COMMUNITY-BASED IVERMECTIN THERAPY FOR ONCHOCERCIASIS: COMPARISON OF THREE METHODS OF DOSE ASSESSMENT

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Abstract. A new method of assessment based on mid-upper arm circumference (MUAC) is described for dosage adjustment for community-based ivermectin distribution. We studied 878 subjects eligible for ivermectin dosing in Awhum, Nigeria. In a previous preliminary study of 40 persons, MUAC (in cm) correlated with weight (kg) in the first 20 male (r = 0.97, r² = 0.95, P < 0.0001) and the first 20 female subjects (r = 0.94, r² = 0.88, P < 0.0001). We therefore studied the use of height, physical appearance, and MUAC for calculating the dose of ivermectin. The MUAC-based schedule underdosed only 4.1% of the population. The methods based on height underdosed 3.3% and 21.1%, and assignment based on physical appearance underdosed 10.2% of the population studied. This MUAC-based method (13—15 cm, 0.5 tablet; 16—20 cm, 1.0 tablet; 21—27 cm, 1.5 tablets; ≥ 28 cm, 2.0 tablets) is more convenient and corresponds closely to dosing by weight. An adaptation of this method with reference to other prevalent tropical diseases and their respective drugs is therefore advocated.

INTRODUCTION

The introduction of ivermectin for the chemotherapy of onchocerciasis has been associated with mild adverse reactions.1–4 Community trials indicate that a single dose (150 μg/kg) markedly reduces skin microfilarial levels for up to 12 months, with a transient fall in transmission levels.5 It also reduces the prevalence of some intestinal nematodes6 and ectoparasitic infections.7

Distribution of ivermectin based on the subject’s body weight has several inherent problems.8,9 The major ones are cost, transportation, and inability of the community-based distributors (CBDs) to read the weighing scales. There is thus a need for easy, cheap, and reliable alternative methods for assessing the dose of ivermectin. In the course of this search, height9,10 and physical appearance10 were used as surrogates for weight. Although height and physical appearance are feasible in mass dosing exercises, they are not without disadvantage since they are subjective. Moreover, field experience shows that a small proportion of the population may refuse the height measurement.

The prevalence of protein-calorie malnutrition appears to be best indicated by weight deficiency in all age-groups and by growth failure in children.11 Since poor muscle development or muscle wasting are cardinal features of all forms of protein-calorie malnutrition, measurement of the mid-upper arm circumference (MUAC) gives an approximate indication of calorie reserve11 and by implication weight status. The MUAC could thus be a valuable method for predicting the dose of ivermectin in mass chemotherapy of onchocerciasis.

This study was necessitated by the fact that during an ivermectin dosing exercise we found a relationship between the body weights and corresponding MUACs in the first 20 male and 20 female subjects. As a follow-up, we therefore examined the use of the MUAC to assess the dose of ivermectin. It was compared with previous methods based on height9,9 and physical appearance,10

MATERIALS AND METHODS

Study site. The study was carried out in Awhum in a rain-forest savannah area of southeast Nigeria. The landscape in this area is bounded by hills, valleys, and evergreen forests. Fast-flowing streams are located at the outskirts of this community where subsistence farming is the main occupation.

Rapid assessment of onchocerciasis in 50 male subjects aged 20 years and above revealed that 51.5% had nodules in non-lymph node areas, 18.2% depigmentation, 6.1% hanging groin, and 63.6% complained of itching. A survey of a larger population (209 subjects) showed that the prevalence of onchocerciasis was 53.1% and the community microfilarial load (CML) was 41.7 microfilariae/mg skin.

Study population. In September 1995, a total of 878 subjects 8–75 years old were administered ivermectin based on the currently recommended dose of 150 μg/kg body weight.9 On the day of dosing, all participants were registered and cards issued to them. Exclusion criteria for ivermectin therapy were pregnancy, breast feeding < 3 months, age < 5 years, or concurrent non-onchocerial illness. Oral informed consent was obtained from all adult participants and from the parents or legal guardians of minors. Approval for the study was given by the Ethics Committee of the University of Nigeria Teaching Hospital, Enugu, Nigeria.

