Short communication

Impact of single dose of diethylcarbamazine and other antifilarial drug combinations on bancroftian filarial infection variables: Assessment after 2 years

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Abstract

The impact of single dose mass drug administration of diethylcarbamazine (DEC), DEC with albendazole (ALB), and ivermectin (IVR) with albendazole, was examined on the human bancroftian filarial infections in village scale trials in south India, from a follow-up study after 2 years. The treatment arms administered with DEC alone and DEC + ALB demonstrated long-term benefits in reducing microfilaraemia significantly (P<0.05), while antigenaemia reduction was negligible. The arm with ALB + IVR did not show such reductions. Among the antigenaemic and microfilaraemic individuals, 87% became amicrofilaraemic in DEC + ALB arm, which were higher than that observed in the other 2 treatment arms. Among amicrofilaraemics (but Ag+), nearly 35% cleared of infection in DEC + ALB, while 26% and 6% in DEC alone and IVR + ALB arms, respectively. The drug combination DEC + ALB was observed to demonstrate a significant impact in reducing filarial infection even after 2 years post treatment.

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1. Introduction

The revised elimination strategy for lymphatic filariasis (LF) has been launched in many countries, and is designed to block the transmission in populations exposed to infection by a single dose of two drugs annually for 5–6 years [1]. Globally, over 120 million people have been affected by it; over 40 million of them are seriously incapacitated and disfigured by the disease. One third of the people infected with the disease live in India [2]. The global programme for elimination of lymphatic filariasis (GPELF) has identified the Indian subcontinent as the region in which the greatest number of people is at risk from lymphatic filariasis: 514 million, 454 million of whom are in India alone [3]. In the global effort to eliminate lymphatic filariasis the major strategy used to interrupt transmission is reducing the reservoir of infection in humans by annual single-dose mass treatment with antifilarial drugs [4]. Several new and effective combinations and strategies are being proposed for elimination of lymphatic filariasis. Although investigations have been carried out to bring out the impact of combination effect of DEC (diethylcarbamazine), IVR (ivermectin) and ALB (albendazole), most of them are hospital-based studies [5,6] and few community trials have been carried with drug combinations DEC + ALB and IVR + ALB [7,8]. But there are no community trials comparing the effect of DEC alone with DEC + ALB and IVR + ALB, two years after the single dose of drug was given. Therefore, the effectiveness of single dose of 1) DEC alone 2) a combination of DEC and ALB and 3) a combination of ivermectin and ALB, in reducing filarial infection after 2 years of treatment, in followed-up human subjects was carried out in a field setting in south India.
2. Materials and methods

Three filariasis endemic villages in Tirukoilur area (latitude: 11°57′00″; longitude: 79°12′00″) of Vellore district, southern India, with a human population of 1026, 2429 and 3258, respectively, were chosen for mass drug administration (MDA) in the year 1999. The average age group of the study population was 19.32, 21.03 and 18.62 years in the 3 villages, respectively. Baseline status of microfilaraemia and antigenaemia were determined prior to this MDA from all the eligible subjects [9]. Blood survey was carried out during 21.00−24.00 h by finger prick method. For microfilaraemia 20 μl blood was collected, while 100 μl for determining the antigenaemia status using ICT card test kit (Binax, USA).

Treatment strategy administered in each village was (i) DEC (6 mg/kg body wt), (ii) DEC with ALB (400 mg/person) and (iii) I.V.R (200 μg/kg bodyweight) with ALB. The MDA was carried out by door-to-door visit, and more than 95% of the eligible residents were treated (children <2 years, pregnant and lactating women were excluded from MDA). Prior oral consent was obtained from villagers at the time of drug administration. Post treatment survey for microfilaraemia (Mf) and antigenaemia was carried out in 10% of the population covering equal proportion in all the age groups, after a gap of 2 years (i.e., in the year 2001). The procedure of sampling was similar in all the 3 drug regimens. In this communication, the analysis was restricted to those subjects who were screened during both the time points (i.e. in 1999 and in 2001). Thus a total of 121, 193 and 223 subjects were screened in I.V.R +ALB, DEC+ALB and DEC alone arms, respectively, during both the years. This project has been cleared by the institutional ethical committee.

