ADVERSE REACTIONS FOLLOWING MASS DRUG ADMINISTRATION WITH DIETHYLCARBAMAZINE AND ALBENDAZOLE FOR LYMPHATIC FILARIASIS ELIMINATION IN WEST SUMATERA, INDONESIA

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Abstract. The Indonesian government has instituted annual mass drug administration (MDA) of diethylcarbamazine (DEC) and albendazole in filarial endemic districts in West Sumatera, Indonesia to control this disease but adverse drug reactions can influence the uptake of the medication by the target population. In this study, we aimed to determine the types and frequencies of adverse drug reactions to these two medications to inform the lymphatic filariasis control program in this area. Study subjects were interviewed and asked about demographics, when they took the medicines and any perceived adverse reactions. This cross-sectional study was conducted during April-November 2017 in two filaria endemic districts of West Sumatera: West Pasaman and South Pesisir. Of the 369 subjects in West Pasaman, 42.0% were males; the mean age was 28.7 years; 26.3% had adverse reactions. Of the 400 subjects in South Pesisir, 35.8% were males; the mean age was 34.6 years; 37.5% had adverse reactions. The most commonly reported adverse reactions were headaches (30.3% in South Pesisir and 19.2% in West Pasaman), vomiting (30.3% in South Pesisir and 19.2% in West Pasaman), abdominal pain (30.3% in South Pesisir and 19.2% in West Pasaman), and drowsiness (30.3% in South Pesisir and 19.2% in West Pasaman). None of the adverse reactions were severe. In this study, the frequency of adverse reactions to lymphatic filariasis treatment was high but none of the reactions were severe. Those receiving these lymphatic filariasis drugs need to be educated about these side effects and the benefits of treatment to optimize lymphatic filariasis control programs in the study area.

Keywords: adverse drug reaction, diethylcarbamazine, albendazole, filariasis, elimination, Indonesia

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INTRODUCTION

In Indonesia, lymphatic filariasis (LF) is caused by three types of nematodes: *Wuchereria bancrofti, Brugia malayi* and *Brugia timori* (Chandy *et al*, 2011) spread

by mosquito bite. The common genera of mosquitoes that transmit LF in Indonesia are *Culex, Anopheles*, and *Aedes* (Hoedojo, 1989). *Mansonia, Couillettidia,* and *Ochlerotatus* spp (de Souza *et al*, 2012) are estimated to have infected 856 million people in 52 countries worldwide (WHO, 2018). The Global Program to Eliminate LF (GPELF) was launched by the World Health Organization (WHO) in 2000 to eliminate LF by 2020 (WHO, 2016). The program consists of mass drug administration (MDA) with antifilariasis drugs. The GPELF uses MDA among at-risk populations to reduce the density of microfilariae in the bloodstream, reducing the risk of transmission of the parasite by mosquitoes (Ichimori, 2014). The WHO recommends the following regimen be used for MDA: albendazole (400 mg) alone twice per year for areas co-endemic with LF and loiasis, ivermectin (200 μg/kg) combined with albendazole (400 mg) for areas with onchocerciasis, and diethylcarbamazine citrate (DEC) (6 mg/kg) combined with albendazole (400 mg) for areas without onchocerciasis (WHO, 2020). In 2009, 385 million people worldwide were treated with the MDA program with two billion doses of antifilaria drugs in 53 endemic filariasis countries (WHO, 2011; WHO, 2010). It is estimated this effort prevented the occurrence of 32 million cases of LF and protected 6.6 million neonates from contracting the disease (Ottesen *et al*, 2008).

In Indonesia, filaria cases were first reported in 1889; during 2014 more than 14.000 people in Indonesia were reported to have elephantiasis due to LF (Arsin, 2016). In 2014, there were 235 LF endemic districts in Indonesia out of a total of 514 districts with >120 million people at risk for contracting LF (Supali, 2014). Of these 235 districts, 55 have been treated using MDA yearly for 5 years, the remaining 181 districts with a population of 76 million will begin MDA in 2020 (Wijayanti and Ikawati, 2017).

