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Do Leprosy Patients Take Dapsone Regularly?

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Urine dapsone/creatinine (D/C) ratios were determined repeatedly in 15 hospital patients on a supervised daily dosage of dapsone. Figures for the group as a whole covered a wide range, but those for individual patients clustered within that range and were much less variable.

D/C ratios were also determined in 89 out-patients prescribed daily dosage of dapsone. Thirty-nine patients gave figures lower than any found in the supervised group, and it was estimated that this group of patients had taken about 42% of their prescribed dosage in the previous 24 to 28 h.

Estimation of the D/C ratio can be utilized to assess regularity of drug taking by a group of patients. Individual patients however can be reliably monitored only if their D/C ratios on supervised treatment are known.

The majority of patients with leprosy are treated outside hospitals, and often in very simple and remote clinics where close supervision of treatment is virtually impossible. Furthermore, the staff who administer treatment have usually themselves undergone only elementary medical training, and the patients may be the first in their area to be exposed to "western" treatment, as leprosy control often pioneers rural health services. Under these circumstances it would be surprising if treatment regimens were rigidly adhered to.

Nevertheless it is valuable in the evaluation of leprosy control programmes to know if patients are taking treatment in the prescribed dosage and frequency; if they are only taking half the prescribed dosage, this fact should be known—and the reasons investigated. In addition it is sometimes important to know whether individual patients are taking dapsone regularly. Any patient, for instance, whose urine tests regularly confirm he is absorbing the drug, but who nevertheless deteriorates clinically must be harbouring dapsone resistant organisms.

The majority of leprosy patients are treated with dapsone (4′4-diamino-diphenylsulphone, DDS). This drug offers few technical problems in analysis or interpretation of results. It is almost completely absorbed from the gastro-intestinal tract, and up to 90% is excreted in the urine (Israili *et al.*, 1973): the

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half life of about one day is not affected by the variable rates at which dapsone is acetylated (Ellard *et al.*, 1974). Thus estimation of the amount of dapsone in the urine should indicate whether a patient is taking treatment in the prescribed dosage and regularity.

When urine tests however are taken from a group of patients who received the same dosage of dapsone, say 100 mg given 24 h previously, there is a very wide range of concentrations of dapsone in the urine. The major factor accounting for this is the urine concentration, for the more a patient drinks, the more dilute is the urine and the lower will be the dapsone concentration.

The wide range of dapsone concentration makes it impossible for tests of urine dapsone concentration to give a reliable indication of regularity of treatment. However this problem can to some extent at least be overcome if the urine creatinine concentration is also estimated, and the result expressed as the ratio of dapsone to creatinine (D/C ratio). Creatinine is a breakdown product of striated muscle, and for any individual the creatinine output per 24 h is very constant. Thus if the urine is concentrated the urine creatinine concentration is increased; with dilute urine it is decreased. The concentration of dapsone in the urine varies in much the same way, and so the D/C ratio varies less than does the dapsone concentration.

This paper describes the results of urine tests carried out on patients attending the hospital service and a leprosy control clinic of the All Africa Leprosy and Rehabilitation Training Centre (ALERT).

Patients and Methods

The study was divided into two parts. In the first stage patients receiving dapsone daily under full supervision provided urine specimens immediately before swallowing their next tablets. These patients were in the hospital service of ALERT; the tablets were administered by nursing staff and seen to be swallowed. These tests provided information on the range of figures to be expected 24 h after various doses of dapsone. Control urines were also obtained from patients and staff not receiving dapsone.

In the second stage of the study patients attending an ALERT leprosy control clinic were requested to provide a urine specimen, but not informed of the reason; the majority agreed to do so. They were receiving daily dosage, but attended usually once a month for routine examination and issue of tablets. The results of these tests gave some indication of the overall regularity of treatment attained at this leprosy control clinic.

Dapsone was estimated by a modification of the method of Bratton and Marshall (1939); creatinine was estimated by the alkaline picrate method. Further details are given elsewhere (Ellard, Gammon and Harris, 1974). A duplicated sheet describing the actual technique in step by step detail is available (request as for reprints).

Results

(1) *Control urines and specimens from patients under fully supervised treatment*

The urine dapsone levels of subjects not receiving dapsone (control blanks) and of patients receiving different fully supervised dapsone dosages are shown in Fig. 1. There is considerable overlap of the dapsone levels at different dosages: a

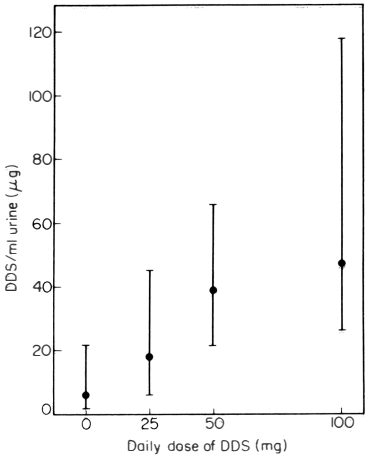

Fig. 1. Urine dapsone concentrations of patients receiving different dosages of dapsone under supervision.

