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Clinical trials of amodiaquine in onchocerciasis

OLADELE O. KALE[1]

Twenty onchocerciasis patients from the rain-forest zone of Western Nigeria were treated with amodiaquine in total dosages ranging from 22 to 68 mg/kg of body weight given over 2-9 days. There was no activity against either the microfilariae or adult forms of Onchocerca volvulus. *It is concluded that the drug, which was poorly tolerated by 12 patients, is ineffective against human onchocerciasis.*

The antimalarial drug amodiaquine, a quinoline derivative, has been shown in laboratory experiments to be very active in high doses against the adult worms of *Litomosoides carinii*, but ineffective against the microfilariae (*1-3*). In a total dose of 40 mg/kg of body weight it also appears to be active against adult *Wuchereria bancrofti* (*4*). It has not previously been tested for activity against *Onchocerca volvulus* infection in man.

This paper describes the results of clinical chemotherapeutic studies of the drug in onchocerciasis.

METHODS

Twenty adult male onchocerciasis patients, with intensity of infection ranging from 19 to 114 microfilariae per mg of skin at the buttocks, were enrolled, with their consent, for the study. They were recruited from onchocerciasis endemic villages in the rain-forest zone of Western Nigeria.

Tablets of amodiaquine hydrochloride, each containing the equivalent of 200 mg of base, were used. The dosage regimens are given in Tables 1 and 2. About 4-12 weeks after the last dose of amodiaquine, 12 patients each received a total of 3-4 g of diethylcarbamazine citrate (DEC) in divided doses spread over 7-10 days, to clear the skin of residual microfilariae. The remaining eight patients were not given DEC. All patients, except three who defaulted early in the post-treatment period, were seen and examined at scheduled intervals over the following 24 months, as shown in Tables 1 and 2.

The methods used for assessing activity of the drug against the microfilariae and adult worms of *O. volvulus* were similar to those described previously (*5, 6*). At each examination before and after treatment, six skin snips were taken from both scapulae, buttocks, and calves of each patient using a corneoscleral punch (Holth). The snips were weighed on a torsion balance and placed in physiological saline in microtitration plates at room temperature for 24 h, after which the microfilariae that had emerged were counted. The snips were then digested in collagenase in the manner described by Schulz-Key (*7*), the additional microfilariae detected were counted, and the number added to the initial count. The mean microfilarial count per mg of skin from the six snips was recorded as the microfilarial load at the time of examination. Nodules were excised 4-6 months after treatment with amodiaquine, from 7 patients, 4 of whom received amodiaquine followed by DEC and 3 of whom received amodiaquine only. The nodules were either digested in collagenase, as described by Schulz-Key (*8*), and the isolated worms examined for viability and living embryos, or sectioned and examined histologically for evidence of possible drug-induced changes.

Standard hepatic and renal function tests as well as total white blood cell and differential counts were carried out, before and 2, 7, and 14 days after treatment to monitor any toxic side-effects.

RESULTS

The parasitological results are summarized in Tables 1 and 2.

Effect on the microfilariae

The results show that the microfilarial counts 4-12 weeks after the administration of amodiaquine were the same or higher than the pretreatment value in 10 patients (50%). In the remaining 10 patients, a slight but insignificant reduction in microfilarial count was

[1] Reader and Consultant Physician in Community Medicine, Department of Preventive and Social Medicine, College of Medicine, University of Ibadan, Ibadan, Nigeria.

Table 1. The mean concentration of microfilariae in the skin of 12 male patients before and after treatment with amodiaquine followed by diethylcarbamazine (DEC)

Patient no.	Age (years)	Weight (kg)	Amodiaquine regimen	Mean microfilarial count per mg of skin[a]						
				Before amodiaquine	4–12 weeks after amodiaquine	1–2 weeks after DEC	1 month after DEC	6 months after DEC	12 months after DEC	24 months after DEC
1	32	60	200 mg, twice daily, ×5 days	102	132 (129.4)	3 (2.9)	27 (26.5)	–	–	–
2	44	51	200 mg, twice daily, ×5 days	40	48 (120.0)	1 (2.5)	6 (15.0)	8 (20.0)	17 (42.5)	20 (50.0)
3	52	43	200 mg, twice daily, ×5 days	52	37 (71.2)	0	0	–	3 (5.8)	27 (51.9)
4	47	54	200 mg, twice daily, ×5 days	37	20 (54.1)	0	0	2 (5.4)	23 (62.2)	38 (102.7)
5	45	48	600 mg, alternate days, ×5 doses	44	31 (70.5)	1 (2.3)	0	–	–	–
6	44	67	600 mg, alternate days, ×5 doses	27	27 (100.0)	0	0	3 (11.1)	2 (7.4)	18 (66.7)
7	20	44	600 mg, alternate days, ×5 doses	19	15 (78.9)	0	3 (15.8)	10 (52.6)	12 (63.2)	31 (163.2)
8	43	57	600 mg, alternate days, ×5 doses	49	68 (138.8)	2 (4.1)	5 (10.2)	–	–	–
9	22	52	600 mg, alternate days, ×5 doses	22	29 (131.8)	0	2 (9.1)	7 (31.8)	11 (50.0)	19 (86.4)
10	29	54	600 mg, daily, ×2 days	66	80 (121.2)	11 (16.7)	–	–	76 (115.2)	61 (92.4)
11	40	43	600 mg, daily, ×3 days	33	21 (63.6)	0	0	4 (12.1)	3 (9.1)	10 (30.3)
12	46	55	600 mg, daily, ×5 days	38	73 (192.1)	3 (7.9)	4 (10.5)	4 (10.5)	3 (5.3)	14 (36.8)
			Geometric mean:	40.4	40.6 (100.5)	1.9 (4.7)	2.8 (7.1)	5.9 (19.0)	9.7 (27.1)	24.2 (67.8)

[a] Figures in parentheses are post-treatment counts expressed as a percentage of pretreatment value.

