Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals

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Abstract

Praziquantel and artemether are safe and efficacious antischistosomal drugs that act against different developmental stages of the parasite: praziquantel against adult worms and artemether against schistosomula. A combined treatment has been suggested as a strategy for transmission control. Recent laboratory experiments with rabbits with a mixed infection of *Schistosoma japonicum* parasites of different ages confirmed the effectiveness of a combination therapy. In the present work, we assessed the effect of a combined treatment on adult worms of *S. japonicum* and found significantly higher worm reduction rates than with a single dose of praziquantel. In a next step, we extended the study of the combined treatment to *Schistosoma mansoni*. A combined treatment with 75 mg/kg praziquantel and 150 mg/kg artemether was administered to hamsters infected with juvenile and adult *S. mansoni*. The two drugs, administered simultaneously or spaced by 6 h, 1, 3 or 7 days, resulted in significantly higher worm reduction rates than a single treatment with praziquantel. A combination therapy with increased doses of 100 mg/kg praziquantel and 300 mg/kg artemether showed very high worm reduction rates of 90% and above, however, some hamsters died in five different combined treatment experiments, suggesting that these drug concentrations were too high. We conclude that a combined treatment with praziquantel and artemether at the lower doses is safe and more effective than praziquantel alone, which forms a foundation for designing respective clinical trials in humans. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Schistosomiasis; *Schistosoma japonicum*; *Schistosoma mansoni*; Praziquantel; Artemether; Combined treatment

1. Introduction

Human schistosomiasis remains one of the most important parasitic diseases in the tropics with an estimated 200 million people infected...
out of 50 patients infected with Schistosoma infections have been reported upon use of praziquantel in northern Senegal (Gryseels et al., 1994; Stelma et al., 1995; Guissé et al., 1997). In a field study in Egypt, one out of 50 patients infected with S. mansoni continued to excrete parasite eggs after three doses of praziquantel (Ismail et al., 1996). Furthermore, a major drawback, which hampers the sustainability of most chemotherapy campaigns is that successfully treated individuals become rapidly re-infected (Wilkins, 1989).

In view of these observations, there is clearly a need for research and development of novel antischistosomal drugs (Cioli, 1998, 2000) or to make more effective use of existing ones. Combined treatment with two drugs, acting on early and later stages of the parasite could be expected to have an additive effect. Artemether, a derivative of artesinin, which is already being widely used against malaria (McIntosh and Olliaro, 2001), has been shown to have antischistosomal properties and to act on the juvenile stages of the parasite (Xiao et al., 2000a). Laboratory animals infected with Schistosoma japonicum, S. mansoni or Schistosoma haematobium showed highly significant worm reduction rates after administration of artemether 7–21 days after infection (Xiao and Catto, 1989; Xiao et al., 1995, 1998, 2000b,c). Considerably lower worm reduction rates were observed when artemether was administered to infections with adult worms. Consequently, randomized controlled trials assessed the effect of artemether to prevent the adult egg-laying worms in humans. The incidence of S. japonicum was reduced by 60–100% in trials carried out in low endemicity areas of China (Xiao et al., 2000a), and that of S. mansoni was reduced by 50% in a trial done in a highly endemic area of Côte d’Ivoire (Utzinger et al., 2000b). The first trial with S. haematobium is currently under way in Côte d’Ivoire and results are expected by mid-2001.

Since praziquantel and artemether act against different developmental stages of the parasite, a combined treatment has been suggested for transmission control strategies in specific endemic settings. In a laboratory study with S. japonicum parasites of different ages in rabbits, a combination therapy showed significantly higher worm reduction rates than a single dose of praziquantel or artemether (Xiao et al., 2000d). In the present study, we investigate the effect of a combined treatment on adult worms of S. japonicum and extend the experiments to mixed infection of S. mansoni parasites of different ages harbored in hamsters.

2. Materials and methods

2.1. Parasites and infection of experimental animals

Cercariae of S. japonicum (Anhui strain) released from infected Oncomelania hupensis snails, were provided by the Institute of Parasitic Diseases, Chinese Academy of Preventive Medicine (IPD-CAPM, Shanghai, China). Male and female rabbits (New Zealand strain), weighing 2.0–2.4 kg, were provided by the Animal Facility of IPD-CAPM. Rabbits were infected with 200 S. japonicum cercariae each, through the shaved abdominal skin, and treated 42 or 56 days after infection.