Methods. A member of the field team estimated the dose of ivermectin based on the subject’s physical appearance. The estimated dose was then noted in the recipient’s registration card and later entered into the register. Another member of the field team measured the height of each subject with a vertical scale fixed to the wall. The measuring scale was two meters high and accurate to the nearest 0.5 cm. After removal of shoes, the subject was asked to stand on a flat floor by the scale and the hands were made to hang at the sides in a natural manner. A wooden block was lowered to make contact with the top of the head. The same worker measured MUAC to the nearest 0.1 cm with a glass-fiber measuring tape as previously reported.12 The tape was placed firmly around the mid-point of a freely flexed arm avoiding compression of soft tissues. This technique was validated by four MUAC measurements of nine persons: three at low MUAC, three at median MUAC and three at high MUAC.

The coefficient of variation (CV) for the three groups were 5.7, 4.4, and 5.2 with an average of 5.1. The subjects were weighed using a standard scale (Hansen Ireland). All three operations were supervised by one of the authors.
DOSAGE ADJUSTMENT OF IVERMECTIN

FIGURE 1. Relationship between weight and mid-upper arm circumference (MUAC) of (a) the first 20 male and (b) the first 20 female subjects involved in a preliminary study.

TABLE 1
Standard and proposed dosing schedules for ivermectin based on the body weight and mid-upper arm circumference (MUAC)

<table>
<thead>
<tr>
<th>Recommended schedule based on weight (kg)</th>
<th>Proposed schedule based on MUAC (cm)</th>
<th>No. of 6-mg tablets</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 15</td>
<td>&lt; 13</td>
<td>0</td>
</tr>
<tr>
<td>15–25</td>
<td>13–15</td>
<td>0.5</td>
</tr>
<tr>
<td>26–44</td>
<td>16–20</td>
<td>1</td>
</tr>
<tr>
<td>45–64</td>
<td>21–27</td>
<td>1.5</td>
</tr>
<tr>
<td>&gt; 64</td>
<td>≥ 28</td>
<td>2</td>
</tr>
</tbody>
</table>

Data analysis. Using the register, data from the 878 subjects were arranged according to body weight into five groups as < 15 kg, 15–25 kg, 26–44 kg, 45–64 kg and > 64 kg. The range of MUAC for each of the five groups was also determined as < 13 cm, 13–15 cm, 16–20 cm, 21–27 cm, and ≥ 28 cm, respectively. The average MUAC in each group was calculated and plotted against the corresponding average body weight in kg.

Underdose or overdose was calculated by the comparison of the dose the subject would have been given if he/she was dosed using the proposed MUAC, height schedules, or physical appearance with that actually administered based on body weight.

RESULTS

Figures 1(a) and 1(b) describe the relationship between body weight and MUAC of the first 20 male and the first 20 female subjects in a preliminary study. The associations were positive and highly significantly correlated for the males (r = 0.97, r² = 0.95, P < 0.0001) and females (r = 0.94, r² = 0.88, P < 0.0001).

Table 1 summarizes the schedule based on the MUAC of subjects in each of the five groups dosed by weight. There was also a positive and highly significant correlation (r = 0.99, r² = 0.99, P < 0.0001) between the average weight and the corresponding average MUAC (Figure 2).

Figure 3 describes the results of dosing based on height, physical appearance, and MUAC. Out of the 878 subjects, the height-based schedule advanced by Taylor and others 8 gave the highest (185, 21.10%) and the lowest (88, 10.02%) number of subjects with an underdosing and overdosing, respectively. In contrast, the height-based schedule proposed by Alexander and others 9 gave the lowest (29, 3.00%) and highest (474, 54.10%) number with an underdosing and overdosing. Dosing by physical appearance 10 resulted in 10.20% (89) underdosing and 16.70% (146) overdosing. There was 4.10% (36) underdosing and 14.90% (131) overdosing by the proposed MUAC schedule.

