Adverse reactions following mass drug administration with diethylcarbamazine in lymphatic filariasis endemic areas in the Northeast of Brazil

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ABSTRACT

Introduction: The Global Programme to Eliminate Lymphatic Filariasis was launched with the goal of eliminating this disease via the annual mass drug administration (MDA) of a single dose of antifilarial drugs. Adverse drug reactions following MDA are a major factor of poor treatment adherence in several countries. This study assessed the occurrence of adverse drug reactions (ADRs) following the first round of mass treatment in two communities treated with different dosages of diethylcarbamazine (DEC) in the City of Recife, Brazil. **Methods:** Population-based cross-sectional surveys were conducted in a random sample of the population living in both communities (Areas I and II). The dose of DEC recommended by the WHO (6mg/kg) was calculated based on the individual's weight-for-age. In Area II, weight differences between the genders were also considered when determining dosage. Data were obtained through interviews conducted in the first 12 to 48h and on the 5th day after MDA during household visits. **Results:** A total of 487 and 365 individuals were interviewed in Areas I and II, respectively. The prevalence of ADRs in Area I (23.6; 95%CI: 19.1-29.5) was higher than in Area II (16.2; 95%CI:11.9-21.5)(p=0.0078). The prevalence of ADRs among females was higher than in males in Area I (p=0.0021). In Area II, no significant difference between the genders was observed (p=0.1840). Age was not associated with ADRs in either area. **Conclusions:** Adjusting MDA dosage schedules according to weight-for-age and sex may be may contribute to reduce the occurrence of adverse drug reactions in the population.

Keywords: Lymphatic filariasis. MDA program. Adverse drug reactions. Prevalence study.

INTRODUCTION

Since the launch of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) by the World Health Organization (WHO) in 1997[1], mass drug administration (MDA) programs have been conducted in a large number of endemic countries. By 2009, 385 million people had been treated, and two billion doses of antifilarial drugs had been distributed in 53 endemic countries[2,3]. It is estimated that these actions resulted in approximately 32 million disability-adjusted life years averted and protected 6.6 million neonates from clinical disease[3].

Low treatment-coverage rates in MDAs (<70%) place the success of elimination programs at risk[4] and have been linked to failures in drug distribution, lack of perceived treatment benefit by the population and fear of adverse reactions[5-7].

Due to the potent microfilaricidal effect of diethylcarbamazine citrate (DEC) on *Wuchereria bancrofti*, with or without other drugs (Albendazole or Ivermectin), it has been the drug of choice in most lymphatic filariasis (LF) mass treatment programs in areas without co-endemic onchocerciasis[4,8,9]. Despite good tolerability, the drug can produce adverse reactions such as drowsiness, nausea, fever, headache, arthralgia, lymphangitis, lymphadenitis, orchitis, epididymitis and other symptoms. These reactions are associated with the dose-related chemical toxicity of the drug or, occasionally, with the death of the parasite[10].

Adverse drug reactions (ADRs) in MDA programs have been a major factor related to poor treatment adherence in several countries[5,6,11,12]. Variations in the occurrence of adverse reactions across MDA programs using different treatment schemes have been observed among people of different ages[13], sexes[13,14] and microfilaraemia statuses[14].

The Metropolitan region of the State of Pernambuco in northeastern Brazil is the remaining focus of lymphatic filariasis in Brazil[15,16-18], and MDAs with annual single doses of DEC only (≈6mg/kg) have been implemented since 2003[17]. According to a parasitological survey conducted between 1999 and 2000 (n=18,279) in the City of Recife, the capital of the state, two neighborhoods (Agua Fria and Alto Santa Terezinha) reached the highest levels of endemicity in the city, with a prevalence of 6.2% and 10.4%, respectively (Health Department of Recife, unpublished data). Initially, two areas in these neighborhoods were selected for MDA with distinct dosages of DEC. This article reports the occurrence of adverse drug reactions following the first round of MDA in these areas.