Cercariae of S. mansoni (Liberia strain) were released by infected Biomphalaria glabrata snails after exposure to artificial light for 5 h. The parasites had been maintained at the Swiss Tropical Institute for the last 20 years, by repeated passages through hamsters and B. glabrata. Male hamsters, weighing 60–80 g, were obtained from Biological
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don, Switzerland). They were maintained on Rodent Blox purchased from Eberle NAFAG (Gossau, Switzerland) and water ad libitum. Hamsters were infected subcutaneously with 120 *S. mansoni* cercariae each, with 40 cercariae on three occasions: days 0, 28 and 35.

### 2.2. Drugs

Praziquantel was the product of Shanghai No. 6 Pharmaceutical Factory (lot 871212) and artemether of Kunming Pharmaceutical Corp. (lot 970801). Both drugs were suspended in 7% Tween-80 and 3% ethanol at 100 mg/ml for treatment of *S. mansoni*-infected hamsters, or suspended in 1% Tragacanth at 10 mg/ml for treatment of *S. japonicum*-infected rabbits.

### 2.3. Treatment regimens

In a first series of experiments, six groups of five to seven rabbits were treated intra-gastrically 42 or 56 days after infection with *S. japonicum* either by a single dose of 40 mg/kg praziquantel, or a single dose of 15 mg/kg artemether, or a combined treatment with these two drugs at the above-mentioned concentrations.

In the second and third set of experiments, hamsters were treated intra-gastrically at day 49 after the first infection with *S. mansoni*. A first group of five hamsters received a single dose of 75 mg/kg praziquantel and a second group was treated with 150 mg/kg artemether singly. Nine groups of hamsters received a combined treatment with praziquantel (75 mg/kg) and artemether (150 mg/kg) at different regimens. The two drugs were administered at the same time or praziquantel was given first, followed by artemether 6 h, 1, 3 or 7 days apart. Alternatively, artemether was administered before praziquantel, at the same concentrations and intervals. Finally, the experiments were repeated with increased doses of praziquantel (100 mg/kg) and artemether (300 mg/kg).

### 2.4. Assessment of the therapeutic effect

In all experiments, one group of infected animals received no drug treatment and served as control to assess the therapeutic effect of a single dose of praziquantel or artemether. The therapeutic effect of the combined treatment with praziquantel together with artemether was compared with that of a single dose of praziquantel. All groups of animals were sacrificed by blood-letting and dissected 28 days after the final treatment. In rabbits, schistosomes were collected by the perfusion technique (Yolles et al., 1947), sexed and counted. In hamsters, the liver, the small and large intestines were removed and separated. The liver was placed in a 21 × 21 cm plastic folder and gently compressed between two 22 × 22 cm glass plates until the parenchyma was evenly dispersed into a thin transparent layer. Subsequently, it was examined with a stereoscopic microscope at 10 × magnification and living worms were sexed and counted. The small and large intestines were placed in a Petri dish and the worms lodged in the mesenteric veins were removed under a stereoscopic microscope, sexed and counted.

For assessment of the therapeutic effect of a combined treatment, the mean total and the mean female worm burden were calculated for the different groups and compared using Student *t*-test, assuming for unequal variances.

### 3. Results

#### 3.1. *S. japonicum*: adult worms in rabbits

In the first series of experiments, rabbits infected with 42- or 56-day-old adult *S. japonicum* received a single or combined treatment of praziquantel and/or artemether (groups 1–8, Table 1). Praziquantel (40 mg/kg) administered alone showed highly significant total worm reduction rates of 87% (groups 2 and 6). A single dose of 15 mg/kg artemether resulted in much lower total worm reduction rates of 25–33% (groups 3 and 7), however, these reductions were still significant when compared with the untreated control groups. A combined treatment with the two drugs administered simultaneously increased the total worm reduction rates to 96–99% (groups 4 and 8). These worm reduction rates were significantly
Table 1
Rabbits infected with 42- (groups 1–4) or 56-day-old adult S. japonicum (groups 5–8): effect of a single drug treatment with praziquantel (PZQ) or artemether (ART) compared with a combined treatment with these two drugs