Table 2 represents the actual dose range in μg/kg for sub-
The MUAC is a relatively simple measurement that requires no calculation. Most villagers own and use glass-fiber tapes for domestic purposes. This is an indication that it may be used for ivermectin dose assessment despite the low level of literacy. Our results therefore show that the use of MUAC as the basis for administering ivermectin is comparable with that based on weight. In earlier reports, extreme cases of protein-calorie malnutrition in starvation during famine showed severe weight loss. The skin in such circumstances was loose and inelastic and muscle and fat wasting were strikingly obvious. This was demonstrable quantitatively by decrease in limb measurements, including the arm circumference. It was an indication of a relationship between arm circumference and body weight. The MUAC was also comparable with the height-based schedule proposed by Alexander and others, in minimizing the number of subjects understated. One problem with this height-based schedule was that it showed a marked overdosing of subjects (Table 2), although ivermectin is safe at doses well in excess of the standard schedule (150 μg/kg). Although a dose-finding study of ivermectin for treatment of onchocerciasis suggested that 150 μg/kg might be the optimal initial therapy, a single dose of 5 mg/kg was still administered to cattle against *Onchocerca gibsoni* (Copeman DB, personal communication). In the Nice region of France, four 6 mg tablets (24 mg) of the drug were administered to

<table>
<thead>
<tr>
<th>Range of dose (μg/kg)</th>
<th>Height†</th>
<th>Height‡</th>
<th>Physical appearance</th>
<th>MUAC</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
<td>No. (%)</td>
</tr>
<tr>
<td>&lt; 100</td>
<td>17 (1.94)</td>
<td>2 (0.23)</td>
<td>13 (1.48)</td>
<td>0 (0.00)</td>
</tr>
<tr>
<td>100–120</td>
<td>73 (8.31)</td>
<td>7 (0.80)</td>
<td>37 (4.21)</td>
<td>17 (1.94)</td>
</tr>
<tr>
<td>Total</td>
<td>90 (10.25)</td>
<td>9 (1.03)</td>
<td>50 (5.69)</td>
<td>17 (1.94)</td>
</tr>
<tr>
<td>181–200</td>
<td>69 (7.86)</td>
<td>214 (24.37)</td>
<td>73 (8.31)</td>
<td>84 (9.54)</td>
</tr>
<tr>
<td>&gt; 200</td>
<td>8 (0.91)</td>
<td>231 (26.31)</td>
<td>0 (0.00)</td>
<td>23 (2.62)</td>
</tr>
<tr>
<td>Total</td>
<td>87 (8.71)</td>
<td>445 (50.68)</td>
<td>73 (8.31)</td>
<td>107 (12.19)</td>
</tr>
</tbody>
</table>

**DISCUSSION**

The introduction of ivermectin for control of onchocerciasis particularly in highly endemic rural areas of developing countries led to the development of a dosing schedule based on body weight. In Africa, drug supplies are often poor or uncontrolled and in ivermectin distribution, absent farmers or workers are often missed by delivery teams. As a result WHO-supported studies in some African countries investigated methods of ivermectin delivery, either by use of community-based distributors or by self-treatment. That was reasonable because the methods did not tax the overburdened health services. To be sure that such delivery methods work in practice and the problem associated with the use of weighing scales can be overcome, there has been a need for another assessment method. This study constitutes the first known effort in Nigeria or elsewhere to establish a link between MUAC and weight and an acceptable dosing schedule that can be used in different zones endemic for onchocerciasis. We show in the present study (Figures 1a and 1b) that there is a linear relationship between MUAC and weight irrespective of sex. Body weight is mainly made of muscle, fat, bone, and intestinal organs. In a younger age group with minimum level of muscle wasting and normal growth, we expect a linear correlation between weight and age. In older age groups where muscle wasting sets in, weight will decrease with the degree of wasting and not with increase in years.

