

## Evaluation of a Continual Compliance Monitoring Program for Dapsone in an Outpatient Hansen's Disease Clinic<sup>1</sup>

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Daily self-administration of dapsone remains an integral part of most pharmacotherapeutic regimens recommended for the treatment of Hansen's disease (26). Regularity of dapsone administration either as monotherapy or as part of multidrug therapy is an important factor to ensuring a successful therapeutic outcome (13). Previous reports have estimated that from 30% to 60% of outpatients with Hansen's disease are noncompliant in their self-administration of dapsone (4, 7, 10, 12). Noncompliance with therapeutic regimens has been shown to be a major cause of treatment failure with other chronic diseases (17, 20, 23). Barton, *et al.*, in an investigation of 62 patients with lepromatous leprosy receiving treatment with dapsone monotherapy, found that failure to achieve quiescence was associated in the majority of patients with poor dapsone compliance (1). In addition, with the emergence of sulfone-resistant *Mycobacterium leprae* (16), the assessment of compliance in Hansen's disease patients is important to help distinguish between treatment failure secondary to noncompliance or to the development of resistance. Also, several reports suggest that irregularity of dapsone administration may be a major factor contributing to the development of dapsone-resistant strains of *M. leprae* (11, 24, 27). These

factors emphasize the importance of developing a method for identifying and minimizing noncompliance in patients with Hansen's disease.

A common method used to assess dapsone compliance is the determination of the urinary dapsone (dapsone plus its diazotizable metabolites) to creatinine (D/C) ratio (8). The application of this method in quantitating the level of compliance in various populations of outpatients with Hansen's disease has been reported (4, 8, 10, 14). However, a large inter-patient variability in the D/C ratio has been reported by several authors even among compliant patients (4, 8, 10, 14, 15). This variability complicates the use of the D/C ratio for monitoring compliance in a given patient (28). Reasons for this large inter-patient variability include differences among patients as to the amount of dapsone being administered on a mg/kg basis; sampling time in relation to dose administration; inter-patient differences in elimination rates for both dapsone and creatinine; gender-related differences in creatinine production and excretion; and the nonspecificity of the assay procedure, which results in measurable D/C ratios in dapsone-free urine samples due to the presence of endogenous diazotizable compounds (8, 14).

This study was designed to develop a method for assessing individual patient compliance to dapsone on a continual basis in an outpatient Hansen's disease clinic. In order to reduce the inter-patient variability and allow the development of useful monitoring guidelines, the measured D/C ratio was standardized in each patient by: a) correcting for the presence of interfering compounds by measuring the D/C ratio in patients not receiving dapsone, b) extrapolation of the D/C ratio to 24 hr postdose to standardize the time since last dose in each patient, and c) correcting for differ-

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ences in body weight among patients. Correction of the D/C ratio by body weight was performed to account for individual differences in urinary dapsone and creatinine excretion. Both total body weight (TBW) and ideal body weight (IBW) were evaluated. Creatinine production and elimination are proportional to lean body mass (<sup>3,19</sup>). This relationship may explain some of the variability in D/C ratios between individual patients and the larger D/C ratio reported in females. The use of body weight in standardizing the D/C ratios may also reduce some of the variability that occurs secondary to inter-patient differences in the total body clearance of dapsone, which is also dependent on body size (<sup>22</sup>). The total body clearance can be approximated by dividing the dosing rate by the steady-state serum concentration. Since the urinary D/C ratio reflects the serum dapsone concentration (<sup>6</sup>), inter-patient variability in the D/C ratio which occurs secondary to individual differences in dapsone total body clearance may be accounted for by standardizing the D/C ratio by dose and body weight.

Urinary D/C ratios standardized by the above factors were used to develop compliance guidelines for Hansen's disease patients being treated with dapsone. This investigation assessed the effect of a continual compliance monitoring program based on these guidelines in altering patient compliance to dapsone therapy and therapeutic response.