Data were analyzed using SPSS software package version 11.0. The chi-square test was used to assess the significance of the difference in prevalence of microfilaraemia between treatment arms, before and after treatment. Geometric mean intensities (GMI’s) of microfilaraemia were calculated as antilog [Σ log(x+1)/n]−1, with ‘x’ being the number of Mf/20 μl of blood and ‘n’ the number of individuals examined, including the Mf negative persons.

3. Results and discussion

The antigenaemia prevalence (AGP) in the followed-up population was 36.4%, 21.8% and 22.9% during the baseline survey in the year 1999, in I.V.R.+ALB, DEC+ALB and DEC alone arms, respectively. After 2 years (i.e., during post treatment period), there was no change in AGP values in any of the treatment arms. Even though albendazole was suggested to have an antifilarial effect on the adult filarial worm [10,11], the impact (assessed by the AGP levels) could not be demonstrated after a gap of 2 years. However, the change in infection levels in the longitudinally followed-up subjects after 2 years of MDA was analysed to determine the loss and gain of infection in the 3 communities with different treatment strategies (Table 1). In this community trial, those persons who were negative for Mf were also administered treatment by which the loss and gain of infection in the study subjects can be examined. This was an advantage in a community trial, which is difficult to infer in a hospital-based approach. The disadvantage is that, the side effects occurring after drug administration cannot be systematically assessed and quantified as in a hospital study.

The individuals followed up were grouped into 3 categories for the purpose of analysis with respect to the loss and gain of infection over a period of 2 years. The 3 categories include (i) Ag+/Mf−, (ii) Ag−/Mf+, (iii) Ag−/Mf−. In I.V.R.+ALB, the infection status in >70% of individuals did not change in the 3 categories, while in the other two arms, there was greater clearance of infection. Under normal circumstances, the prevalence reduction is likely to be greater in areas with high prevalence and intensity. It is difficult to reduce infection levels in areas, which are already at a low level. Therefore, in the present study, the infection in I.V.R.+ALB is the highest and the reduction was expected to be more in this village than in the other 2 villages where the pre-treatment prevalences are lower. Of the individuals who were found microfilaraemic in 1999 (Ag+/Mf+), 87.6% and 60.7% became amicrofilaraemic in DEC+ALB and DEC alone arms, respectively during 2001 survey. In the arm administered with I.V.R.+ALB, only 26.9% became amicrofilaraemic (including those cleared of antigenaemia). The percentage

| Table 1 Changes in filarial infection status among human subjects after 2 years of single dose MDA |
|---|---|---|---|---|---|---|---|
| Pre treatment infection status during 1999 | Treatment arm | Number of persons followed | Infection status after 2 years in 2001 |
| | | | Microfilaraemic (Ag+/Mf+) | Amicrofilaraemic (Ag−/Mf−) | Negative (Ag−/Mf−) |
| | | | Number | % | Number | % | Number | % |
| Microfilaraemic (Ag+/Mf+) | I.V.R.+ALB | 26 | 19 | 73.1 | 6 | 23.1 | 1 | 3.8 |
| | DEC+ALB | 16 | 2 | 12.5 | 13 | 81.3 | 1 | 6.3 |
| | DEC alone | 28 | 11 | 39.3 | 16 | 57.1 | 1 | 3.6 |
| Amicrofilaraemic (Ag−/Mf−) | I.V.R.+ALB | 18 | 4 | 22.2 | 13 | 72.2 | 1 | 5.6 |
| | DEC+ALB | 26 | 1 | 3.8 | 16 | 61.5 | 9 | 34.6 |
| | DEC alone | 23 | 2 | 8.7 | 15 | 65.2 | 6 | 26.1 |
| Negative (Ag−/Mf−) | I.V.R.+ALB | 77 | 1 | 1.3 | 8 | 10.4 | 68 | 88.3 |
| | DEC+ALB | 151 | 0 | 0.0 | 10 | 6.6 | 141 | 93.4 |
| | DEC alone | 172 | 0 | 0.0 | 12 | 7.0 | 160 | 93.0 |

a, b—significant difference with respect to other 2 treatment arms separately.
of subjects remained positive for both the infection variables after 2 years was higher in this arm (73.1%), compared to arms administered using DEC with or without albendazole. The persistence of antigenaemia, despite loss of microfilaraemia has been reported from other longitudinal studies [12,13]. Despite persistence of antigenaemia, despite loss of microfilaraemia has been administered using DEC with or without albendazole. The clearance in DEC+ALB was significantly higher (P<0.05) demonstrating the importance of this drug combination as an adulticide.

