Ivermectin dose assessment without weighing scales

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Described are two alternatives to the weighing of patients for assessing the dose of ivermectin for use in mass chemotherapy campaigns against onchocerciasis. The first method uses height to separate patients into four dosing categories (1/2, 1, 1 1/2 and 2 tablets), while the second involves estimating one of these dosing categories according to an individual's physical appearance, without making any measurements. Data for the height-based method were obtained from 6373 people who were taking part in a placebo-controlled trial of ivermectin in northern Nigeria. Use of an arbitrary trade-off of approximately 100 people "overdosed" for every person "underdosed" would lead to 0.5% of the population being underdosed by 1/2 tablet, 46.5% being dosed correctly, 51.7% being overdosed by 1/2 tablet, and 1.2% being overdosed by 1 tablet. The physical appearance approach involved three observers and 779 subjects. A total of 82% of the observers' estimates were "correct", with all the incorrect dosing deviating by only 1/2 tablet from the dose that the subjects should have received.

Introduction

Ivermectin is a microfilaricide that is used in the treatment of onchocerciasis, a disease from which about 0.5 million people are blind, mostly in rural areas of Africa and northern South America. Onchocerciasis is caused by a parasitic worm, *Onchocerca volvulus*, and is spread by blackflies of the genus *Simulium*; large numbers of microfilariae are found in the skin and eyes of infected individuals, and these cause the dermatological and ocular symptoms that constitute the main burden of the disease. As described by several workers (*1–4*) ivermectin (Mectizan ®, Merck, Sharp & Dohme), a recently developed drug, is a safe and effective microfilaricide. The drug is available in 6-mg tablets, and the dosing schedule, which is based on 150 µg/kg body weight, is shown in Table 1.

Unfortunately, provision of sufficient numbers of weighing scales to maintain long-term, mass dosing programmes in the rural areas of developing countries presents major problems. Although ivermectin itself is provided free by the manufacturers, the cost of the large number of scales needed is substantial; also, scales can easily lose their calibration or break completely under field conditions. In practice, delays in replacing broken or stolen scales could lead to doses of the drug being administered haphazardly or to people failing to be dosed at all. Furthermore, use of standard scales requires basic literacy skills, and even then confusion may arise if they are calibrated not only in kg but also in other units. An alternative method of reliably assessing the dose of ivermectin is therefore highly desirable.

One candidate measure for this purpose is height. A height scale could easily be produced by marking a straight cane or piece of wood in units of ivermectin tablets. Such canes are cheap and easy to make and could be distributed widely to all the individuals entrusted with the dosing. Canes would be less likely than scales to lose calibration, except pos-

Table 1: **Standard dosing schedule for ivermectin, based on body weight**

Patient's weight (kg)	No. of 6-mg tablets
<15	0
15–25	1/2
26–44	1
45–64	1 1/2
>64	2

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sibly through wear of the bottom end, although this could be reduced by reinforcing the end with metal from a tin can. The canes would have few uses other than for dose assessment and so would be less likely than scales to be stolen; furthermore, health workers travelling on bicycles could carry measuring tapes that would enable them to calibrate a measuring cane in each village.

Use of height as a proxy measure for weight poses the difficulty that people of the same weight vary considerably in height, i.e., if dose is assessed by height many people would be assigned to the "wrong" dosing category. A trade-off would have to be made between the number of people "underdosed" because they are short for their weight and the number "overdosed" because they are tall for their weight. Since ivermectin is safe even at doses well in excess of the standard schedule (*5, 6*), we suggest minimizing the number of people underdosed at the cost of overdosing many.

A second alternative to weighing would simply be to estimate the correct dose on the basis of each individual's physical appearance. This would have the advantages of not requiring any equipment and of allowing some discretion in, for example, dosing very thin people for whom a rigid height-based approach would result in too large a dose. On the other hand, this could lead to incorrect dosing, depending on the mood of the individual assessing the dose or because of pressure from those receiving the drug.

Materials and methods

The subjects for the study were inhabitants of 34 rural communities in Kaduna State, northern Nigeria, who were participating in a double-blind, placebo-controlled trial of ivermectin for onchocerciasis, having given their free and informed consent. Each individual's dose was assessed, as shown in Table 1, by weighing the patient on a standard set of household scales. Height was recorded at the same time, being read off a vertical scale by placing a flat piece of wood horizontally on each subject's head. These measurements were made between December 1988 and October 1989 by a field worker who was a trained entomology technician.

