discussion, as follows.

Because of the uncertainty of overlap in D/C concentration ratios between patients who are fully compliant and those not compliant with DDS therapy, no attempt was made to classify out-patients into those taking their doses regularly, irregularly or grossly irregularly (Ellard *et al.*, 1974*b*). Instead urines were classified as either positive or negative, by the use of the highest D/C concentration ratio in the blank values range. It is inevitable that some patients will be misclassified by this procedure and this is borne out by the finding that 5% of the in-patients from Mandalay and 9% of those from Rangoon had negative urines. It is, however, also possible, although unlikely, that even supervised in-patients do not absolutely reliably receive their medication, some patients consistently evading it.

The number of hospital out-patients found to have negative urines represents an unacceptable level of non-compliance. Those who attend hospital clinics are known to be well motivated to take their prescribed therapy and most are regular attenders. Even so, the finding that 24% of those attending the clinics had negative urines is of major concern. Urban and rural patients attending mobile clinics, however, present a more serious problem. These patients, by virtue of their isolation and life in a leprosy community, lack the motivation to be cured. They often fail to collect supplies of tablets, so it is not surprising to find many of them with negative urines. In the Taik Kyi, Hlegu and Hmawbi areas of Rangoon, the patients are prescribed higher doses of DDS than hospital out-patients in an attempt to compensate for the lack of motivation in taking their therapy.

The consequences of non-compliance with DDS therapy have been emphasized (Ellard, 1975) and it is clearly reasonable to conclude that the current prevalence of the disease in Burma (Tin Shwe, 1970) is at least partly a consequence of poor compliance among inadequately supervised patients. The practical solution appears to be to increase supervision with medication and our results support Ellard's suggestion that those patients who are relied upon to self-administer their DDS therapy require fully supervised intermittent therapy. This additional supervision could be given at clinic sessions with the proviso that those patients who default clinic attendances would be followed up.

This study has reinforced the idea that increased supervision with DDS therapy, both in hospital out-patients and urban and rural clinic patients in Burma, is urgently needed in order to reduce the prevalence of leprosy and the persistent emergence of new cases of this disease.

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