Interactions of mefloquine with praziquantel in the Schistosoma mansoni mouse model and in vitro

Jennifer Keiser1,2*, Theresia Manneck1,2 and Mireille Vargas1,2

1Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, CH-4002 Basel, Switzerland; 2University of Basel, CH-4003 Basel, Switzerland

*Corresponding author. Tel: +41-61-284-8218; Fax: +41-61-284-8105; E-mail: jennifer.keiser@unibas.ch

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Objectives: Mefloquine has interesting antischistosomal properties, hence it might be an attractive partner drug for combination treatment with praziquantel. The aim of this study was to evaluate activities of mefloquine/praziquantel combinations against Schistosoma mansoni in vitro and in vivo.

Methods: Dose–response relationships were established following exposure of adult S. mansoni to mefloquine, praziquantel and fixed dose combinations of mefloquine/praziquantel in vitro. S. mansoni-infected mice were treated orally with selected doses of single drugs and drug combinations 7 weeks post-infection.

Results: We calculated in vitro LC50 values of 0.024 and 1.9 μg/mL for praziquantel and mefloquine, respectively. Mefloquine/praziquantel combinations showed synergistic effects, with combination index (CI) values <1 when adult S. mansoni were simultaneously incubated with both drugs in vitro. Reduced viabilities were also observed when schistosomes were first exposed to mefloquine followed by praziquantel in vitro. ED50s of 62 mg/kg and 172 mg/kg were determined for mefloquine and praziquantel against adult S. mansoni in vivo, respectively. Combinations of praziquantel (50 or 100 mg/kg) followed the next day by mefloquine (50 or 100 mg/kg) treatment revealed only moderate total worm burden reductions of 47.8%–54.7%. On the other hand, when both drugs (100 mg/kg each) were either given simultaneously or mefloquine was given prior to praziquantel, high total and female worm burden reductions of 86.0%–93.1% were observed. For the later treatment regimen, synergistic effects (CI<1) were calculated when mefloquine and praziquantel were combined using a fixed dose ratio based on their ED50s.

Conclusions: Combinations of mefloquine and praziquantel may have clinical utility in the treatment of schistosomiasis.

Keywords: schistosomiasis, combination chemotherapy, activity, combination index, isobolography

Introduction

In the treatment of tuberculosis, cancer or malaria, drugs are often given in combination to increase their therapeutic advantages.1–3 The clinical effect of a combination of two drugs should either be the sum (additive behaviour) or ideally even exceed (synergy) the individual effect of each drug. On the other hand, for adverse events, antagonism (the effect of the two drugs being less than the effect of each drug) is preferable. In addition, combination chemotherapy is a viable therapeutic strategy to delay the development of drug resistance.4

There is scarce information available as to whether antischistosomal drug combinations provide an increased therapeutic efficacy over monotherapy. A few clinical trials have evaluated praziquantel plus oxamnique combinations and combinations of praziquantel with an artemisinin derivative.5,6 In the laboratory, combinations of ‘something old’ (praziquantel) with ‘something new’, e.g. novel experimental drugs such as Ro 15-54587 or nilutamide,8 were studied. However, the great disadvantage of these combinations (involving novel drug candidates) is the long drug development process (12–15 years), and therefore the associated high costs, in the order of $1 billion.9

Another possibility for an antischistosomal drug combination might be a polytherapy with praziquantel and the antimalarial drug mefloquine. Several laboratory studies have demonstrated interesting antischistosomal properties of mefloquine. For example, a single 200 mg/kg oral dose of mefloquine achieved a worm burden reduction of 72% in mice harbouring a chronic Schistosoma mansoni infection.10 In addition, in a randomized, exploratory open-label trial in Côte d’Ivoire in Schistosoma
haematobium-infected schoolchildren, a mefloquine/artesunate combination achieved a cure rate of 61% and an egg reduction rate of 95%.11

The aim of the present study was to evaluate the effect of mefloquine/praziquantel combinations against *S. mansoni* in vitro and in vivo. A preliminary study has already pointed to significant worm burden reductions following treatment with praziquantel plus mefloquine in mice infected with *Schistosoma japonicum*.12 We determined whether the potency of this drug combination is additive, antagonistic or synergistic.13 In addition, we analysed whether mefloquine/praziquantel combinations should be given simultaneously or in sequence.