The endemicity of LF was determined based on the results of a baseline survey of the prevalence of microfilaria; a prevalence of $\geq$1% is defined as being endemic by the WHO (WHO, 2013). Efforts to tackle areas with a high prevalence of lymphatic filariasis microfilaria (LF MF) greater than 1% are carried out by the mass treatment program which is conducted annually for 5 years. An evaluation was carried out after 5 years of treatment with a blood test to calculate the MF rate. If 5-year therapy does not succeed, MDA is repeated every year for 2 years (Titaley *et al*, 2018).

The success of a LF control program depends on compliance with taking the MDA medicine regularly. Several previous studies have reported low compliance rates are associated with program failure (Cantey *et al*, 2010; Babu and Babu, 2014; Hussain *et al*, 2014). Factors associated with low compliance include inadequate knowledge about the drugs, inadequate knowledge about MDA, no home visits by health workers during MDA, not believing in the efficacy of MDA drugs, and adverse effects of the MDA drugs (Adhikari *et al*, 2014). Fear of adverse reactions may decrease compliance with MDA by the community. Previous studies have reported adverse effects of LF treatment (Ikawati *et al*, 2018; Lima *et al*, 2012; Budge *et al*, 2018; Anderson, 2008). However, there is little data regarding the adverse effect of LF medication during MDA in Indonesia.

In this study, we aimed to determine the types and frequencies of adverse effects of taking DEC combined with albendazole for MDA to treat LF in two

districts of West Sumatera, Indonesia: West Pasaman and South Pesisir, in order to inform LF control programs in the study area.

MATERIALS AND METHODS

Study area

The study was conducted in West

Fig 1-Study areas in West Pasaman (top) and South Pesisir (bottom).

Maps were obtained from Google Earth (Available from: URL: https://earth.google.com/web/search/Pasaman+Barat/ and https://earth.google.com/web/search/Pesisir+selatan/ cited on 2019 Dec 01).

Pasaman and South Pesisir, West Sumatra, Indonesia from April - November 2017 (Fig 1). West Pasaman covers an area of 3878 km^2 and has a population of 427,295 (West Pasaman District Statistics Agency, 2017). South Pesisir covers an area of 5750 km^2 and has a population of 457,285 (South Pesisir District Statistics Agency, 2017). MDA for LF in West Pasaman was initiated in 2007, and in South Pesisir in 2006. MDA was completed in 2011 (Wijayanti and Ikawati, 2017). Post-MDA, transmission assessment surveys (TAS) were conducted in 2012 at both sites. The results of these surveys showed the MDA did not reach its goal so MDA was re-implemented during 2014 and 2015 (Ikawati *et al*, 2018).

Study design and sampling

We used a cross-sectional study design. Study subjects were selected randomly. Inclusion criteria for study subjects were being aged ≥5 years and living in the study area for at least five years; the exclusion criterion was having a psychiatric disorder (Budge *et al*, 2018; Wijayanti and Ikawati, 2017).

Data collection

Each subject was interviewed using a validated questionnaire and asked about demographics, frequencies, and types of adverse reactions from medication given for MDA 2 years previously. For subjects aged <13 years, a parent/guardian of the subject was interviewed. The adverse reactions of the medicine were self-reported.

Data Analysis

Descriptive analysis was conducted to describe demographic characteristics (age and gender) and adverse effects reported by the subject. Means, interquartile ranges (IQR), ages, frequencies, and proportions were calculated. Proportions were compared between groups with a Chi-square or Fisher's exact test. Associations between dependent variables (having an adverse effect) and independent variables (age, gender, and when the medication was taken) were evaluated through univariate and multivariate logistic regression analysis. Age was categorized into 4 groups (5-14, 15-38, 39-55, and ≥56 years). Odds ratios and their 95% confidence intervals were calculated. Significance was set at $p < 0.05$.

Ethics Statement

This study was approved by the Ethics Committee of the Indonesian Health Research and Development Institute (Approval No. LB.02.01/2/KE./67/2017). Subjects or their guardians/parents (if aged <13 years) gave written informed consent before participation in the study.