Table 2. The mean concentration of microfilariae in the skin of 8 male patients who did not receive DEC, before and after treatment with amodiaquine

Patient no.	Age (years)	Weight (kg)	Amodiaquine regimen	Mean microfilarial count per mg of skin[a]				
				Before amodiaquine	1 month after amodiaquine	6 months after amodiaquine	12 months after amodiaquine	24 months after amodiaquine
13	49	50	200 mg, twice daily, × 5 days	28	12 (42.4)	18 (64.3)	–	23 (82.1)
14	49	73	200 mg, twice daily, × 5 days	86	82 (95.3)	67 (79.9)	70 (81.4)	91 (86.0)
15	39	71	200 mg, twice daily, × 7 days	60	68 (113.3)	30 (50.0)	46 (76.7)	56 (93.3)
16	42	55	200 mg, twice daily, × 7 days	43	28 (65.1)	29 (67.4)	36 (83.7)	34 (79.1)
17	40	68	600 mg, alternate days, × 5 doses	91	70 (76.9)	66 (72.5)	85 (91.2)	75 (82.4)
18	40	61	600 mg, alternate days, × 5 doses	37	50 (135.1)	45 (121.6)	33 (89.2)	44 (118.9)
19	39	49	600 mg, daily, × 3 days	114	82 (71.9)	88 (77.2)	120 (105.3)	98 (86.0)
20	51	63	600 mg, daily, × 3 days	29	33 (113.8)	18 (62.1)	34 (117.2)	33 (113.8)
			Geometric mean:	54.8	46.6 (85.0)	39.8 (72.6)	55.0 (91.7)	51.6 (94.3)

[a] Figures in parentheses are post-treatment counts expressed as a percentage of pretreatment value.

recorded. Clearly, amodiaquine has no demonstrable antimicrofilarial activity.

Effect on the adult worm

The administration of DEC to 12 patients produced a reduction in microfilarial counts to near zero; in the 9 patients who received DEC and remained in the trial for the following 24 months, the microfilarial counts rose gradually to an average of 67.8% (range, 30.3–163.2%) of the pretreatment level (Table 1). This indicates a lack of activity of amodiaquine against the adult worm. The slowest build-up occurred in the two patients (nos. 11 and 12) who received 600 mg of amodiaquine daily for 3 and 5 days, respectively.

In the 8 patients who did not receive DEC the skin microfilarial concentrations remained high throughout the follow-up period (Table 2), again indicating a lack of activity against the adult worms.

Altogether, 16 nodules were recovered from the 7 patients who underwent nodulectomy. None of the worms isolated by collagenase digestion or examined histologically showed any evidence of the type of drug-induced changes that have been described elsewhere (*9–11*).

Side-effects

Of the 20 patients, 12 (60%) suffered various side-reactions to treatment with amodiaquine. Seven had gastrointestinal disturbances; of these, 5 had nausea and vomiting accompanied by colic in two; 3 patients had diarrhoea and 2 were constipated. Twelve patients suffered a moderate to severe degree of lassitude, three of these (nos. 8, 12, and 19) being confined to bed for 1–2 days after completion of treatment. Three patients (nos. 9, 11, and 19) had a slight and transient, but insignificant, reduction in blood granulocyte count (range of reduction, 18–27%, lasting 7–14 days).

CONCLUSION

Amodiaquine has been found to be ineffective against the adult worms and microfilariae of *O. volvulus*. The high frequency of side-effects recorded at the dosages used precludes further trials with the drug at higher doses.

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RÉSUMÉ

ESSAIS CLINIQUES DE L'AMODIAQUINE DANS L'ONCHOCERCOSE

Vingt hommes adultes atteints d'onchocercose dans la zone de forêt ombrophile de l'ouest du Nigéria, dont l'infection avait une intensité allant de 19 à 114 microfilaires par mg de peau, ont été traités par l'amodiaquine, médicament antipaludique. Les doses ont été comprises entre 22 et 68 mg/kg de poids corporel, administrées pendant 2 à 9 jours. Les malades ont été suivis pendant une période allant jusqu'à 24 mois, et à chaque examen des biopsies cutanées exsangues ont été prélevées sur les deux omoplates, fesses et mollets. Des nodules ont également été excisés chez sept malades 4 à 6 mois après traitement.

Il a été constaté que l'amodiaquine n'a aucun effet démontrable ni sur les vers adultes, ni sur les microfilaires. Douze malades ont souffert de diverses réactions secondaires, notamment de troubles gastro-intestinaux et de lassitude modérée à grave. Il en est conclu que le médicament est inefficace dans l'onchocercose humaine à la posologie éprouvée et que la fréquence élevée des effets secondaires exclut l'essai de doses supérieures.

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