**Materials and methods**

**Animals and parasites**

Female NMRI mice (*n* = 125, age = 3 weeks, weight ~35 g), obtained from Harlan Laboratories (Horst, The Netherlands), were kept under standard conditions (temperature, ~25°C; humidity, 70%; 12 h light and 12 h dark cycle) with free access to water and rodent diet in accordance with the Swiss national and cantonal regulations on animal welfare. Experiments were approved by the local veterinary agency (permit 2070). *S. mansoni* cercariae (Liberian strain) were collected after exposing *Biomphalaria glabrata* to light for 3 h. Mice were infected subcutaneously with ~80 cercariae.

**Drugs**

Praziquantel was purchased from Sigma (Buchs, Switzerland), and mefloquine hydrochloride was kindly provided by Mepha Pharma AG (Aesch, Switzerland). For *in vitro* studies, drugs were dissolved in 100% DMSO (Fluka, Buchs, Switzerland) to obtain stock solutions of 10 mg/mL. For *in vivo* studies, drugs were prepared as suspensions in 7% (v/v) Tween 80 and 3% (v/v) ethanol before oral administration to mice (10 mL/kg).

**In vitro assay procedures**

**Preparation of adult *S. mansoni* and culture conditions**

Forty-nine-day-old adult schistosomes, removed by picking from the hepatic portal system and mesenteric veins from infected NMRI mice, were washed with PBS (pH 7.4) and kept in RPMI 1640 culture medium [supplemented with 5% inactivated fetal calf serum (IFCS) and 100 U/mL penicillin and 100 μg/mL streptomycin (Invitrogen, Carlsbad, CA, USA)] at 37°C in an atmosphere of 5% CO₂ until use.

**Combination chemotherapy studies on adult *S. mansoni* in vitro**

In a first step, the lethal concentrations (*LC*100) that kill all schistosomes within 72 h of in vitro drug exposure and the median effective concentrations (*LC*50) were determined for praziquantel and mefloquine. Drugs were serially diluted in 24-well plates (Costar) in RPMI 1640 culture medium and 2 male and 2 female worms were added to each well. Praziquantel concentrations of 1, 0.5, 0.2, 0.1, 0.05, 0.025 and 0.001 μg/mL and mefloquine concentrations of 10, 9, 6, 5, 2, 1, 0.5, 0.2, 0.1 and 0.01 μg/mL were tested. Each drug concentration was assessed in duplicates and repeated once (*n* = 12 worms/drug concentration). For the interaction studies, mefloquine and praziquantel were added simultaneously in a first experiment at a fixed dose ratio based on the calculated *LC*50 values (1.9 μg/mL for mefloquine and 0.024 μg/mL for praziquantel) and 2-fold dilutions were carried out up and down (7.6 and 0.1 μg/mL; 3.8 and 0.05 μg/mL; 1.9 and 0.024 μg/mL; 0.95 and 0.0125 μg/mL; 0.475 and 0.006 μg/mL; and 0.238 and 0.003 μg/mL of mefloquine and praziquantel, respectively). In addition, we studied a 5-fold dilution of the *LC*50 value (combination of 0.03 μg/mL mefloquine and 0.0004 μg/mL praziquantel). Worms were incubated at 37°C and 5% CO₂ for 72 h, their viabilities recorded using a microscope (8–40-fold magnification; Carl Zeiss AG, Germany) and the mean viability of the 12 examined worms calculated as described previously.14 Worms were classified as dead if no movement was observed for 2 min and worms had a dark colour. In a second experiment, schistosomes were exposed to *LC*50LC50 (1.9 μg/mL for mefloquine and 0.024 μg/mL for praziquantel) and 0.5 LC50LC50 (0.95 μg/mL for mefloquine and 0.0125 μg/mL for praziquantel) and drug addition was spaced by the respective half-life of the drugs in mice.15,16 In more detail, schistosomes were exposed to (i) praziquantel followed by mefloquine 1 h post-incubation and (ii) mefloquine followed by praziquantel 17 h post-exposure. The viabilities of these worms were assessed 72 h after drug incubation. Worms incubated in medium containing the highest solvent concentration used (1% DMSO) served as controls in all experiments.

