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Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Disease

journal homepage: www.elsevier.com/locate/apjtd

Document heading doi: 10.1016/S2222-1808(14)60797-0

School-based combined mass drug administration for soil-transmitted helminthiases and schistosomiasis among school-age children: lessons from two co-endemic areas in the Philippines

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PEER REVIEW

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Comments

This paper is well written and clearly describes their experience of MDAs. The findings reconfirmed that MDA was safe and acceptable, which is well known.
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ABSTRACT

Objective: To demonstrate the safety and feasibility of school-based combined mass drug administration (MDA) using albendazole and praziquantel in selected areas in the Philippines.

Methods: This study consisted of two phases: Phase I assessed the safety and feasibility of combined MDA; Phase II assessed the feasibility of teacher-assisted combined MDA. Sites chosen had ongoing school-based MDA of albendazole for soil-transmitted helminthiases in order to demonstrate integration of services by adding MDA of praziquantel for schistosomiasis onto the manpower and infrastructure of the existing program.

Results: School-based combined MDA coverage rates were 80.1% and 75.5% in Phases I and II, respectively. Of students treated, 5.2% in Phase I and 5.4% in Phase II experienced adverse events, which were mostly mild and transient. In Phase II, the average time for combined treatment was less than one minute per student, with shorter times observed in older age groups.

Conclusions: Integration of MDA in schools may help in achieving good treatment coverage for soil-transmitted helminthiases and schistosomiasis control among school-age children. The safety profile and feasibility of school-based combined MDA as demonstrated by this study may provide basis for larger scale implementation in other co-endemic areas.

KEYWORDS

Intestinal helminthiasis, Schistosomiasis, School-age population, Neglected diseases, Praziquantel, Albendazole

1. Introduction

Neglected tropical diseases (NTDs) are a group of chronic and disabling conditions which are mostly infectious diseases of poverty[1]. In many developing countries including the Philippines, NTDs such as soil-transmitted helminthiases (STH) and schistosomiasis, remain highly prevalent. The highest burden of STH and schistosomiasis among all age groups is found among school-age children[2], contributing to undernutrition, permanent growth deficits, anemia, micronutrient deficiency, school absenteeism, and poor academic performance[3-5].

To reduce morbidity and transmission of NTDs, the World

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Foundation Project: The study was supported by Johnson & Johnson, Inc. and Asian Community Trust.

Article history:
Received 21 Nov 2014
Received in revised form 29 Dec 2014
Accepted 10 Jan 2015
Available online 19 Mar 2015

Health Organization (WHO) recommends preventive chemotherapy involving large-scale distribution of anthelminthics to population groups at risk[1,6,7]. In developing countries, geographic overlap of some NTDs is common, signifying co-endemicity and the need for co-administration of anthelminthics by integrating mass drug administration (MDA) activities[6,8]. This strategy offers opportunities for cost-effectiveness especially in low-resource rural communities[8,9].

Despite evidence that combining MDA is safe, many NTD control programs in developing countries cover only a single disease[10,11]. Little integration has been advocated[10-12], with separate MDA schemes and schedules for each type of helminth infection. This study aimed to demonstrate the safety and feasibility of school-based, teacher-assisted combined MDA using albendazole (ALB) and praziquantel (PZQ) in two co-endemic areas for STH and schistosomiasis in the Philippines.

2. Materials and methods

2.1. Phase I: pilot assessment of safety and feasibility of school-based combined MDA study sites

The study sites were two villages, Hinab-Ongan and Marcelo, in the municipality of Calatrava, Negros Occidental Province in Central Philippines. In these sites, the University of the Philippines Manila has provided technical support to the Department of Health (DOH) for implementation of the Integrated Helminth Control Program, providing basis for their selection. Combined MDA with ALB and PZQ was administered to school children in one public elementary school per village. All students in grades four to six (10-12 years old) enrolled in Hinab-Ongan and Marcelo Elementary Schools were targeted for school-based combined MDA.