In December 1991 we investigated the feasibility of estimating the correct dose of ivermectin, based on the recipient's physical appearance, using no equipment. The estimations were performed by two members of the field team and one local person; all estimates were made before the patients were weighed, without knowledge of the correct dose. The process was supervised and the data were recorded by one of the authors (*S.N.C.*). The two field-team members were entomology technicians, but had previously been involved in making anthropometric measurements, and were asked to use their experience to estimate the dose for all the people who presented. The local person was a 28-year-old man who had been educated to secondary-school level and worked as a subsistence farmer; such people can be found in most northern Nigerian villages. He was chosen because he appeared to be intelligent and was interested in the study. It was explained to him that the purpose of the exercise was to determine whether patients could be dosed correctly with ivermectin without using a set of scales. He was then told that there were four dosing categories and that, in general, young children received 1/2 tablet, adolescents 1 tablet, most adults 1 1/2 tablets, and large adults 2 tablets. A few (<10) project staff and onlooking children were then used as practice subjects before his estimates for those who presented for dosing were recorded.

Results

Of the 8230 people who were aged ≥5 years and registered in the trial, 6373 (77%) had a pair of simultaneous weight and height readings available. Excluded were individuals who were not dosed because they were ill, pregnant, or underweight, but the included breast-feeding women, since under current criteria these would almost all have been dosed. The height data, according to standard dosing category, are summarized in Table 2 and shown graphically in Fig. 1. The curves in Fig. 1 can be used to read off the number of people in any dosing category whose height was above or below any given value. For example, there were about 1500 people in the 1 1/2-tablet category with heights <160 cm and about 250 with heights <150 cm. The number taller than any given height may be obtained by subtraction from the total in that category.

Dose assignment by height corresponds to the three broken perpendiculars shown in Fig. 1 at the heights chosen as the thresholds between the four dosing categories.We selected a ratio of overdosings to underdosing of 100:1, and this leads to the assignments shown in Table 3.

Only 43 people weighed <15 kg, which does not permit assignment of a height below which no tablets should be given; all 43 would have received 1/2 tablet according to the criteria in Table 2.

Table 4 compares the assignments according to the height schedule in Table 3 with those according to the weight schedule in Table 1.

Use of the height schedule indicates that, relative to the weight schedule, 34 people would have been underdosed, 3374 overdosed, and 2965 correct-

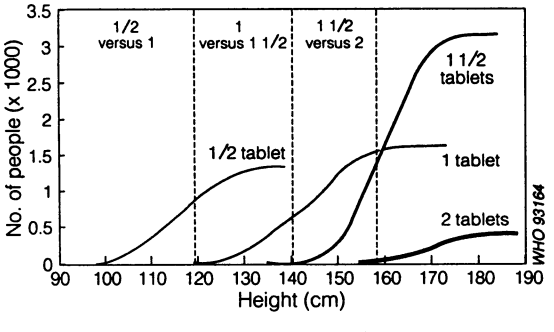
Table 2: **Heights of people in the four dosing categories for ivermectin**

No. of tablets	Height (cm)					No. of people
	Minimum	25th percentile	Median	75th percentile	Maximum	
0	90	97	99	103	119	43
1/2	92	110	116	123	139	1310
1	109	136	145	151	173	1575
1 1/2	135	155	160	165	185	3109
2	150	166	170	174	188	336
Overall	90	133	153	162	188	6373

ly dosed. The 34 underdosed would all have received only 1/2 tablet less than the correct dose. Of the 3374 overdosings, 3298 (98%) would have received only 1/2 tablet more than the correct dose and the remaining 76 (2%) just 1 tablet more. The proportion of the study population who would have received a dose at most 1/2 tablet greater or less than the correct dose was 99%.

Table 5 compares the height-based with the standard weight-based categories in terms of the latter's original source—the number of μg of ivermectin per kg body weight. The standard categories give a dose ranging from 231 μg/kg, for a 26-kg individual to 120 μg/kg, for someone weighing 75 kg (and even less for anyone >100 kg). Use of the height-based categories would result in the vast majority (98%) of people receiving a dose in the range 100–299 μg/kg. Of the remainder, two individuals would have received <100 μg/kg (i.e., 97 and 98 μg/kg) and the rest 300–400 μg/kg.

Fig. 1. **Height distribution by dosing category.** The curves show the cumulative height distribution for each weight-based tablet dosing category. The broken perpendiculars show the division of population into height-based tablet dosing categories.



The choice of trade-off between underdosing and overdosing is arbitrary, and Fig. 1 permits investigation of other thresholds. For example, increasing the threshold between 1 1/2 and 2 tablets from 158 cm to 170 cm would mean that virtually no one in the 1-tablet category would receive 2 tablets; this would nevertheless increase to over 100 the number of people in the 2-tablet category who are underdosed.