**In vivo studies**

**Monotherapy**

Forty-nine days post-infection, groups of 6–11 mice were treated orally with subtherapeutic single oral doses of mefloquine (50 and 100 mg/kg) and praziquantel (50, 100, 150 and 200 mg/kg). Untreated mice served as controls. At 21 days post-treatment, animals were killed by the CO₂ method and dissected. Worms were removed by picking, then sexed and counted as described in previous publications.17 For the calculation of the *ED*₅₀ values, worm burden reductions obtained in recent experiments with effective doses of mefloquine (200 mg/kg) and praziquantel (400 mg/kg) were included.10,17

**Effect of treatment schedule**

We evaluated whether the administration schedule has an influence on the activity of the drug combination. Six groups of mice were treated with combinations of mefloquine and praziquantel (50 mg/kg mefloquine plus 50 mg/kg praziquantel, 100 mg/kg mefloquine plus 100 mg/kg praziquantel) administered either simultaneously or on subsequent days (mefloquine followed by praziquantel or praziquantel followed by mefloquine). Untreated mice were included as controls. At 21 days post-treatment, worms were killed and processed as described above.

**Effect of drug interactions**

To determine the combination dose effect, four groups of mice were treated with combinations based on their *ED*₅₀ (1:2.8 ratio and 2-fold dilutions up and down). The treatment was administered on subsequent days (mefloquine followed by praziquantel), as this regimen has shown the highest activity in our experiments *in vitro* and *in vivo*. Three weeks post-treatment, mice were killed and processed as described above.

**Scanning electron microscopy study**

We collected adult *S. mansoni* 72 h post-treatment from three mice as described above, which had been treated with (i) mefloquine (60 mg/kg), (ii) praziquantel 170 mg/kg, and (iii) mefloquine (60 mg/kg) followed on the next day by praziquantel (170 mg/kg). Worms were fixed with 2.5% (v/v) glutaraldehyde in PBS (pH 7.4) for several hours. The schistosomes
were then washed twice with double-distilled water, dehydrated in ascending ethanol concentrations and critically point dried (Bomar SPC-900; Tacoma, WA, USA). Finally, worms were sputter coated with 20 nm gold particles and observed using a high-resolution scanning electron microscope (Phillips XL30 ESEM) at an accelerating voltage of 5 kV.

Statistical analysis

LC$_{50}$ and ED$_{50}$ values, combination index (CI), dose reduction index (DRI) and isobologram plots were calculated using the CompuSyn software package (CompuSyn, Paramus, NJ, USA). LC$_{50}$ plots were drawn using XLfit$^{18}$ (Xlfit5, IDBS, Guildford, UK). We used the Kruskal–Wallis (KW) test to compare the medians of the worm burdens in the monotherapy versus combination chemotherapy treatment groups [version 2.4.5 Statsdirect (Cheshire, UK)]. A difference in median was considered to be significant at a significance level of 5%.

Results

In vitro studies

Determination of LC$_{50}$ values of monotherapy

The dose–response curves of mefloquine and praziquantel are depicted in Figure 1. LC$_{50}$ values of 0.024 and 1.9 µg/mL were calculated for praziquantel and mefloquine, respectively. The corresponding LC$_{75}$ and LC$_{95}$ values are 0.04 and 0.11 µg/mL for praziquantel and 3.4 and 9.2 µg/mL for mefloquine, respectively.

Simultaneous drug administration

In Figure 1, the dose–response curve of adult S. mansoni exposed simultaneously to praziquantel and mefloquine (LC$_{50}$:LC$_{50}$) in vitro is shown. Figure 2 illustrates the combination dose effect using an isobologram.