METHODS

Study design and settings

Recife has an area of 217.5km² and a population of 1,536,934 inhabitants (IBGE, 2010). MDA in this city, with annual single doses of DEC, started in 2003, and nearly 150,000 people were treated by 2009[19].

The population-based cross-sectional survey was conducted in a random sample of the population eligible for MDA in both areas. Area I is located at the intersection between the neighborhoods of

Agua Fria and Alto Santa Terezinha. It had a population of 20,891 inhabitants at the time of the survey, and the first round of MDA was conducted in November of 2003. Area II is in the neighborhood of Alto Santa Terezinha (Area II). It had a population of 3,332 inhabitants, and the first round of MDA was conducted in November 2004 **(Figure 1)**. A pre-MDA parasitological survey conducted in a random population sample of the areas found a prevalence of microfilaraemia of 5.5% and an average microfilaraemic density of 55.1mf/mL (ZC Santos: personal communication, 2006).

The populations were comprised primarily of young people (25% were children under 15 years). Approximately 16% of the population was illiterate or had less than one year of schooling, and the average family monthly income was 206.00 USD (United States dollars)[20].

MDA treatment schemes

Residents aged from four years, excluding pregnant women and individuals with severe heart, renal or liver disease, were eligible for treatment. All the residents were registered and treated in treatment units specifically organised for that purpose and distributed at strategic points in the communities. The residents who did not attend these units were treated in their own residence.

The dose of DEC was determined based on the dosage guideline of 6mg/kg, as recommended by the WHO[21]. **Table 1** shows the average weight for the 25th percentile of the National Center for Health Statistics (NCHS) growth curve[22] and the dosage of DEC for each age group. In area I, the dosages were calculated based on the average weight-for-age of each age group. In Area II, the dosages were calculated using the same parameter while also considering differences in weight between the sexes.

Sample size calculation and sampling strategy

The sample size was calculated assuming a prevalence of adverse effects of 10%[23], a standard error of 3%, a 95% confidence interval and design effect of 1.5 (to take into account the variation of positives in each household). This yielded a sample of 450 individuals in each area.