#### MATERIALS AND METHODS

Quantitative determination of the ratio of dapsone (plus its diazotizable metabolites) to creatinine (D/C) in the urine was obtained by the analytical procedure described by Ellard, *et al.* using a Perkin-Elmer Model 200 spectrophotometer (<sup>8</sup>). All urine samples were collected from a mid-stream collection at least 2 hr postdose to allow for sampling during the postabsorption phase (<sup>6</sup>). Urine samples were frozen at  $-20^{\circ}\text{C}$  within 3 hr of collection and analyzed within 2 weeks. Samples from patients receiving concomitant sulfonamides or sulfonamide derivatives were not analyzed due to assay interference. The concentration of dapsone plus metabolites was determined by comparing the change in optical density

(OD) observed for the patient samples (diluted 1:5 with distilled water) to a standard curve constructed from five aqueous standards of known dapsone concentration (2 to 32  $\mu\text{g/ml}$ ). The standard curve samples and a spiked control sample in urine were analyzed with each assay run. The within and between assay precision, expressed as the coefficient of variation, for this procedure in our laboratory was 2.5% and 4.0%, respectively. The urinary creatinine concentration was determined by the Jaffe reaction, as previously described (<sup>8</sup>). The "blank" D/C ratio was determined in 20 patients not receiving dapsone. This was performed to quantitate the urinary concentration of endogenous diazotizable compounds in the clinic population. No interference with the assay procedure was observed for patients receiving rifampin, thalidomide, clofazimine, or prednisone. The study was approved by the Institutional Review Board of the University of Illinois at Chicago, and informed consent was obtained from all patients.

The compliance guidelines were established from D/C ratios obtained in 12 adult outpatients at the University of Illinois Hansen's Disease Clinic who were judged to be compliant with their dapsone therapy by the medical staff. All of these patients had been receiving dapsone 100 mg daily for at least 4 weeks. The urine samples for determination of the D/C ratios were collected at the same approximate time postdose in each patient on three separate occasions over 2 months to confirm compliance. A coefficient of variation on the replicate patient D/C ratios of less than 15% was used to indicate compliance (<sup>12</sup>). The D/C ratio obtained from the assay procedure was standardized in each patient to account for differences in dose, body weight and time since last dose.

The following equation was used to obtain the standardized D/C ratio ( $D/C_{\text{stand}}$ ):

#### Equation 1

$$D/C_{\text{stand}} = (D/C_{\text{pt}} - D/C_{\text{blank}}) \cdot \frac{1}{\text{Dose}} \cdot \text{BW} \cdot e^{-Kc \cdot t}$$

where:

- $D/C_{pt}$  = D/C ratio obtained from assay procedure  
 $D/C_{blank}$  = mean "blank" D/C ratio  
 BW = patient's body weight in kg; use of both total body weight (TBW) and ideal body weight (IBW), as calculated by the method of Devine<sup>(5)</sup>, were evaluated  
 $K_e$  = D/C elimination rate constant, an average value of  $0.0257 \text{ hr}^{-1}$  (equivalent to half-life of 27 hr) was used<sup>(4, 6)</sup>  
 $t$  = 24 hr minus time from last dose

The exponential term is used to standardize patient samples to 24 hr postdose. The "t" value is set equal to zero for noncompliant patients (i.e., last dose greater than 24 hr from sampling time).