RESULTS

Three hundred and sixty-nine participants in West Pasaman and 400 in South Pesisir were included in the study. The numbers of subjects in the 2 districts were not the same due to incomplete data resulting in some subjects not being included in the study. In South Pesisir, 64% of subjects were female. The mean (IQR) age of South Pesisir subjects was 34 (16-48) years. In West Pasaman, 58% of subjects were female. The mean (IQR) age of West Pasaman subjects was 28 (12-42) years (Table 1).

The overall prevalence of adverse drug reaction (ADR) in South Pesisir was 37.5% and in West Pasaman was 26.8%. Thirty-point three percent of subjects in South Pesisir and 19.2% of subjects in West Pasaman reported having headaches after MDA (Table 2). In South Pesisir, the age-group with the highest incidence of ADR was those aged 15-38 years (45.5%) and in

Table 1
Characteristics of study subjects by study location.

Characteristics	Study location	
	South Pesisir	West Pasaman
Age		
Mean (IQR) age in years	34.64 (16-48)	28.70 (12-42)
Gender (*n*, %)		
Male	143 (35.8)	155 (41.9)
Female	257 (64.3)	214 (58.1)

IQR: interquartile range.

Table 2
Adverse reactions of study subjects by gender and study location.

Symptom	South Pesisir ($n = 400$)				West Pasaman ($n = 369$)			
	Male		Female		Male		Female	
	n	%	*n*	%	*n*	%	*n*	%
Headache	37	9.3	84	21.0	27	7.3	44	11.9
Fever	0	0.0	1	0.3	5	1.4	6	1.6
Joint pain	0	0.0	6	1.5	2	0.5	5	1.4
Abdominal pain	1	0.3	6	1.5	6	1.6	7	1.9
Vomiting	5	1.3	9	2.3	8	2.2	7	1.9
Breathlessness	0	0.0	0	0.0	0	0.0	1	0.3
Palpitations	0	0.0	1	0.3	2	0.5	0	0.0
Drowsiness	10	2.5	22	5.5	1	0.3	1	0.3
Others	17	4.3	24	6.5	3	0.8	3	0.8

West Pasaman was those aged ≥56 years (38.5%). The prevalence of ADR in females and males in South Pesisir were 41.2% and 30.8% respectively, and in West Pasaman were 27.4% and 25.8% respectively. The time of day the medicine was taken with the highest proportion of study subjects with ADR was noon for both South Pesisir (52.6%) and West Pasaman (34.4%) (Table 3).

On multivariable regression analysis, the age group in South Pesisir with the greatest prevalence of ADR was those aged 15-38 years (odds ratio (OR): 2.169; 95% confidence interval (CI): 1.170-4.02; $p = 0.014$). In West Pasaman, on multivariable regression analysis, no age group had a higher prevalence of ADR. On multivariable regression analysis the time of day in South Pesisir significantly associated with ADR was noon (OR: 2.148; 95% CI: 1.041-4.432; $p = 0.039$) but in West Pasaman on multivariable regression analysis, no time of day was significantly associated with ADR. No other factors were significantly associated with ADR on multivariable regression analysis (Table 4).

Table 3
Incidence of adverse drug reaction among study subjects by study location by selected variables.

Variables	Adverse drug reaction (ADR)			
	South Pesisir		West Pasaman	
	Number of those who reported having ADR (%)	*p*-value	Number of those who reported having ADR (%)	*p*-value
Age groups in years		0.10		0.25
5-14	30 (34.5)		37 (28.7)	
15-38	65 (45.5)		32 (25.6)	
39-55	33 (32.7)		18 (20.2)	
≥56	22 (31.9)		10 (38.5)	
Gender		0.04[a]	40 (25.8)	0.81
Male	44 (30.8)		59 (27.4)	
Female	106 (41.2)			
Time medication taken		0.001[b]		0.04[a]
Morning	17 (36.2)		19 (26)	
Noon	60 (52.6)		45 (34.4)	
Afternoon	7 (31.3)		1 (7.7)	
Night	66 (31.3)		34 (22.1)	

[a]*p*-value <0.05 chi-square; [b]*p*-value <0.01 chi-square.