The areas were mapped. Households were counted, and resident registration was conducted. A systematic sample of the households in each area was then drawn based on the calculation of a sampling fraction that was determined considering the mean number of people eligible for MDA per household. All the persons who underwent MDA treatment in the selected households participated in the survey.
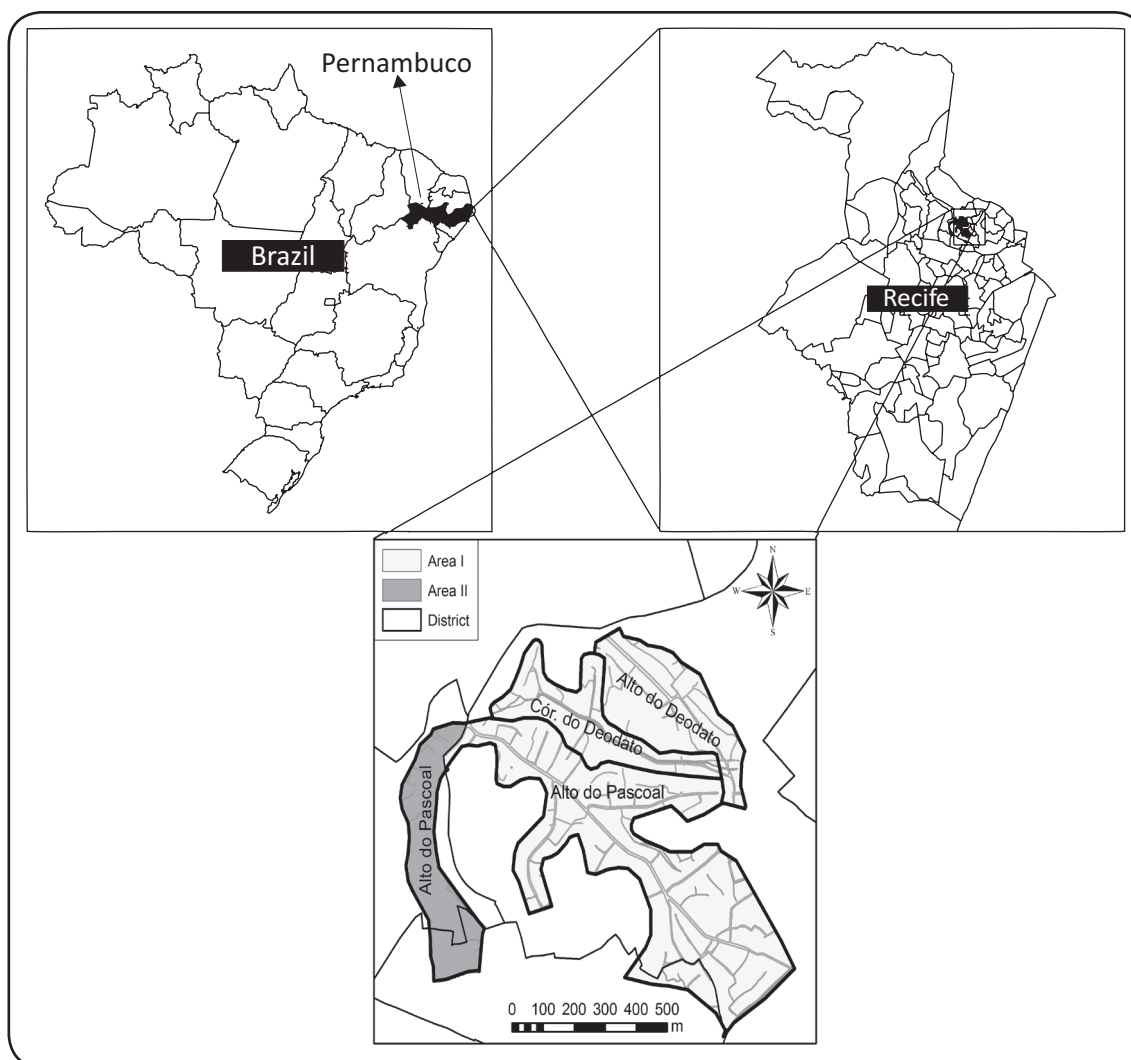

FIGURE 1 - Map of the Recife, State of Pernambuco, Brazil, with emphasis on the two areas of study- Area I (Água Fria) and Area II (Alto Santa Terezinha).

TABLE 1 - Estimated weight (NCHS curves), dosage schedules and average dose (mg/kg) of diethylcarbamazine citrate by age group and sex in mass treatment of the Areas I and II. Recife, Brazil, 2003-2004.

| Age group (years) | Average weight (kg)* | | Area I | | | Area II | | | |
| | | | | average dose of DEC (mg/kg) | | male | | female | |
	male	female	DEC doses (mg)**	male	female	DEC doses (mg)**	average dose of DEC (mg/kg)	DEC doses (mg)	average dose of DEC (mg/kg)
4-8	17	17	100	5.9	5.9	100	5.9	100	5.8
7-10	25	23	150	6.0	6.3	150	6.0	150	6.3
11-14	38	38	200	5.3	5.3	200	5.3	200	5.2
15-17	55	48	250	4.5	5.2	250	4.5	200	4.2
>18	60	50	300	5.5	6.0	300	5.5	250	5.0

DEC: diethylcarbamazine; NCHS: National Center for Health Statistics; DEC: diethylcarbamazine. *25th percentile of the NCHS curve for for the average age of each age group; **50mg tablets.

Data collection and variables

Data collection in Areas I and II was performed in November 2003 and September 2004, respectively.