Compliance guidelines were based on the mean and 99% confidence interval of the D/C ratios from the compliance controls. Three sets of compliance guidelines were constructed based on either unstandardized, TBW-standardized or IBW-standardized D/C ratios. Prior to using the compliance guidelines to assess compliance in the clinic patients, an evaluation of the three sets of compliance guidelines to determine which was the most appropriate to use was performed on 14 D/C ratios obtained from nine inpatients. These urine samples were obtained at varying periods following the last dapsone dose with a range of 12 to 96 hr. Two methods were used in evaluating the compliance guidelines: a) examining the time postdose at which the D/C ratios from the inpatients ( $D/C_{inpt}$ ) fell below the compliance guidelines, and b) comparing actual time postdose to that calculated by Equation 2 below, using the mean D/C ratio from the compliance controls ( $D/C_{control}$ ). Unstandardized, TBW-standardized, or IBW-standardized  $D/C_{inpt}$  was used, depending on which of the three compliance guidelines was being evaluated, i.e., unstandardized, TBW-standardized, or IBW-standardized, respectively.

#### Equation 2

$$\begin{aligned} &\text{Time since last dose} \\ &= 24 - \frac{1}{K_e} * \ln \frac{D/C_{inpt}}{D/C_{control}} \end{aligned}$$

The evaluator was blinded to the actual time that doses were withheld. As a result of this, "t" in Equation 1 was set equal to zero when standardizing the D/C ratios from the inpatients.

Following the establishment and evaluation of the compliance guidelines as described above, urine samples were monitored on a continual basis over the next 24 months in outpatients (N = 30) attending the Hansen's Disease Clinic. Overall percent compliance was assessed at three different periods of time. An initial base-line assessment of compliance was done over a 6-month period during which the results were not revealed to the patients. Following this period, a continual compliance monitoring program was instituted over the next 18 months. Results of the urine testing were explained to the patients, and the importance of compliance stressed to those patients whose D/C ratios were below the lower limit of the compliance guidelines. Compliance was again assessed at 6 and 18 months following initiation of the monitoring program. In assessing compliance during the three time periods, those clinic patients whose D/C ratios fell below the lower limit of the compliance guidelines for the majority of visits during the time period (range 2 to 5 visits per patient) were considered to be noncompliant.

The following clinical data were also collected from each patient: type of Hansen's disease, date of diagnosis, sex, race, height, weight, age, daily dapsone dose, time since last dose, concomitant drug therapy, and patient's assessment of compliance with drug regimen. All medications, including once-monthly rifampin, were self-administered by the patients. Time since last dose ranged from 4 to 24 hr in the compliant patients. In a subgroup of 18 patients who were followed throughout the 24 months with at least one skin smear (and/or biopsy) during each of the three time periods (base line, 6 and 18 months), the therapeutic response in relation to compliance was evaluated from histological (morphological index, bacterial index, percent dermis involved) and clinical findings. The assessment of clinical response was performed by examination of individual patient data by one of the investigators (SMW). The patient data had been compiled by a third party and con-

TABLE 1. *D/C ratios from the compliance controls.*

|  | Unstandardized  | Standardized-TBW <sup>a</sup> | Standardized-IBW <sup>b</sup> |
|--|-----------------|-------------------------------|-------------------------------|
| Mean ( $\mu\text{g}/\text{mg} \pm \text{S.D.}$ ) | 43.1 $\pm$ 16.2 | 25.1 $\pm$ 7.0                | 20.4 $\pm$ 3.8                |
| Range  | 24.0–70.1       | 15.5–42.2                     | 15.3–25.5                     |
| Coefficient of variation                         | 37.6%           | 27.9%                         | 18.6%                         |

<sup>a</sup> D/C ratio standardized by Equation 1 using TBW (total body weight).

<sup>b</sup> D/C ratio standardized by Equation 1 using IBW (ideal body weight).

tained no reference to patient identification or compliance testing results. The patient data were judged as demonstrating improvement or no improvement in disease response over the time of the study.

Statistical analyses performed included: a) test for differences between variances of two related samples, to evaluate the reduction in variability by standardization of the D/C ratio (<sup>2</sup>); b) paired *t* test, to evaluate the actual and predicted times from last dose; c) chi-squared contingency table, to evaluate the compliance changes in the clinic population, and d) Fisher's exact test, to evaluate the differences in disease response in the subgroup of patients (<sup>21</sup>). A  $p < 0.05$  was considered significant.