2.1.1. School-based combined MDA scheme

Prior to MDA, light meals were provided to all students. ALB (400 mg) was administered by trained health workers from the Department of Education (DepEd) and local health unit (LHU) to targeted students in a classroom setting, while PZQ (40 mg/kg) was administered by LHU health workers in a treatment station located within the school premises.

2.1.2. Incidence, assessment of severity and causation of adverse events (AEs)

Teachers received complaints from students during the observation period (four hours post-treatment) in the classrooms and referred them to project physicians for appropriate management. Project team physicians in collaboration with medical officers and nurses from the DepEd and LHU assessed AEs for severity and causality, then managed them, as necessary, in a makeshift clinic inside the school principal's office.

An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the co-administration of ALB and PZQ, regardless of the relationship to the drugs[13]. AEs occurring up to four hours post treatment were recorded on case record forms.

Recording of the AEs included: (a) date and time of onset, (b) duration, (c) severity, and (d) relationship to treatment. Severity and causality were assessed according to the WHO toxicity grading scale[14], and standard operating procedures for clinical investigators described by Karbwang and Pattou (1999), respectively[15]. Management of AEs and observed outcomes were also documented on the case record form.

The incidence and severity of AEs were obtained for the reported signs and symptoms including: dizziness, headache, nausea, vomiting, abdominal discomfort, fever and allergic reaction. Their severity was categorized as: (a) mild, (b) moderate, (c) severe, and (d) life-threatening. Their relationship to combined MDA was categorized as: (a) not related, (b) unlikely, (c) possible, (d) probable, and (e) most probable[14]. Total AEs reported during the four-hour observation period was the overall incidence of AEs. The proportion of participants reporting one or more AEs was recorded separately.

2.2. Phase II: larger-scale assessment of feasibility of school-based combined MDA study sites

Study sites for Phase II were the municipalities of Carmen and Santo Tomas, Davao del Norte Province in Southern Philippines, which had more co-endemic villages than Calatrava. From seven selected villages, eight public elementary schools and two public high schools were included. Students in all grade and year levels were targeted for combined MDA.

2.2.1. School-based combined MDA scheme

Training was conducted for health personnel from the DepEd and LHU (medical officers, nurses, midwives, and village health workers), as well as clinic teachers from selected schools. The clinic teachers and health staff then performed roll-out orientation of all class teachers and parents using instructional powerpoint presentations used in the training. To determine appropriate PZQ dosage, the latest data for body weight of all students participating in the combined MDA was gathered prior to the scheduled MDA through the DepEd semi-annual nutritional status assessment. Coordination with nearby secondary level hospitals was done in preparation for possible referrals for any severe AEs.

Prior to MDA, light meals were provided to all students as facilitated by parents. Support for feeding was provided by DOH Region XI. Trained class teachers co-administered ALB and PZQ to students in classrooms in the presence of a health worker (Figure 1). The trained nurses and midwives assisted in the combined MDA. Teachers accomplished record forms documenting coverage rate and duration of combined MDA.

Figure 1. Administration of deworming tablets.
A trained teacher administered ALB and PZQ tablets to students in the classroom setting in the presence of a health worker.

2.2.2. Incidence, assessment of severity and causation of AEs

During the observation period in classrooms, teachers referred students with complaints to the nurses and midwives, who then performed initial assessment of AEs with assistance from project team physicians (Figure 2). Students with mild AEs were reassured, allowed to rest, and observed by trained nurses and midwives. AEs of at least moderate severity were referred to the project team physicians for further assessment and appropriate management. The methodology for assessment of incidence, severity, and causation was identical to that in Phase I.

Figure 2. Assessment of AEs.
A trained nurse performed initial assessment of AEs.

2.3. Data processing and analysis

Data was double encoded on pre-tested forms prepared from MS Excel 2007 sheets. Safety parameters included incidence, severity, and causation of AEs. Feasibility was described through implementation indicators such as coverage rates, duration of combined MDA, average time for combined MDA, utilization of existing personnel and infrastructure[16].