Demographic data (age, sex) and information on the occurrence of adverse reactions were obtained through interviews conducted directly with the participants or their guardians (if the participant was <13 years of age) during home visits in the first 12 to 48h after treatment. The interviews were conducted by trained nursing graduate students and nurses using a standardised and pre-tested questionnaire.

ADRs were defined as the self-report of local manifestations (swelling/pain of the scrotum or genitals, lymphedema of the lower or upper limb, abscess or lymphangitis) or systemic symptoms (fever, sweating, asthenia, drowsiness, dizziness, lethargy, headache, nausea, vomit, abdominal discomfort or pain or urticaria).

Data analysis

The prevalence of ADRs and their respective 95% confidence intervals (95% CI) were estimated in each area according to sex and age group. The frequency distribution of adverse reactions was described according to type (local and systemic). The association between the prevalence of adverse effects and area, sex and age group was tested by calculating the prevalence ratio (PR) and prevalence difference (PD), 95% CI and p-value (≤ 0.05).

Ethical considerations

The study was reviewed and approved by the Ethics Committee of the Centro de Pesquisas Aggeu Magalhães (CAAE: 0780.0.095.000-05). The participants were interviewed after reading and signing an informed consent form. Cases of adverse reactions were addressed at the local health units and referred to medium or high complexity health services when necessary.

RESULTS

In Area I, a total of 487 individuals were treated in the selected households (n=152) and 438 (90%) were asked about the occurrence of ADRs. Of these, 207 (47.3%) were male, and 231 (52.7%) were female. In area II, all 365 people treated in the selected households (n=85) were interviewed. This included 168 (46%) males and 197 (54%) females. **Table 2** shows the eligible and treated populations, the study sample and the overall prevalence of ADRs in both areas. The prevalence of ADRs in Area I was higher than in Area II (PD=7.6%; 95% CI: 2.1%-14.0%; p= 0.0078).

The prevalence of ADRs among females was almost two times higher than that observed in males in Area I; this difference was statistically significant ($\chi2$=9.43; p=0.0021). Although the prevalence of ADRs was higher among females in Area II, the difference was not statistically significant ($\chi2$=1.76; p=0.1840). Age was not statistically associated with ADRs in either area **(Table 3).**

TABLE 2 - Eligible and treated population, study sample and reported cases of adverse drug reactions following mass treatment with diethylcabamazine in the two selected areas. Recife, Brazil, 2003-2004.

Characteristics	Area I	Area II
Eligible population	20,891	3,332
Population treated (%)	18,491 (88.5)	2,391 (71.6)
Study sample	438	356
Reported cases of ADRs	104	59
Prevalence of ADRs (95% CI)	23.6 (19.1-29.5)	16.2 (11.9-21.5)

ADRs: adverse drug reactions; 95% CI: 95% confidence interval.

TABLE 3 - Frequency distribution and prevalence ratio of adverse drug reactions reported cases following the first dose of mass treatment for bancroftian filariasis according to sex and age groups in the Areas I and II. Recife, Brazil, 2003-2004.

| Characteristics | Area I | | | | Area II | | | |
	population sample	adverse drug reactions (%)	prevalence ratio (95% CI)	P value	population sample	adverse drug reactions (%)	prevalence ratio (95% CI)	p value
Sex								
male	207	35 (16.9)	1.00	0.0021	168	22 (13.1)	1.00	0.1840
female	231	69 (29.9)	1.77 (1.23-2.53)		197	37 (18.8)	1.43 (0.88-2.83)	
Age group (years)								
≤ 14	119	25 (21.0)	1.00	0.7283	111	13 (11.7)	1.00	0.4760
15-44	232	56 (24.2)	0.87 (0.57-1.31)		191	34 (17.8)	0.66 (0.36-1.19)	
≥ 45	22	22 (25.3)	0.83 (0.50-1.37)		63	12 (19.0)	0.61 (0.30-1.26)	

CI: 95% confidence interval.