### RESULTS

D/C ratios in patients not receiving dapsone ("blank values") ranged from 0 to 6.5  $\mu\text{g}/\text{mg}$  with a mean of 3.4  $\mu\text{g}/\text{mg}$ . The mean, range, and coefficient of variation for D/C ratios determined in the 12 compliance controls are listed in Table 1. Inter-patient variability, as represented by the coefficient of variation, was reduced significantly ( $p < 0.01$ ) following standardization of D/C ratios using Equation 1 with IBW, 18.6% versus 37.6% and 27.9% obtained for unstandardized and standardized with TBW D/C ratios, respectively. The accuracy of compliance guidelines determined from the mean and 99% confidence interval of the unstandardized, TBW-standardized, and IBW-standardized D/C ratios from the compliance controls was assessed using D/C ratios from nine inpatients. No significant difference ( $p > 0.05$ ) was observed between actual, 38.9  $\pm$  23.0 hr (mean  $\pm$  S.D.), time since last dose in the inpatients and that predicted, 39.9  $\pm$  23.6 hr, using the mean IBW-standardized D/C ratio from the compliance controls. The difference between ac-

tual and predicted time since last dose was significantly different ( $p < 0.01$ ) using either the mean unstandardized, 45.3  $\pm$  25.3 hr, or TBW-standardized, 32.3  $\pm$  23.6 hr, D/C ratio from the compliance controls. Six of seven D/C ratios from the inpatients at greater than 36 hr postdose were below the lower limit of the IBW-standardized compliance guidelines. Using compliance guidelines based on either unstandardized or TBW-standardized D/C ratios, only 3 of 7 D/C ratios at greater than 36 hr in both cases would have been below the compliance range. Thirty-six hours represents the approximate minimum time, predicted by Equation 2, that patients with D/C ratios below any of the three compliance guidelines would have received their last dapsone dose. As a result of the above findings, the guidelines for assessing patient compliance were based on the IBW-standardized D/C ratios, and D/C ratios from the clinic patients standardized using Equation 1 and IBW prior to assessing for compliance. The 99% confidence interval for the IBW-standardized D/C ratios in the compliance controls was 17.0 to 23.8  $\mu\text{g}/\text{mg}$ .

The demographic data from the compliance controls and clinic patients are summarized in Table 2. No significant difference ( $p > 0.05$ ) was found between the two groups in terms of age, sex, type of Hansen's disease, and concomitant drug therapy. D/C ratios obtained during the base-line assessment period indicated that only 14 of 30 patients (46.7%) attending the clinic were compliant with their dapsone therapy. The level of dapsone compliance in the clinic patients was reassessed at 6 and 18 months following implementation of the compliance monitoring program. A significant increase ( $p < 0.05$ ) in the number of compliant patients was observed at both time periods, 23 (73.3%) and 24 (80%) of 30 pa-

TABLE 2. Demographic data.

|   | Compliance           |                         |
|---|----------------------|-------------------------|
|   | Controls<br>(N = 12) | Outpatients<br>(N = 30) |
| Age (years $\pm$ S.D.)  | 38.4 $\pm$ 12.0      | 37.9 $\pm$ 11.5         |
| Sex   | 7 M, 5 F             | 17 M, 13 F              |
| Weight (kg $\pm$ S.D.)  | 74.7 $\pm$ 18.9      | 69.4 $\pm$ 10.7         |
| Range   | 54.1–81.8            | 47.3–98.2               |
| Type of Hansen's disease  |                      |                         |
| Paucibacillary  | 4                    | 11                      |
| Multibacillary  | 8                    | 19                      |
| Drug therapy regimens   |                      |                         |
| Dapsone 100 mg/<br>day plus rifam-<br>pin 1200 mg<br>once monthly | 9                    | 22                      |
| Dapsone 100 mg/<br>day  | 3                    | 3                       |
| Dapsone 50 mg/<br>day plus rifam-<br>pin 1200 mg<br>once monthly  | —                    | 1                       |
| Dapsone 50 mg/<br>day   | —                    | 2                       |
| Dapsone 100 mg/<br>day plus clofam-<br>izine 100 mg/<br>day       | —                    | 2                       |

tients, respectively, as compared to the base-line assessment period prior to initiation of the monitoring program.