DISCUSSION

In our study, the incidence of ADR was significantly greater among women in South Pesisir but not West Pasaman. Previous studies have reported ADR were significantly more common among women (Babu and Babu, 2014; Gunawardena *et al*, 2008, Rademaker, 2001; Bergiannaki and Kostaras, 2016; Yu *et al*, 2016). A possible explanation for a gender difference could be that women have a higher percent body fat, which can affect the volume of distribution of the drugs (Anderson, 2008). Another possible explanation is the renal clearance of some drugs is lower in women than men due to differences in cytochrome P450 enzyme activity (CYP) and urine diphosphate glucuronosyltransferase (UGT) (Rademaker, 2001).

In our study, the incidence of ADR was significantly more common among subjects aged (15-38 years) in South Pesisir, but not in West Pasaman. The drugs dosage used for MDA are adjusted based on age. A previous study reported the incidence of ADR was more common among subjects aged 20-30 years (Upreti *et al*, 2014), while another study reported ADR were common in subjects aged ≥65 years (Yu *et al*, 2015). The reason for these disparities by age is unclear.

In our study, the incidence of ADR was significantly greater among those who took the drugs at noon in South Pesisir but no association was seen in West Pasaman. The reasons for these and other differences in ADR at 2 study sites

Table 4
Associations between experiencing adverse drug reaction with age, gender and time medication taken.

Variable	South Pesisir		West Pasaman	
	Adverse drug reaction		Adverse drug reaction	
	Crude OR (95%CI)	Adjusted OR (95%CI)	Crude OR (95%CI)	Adjusted OR (95%CI)
Age groups in years				
5-14	1	1	1	1
15-38	1.583 (0.912-2.747)	2.169 (1.170-4.021)[b]	1.169 (0.672-2.034)	1.291 (0.731-2.280)
39-55	0.922 (0.502-1.691)	0.540 (0.185-1.573)	1.586 (0.834-3.017)	1.816 (0.940-3.508)
≥ 56	0.889 (0.454-1.741)	0.691 (0.348-1.373)	0.643 (0.268-1.547)	0.602 (0.240-1.515)
Gender				
Male	1	1	1	1
Female	1.579 (1.024-2.436)[a]	1. 571 (0.989-2.493)	0.920 (0.576-1.469)	0.944 (0.583-1.530)
Time medication taken				
Morning	1	1	1	1
Noon	1.960 (0.974-3.946)	2.148 (1.041-4.432)[b]	0.672 (0.356-1.269)	0.709 (0.368-1.364)
Afternoon	0.588 (0.207-1.667)	0.540 (0.185-1.573)	4.222 (0.512-34.684)	5.598 (0.654-47.947)
Night	0.803 (0.414-1.557)	0.691 (0.348-1.373)	1.242 (0.650-2.371)	1.355 (0.700-2.622)

[a]p-value <0.05 chi square; [b]p-value <0.01 logistic regression.

are unclear. These may be due to study design errors are differences in interviews. Adverse reactions may be related to whether the subject took the drugs on an empty stomach, their activity level, and hydration status.

A study from India reported the factors associated with ADR with MDA included previous experience with MDA, fear of ADR, understanding the benefits of MDA, and belief MDA works (Roy *et al*, 2013). ADR may exaggerated by the media, which may prevent subjects from being compliant with MDA (Gunawardena *et al*, 2008).

Our study had the main limitation in that the ADR was based on self-reports which are subject to recall bias. We tried to account for this by having a large sample size from two areas. We also did not test for the presence of filaria which when present could have caused more side effects due to the inflammation caused by filarial death.

In summary, we found a variety of ADR reported by study subjects. These need to be taken into consideration by the LF control programs to optimize success by developing strategies for dealing with these among the treated population.

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