More than 90% of the symptoms reported by both sexes in the two areas were classified as systemic reactions **(Table 4)**. The number of symptoms reported in Area I was 2 times greater than that reported in the Area II.

In Area I, the most commons ADRs were drowsiness, nausea, headache and dizziness. In Area II, drowsiness, nausea and stomach discomfort/pain were the most commonly reported symptoms. Reports of local reactions comprised less than 3% of the signs and symptoms in both areas. Reported local symptoms included 3 cases of scrotal reaction, 2 cases of lymphangitis and 1 case of lymphedema **(Table 4)**.

DISCUSSION

Annual mass treatment with anti-filarial drugs of populations at risk is one of the main strategies used to achieve the goal of the global elimination of lymphatic filariasis. High MDA compliance rates for more than one round of treatment is an essential requirement of interrupting transmission[24] and has been one of the challenges of elimination programs underway around the world[7,11,25]. The fear of adverse reactions by the population has been a major reason for noncompliance in lymphatic filariasis elimination programs[5-7]. Therefore, new strategies aimed at reducing the adverse effects on treatment programs may contribute to maintaining MDA compliance rates at acceptable levels (≥80%) in LF elimination programs[2].

This study describes the occurrence of adverse reactions following MDA in two contiguous endemic areas with similar socioeconomic characteristics and endemicity levels submitted to distinct DEC treatment schemes. The prevalence rates of ADRs in the two areas of approximately 20% were similar to those described in active surveillance reports of ADRs following the use of DEC alone or in combination with other antifilarial drugs in several endemic Areas[14,26].

The overall prevalence of ADRs in Area I, where the dosage of DEC was calculated with respect to the differences in weight according to age only, was significantly higher than that observed in Area II, where weight differences between the sexes were also considered. It was also observed that the prevalence of ADRs was significantly higher among females than males in area I. While the prevalence of ADRs among women was greater than in men in Area II, this difference was not statistically significant. Moreover, most of the reported adverse reactions in both areas were classified as systemic and mainly reported by the women. Common symptoms included drowsiness, nausea, headache, dizziness and abdominal pain. These manifestations are particularly related to the chemical toxicity of the drug and the death of microfilariae[27,28]. Considering the geographical proximity of the areas, the similarities in their socioeconomic characteristics, their

TABLE 4 - Reported adverse drug reactions following the first dose of mass treatment with diethilcarbamazine citrate according to sex and intervention area. Recife, Brazil, 2003-2004.

Manifestations*	Área I				Área II			
	males (n=207)		females (n=231)		males (n=168)		females (n=197)	
	n	%	n	%	n	%	n	%
Systemic	39	95.1	110	100.0	27	96.4	42	91.3
fever	1	-	5	-	5	-	1	-
chill	-	-	4	-	-	-	1	-
sweating	1	-	5	-	-	-	-	-
headache	9	22.0	16	14.5	3	-	3	-
arthralgia	3	-	7	-	3	-	3	-
stomach discomfort/pain	1	-	6	-	1	-	5	10.9
drowsiness	13	31.7	31	28.2	12	42.3	13	28.3
dizziness	6	14.6	10	9.1	-	-	2	4.3
lethargy	-	-	1	-	-	-	-	-
nausea	4	14.6	21	19.1	-	-	9	19.6
vomiting	-	-	2	-	1	-	1	-
anorexia	-	-	2	-	-	-	1	-
elimination of intestinal worms	1	-	-	-	-	-	1	-
urticária	-	-	-	-	2	-	2	-
Local	2	4.9	-	-	1	3.6	4	8.7
lymphangitis	-	-	-	-	-	-	2	-
abscess	-	-	-	-	-	-	1	-
scrotal swelling/pain	2	-	-	-	1	-	-	-
lymphedema	-	-	-	-	-	-	1	-
Total	41	100.0	110	100.0	28	100.0	46	100.0

*more than one symptom per person.

comparable endemic levels and the surveillance methods adopted, it is reasonable to assume that the lower prevalence of ADRs found in Area II could be attributed to the lower DEC dosage administered to women in area II. This assumption is reinforced by the fact that a two-fold higher number of signs and symptoms were reported by the women from Area I than in Area II.