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment (dose mg/kg)</th>
<th>Rabbits (n)</th>
<th>Total worms (mean ± S.D.)</th>
<th>Total worm reduction rate (%)</th>
<th>Female worms (mean ± S.D.)</th>
<th>Female worm reduction rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Control</td>
<td>6</td>
<td>108.0 ± 15.1</td>
<td>–</td>
<td>50.8 ± 7.5</td>
<td>–</td>
</tr>
<tr>
<td>2</td>
<td>PZQ (40)</td>
<td>6</td>
<td>14.5 ± 9.4/a/**</td>
<td>87</td>
<td>6.2 ± 5.0a/**</td>
<td>88</td>
</tr>
<tr>
<td>3</td>
<td>ART (15)</td>
<td>6</td>
<td>72.5 ± 21.7a/**</td>
<td>33</td>
<td>35.2 ± 10.7a/*</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>PZQ (40) + ART (15)</td>
<td>5</td>
<td>1.6 ± 1.5b/*</td>
<td>99</td>
<td>0.6 ± 0.9b/*</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>Control</td>
<td>7</td>
<td>88.0 ± 9.2</td>
<td>–</td>
<td>27.6 ± 5.4</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>PZQ (40)</td>
<td>7</td>
<td>8.9 ± 4.4c/**</td>
<td>87</td>
<td>1.1 ± 1.5c/**</td>
<td>96</td>
</tr>
<tr>
<td>7</td>
<td>ART (15)</td>
<td>7</td>
<td>51.0 ± 6.4c/**</td>
<td>25</td>
<td>24.4 ± 3.8c</td>
<td>12</td>
</tr>
<tr>
<td>8</td>
<td>PZQ (40) + ART (15)</td>
<td>7</td>
<td>2.7 ± 3.0d/*</td>
<td>96</td>
<td>0d</td>
<td>100</td>
</tr>
</tbody>
</table>

a: Groups 2 and 3 tested versus group 1; *P<0.05; **P<0.01. b: Group 4 tested versus group 2; *P<0.05. c: Groups 6 and 7 tested versus group 5; **P<0.01. d: Group 8 tested versus group 6; *P<0.05. S.D., standard deviation.
higher when compared with a single treatment with praziquantel. Female worm reduction rates were similarly high in the different experiments and reached 99–100% in the combined treatment group.

3.2. _S. mansoni: schistosomula and adult worms in hamsters_

In the second set of experiments, hamsters simultaneously infected with 14- and 21-day-old schistosomula and 49-day-old adult _S. mansoni_ were treated with praziquantel or artemether singly or in combination (groups 9–20, Table 2). A single dose of 75 mg/kg praziquantel resulted in a total worm reduction rate of only 2% and a slightly higher female worm reduction rate of 12% (group 10). Therefore, the total and female worm burden after a single treatment with praziquantel were not significantly lower than in the untreated control group. A single dose of 150 mg/kg artemether showed much higher total and female worm reduction rates of 66 and 81%, respectively (group 11), which were highly significant when compared with the untreated control group.

Combining the two drugs and simultaneous administration at the same concentrations as in the single treatment experiments showed an additive effect. The total and female worm reduction rates increased to levels of 77 and 85%, respectively (group 12), which was significantly higher than a single treatment with praziquantel. Very similar total and female worm reduction rates were obtained when the two drugs were administered with an interval of between 6 h and 7 days. Slightly higher total and female worm reduction rates were observed when artemether was administered first, followed by praziquantel (groups 17–20).