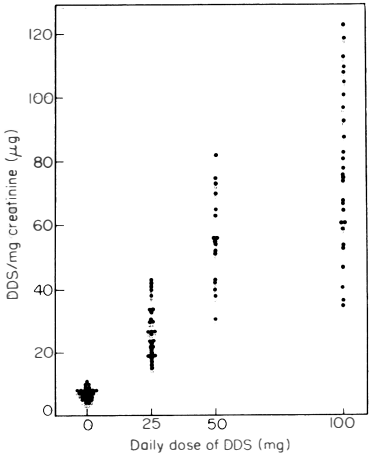

Fig. 2. Urine dapsone/creatinine ratios of patients receiving different dosages of dapsone under supervision.

patient with 40 μg dapsone/ml of urine, for instance, could have taken 25, 50, or 100 mg of dapsone 24 h previously. By contrast, the D/C ratios (Fig. 2) show much better separation. In particular there is complete separation between the control and other groups, and almost complete separation of the 25 mg and 50 mg groups.

The D/C ratio for 4 or more repeated tests on individual patients (in hospital) on different dosages are shown in Fig. 3. The range for a single patient is much less than that of the group as a whole.

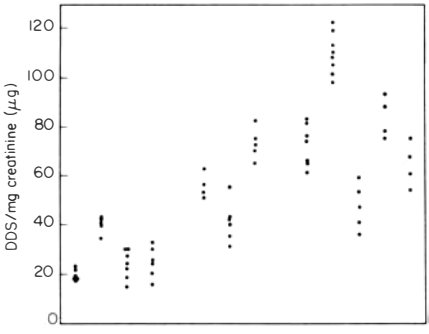

Fig. 3. Urine dapsone/creatinine ratios of individual patients receiving different dosages of dapsone under supervision.

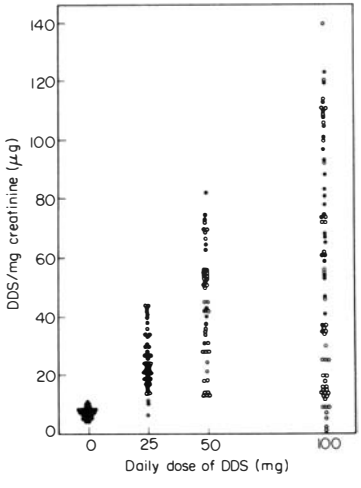

Fig. 4. Urine dapsone/creatinine ratios of patients receiving different dosages of dapsone; ●, under supervision in hospital; ○, prescribed as outpatient treatment.

(2) *Patients attending an ALERT leprosy control clinic*

These patients, though receiving daily dosage of dapsone, were seen usually once a month. Results of their urine tests, taken at routine clinic attendance, are shown in Fig. 4. The patients should have taken their tablets 12 to 24 h previously, but only one test was higher than any under supervised dosage. Thirty-nine of the patients however gave lower figures than the lowest seen in their control groups: and statistical analysis indicated that the group as a whole had taken about 42% of their prescribed dapsone dosage in the previous 24 to 48 h.

Discussion

In the field of leprosy, regularity of clinic attendance is usually considered (at least for the purposes of annual reports) as adequate indication of regularity of

drug taking. This assumption might be considered reasonable in view of the virtual absence of unpleasant side effects of dapsone *per se* in currently accepted dosage (i.e. not greater than about 100 mg daily). Nevertheless the majority of experienced field workers appear to consider that leprosy patients as a group are unreliable, and cannot be trusted to take tablets except under the closest supervision. Thus, one of the benefits of weekly dosage of dapsone is considered to be that the patient (if he can reach the clinic each week) can be "fully supervised", and need not be given tablets to take away, which he may or may not swallow.

The results of this study support those who think that patients often fail to take treatment regularly. Out of 89 patients tested, 39 who should have taken a tablet in the previous 24 h had probably not done so. The attendance rate at this clinic is good (80% are regular attenders) but it is clear that, in this clinic at least, regularity of attendance is no guarantee of regularity of dosage. Similar findings have been reported from the only other control programme where these tests have been performed (Ellard *et al.*, 1974). Both these studies were performed in Africa. However random home visits to check on tablet consumption (carried out in an Indian leprosy control programme) showed that about three-quarters of patients visited had the correct number of tablets remaining (Cap, 1974).

In tuberculosis irregular drug treatment is liable to give rise rapidly to drug resistance. In leprosy this is not the case: dapsone resistance develops only in a small proportion of patients with lepromatous leprosy, and not at all in borderline or tuberculoid cases. Irregular treatment has, however, been shown in leprosy to prolong the period of treatment required for patients to become smear negative (Cap, 1974); and it may also give rise to more complications, probably including an increased risk of dapsone resistance. Moreover it is clearly impossible to evaluate the benefits and hazards of different drug regimes if it is uncertain whether patients are adhering to them.

The results of these tests point clearly to the existence of a group of patients who, though willing to attend clinics regularly, are not taking the prescribed treatment. The reasons for this pattern of behaviour are obscure; possible explanations include:

(1) The patients are sharing out or selling some of their tablets.
(2) They may come to the clinic, but their main interest in doing so may be to obtain other things than medication, such as shoes or clothes, which meet their felt needs. They may not be particularly interested in dapsone.
(3) They may not see their disease improving, and therefore lose trust in their supervisor and interest in their treatment. Patients such as beggars may also have little motivation to be "cured".
(4) They may just forget to take their tablets, or lose them, or find they have crumbled up, and are afraid to say what has happened.

Estimation of the D/C ratios of a group of patients makes it possible to determine whether irregular drug taking is a problem in a clinic or control scheme. Similarly the test can be used to monitor the regularity of an individual patient provided his normal range is first determined by several tests during a period of fully supervised treatment. Evaluation of the medical, social, and personality differences between regular and irregular takers should make it possible to discover why some patients do not take treatment regularly, and to institute preventive measures. Further studies along these lines are planned.

Acknowledgements

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