Data on the frequency distribution of ADRs reported by sex following MDA with DEC alone or in combination with albendazole have been inconsistent[13,25,29]. Our results are in accordance with those reported in Sri Lanka where a significantly higher frequency of ADRs was found among females compared to males (54% versus 46%)[25]. On the other hand, a higher incidence of ADRs was reported among males in Haiti[13], and a lack of association between ADRs and sex was reported in India[14,30].

No variation in the occurrence of ADRs between age groups was observed in the study areas. This result is different from the results of surveys conducted in other endemic areas where an increased frequency of ADRs with age was reported[13,14,25]. Based on these findings, we conclude that variations in the occurrence of ADRs among sex and age groups mainly occur due to differences in the surveillance methods applied, the distinct drug treatment dosages and regimes and local variations in the epidemiological patterns of the disease.

The occurrence of an information bias due to both the interviewer and the surveyed individual having knowledge about the DEC ingestion and the possible ADRs is one possible methodological issue of this study. This problem may have overestimated the prevalence of adverse reactions in both areas; however, the chances of error were similar for the two areas, allowing for a comparative analysis between them.

Epidemiologic studies in large population samples have shown an increased risk of adverse drug effects among females[31,32] however, most MDA dosages in LF elimination programs have been defined based on population parameters of weight-for-age[13,14,33,34] and have not considered sex variations in weight in terms of the tolerability of antifilarial drugs. The data from this study suggest that adjusting dosage schedules in MDA by genders may reduce the occurrence of ADRs, primarily by reducing the number of ADRs in the female population. Based on this result, we conclude that dosage schedules adjusted according to weight-for-age and sex may contribute to reduce the occurrence of adverse drug reactions following MDA. Further studies are needed to assess the impact of these treatment regimens on the incidence of ADRs in other endemic areas.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABSTRACT IN PORTUGUESE

Reações adversas após tratamento em massa com dietilcarbamazina em áreas endêmicas de filariose linfática no nordeste do Brasil

Introdução: O Programa Global de Eliminação da Filariose Linfática foi lançado visando à eliminação da doença pela administração de medicamentos em massa (MDA). As reações adversas seguidas ao MDA são um importante fator de baixa adesão ao tratamento em vários países. Este estudo avaliou a ocorrência de reações adversas medicamentosas (ADRs) após a primeira dose de tratamento em massa em duas comunidades tratadas com diferentes doses de dietilcarbamazina (DEC), na Cidade de Recife, Brasil. **Métodos:** Estudos transversais foram realizados em uma amostra aleatória da população de duas áreas (Áreas I e II). A dose de DEC recomendada pela OMS (6mg/kg) foi calculada com base em parâmetros populacionais de peso para a idade. Na Área II, diferenças de peso entre os sexos também foram consideradas no cálculo. Dados foram obtidos através de entrevistas nas primeiras 12 às 48h e 5º dia após o tratamento durante visitas domiciliares. **Resultados:** Um total de 487 e 365 pessoas foi entrevistado nas Áreas I e II, respectivamente. A prevalência de ADRs na Área I (23,6; IC95%: 19,1-29,5) foi maior do que na Área II (16,2; IC 95%:11,9-21,5)(p=0,0078). Na Área I, a prevalência de ADRs foi maior nas mulheres do que nos homens (p=0,0021), não se observando diferença na Área II (p=0,1840). Idade não esteve associada à ADRs. **Conclusões:** Doses de tratamento em massa (MDA) ajustadas por peso para a idade e sexo parecem contribuir para redução da ocorrência de ADRs na população.

Palavras-chaves: Filariose linfática. Tratamento em massa. Reações adversas medicamentosas. Estudo de prevalência.

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