A similar increase in compliance was observed in the subgroup of 18 patients. The proportion of compliant patients in this group increased from 50% during the base-line period to 72% and 78% at 6 and 18 months, respectively. A significant improvement ( $p < 0.05$ ) in disease response, as determined from the histological and clinical data summarized in Table 3, was seen in nine patients compliant throughout the study period and four patients noncom-

pliant during the base line but compliant at 6 and 18 months. No significant change ( $p > 0.05$ ) in the histological findings was seen in the five patients noncompliant throughout the study period. Only two of these patients had an improvement in their disease response based on the clinical assessment of the physician. The difference in therapeutic response between the compliant and noncompliant patients was statistically significant ( $p < 0.05$ ). No significant difference ( $p > 0.05$ ) was found between the noncompliant and compliant patients in terms of base-line bacterial index, morphological index, percent dermis involved, type of Hansen's disease (4 of 5 patients multibacillary versus 10 of 13 patients multibacillary, respectively) and concomitant drug therapy (5 patients receiving dapsone plus once-monthly rifampin versus 11 patients on dapsone plus once-monthly rifampin and 2 patients on dapsone plus clofazimine, respectively).

## DISCUSSION

The large inter-patient variability for unstandardized D/C ratios observed in our compliance controls is similar to that reported by others (<sup>4, 8, 10, 14, 15</sup>). This large variability in D/C ratios interferes with the development of accurate guidelines for assessing compliance in individual patients (<sup>4, 8</sup>). Standardization of the D/C ratios by factors known to account for this inter-patient variability in drug concentrations resulted in a significant reduction of variability and in the establishment of practical guidelines for assessing compliance. The accuracy of these guidelines in assessing compliance was confirmed in a group of inpatients receiving supervised doses of dapsone. Because of the lack of clinical or experi-

TABLE 3. Therapeutic response in subgroup (mean  $\pm$  standard deviation).

|                      | Compliant patients |               | Noncompliant patients |                |
|----------------------|--------------------|---------------|-----------------------|----------------|
|                      | Base line          | 18 months     | Base line             | 18 months      |
| Bacterial index      | 2.5 $\pm$ 2.5      | 1.0 $\pm$ 1.6 | 2.6 $\pm$ 2.3         | 2.0 $\pm$ 2.0  |
| Morphological index  | 3.3 $\pm$ 6.1      | 0             | 3.0 $\pm$ 5.4         | 1.6 $\pm$ 2.2  |
| % Dermal involvement | 23.7 $\pm$ 27.6    | 7.5 $\pm$ 9.9 | 17.0 $\pm$ 13.0       | 12.5 $\pm$ 7.1 |
| Clinical Assessment  |                    |               |                       |                |
| Improvement          |                    | 13            |                       | 2              |
| No improvement       |                    | 0             |                       | 3              |

mental data to predict the minimum level of compliance required to prevent therapeutic failure with dapsone either as monotherapy or as part of a multidrug regimen and the greater development of resistance attributed to low-dose dapsone regimens<sup>(11, 13)</sup>, our monitoring guidelines were developed to provide a strict assessment of patient compliance while allowing for the degree of inter-patient variability determined from the standardized D/C ratios in our compliance controls. The risk associated with this approach may be the false classification of compliant patients with extremely rapid rates of dapsone elimination as being noncompliant. Despite the risk associated with the relatively narrow range of our compliance guidelines, they appeared to appropriately determine the regularity of drug intake in our clinic population. This assertion is supported by the close agreement between predicted and actual time since last dose using the D/C ratios from the inpatients; the increase in D/C ratios into the compliance range in the majority of initially noncompliant patients following the feedback of results, and the greater sample-to-sample fluctuation in D/C ratios observed for the noncompliant patients (>30%) versus the compliant patients (<20%). This greater fluctuation in replicate samples would suggest a higher degree of inconsistency in drug administration.