The use of different thresholds for males and females gave only a minimal increase in performance. For males the following dosing categories were used: 1/2 tablet (height, 90–119 cm); 1 tablet

Table 3: **Dosing schedule for ivermectin based on height**[a]

Patient's height (cm)	No. of tablets
90–119	1/2
120–140	1
141–158	1 1/2
>158	2

[a] Based on an assignment of approximately 100 overdosings for every underdosing.

Table 4: **Number of people in the standard dosing categories by weight (see Table 1) compared with those in the categories based on height**

No. of tablets by weight	No. of tablets by height					Total
	0	1/2	1	1 1/2	2	
0	0	43	0	0	0	43
1/2	0	781	529	0	0	1310
1	0	6	588	905	76	1575
1 1/2	0	0	13	1275	1821	3109
2	0	0	0	15	321	336
Total	0	830	1130	2195	2218	6373

Table 5: **Numbers of individuals according to the dose of ivermectin they would have received using the standard dosing categories (by weight) and those based on height**

No. of individuals in weight-based categories (μg/kg)	No. of individuals in height-based categories (μg/kg):				
	0–99	100–199	200–299	300–400	Total
0–99	0	0	42	1	43
100–199	2	2628	2850	92	5572
200–299	0	6	720	32	758
300–400	0	0	0	0	0
Total	2	2634	3612	125	6373

(120–144 cm); 1 1/2 tablets (145–162 cm); and 2 tablets (≥163 cm). For females the corresponding categories were: 1/2 tablet (90–119 cm); 1 tablet (120–138 cm); 1 1/2 tablets (139–155 cm); and 2 tablets (≥156 cm). Use of these categories reduced the number overdosed from 3374 to 3302, the number underdosed from 34 to 33, while the number correctly dosed increased from 2965 to 3038. Nevertheless, these improvements seem insufficient to warrant the use of separate threshold values according to sex.

Table 6 compares the results obtained by three observers using the physical appearance method. Of the two project staff, one (A) correctly estimated the dose for 272 of 332 people (81.9%), while the other (B) correctly estimated the dose for 188 of 228 people (82.5%). The local person (C) correctly estimated the dose for 179 of 219 people (81.7%). For each of the three observers, all of the incorrect estimates deviated only by 1/2 tablet from the correct dose.

The proportion of correct estimates was much greater for physical appearance (Table 6) than for height (Table 4), but the observers were asked to make their estimates as accurately as possible and to overdose if in doubt. The best proportion obtained for correct dosing using height was 81.2%, which is similar to the levels shown in Table 6. This value was obtained using the following assignments: 90–128 cm (1/2 tablet); 129–149 cm (1 tablet); 150–181 cm (1 1/2 tablets); and ≥182 cm (2 tablets). It should be noted that the populations used to compare the two methods were not identical, since 122 (15.7%) of the 779 individuals shown in Table 6 were not in the placebo-controlled trial, whereas all those shown in Table 4 were. However, this is unlikely to invalidate general comparisons between the two groups.

Discussion

The guidelines for the use of ivermectin are that the number of tablets given to each person should be based on the recipient's weight on the day of treatment. However, the practical problems of providing and maintaining large numbers of weighing scales mean that weighing everyone is probably not realistic. Our findings show that the vast majority of rural Africans can be assigned a dose of ivermectin that deviates by at most 1/2 tablet from the correct dose,

Table 6: **Number of individuals in the standard dosing categories (by weight) compared with the numbers in the categories estimated by two entomology technicians (A and B) and a local person (C)**

No. of tablets by weight	Estimated number of tablets:															
	A				B				C				Total			
	1/2	1	1 1/2	2	1/2	1	1 1/2	2	1/2	1	1 1/2	2	1/2	1	1 1/2	2
1/2	27	15	0	0	27	2	0	0	34	3	0	0	88	20	0	0
1	1	83	19	0	10	47	11	0	4	39	13	0	15	169	43	0
1 1/2	0	13	153	4	0	8	109	5	0	3	98	9	0	24	360	18
2	0	0	8	9	0	0	4	5	0	0	8	8	0	0	20	22
Total	28	111	180	13	37	57	124	10	38	45	119	17	103	213	423	40

either using a set of height-based dosing categories or based on the individual's physical appearance without the use of any equipment.