Acquisition of new infections (as indicated by the presence of adult filarial antigen) in the year 2001 (i.e., after 2 years post treatment) was low in DEC+ALB and DEC alone arms (7%), as compared to IVR+ALB arm (12%) (Table 1). Since the baseline prevalence of antigenaemia (36%) and microfilaraemia (22%) in longitudinally followed individuals were highest in IVR+ALB arm, transmission in this village is likely to be on the higher side and hence acquiring of new infections can occur much faster in this arm than in the other 2 treatment strategy arms. Ivermectin was reported to result in a rapid decline in parasite intensities than parasite prevalence, as reported in other studies [15,16]. Even though a mere 8% reduction in MFP was recorded in IVR+ALB arm; the Mf intensity declined insignificantly by 41% (P>0.05). With this drug combination, a slightly higher reduction was observed in MFP (10.5%) and Mf intensities (72.5%) after 2 years of post treatment in Ghana [7], but all the subjects included in the study were microfilaraemic during pre-treatment. In a clinical trial [5], a reduction of 27% in MFP was observed, with IVR+ALB drug combination. Reduction in levels of antigenaemia (69.5%) and microfilaraemia (>99%) was observed to be greatest with DEC+ALB than by other drug combinations after 2 years post treatment [5].

<table>
<thead>
<tr>
<th>Treatment arm</th>
<th>Treatment period</th>
<th>Number positive</th>
<th>% Positive</th>
<th>% Reduction</th>
<th>GMI (Mf)</th>
<th>% Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVR+ALB (n=121)</td>
<td>Pre MDA (1999)</td>
<td>26</td>
<td>21.5</td>
<td>7.7</td>
<td>0.9011</td>
<td>41.3</td>
</tr>
<tr>
<td></td>
<td>Post MDA (2001)</td>
<td>24</td>
<td>19.8</td>
<td>5.293</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEC+ALB (n=193)</td>
<td>Pre MDA (1999)</td>
<td>16</td>
<td>8.3</td>
<td>81.3**</td>
<td>0.2123</td>
<td>92.9**</td>
</tr>
<tr>
<td></td>
<td>Post MDA (2001)</td>
<td>3</td>
<td>1.6</td>
<td>0.0151</td>
<td></td>
<td></td>
</tr>
<tr>
<td>DEC alone (n=223)</td>
<td>Pre MDA (1999)</td>
<td>28</td>
<td>12.6</td>
<td>53.6**</td>
<td>0.3954</td>
<td>74.9**</td>
</tr>
<tr>
<td></td>
<td>Post MDA (2001)</td>
<td>13</td>
<td>5.8</td>
<td>0.0992</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Post MDA = Survey was carried out 2 years after MDA.
** P<0.05 by chi square and t test.

Similarly, this drug combination reduced filarial antigenaemia by 75%, while the decline in MFP and GMI (Mf) were 28% and 95%, respectively, after 1-year post treatment [17]. In the present study, there was 81% and 93% decline in MFP and GMI (Mf) with this combination. Almost similar reduction of 86% in GMI (Mf) was observed in Egypt with a single dose of DEC+ALB [8]. In the DEC alone arm there was 54% reduction in MFP (Table 2), which coincided well with the results of Pondicherry study [18], where 48% decline was reported after 2 years of treatment. Since DEC was a common drug used in the study arms of the present study, and by considering DEC alone arm as the control group, the relative impact of albendazole on microfilaraemia was estimated by using Mulla’s formula [19], which demonstrated a reduction of 60% and 72% in MFP and GMI (Mf), respectively.

International Filariasis Group [20] concluded that there is insufficient reliable research to confirm or refute the additional benefit of albendazole inclusion in reducing filarial infection variables. However, our findings indicate that DEC and DEC+ALB combination showed long-term benefits in reducing lymphatic filarial infection at least for a period of 2 years, with the later having a better edge. This is in confirmation to our findings in a different study [21]. In a review article [22], the drug combinations containing DEC were reported to be more effective against microfilaria prevalence and intensity than single drug. The combination of DEC+ALB demonstrated greatest clearance for microfilaraemia and hence repeated annual drug administration with this drug combination could possibly decrease the filarial infection to a level at which further transmission is blocked.

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Conflicts of interest statement
The authors have no conflicts of interest concerning the work reported in this paper.

References