The use of ideal body weight (IBW) to standardize the D/C ratio resulted in a significant decrease in the inter-patient variability as compared to total body weight (TBW). Since urinary creatinine excretion is directly related to lean body mass, IBW would be expected to better correct for individual differences in creatinine excretion. IBW also corrected for gender-related differences in the D/C ratio. Previous reports have shown a larger D/C ratio in female than in male patients<sup>(12, 14)</sup>. This difference appears to occur secondary to lower urinary creatinine excretion in females. The mean unstandardized and TBW-standardized D/C ratios from our compliant patients were significantly larger in female than in male patients, 61.1 (females) versus 49.2 (males)  $\mu\text{g}/\text{mg}$  and 31.1 (females) versus 25.5 (males)  $\mu\text{g}/\text{mg}$ , respectively. Following standardization using IBW, the D/C ratios were similar between female and male patients, 21.6 ver-

sus 20.9  $\mu\text{g}/\text{mg}$ , respectively. The lower variability associated with the use of IBW as compared to TBW in standardizing the D/C ratio may also indicate a poor distribution of dapsone into adipose tissue<sup>(25)</sup>.

Huikeshoven reported, in a review of previous compliance studies utilizing the D/C ratio method, that approximately 50% of leprosy patients receiving dapsone were compliant<sup>(12)</sup>. A similar level of compliance was observed in our patients during the base-line period. However, previous studies have been primarily concerned with quantitating the level of compliance for a group of patients in leprosy clinics or control centers. The present study has investigated the use of continual monitoring of urine D/C ratios with feedback of results to the patients to improve dapsone compliance. Studies in epileptic patients have shown that continual monitoring of drug concentrations with feedback to the patients can improve compliance<sup>(23)</sup>. The results in our clinic demonstrate that such a monitoring program can be successfully applied to improving medication compliance in patients with Hansen's disease. Ganapati, *et al.* reported a similar improvement following the feedback of urine test results<sup>(9)</sup>. The value of objective guidelines for assessing compliance is shown by comparing the level of compliance determined from the D/C ratio results to that determined by direct questioning of patients. During the base-line assessment period, only 5 of 30 patients admitted to being noncompliant versus 16 of 30 based on the D/C ratios. Following the initiation of the monitoring program with feedback of results to the patients, D/C ratios in the majority of these 16 patients, including most of those who originally stated to be compliant, increased into the range of the compliance guidelines. Dependence on patient history alone would not have provided a satisfactory indication of drug compliance.

Previous studies showing a direct relationship between compliance and therapeutic response are lacking. The examination of clinical and histological data in our subgroup demonstrated a significant relationship between compliance and therapeutic response. It should be stressed that therapeutic response in these patients was not dependent on dapsone alone, since most

were receiving dapsone as one component of a multidrug regimen. The other medications, including the once-monthly rifampin, were also being self-administered. The degree of compliance with the other components was not determined. These initial findings do, however, suggest that compliance is as important in present multidrug regimens as in dapsone monotherapy; a similar observation was made in a recent editorial (13). Further study is needed to quantitate the level of compliance for the individual components in the multidrug regimens required to ensure a successful therapeutic response.

