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The Pharmacology of Sulphetrone and Its Implications in Sulphone Resistance

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Spectrofluorometric techniques were utilized to quantitate dapsone (DDS) and N^4-acetyldapsone (MADDS) contamination of a sulphetrone preparation used for leprosy in Malaysia between 1947 and 1951. Also plasma levels of DDS and MADDS following administration of a standard intramuscular dose of this preparation were studied. The preparation was contaminated with trace amounts of DDS but no MADDS. Following injection the plasma levels were substantial and suggested that sulphetrone was converted *in vivo* to DDS. The importance of these findings to the problem of sulphone resistance is discussed.

Introduction

Sulphetrone (solapsone), a sulphone, was prepared in 1936 (Buttle *et al.*, 1938) and subsequently attracted attention because of its antituberculosis activity (Brownlee and Kennedy, 1948) and low toxicity (Brownlee, 1948). Sulphetrone was first shown to be effective in the treatment of lepromatous leprosy in 1942 (Harkness and Brownlee, 1948) and was widely used for some 12 years (Dharmendra, 1950; Cochrane *et al.*, 1949; Austin, 1950). However, it fell into disrepute because it is poorly absorbed in the gastrointestinal tract (Smith, 1949*a*), causes pain following intramuscular injection, and was thought to act

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against *Mycobacterium leprae* only because of contamination with dapsone (DDS) (Lowe, 1952) or conversion *in vivo* to it (Smith, 1959*b*). Deavin *et al.* (1967), utilizing a semiquantitative assay, demonstrated that sulphetrone was contaminated with 0.5-2% DDS.

A recent retrospective analysis by Meade *et al.* (1973) of the emergence of sulphone resistance among lepromatous leprosy patients at the National Leprosy Control Center, Sungei Buloh, Malaysia, showed an incidence of 8% in patients initially treated between 1947 and 1951 with sulphetrone, compared to an incidence of 2% in patients begun on DDS. Highly sensitive and specific spectrofluorometric techniques for the assay of DDS and its monoacetyl metabolite (MADDS) have now been developed (Peters *et al.*, 1970). We applied these methods to determine the amount of DDS and MADDS in the same sulphetrone preparation used earlier in Malaysia and also to determine plasma concentrations obtained in patients following the usual therapeutic dose of this preparation. It was hoped that information from these studies might prove useful in assessing the efficacy of other sulphone preparations, as well as different DDS regimens.

Methods

Two vials of aqueous 30% sulphetrone (Ph Lab Kuala Lumpur) were diluted serially with distilled water to 1/2500 and 1/5000, and the concentrations of DDS and MADDS determined fluorometrically (Peters *et al.*, 1970) in duplicate samples. This method was modified to avoid sulphetrone breakdown by omitting sodium hydroxide during the initial extraction.

Eight adult patients volunteered to discontinue all sulphones for two weeks. After this period a baseline urine was analysed for sulphone content by a modification of the procedure of Bratton and Marshall (1939), sensitive to 0.3 μg/ml. Five ml of the 30% sulphetrone preparation was then injected intramuscularly, and heparinized plasma was obtained generally just before and 4, 8, 24, 48, 72 and 96 h after administration. Plasma concentrations of DDS and MADDS were determined fluorometrically. No specimens were studied after four days because in Malaysia the standard practice had been to treat leprosy patients with 5 ml sulphetrone twice weekly.

Results

There was no (0.02 mg/ml) MADDS found in either of the two vials of sulphetrone studied. Duplicate specimens and at the two dilutions studied showed no greater than 1% discrepancy in the amount of DDS contamination of the sulphetrone preparation. DDS concentration in the two vials was 0.70 and 0.75 mg/ml.

Plasma levels of DDS and MADDS following a single intramuscular injection of sulphetrone in each of the eight patients studied are presented in Table 1.

Discussion

These studies confirm that sulphetrone is contaminated with trace amounts of DDS. The average plasma DDS concentrations found in subjects 24 and 48 h after sulphetrone administration were 93 and 78 mg/ml respectively. Twenty-four and 48 h after a 50-mg oral dose of DDS in patients from this institution, the mean

TABLE 1

MADDS and DDS plasma levels following intramuscular administration of 5ml 30% sulphetrone

Patient (Wt in kg)	Substance	Plasma concentration (mg/ml) Hours after injection 0	4	8	24	48	72	96
Indian male	DDS	–	90	80	100	80		30
(58.2)	MADDS	–	20	20	20	20		10
Chinese female	DDS	0	100	90	120	120		100
(40.9)	MADDS	0	70	70	120	120		80
Chinese male	DDS	10	90	90	70	70		
(60.0)	MADDS	10	50	50	40	40		
Chinese male	DDS	10	60	60	60	40	30	10
(48.2)	MADDS	20	70	60	50	50	30	20
Chinese male	DDS	10	70	70	70	70	40	20
(53.2)	MADDS	30	40	50	30	30	30	20
Malay male	DDS	0	–	–	90	60	30	20
(52.0)	MADDS	0	–	–	10	10	0	0
Malay male	DDS	10	–	–	120	110	100	80
(48.0)	MADDS	20	–	–	60	50	50	30
Chinese male	DDS	0	–	–	110	70	40	20
(48.0)	MADDS	0	–	–	80	50	30	20
Average	DDS	6	82	78	93	78	48	40
	MADDS	11	50	50	51	46	28	26

Tests for urinary DDS concentration, sensitive to 0.3 μg ml, were negative for all patients before injection of sulphetrone.

plasma levels were 260 and 128 mg/ml respectively (Gelber and Rees, unpublished results). Since plasma concentration of DDS has been found to be linearly related to dose (Ellard *et al.*, 1971), certainly the 3.5 or 3.75 mg DDS contaminating each sulphetrone injection is too little to account for the circulating levels of DDS. Hence significant *in vivo* metabolism of sulphetrone to DDS must occur.

Patients treated with the intramuscular repository sulphone acedapsone (DADDS) in the usual dose of 225 mg every 77 days averaged 25 to 31 mg/ml DDS in the plasma just before the next injection (Murray *et al.*, in press; Gordon *et al.*, in press). As plasma levels of DDS in patients treated with sulphetrone in Malaysia on the average would not have fallen below 40 mg/ml, DADDS therapy of bacilliferous leprosy might similarly result in an unacceptable frequency of relapse with DDS-resistant *Myco. leprae*. We therefore would be reluctant to recommend DADDS as monotherapy of lepromatous leprosy in areas where other alternatives are possible.

It has been demonstrated that 1-10 mg/ml DDS in plasma will prevent multiplication of *Myco. leprae* in the footpads of mice (Shepard *et al.*, 1969; Ellard *et al.*, 1971) and rats (Peters *et al.*, 1972). Patients treated with sulphetrone maintained levels that were at all times above this minimal inhibitory concentration, and yet 8% of them relapsed with dapsone-resistant leprosy, which must be considered unacceptable. Thus it may be hazardous to extrapolate from levels of dapsone effective for preventing multiplication in the local self-limited infection in mice and rats to the treatment of the severe and progressive systemic disease that *Myco. leprae* may cause in man, because of differences in bacterial load and hence the numbers of DDS-resistant mutants. Results from this study suggest that the currently fashionable low-dose DDS regimens may be hazardous.

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