Underdosing is probably more serious than overdosing, and our set of height-based categories was chosen to minimize the number of underdosings. Less than 1% of our study population would have been underdosed and <2% would have been overdosed by more than 1/2 tablet had our height-based categories been used. One disadvantage of the method, however, is that any set of height-based categories derived from our data might not be appropriate in other populations drawn from different ethnic groups. In addition, the age structure of the population is relevant, since it affects the proportions in the various dosing categories. For example, the majority of people in the 1/2 tablet category would be dosed correctly using the height criteria, compared with a minority overall. This means that in a population with fewer children, the height-based categories will tend to have a lower success rate (proportion correctly dosed) than we have estimated, and vice versa. However, the large proportion of children in our population (24% were aged 5–9 years) is likely to be a feature of most populations targeted for mass dosing with ivermectin. Using height to assess the dose of ivermectin will inevitably result in a large number of people being incorrectly dosed, although, with the cut-off points we used, almost all of these incorrect dosings would only have been by a 1/2 tablet.

We also investigated dose assessment based on the individual's physical appearance alone, without the use of any equipment. In our sample, around 80% of people assessed in this way would have received the correct dose, with no incorrect dosings of more than 1/2 tablet; this compares favourably with the results obtained using height. The three observers all achieved very similar success rates, suggesting that such a rate might be widely obtainable by intelligent, motivated staff. On the other hand, under less well controlled conditions there may be pressures on the individual dispensing the ivermectin to alter the dose, particularly once recipients see that it varies from person to person. While such pressure will generally be for overdosing, which is probably preferable to underdosing, we do not currently have sufficient data to predict the likely magnitude and prevalence of incorrect dosings that might occur if this method were to be applied by large numbers of staff in a mass campaign.

If ivermectin is to reach, on a regular basis, the remote rural communities most in need of the drug, an alternative to using weight as the basis of assessing the dose needs to be found. We have investigated two alternatives, height and physical appearance. Either of these methods is, in our view, acceptable, and further research in different populations would help to clarify which should become the method of choice.

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Résumé

Détermination des doses d'ivermectine sans balance

L'ivermectine est actuellement le médicament de choix pour le traitement de l'onchocercose. La posologie est déterminée en fonction du poids corporel, ce qui nécessite l'emploi de balances. Comme la fourniture de balances pour les programmes de traitement de masse dans les pays en développement pose des problèmes financiers et logistiques, nous avons examiné deux alternatives à la pesée pour la détermination de la dose d'ivermectine à administrer. Il est ainsi possible d'utiliser la taille pour classer les sujets dans les quatre catégories posologiques (1/2, 1, 1 1/2 et 2 comprimés); les catégories basées sur la taille permettraient d'utiliser des bâtons directement gradués en nombre de comprimés, ce qui constituerait une solution plus économique, plus facile d'emploi et plus fiable que les balances. L'autre possibilité serait d'évaluer la dose convenant à chaque sujet en fonction de son aspect physique, sans aucun matériel.

Pour la méthode basée sur la taille, nous avons été amenés, au vu de données sur le surdosage en ivermectine, à adopter un compromis permettant de limiter le nombre de sujets "sous-dosés", parce que petits pour leur poids, quitte à "surdoser" de nombreux sujets relativement grands pour leur poids. Nous avons expérimenté cette méthode sur 6373 sujets participant à un essai contre placebo de l'ivermectine dans le nord du Nigéria. En adoptant une solution de compromis conduisant à surdoser environ 100 sujets pour un sujet sous-dosé, nous avons conclu que 0,5% des sujets seraient sous-dosés d'un demi-

comprimé, 46,5% seraient correctement dosés, 51,7% seraient surdosés d'un demi-comprimé et 1,2% seraient surdosés d'un comprimé. Les catégories de taille proposées sont les suivantes: 90–119 cm: 1/2 comprimé; 120–140 cm: 1 comprimé; 141–158 cm: 1 1/2 comprimé; plus de 158 cm: 2 comprimés. Dans ces catégories, aucun sujet ne reçoit plus de 400 µg/kg (dose standard: 150 µg/kg). Nous avons tenté d'établir des catégories de taille différentes pour les hommes et les femmes, mais l'amélioration était négligeable.

En ce qui concerne la méthode fondée sur l'aspect physique du sujet, nos données ont été fournies par trois observateurs (deux techniciens en entomologie et un agriculteur local) sur 779 sujets. Au total, 82% des doses estimées étaient correctes, toutes les doses incorrectes n'étant fausses que d'un demi-comprimé. Nous pensons que s'il faut administrer régulièrement de l'ivermectine aux communautés rurales reculées qui en ont le plus besoin, il faut trouver une méthode d'estimation des doses qui ne fasse pas appel à la pesée. Les deux méthodes que nous décrivons sont, à notre avis, acceptables; chacune a ses avantages et ses inconvénients. En poursuivant les essais dans différentes populations, il serait possible de déterminer laquelle devra être retenue.

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