In the third series of experiments, the dose of praziquantel was increased to 100 mg/kg and that of artemether to 300 mg/kg. As in the earlier experiments, the drugs were administered singly or in combination to hamsters harboring juvenile and adult _S. mansoni_ (groups 21–29, Table 3). A single dose of praziquantel at this higher concentration showed increased total and female worm reduction rates of 36 and 27%, respectively (group 22). Doubling the dose of artemether to 300 mg/kg showed no increased levels of total and female worm reduction rates, since they were similarly high as the ones observed after administration of 150 mg/kg artemether. However, one of five hamsters died within 24 h following artemether treatment at this higher dose, indicating that this dose might be toxic (group 23). This observation was confirmed in the first combined treatment experiment, as all five hamsters died within 24 h after administration of 100 mg/kg praziquantel together with 300 mg/kg artemether. In six subsequent experiments, with the two drugs administered 1, 3 or 7 days apart, six hamsters died in four different groups (groups 25, 27–29). In those hamsters that survived, the combined treatment resulted in very high total worm reduction rates of 90–99% (groups 24–29). The female worm reduction rates were similarly high. These worm reductions were all significant when compared with the group of infected hamsters that received praziquantel alone (_P_ < 0.05). It seemed of little importance whether praziquantel or artemether was administered first, since very similar total and female worm reduction rates were calculated.

4. Discussion

Our results confirm earlier observations that praziquantel and artemether, two currently available antischistosomal drugs, act against different developmental stages of the parasite (Gönnert and Andrews, 1977; Sabah et al., 1986; Xiao and Catto, 1989; Araújo et al., 1991; Xiao et al., 1995, 1998, 2000a,b). In the first series of experiments, a single dose of praziquantel was administered to rabbits harboring adult _S. japonicum_, which resulted in high worm reduction rates. In contrast, a single dose of artemether only reduced the number of worms slightly. In the second and third set of experiments, with hamsters that harbour schistosomula and, to a lesser extent, adult _S. mansoni_, a single dose of praziquantel showed only a little effect in killing the parasites, especially at the lower dose of 75 mg/kg. However, artemether had a significantly stronger effect on reducing the total and female worm burden.
<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment (dose mg/kg)</th>
<th>Interval</th>
<th>Hamsters (n)</th>
<th>Total worms (mean ± S.D.)</th>
<th>Total worm reduction rate (%)</th>
<th>Female worms (mean ± S.D.)</th>
<th>Female worm reduction rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9</td>
<td>Control</td>
<td>–</td>
<td>5</td>
<td>36.0 ± 11.5</td>
<td>-</td>
<td>14.8 ± 4.1</td>
<td>–</td>
</tr>
<tr>
<td>10</td>
<td>PZQ (75)</td>
<td>–</td>
<td>5</td>
<td>35.2 ± 14.6a</td>
<td>2</td>
<td>13.0 ± 5.4a</td>
<td>12</td>
</tr>
<tr>
<td>11</td>
<td>ART (150)</td>
<td>–</td>
<td>5</td>
<td>12.2 ± 5.2a/**</td>
<td>66</td>
<td>2.8 ± 1.3a/**</td>
<td>81</td>
</tr>
<tr>
<td>12</td>
<td>PZQ (75)+ART (150)</td>
<td>Together</td>
<td>5</td>
<td>8.4 ± 3.4b/**</td>
<td>77</td>
<td>2.2 ± 1.9b/**</td>
<td>85</td>
</tr>
<tr>
<td>13</td>
<td>PZQ (75)+ART (150)</td>
<td>6 h</td>
<td>5</td>
<td>11.4 ± 1.1b/**</td>
<td>68</td>
<td>3.2 ± 1.1b/**</td>
<td>78</td>
</tr>
<tr>
<td>14</td>
<td>PZQ (75)+ART (150)</td>
<td>1 day</td>
<td>5</td>
<td>8.8 ± 5.2b/**</td>
<td>76</td>
<td>3.2 ± 1.5b/**</td>
<td>78</td>
</tr>
<tr>
<td>15</td>
<td>PZQ (75)+ART (150)</td>
<td>3 days</td>
<td>5</td>
<td>9.8 ± 3.6b/**</td>
<td>73</td>
<td>3.2 ± 1.8b/**</td>
<td>78</td>
</tr>
<tr>
<td>16</td>
<td>PZQ (75)+ART (150)</td>
<td>7 days</td>
<td>5</td>
<td>6.8 ± 4.1b/**</td>
<td>81</td>
<td>2.8 ± 1.9b/**</td>
<td>81</td>
</tr>
<tr>
<td>17</td>
<td>ART (150)+PZQ (75)</td>
<td>6 h</td>
<td>5</td>
<td>7.0 ± 2.5b/**</td>
<td>81</td>
<td>2.4 ± 1.5b/**</td>
<td>84</td>
</tr>
<tr>
<td>18</td>
<td>ART (150)+PZQ (75)</td>
<td>1 day</td>
<td>5</td>
<td>5.6 ± 4.2b/**</td>
<td>84</td>
<td>2.2 ± 1.5b/**</td>
<td>85</td>
</tr>
<tr>
<td>19</td>
<td>ART (150)+PZQ (75)</td>
<td>3 days</td>
<td>5</td>
<td>6.6 ± 4.4b/**</td>
<td>82</td>
<td>2.2 ± 1.1b/**</td>
<td>85</td>
</tr>
<tr>
<td>20</td>
<td>ART (150)+PZQ (75)</td>
<td>7 days</td>
<td>5</td>
<td>5.8 ± 2.0b/**</td>
<td>84</td>
<td>2.2 ± 1.5b/**</td>
<td>85</td>
</tr>
</tbody>
</table>