Although various anthropometric measurements (arm circumference for age, weight for height, weight for head circumference, height for age) have been used to assess the nutritional status of a community, the relationship between MUAC and weight has not been examined except in Papua New Guinea where MUAC was used in nutritional assessment of adults.

The MUAC is a relatively simple measurement that requires no calculation. Most villagers own and use glass-fiber tapes for domestic purposes. This is an indication that it may be used for ivermectin dose assessment despite the low level of literacy. Our results therefore show that the use of MUAC as the basis for administering ivermectin is comparable with that based on weight. In earlier reports, extreme cases of protein-calorie malnutrition in starvation during famine showed severe weight loss. The skin in such circumstances was loose and inelastic and muscle and fat wasting were strikingly obvious. This was demonstrable quantitatively by decrease in limb measurements, including the arm circumference. It was an indication of a relationship between arm circumference and body weight. The MUAC was also comparable with the height-based schedule proposed by Alexander and others in minimizing the number of subjects understated. One problem with this height-based schedule was that it showed a marked overdosing of subjects (Table 2), although ivermectin is safe at doses well in excess of the standard schedule (150 μg/kg).

**FIGURE 2.** Relationship between the average weight and the corresponding average MUAC.

**FIGURE 3.** Percentage of subjects dosed by weight who would have been underdosed or overdosed if the height, physical appearance, or mid-upper arm circumference (MUAC) schedules were employed.
each of 53 subjects for the treatment of Norwegian scabies.\textsuperscript{21} Although body weights were not mentioned, it could be assumed that all weighed 60–70 kg and that they received doses above 400 μg/kg. These findings suggest that the dose of ivermectin could be greater than the standard dose of 150 μg/kg. Awadzi and others\textsuperscript{22} determined the clinical and laboratory tolerance in onchocerciasis patients by successfully increasing total doses of ivermectin from 150 to 950 μg/kg and with 800 μg, administered as a single dose. They found that for a given intensity of infection the severity of Mazzotti reaction was independent of the dose in the 150–950 μg/kg range. Moreover, WHO\textsuperscript{13} reported that multiple doses of 1600 μg/kg given over two weeks were clinically acceptable. A clearing dose of ivermectin could be as low as 20 μg/kg in lymphatic filariasis but is 150 μg/kg in onchocerciasis.\textsuperscript{20} It is therefore safer to err on the side of overdosing rather than underdosing.

It has been reported\textsuperscript{11} that in some circumstances helminth burden can increase body weight. This increase may not be reflected in a corresponding increase in arm circumference. This may contribute to the percentage of underdosed subjects when the MUAC was employed.

The results of the MUAC are not similar to those of the height-based schedule proposed by Taylor and others.\textsuperscript{4} This may be due to the fact that subjects who would have received two 6 mg tablets, if the MUAC were used, only received 1.5 6 mg tablets by the height-based schedule. The height-based schedule by Taylor and others\textsuperscript{4} therefore has a more serious disadvantage than that of Alexander and others\textsuperscript{6}. Both schedules may however not be appropriate in other populations of different ethnic groups. This was reflected in the results of this study (Figure 3). Moreover, it has been shown that during starvation there is weight loss with no increase in lymphatic filariasis. This increase may not be correlated with weight because of malnutrition.

The method based on physical appearance\textsuperscript{10} compared with the MUAC or height-based schedule by Alexander and others\textsuperscript{6} showed a high number of underdosed subjects (Figure 3). This was probably due to the fact that distribution by this method was subjective and depended on the level of literacy of the distributor. If the WHO-supported community-based treatment with ivermectin turns out to be practicable, the MUAC may be useful. We propose that this schedule be considered for adoption in communities, especially where height is not easily correlated with weight because of malnutrition.

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