The coverage rate of school-based combined MDA was computed as:

$$\text{Combined MDA coverage rate} = \frac{\text{Number of students who took ALB and PZQ tablets}}{\text{Number of students enrolled}} \times 100$$

In Phase II, duration of combined MDA was measured by the difference between the time of treatment of the first student and the time of treatment of the last student in each classroom. Coverage and duration were determined for the following groups: Grades 1-3, Grades 4-6, and high school. The average time for combined MDA per student was computed as:

$$\text{Average time for combined MDA} = \frac{\text{Duration of combined MDA (minutes)}}{\text{Number of students who took ALB and PZQ tablets}}$$

Fisher's exact tests were conducted using STATA 12 to determine the significant difference of incidence of AEs among study sites and grade levels. Level of significance was set at $P < 0.05$.

2.4. Ethical considerations

Both protocols for Phases I and II were reviewed and approved by the University of the Philippines Manila-Research Ethics Board (UPMREB-2012-041-NIH and UPMREB-2012-0181-NIH, respectively). Individual informed consent was obtained by properly oriented class teachers from the parents of study participants. Assent of students (12-15 years old) was also obtained prior to participation in the study. Medical interventions conducted by trained physicians for moderate or severe AEs complied with DOH guidelines (*i.e.*, DOH - Administrative Orders No. 2006-28, 2007-15, and 2010-23).

3. Results

3.1. Phase I: pilot assessment of safety and feasibility of school-based combined MDA

A total of 408 students were enrolled in grades four to six in the two selected schools in Calatrava, Negros Occidental, of whom 327 (80.1%) received both ALB and PZQ. Of these, 17 (5.2%) were assessed to have AEs. The number of students who were assessed to have AEs was significantly higher in Hinab-Ongan Elementary School (9.8%) than in Marcelo Elementary School (3.7%) ($P = 0.043$).

Reported AEs following the combined MDA included dizziness, headache, nausea, vomiting, and abdominal pain. Dizziness was most common with an incidence of 3.1%, all assessed as mild. Moderate AEs comprised one case each of headache, nausea, and vomiting. Most AEs were assessed as "possibly" or "most probably" caused by co-administration of ALB and PZQ (Table 1).

Table 1
Incidence, severity, and causality of AEs in Calatrava, Negros Occidental (July 2012) [*n* (%)].

Clinical signs/ symptoms	Incidence ($n = 327$)	Severity		Causality			
		Mild	Moderate	Unlikely	Possible	Probable	Most Probable
Dizziness	10 (3.1)	10 (100.0)	0 (0.0)	0 (0.0)	7 (70.0)	2 (20.0)	1 (10.0)
Headache	8 (2.4)	7 (87.5)	1 (12.5)	0 (0.0)	3 (37.5)	2 (25.0)	3 (37.5)
Nausea	7 (0.4)	6 (85.7)	1 (14.3)	0 (0.0)	2 (28.6)	2 (28.6)	3 (42.9)
Vomiting	5 (0.3)	4 (80.0)	1 (20.0)	0 (0.0)	2 (40.0)	1 (20.0)	2 (40.0)
Abdominal Pain	4 (0.2)	4 (100)	0 (0.0)	0 (0.0)	4 (100.0)	0 (0.0)	0 (0.0)
Sleepiness	1 (0.1)	1 (100.0)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)

3.2. Phase II: larger-scale assessment of feasibility of school-based combined MDA

A total of 2 410 (75.5% coverage) students were treated with both ALB and PZQ. Of these, 767 (82.0% coverage) were from Carmen and 1 643 (72.8% coverage) were from Santo Tomas. In Carmen, Grades 4-6 required the longest time to finish combined MDA at a rate of 0.94 minutes/student, while high school students required the shortest time at a rate of 0.43 minutes/student. However, some high school classes in Carmen were not included in computation of average time of combined MDA due to the failure of teachers to fill out time record forms properly. In Santo Tomas, Grades 1-3 took the longest at a rate of 0.77 minutes/student, while high school students required the least amount of time to finish treatment, at a rate of 0.50 minutes/student. Of the 2 410 students who received the two drugs, 131 (5.4%) were assessed to have AEs. This percentage was slightly higher in Carmen (7.0%) than in Santo Tomas (4.7%) ($P = 0.020$). The number of AEs reported in Grades 1-3 and 4-6 was significantly higher than that reported in first to fourth year high school students ($P = 0.049$ and 0.000, respectively) (Table 2).