a: Groups 10 and 11 tested versus group 9; **P<0.01. b: Groups 12–20 tested versus group 10; **P<0.01. S.D., standard deviation.
Table 3

Hamsters infected with 14- and 21-day-old schistosomula and 49-day-old adult *S. mansoni*: effect of a single drug treatment with praziquantel (PZQ) or artemether (ART) compared with a combined treatment with these two drugs.

<table>
<thead>
<tr>
<th>Group</th>
<th>Treatment (dose mg/kg)</th>
<th>Interval (days)</th>
<th>Hamsters (n)</th>
<th>Hamsters (†)</th>
<th>Total worms (mean ± S.D.)</th>
<th>Total worm reduction rate (%)</th>
<th>Female worms (mean ± S.D.)</th>
<th>Female worm reduction rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>21</td>
<td>Control</td>
<td>–</td>
<td>4</td>
<td>0</td>
<td>42.5 ± 9.3</td>
<td>-</td>
<td>21.0 ± 5.0</td>
<td>–</td>
</tr>
<tr>
<td>22</td>
<td>PZQ (100)</td>
<td>–</td>
<td>5</td>
<td>0</td>
<td>27.2 ± 14.4a</td>
<td>36</td>
<td>15.4 ± 7.5a</td>
<td>27</td>
</tr>
<tr>
<td>23</td>
<td>ART (300)</td>
<td>–</td>
<td>5</td>
<td>1</td>
<td>10.3 ± 3.5a/**</td>
<td>76</td>
<td>5.0 ± 1.8a/**</td>
<td>76</td>
</tr>
<tr>
<td>24</td>
<td>PZQ (100)+ART (300)</td>
<td>1</td>
<td>5</td>
<td>0</td>
<td>3.6 ± 3.8b/*</td>
<td>92</td>
<td>1.8 ± 1.9b/*</td>
<td>91</td>
</tr>
<tr>
<td>25</td>
<td>PZQ (100)+ART (300)</td>
<td>3</td>
<td>5</td>
<td>2</td>
<td>1.7 ± 2.3b/*</td>
<td>96</td>
<td>0.7 ± 1.2b/*</td>
<td>97</td>
</tr>
<tr>
<td>26</td>
<td>PZQ (100)+ART (300)</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>4.4 ± 3.0b/*</td>
<td>90</td>
<td>2.0 ± 1.4b/*</td>
<td>90</td>
</tr>
<tr>
<td>27</td>
<td>ART (300)+PZQ (100)</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>2.3 ± 2.5b/*</td>
<td>95</td>
<td>1.0 ± 1.0b/*</td>
<td>95</td>
</tr>
<tr>
<td>28</td>
<td>ART (300)+PZQ (100)</td>
<td>3</td>
<td>5</td>
<td>1</td>
<td>0.3 ± 0.5b/*</td>
<td>99</td>
<td>0.3 ± 0.5b/*</td>
<td>99</td>
</tr>
<tr>
<td>29</td>
<td>ART (300)+PZQ (100)</td>
<td>7</td>
<td>5</td>
<td>1</td>
<td>3.3 ± 3.9b/*</td>
<td>92</td>
<td>1.8 ± 1.7b/*</td>
<td>91</td>
</tr>
</tbody>
</table>