The results from this investigation suggest that important elements for a compliance monitoring program include: a simple method for assessing the amount of dapsone ingested, rapid availability of results, and the consistent feedback of the results to the patients. While we have described one method for assessing patient compliance to their dapsone therapy, different methods described by others may be equally valid and useful (12, 15, 28). We would recommend that the method be validated in patients from that clinic population, since significant differences in patient populations and laboratory techniques may occur between different clinic centers. The importance of some type of monitoring program is demonstrated by the poor therapeutic response seen in patients who were consistently noncompliant. Since the majority of these patients were all receiving multidrug therapy for their Hansen's disease, these findings suggest that the assessment of compliance is important whether dapsone is administered as monotherapy or as part of a multidrug regimen.

#### SUMMARY

Guidelines for the assessment of patient compliance to dapsone were developed and evaluated. The urinary dapsone-to-creatinine (D/C) ratio following standardization by dose, ideal body weight, and time since last dose was used for assessment of compliance. Compliance standards were established in 12 patients of known compliance and confirmed prospectively in nine inpatients on 14 occasions. Compliance increased significantly among outpatients (N = 30) attending the University of Illinois Hansen's Disease Clinic from 47% at base line

to 73% at 6 months and 80% at 18 months after establishing the monitoring program. In a subgroup of 18 patients, a similar increase in compliance was observed from 50% to 80%. A good therapeutic response was seen in the subgroup patients who were compliant. A poor therapeutic response was seen in the consistently noncompliant patients. These results demonstrate that use of a continual compliance monitoring program can improve patient drug compliance in an outpatient Hansen's disease clinic.

#### RESUMEN

Se desarrollaron y evaluaron lineamientos para establecer la constancia de los pacientes en cuanto a su medicación con dapsona. Para establecer dicha constancia de medicación, se determinó el índice dapsona/creatinina (D/C) urinarios, después de hacer la estandarización por dosis, peso corporal ideal, y tiempo desde la última dosis. Los estándares de constancia se establecieron en 12 pacientes de constancia reconocida y se confirmaron posteriormente en 9 pacientes internos, en 14 ocasiones. El grado de constancia aumentó significativamente entre los pacientes externos (N = 30) de la Clínica de la Enfermedad de Hansen de la Universidad de Illinois, del 47% al inicio, al 73% y al 80%, 6 y 18 meses después de establecer el programa de seguimiento. En un subgrupo de 18 pacientes se observó un aumento similar en la constancia del 50% al 80%. En el subgrupo de pacientes que fueron constantes se observó una buena respuesta terapéutica. En los pacientes muy inconsistentes la respuesta fue pobre. Estos resultados demuestran que el uso de un programa de seguimiento continuo puede mejorar el cumplimiento de los pacientes al tratamiento en clínicas para pacientes externos con la enfermedad de Hansen.

#### RÉSUMÉ

On a développé et évalué des directives en vue de l'évaluation de l'assiduité des malades de la lèpre à la dapsona. Pour cette évaluation, on s'est basé sur le ratio dapsona/créatinine (D/C), standardisé pour la dose, le poids corporel idéal, et le temps écoulé depuis la dernière administration. Des normes d'assiduité ont été établies chez 12 malades dont on connaissait l'assiduité. Ces normes ont été confirmées de manière prospective à 14 reprises chez neuf malades hospitalisés. L'assiduité s'est améliorée significativement chez les malades ambulatoires, au nombre de 30, qui fréquentaient le dispensaire de la lèpre (Hansen Disease Clinic) de l'Université de l'Illinois. Cette assiduité est montée de 47% à 73% en six mois, et à 80% en 18 mois, à la suite de la mise en oeuvre de ce programme de surveillance. Dans un sous-groupe de 18 malades, on a noté une amélioration semblable de l'assiduité, de 50% à 80%. Une réponse thérapeutique satisfaisante a été constatée chez les malades qui étaient assidus au trai-

tement. Chez les malades qui, de façon irréductible, étaient peu assidus, la réponse thérapeutique fût faible. Ces résultats démontrent que le recours à un programme de surveillance continu de l'assiduité peut améliorer l'assiduité thérapeutique des malades ambulatoires dans un dispensaire pour la lèpre.

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