Spaced drug administration

When praziquantel and mefloquine were added to the in vitro cultures with a time lag corresponding to their respective half-lives, only schistosomes exposed first to mefloquine and 17 h later to praziquantel were affected and showed reduced viabilities (a viability of 1 for the combination of 1.9 µg/mL mefloquine and 0.024 µg/mL praziquantel and a viability of 1.5 for the combination of 0.95 µg/mL mefloquine and 0.0125 µg/mL praziquantel) within 72 h. Parasites exposed to praziquantel for 1 h followed by mefloquine revealed only a slight loss of viability (viability of 2.0 for both combinations tested) in comparison with the untreated controls.

In vivo studies

ED$_{50}$ calculation for mefloquine and praziquantel

For the ED$_{50}$ calculation we also included results obtained from previous experiments in our laboratories.$^{10,17}$ Treatment of S. mansoni-infected mice with 50, 100 or 200 mg/kg mefloquine resulted in total worm burden reductions of 44.1, 64.0 (Table 1) and 93.4%,$^{17}$ respectively. We calculated an ED$_{50}$ of 62 mg/kg and an ED$_{95}$ of 262 mg/kg.

Worm burden reductions of 13% (50 mg/kg; Table 1) up to 96% (400 mg/kg)$^{10}$ were observed following treatment with praziquantel. Praziquantel given at 172 mg/kg and 592 mg/kg is estimated to achieve worm burden reductions of 50% and 95%, respectively.
Effect of combination treatment regimen on efficacy

Based on the results obtained in our in vitro experiments, which showed differences depending on the treatment schedule used (simultaneous or spaced incubation), we were interested whether these findings could also be documented in vivo. Mice were divided in three groups. Group 1 was treated with both drugs simultaneously, group 2 was treated with mefloquine followed by praziquantel 24 h later, and group 3 was treated with praziquantel followed by mefloquine 24 h later. We used subtherapeutic doses of 50 and 100 mg/kg for each of the drugs. The results are summarized in Table 1. When mefloquine and praziquantel were administered simultaneously at doses of 50 mg/kg each, low total (25.9%) and female (29.0%) worm burden reductions were observed, which were even lower than worm burden reductions observed with mefloquine (50 mg/kg) alone. When both drugs were given at 100 mg/kg simultaneously, high total and female worm burden reductions of 86.0% (P = 0.014) and 86.9% (P = 0.091), respectively, were calculated. High significant worm burden reductions (total worm burden reduction of 93.1% (P = 0.001) and female worm burden reduction of 93.0% (P = 0.008) were observed when mice were treated with 100 mg/kg mefloquine followed by 100 mg/kg praziquantel 24 h later. When half of these doses were given, total and female worm burden reductions decreased to 61.5% and 58.0%, respectively.

Combination dose–effect analysis

We used a constant ratio design based on the ED50s of both drugs (1:2.8) to analyse whether a mefloquine/praziquantel combination reveals additive, antagonistic or synergistic effects. Since the highest worm burden reductions were obtained when praziquantel followed mefloquine administration, this treatment schedule was employed to determine the combination dose effect. Significant total worm burden reductions of 91.8% and 97.8% were observed at the two highest concentrations tested (Table 2). At a dose of 30 mg/kg mefloquine and 85 mg/kg praziquantel, total and female worm burden reductions of 51.6% and 48.8%, respectively, were observed, which were not statistically significant. At the lowest dose tested (15 mg/kg mefloquine, 42.5 mg/kg praziquantel), low total and female worm burden reductions of 19.2% and 19.8%, respectively, were achieved. The ED50 dose of the combination was calculated as 101.8 mg/kg (26.8 mg/kg mefloquine and 75.1 mg/kg praziquantel, corresponding to a 2.3-fold dose reduction for each drug). A CI of 0.87 was determined at the median dose–effect level. At the ED75, ED90 and ED95, CI values were below 0.8. Hence, at the dose ratio for combined praziquantel and mefloquine (1:2.8), synergistic interactions were observed.