a: Groups 22 and 23 tested versus group 21; **P<0.01. b: Groups 24–29 tested versus group 22; *P<0.05. S.D., standard deviation; †, dead.
In rabbits, which have been shown to be a suitable host for *S. japonicum* (Xiao et al., 1998), it has been shown recently that a combined treatment with praziquantel and artemether is highly effective in killing parasites of different ages (Xiao et al., 2000d). Our experiments presented here were an extension of our earlier work on mixed infections to adult *S. japonicum*. The combined treatment showed significantly higher worm reduction rates than a single dose of praziquantel. Therefore, our results further support the idea that combination therapy with praziquantel and artemether has an additive effect when used against *S. japonicum* infections, even if only adult worms are present.

We then explored the possibility of extending the combined treatment initially tested in mixed infections of *S. japonicum* parasites of different ages to *S. mansoni*. In a first step, the effect of a combined treatment with 75 mg/kg praziquantel together with 150 mg/kg artemether was evaluated in *S. mansoni*-infected hamsters, which has earlier shown to be a suitable host-parasite model (Xiao et al., 2000b). The experiments clearly revealed the expected additive effect of the combined treatment, with significantly higher total and female worm reduction rates than observed after a single dose of praziquantel. Therefore, our results confirm the earlier findings obtained with a combination therapy administered to rabbits simultaneously infected with juvenile and adult *S. japonicum* (Xiao et al., 2000d). Increasing the doses of praziquantel and artemether to 100 and 300 mg/kg, respectively, and administration of the two drugs in combination boosted the total and female worm reduction rates to 90% and above. However, a total of 11 hamsters died in five different combined treatment experiments, indicating that drug concentrations were somewhat too high. In view of one dead hamster also observed following a single dose of 300 mg/kg artemether, we assume that this concentration is borderline toxic, when administered to hamsters simultaneously infected with juvenile and adult stages of *S. mansoni* parasites.

Interestingly, we found in our own preceding work that hamsters only infected with juvenile *S. mansoni* tolerated two to five doses of 300 mg/kg artemether well (Xiao et al., 2000b). However, another study with hamsters inoculated with adult *S. mansoni* reported 100% death rates when artemether was administered at a single dose of 100 or 200 mg/kg by intramuscular route (Araújo et al., 1991). Although the cause of killing the hamsters is not known, one possibility is that rapid death of many adult *S. mansoni* worms may have caused collapse of liver function.

We conclude that a combined treatment with praziquantel together with artemether is more effective in killing *S. japonicum* and *S. mansoni* worms than a single treatment with either of the two drugs. The strategy of a combination therapy has the additional advantage that it might significantly delay the possible development of drug resistant parasites. This is of pivotal importance and has been reviewed in great detail in the case of malaria, where a combination therapy has been proposed as an approach to delay or reverse resistance in the *Plasmodia* parasites (White, 1999). Additional laboratory studies should be carried out to assess the effect of a combined treatment with praziquantel and artemether on *S. haematobium*. Special attention should be paid to dose-finding and potential drug-induced toxicity, especially when the two drugs are administered at the same time. While there is firm evidence that both praziquantel and artemether are rapidly metabolized (Mandour et al., 1990; White et al., 1999), little is known about potential pharmacokinetic interactions. In view of the very short terminal half-lives of both drugs (Gönnert and Andrews, 1977; White et al., 1999), it is, however, assumed that such interactions will decrease sharply, especially if drug administration is spaced by a few hours. The results of animal studies as described here will form a strong foundation for subsequent clinical trials in humans. A first preliminary study in an *S. mansoni* endemic area of Senegal investigated the effectiveness of a combined treatment with praziquantel and artesunate, which is another derivative of artemisinin. The parasitological cure rate, assessed 5 weeks after intervention, was significantly higher in patients who received a combined treatment when compared with those who received praziquantel or artesunate singly (De Clercq et al., 2000).
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