AEs reported following the combined MDA included headache, dizziness, abdominal pain, vomiting, nausea, fever, and allergic reaction. Among these AEs, headache was most common at 3.3%. In terms of severity, 93.7% of complaints were mild and 6.3% were moderate in severity. Most AEs were assessed as "possibly" or "probably" caused by co-administration of ALB and PZQ (Table 3).

Table 2

Coverage rate of and duration of combined MDA with ALB and PZQ and number of consults for AE/s in Carmen and Santo Tomas, Davao del Norte (September 2012).

School district	School level	No. of enrolled students	Combined MDA coverage [*n* (%)]	Duration of combined MDA (minutes)		Students with AE/s [*n* (%)]
				Total time	Average time	
Carmen	Grades 1-3	312	258 (82.7)	229	0.89	16 (6.2)
	Grades 4-6	319	279 (87.5)	261	0.94	31 (11.1)
	1st-4th year HS	304	230 (75.7)	56	0.43[a]	6 (2.6)
Subtotal		935	767 (82.0)	546	0.82[b]	54 (7.0)
Santo Tomas	Grades 1-3	904	633 (70.0)	489	0.77	31 (4.9)
	Grades 4-6	709	520 (73.3)	353	0.68	29 (5.6)
	1st-4th year HS	644	490 (76.1)	247	0.50	17 (3.5)
Subtotal		2 257	1 643 (72.8)	1 089	0.66	77 (4.7)
Total		3 192	2 410 (75.5)	1 635	0.71[c]	131 (5.4)

[a]denominator used was 131 students (classes with incomplete data for time were excluded); [b]denominator used was 668 students; [c]denominator used was 2 311 students. HS: high school.

Table 3

Incidence, severity, and causality of AEs in Carmen and Santo Tomas, Davao del Norte (September 2012) [*n* (%)].

Clinical signs/ Symptoms	Incidence (n = 2 410)	Severity		Causality			
		Mild	Moderate	Unlikely	Possible	Probable	Most Probable
Headache	79 (3.3)	74 (93.7)	5 (6.3)	28 (35.4)	30 (38.0)	21(26.6)	0 (0.0)
Dizziness	49 (2.0)	47 (95.9)	2 (4.1)	11(22.4)	19 (38.8)	19 (38.8)	0 (0.0)
Abdominal pain	30 (1.2)	27 (90.0)	3 (10.0)	5 (16.7)	10 (33.3)	15 (50.0)	0 (0.0)
Vomiting	29 (1.2)	27 (93.1)	2 (6.9)	5 (17.2)	8 (27.6)	16 (55.2)	0 (0.0)
Nausea	21 (0.9)	21 (100)	0 (0.0)	2 (9.5)	8 (38.1)	11 (52.4)	0 (0.0)
Fever	3 (0.1)	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)	1 (33.3)	0 (0.0)
Allergic reaction[a]	1 (0.04)	1 (100)	0 (0.0)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)
Chest pain	1 (0.04)	1 (100)	0 (0.0)	1 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)

[a]erythematous pruritic wheals, without difficulty of breathing or facial swelling.

4. Discussion

This study has demonstrated that school-based teacher-assisted combined MDA was feasible in terms of a number of implementation indicators. First, both phases of this study demonstrated at least 75% to 80% coverage rates in elementary and high school, reaching the WHO target of 75%[6]. Second, combined MDA was completed from just one to two mornings covering a total of 2 737 students from both phases. Third, less than one minute was required for combined MDA per student in Phase II, ranging from 0.43 minute in high school to 0.94 minute in elementary school. Notably, the rate of combined MDA was fastest in high school levels possibly due to age-related factors such as capacity to understand instructions and swallow drugs more easily. Lastly, local health and education personnel participated in the implementation of combined MDA in an existing infrastructure, in this study, the school setting.

Schools offer readily available infrastructure which easily covers students, utilizing skilled teachers and local health workers who are in close contact with the community, thus helping minimize costs and time spent for MDA. Administration of a combination of two anthelminthics to students by teachers, with supervision from local nurses or midwives, may allow achievement of higher coverage rates and diminished period of implementation. In this manner, local health workers may focus on oversight of the MDA implementation as well as assessment and monitoring of AEs.

Safety of combined MDA was demonstrated in both phases of the study. Generally, lower percentage levels of students were assessed to have AEs (5.2% and 5.4% in Phases I and II, respectively) than in another local study, in which 35% of schoolchildren reported symptoms following treatment with both ALB and PZQ[17]. Headache and dizziness were of highest incidence ranging from 2.0% to 3.3%, while in the study by Olds *et al*., these symptoms had incidence rates of at least 20%. It should be noted, however, that the prevalence of schistosomiasis reported in the study of Olds *et al*. was at least 50%, compared to the 3.8% to 6.0% prevalence reported in this study prior to the conduct of combined MDA. The rate and intensity of side effects following treatment with PZQ have long been correlated with the dose of PZQ and the intensity of infection[17-19]. Thus, the lower AE rates currently observed may be attributed to the lower prevalence and intensity of schistosomiasis resulting from previous rounds of community-based MDA for schistosomiasis in the study sites.

Assessment of severity of AEs showed that most were mild and not requiring referral to the health center or hospital. Additionally, all AEs resolved in the schools within the four-hour observation period, consistent with the findings of other studies[19-21]. It has been reported that AEs following treatment with PZQ are transient and dose related[17,21].

In this study, initial assessment and management of AEs (*i.e.*, reassurance and rest) did not require physicians, provided local health workers were given adequate orientation and instructions beforehand. In order to build confidence among teachers and health workers in implementing combined MDA in the future, a scheme for assessment and management of AEs demonstrated in this study may be utilized. A referral system linking schools to the LHUs and referral hospitals may also be established.

An important component that contributed to the implementation of school-based combined MDA in the project sites was the multisectoral collaboration among stakeholders. The DOH provided the drugs and support for feeding prior to MDA, while the DepEd provided the infrastructure and manpower, LHUs provided local health workers, and the project team from the academe provided technical support. More specific tasks including advocacy, capacity building, social mobilization, and monitoring and evaluation may also be assigned to concerned stakeholders in order to implement school-based combined MDA in a comprehensive manner[22].

The results of this study may help provide basis for formulation of policy and improvement of guidelines in conducting combined MDA for STH and schistosomiasis. School-based teacher-assisted combined MDA may be further scaled up so that this may be implemented in other co-endemic provinces or areas.

Conflict of interest statement

We declare that we have no conflict of interest.

Acknowledgements

The authors wish to extend their gratitude to the Department of Education Division Office of Davao del Norte and Negros Occidental, Department of Health - Centers for Health and Development of Region VI and XI, Provincial Health Team Office of Davao del Norte, Local Government Units of Calatrava, Negros Occidental and Carmen and Santo Tomas, Davao del Norte, and Dr. Carlos Miguel Perez. The authors are also thankful to Dr. Peter San Martin, Dr. Jolene Gatmaitan, and Dr. Harvy Joy Liwanag for providing suggestions on improvement of the manuscript.

Comments

Background

MDA is commonly implemented in developing countries for control of NTDs. This study focused on adverse reactions by Phases 1 and 2 MDAs after medication for STH & schistosomiasis in the Philippines.

Research frontiers

This paper describes their experience of MDAs for NTDs in a locality. It is not a study for any scientific hypothesis but check safety of MDAs for school children. They suggested school-based MDAs for cost-effectiveness of NTDs control.

Related reports

Most of the cited references and much more articles are published on this topic. School-based MDA is strongly recommended by WHO for control of NTDs in developing countries.

Innovations & breakthroughs

Low incidence (5.2% and 5.4%) of adverse reactions after medication were reported.

Applications

The present finding may be referred to for further MDA program of STH and *Schistosomiasis japonicum*.

Peer review

This paper is well written and clearly describes their experience of MDAs. The findings reconfirmed that MDA was safe and acceptable, which is well known.

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