Table 1. Effect of praziquantel and mefloquine monotherapies administered at single oral doses of 50–100 mg/kg and praziquantel/mefloquine combinations (50/50 and 100/100 mg/kg) following three different treatment schedules to mice harbouring a 49-day-old S. mansoni infection

<table>
<thead>
<tr>
<th>Drug Dose</th>
<th>Drug</th>
<th>Dose</th>
<th>No. of mice investigated</th>
<th>No. of mice cured</th>
<th>Mean number of worms (SD)</th>
<th>Total worm burden reduction (%)</th>
<th>Female worm burden reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>20</td>
<td>0</td>
<td>24.7 (14.7)</td>
<td>14.1 (7.6)</td>
<td>10.7 (7.6)</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>praziquantel</td>
<td>50</td>
<td>4</td>
<td>0</td>
<td>21.5 (10.5)</td>
<td>10.0 (3.4)</td>
<td>11.5 (7.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>6</td>
<td>0</td>
<td>21.0 (9.5)</td>
<td>11.5 (5.8)</td>
<td>9.5 (3.8)</td>
</tr>
<tr>
<td></td>
<td>praziquantel</td>
<td>50</td>
<td>11</td>
<td>0</td>
<td>13.8 (9.4)</td>
<td>8.0 (11.6)</td>
<td>5.8 (4.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>100</td>
<td>9</td>
<td>0</td>
<td>8.9 (3.9)</td>
<td>6.4 (3.4)</td>
<td>2.4 (1.4)</td>
</tr>
<tr>
<td>Combination chemotherapy, simultaneous application</td>
<td>praziquantel/mefloquine</td>
<td>50/50</td>
<td>8</td>
<td>0</td>
<td>18.3 (8.5)</td>
<td>10.6 (5.7)</td>
<td>7.6 (3.1)</td>
</tr>
<tr>
<td></td>
<td>praziquantel/mefloquine</td>
<td>100/100</td>
<td>8</td>
<td>1</td>
<td>3.5 (3.9)</td>
<td>2.1 (2.9)</td>
<td>1.4 (1.1)</td>
</tr>
<tr>
<td>Combination chemotherapy, mefloquine followed by praziquantel</td>
<td>praziquantel/mefloquine</td>
<td>50/50</td>
<td>8</td>
<td>0</td>
<td>9.5 (6.8)</td>
<td>5.0 (3.6)</td>
<td>4.5 (3.3)</td>
</tr>
<tr>
<td></td>
<td>praziquantel/mefloquine</td>
<td>100/100</td>
<td>9</td>
<td>4</td>
<td>1.7 (2.0)</td>
<td>0.9 (1.1)</td>
<td>0.8 (1.0)</td>
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<tr>
<td>Combination chemotherapy, praziquantel followed by mefloquine</td>
<td>praziquantel/mefloquine</td>
<td>50/50</td>
<td>8</td>
<td>0</td>
<td>12.9 (7.8)</td>
<td>6.6 (4.3)</td>
<td>6.3 (3.7)</td>
</tr>
<tr>
<td></td>
<td>praziquantel/mefloquine</td>
<td>100/100</td>
<td>9</td>
<td>0</td>
<td>11.2 (8.8)</td>
<td>8.2 (6.6)</td>
<td>3.0 (3.1)</td>
</tr>
</tbody>
</table>

*p < 0.05. **p < 0.001.

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observed on adult schistosomes collected from mice treated with 60 mg/kg mefloquine and 170 mg/kg praziquantel, respectively (Figure 3a–d). Many worms revealed no tegumental damage. On the other hand, the majority of worms had already been expelled from a mouse treated with a combination of mefloquine and praziquantel 72 h post-treatment. Only a single worm could be recovered that showed extensive blebbing on its mid-body (Figure 3e).

Discussion

In several medical fields the search for effective drug combinations has been recognized as an important strategy for a successful treatment outcome and to delay drug resistance.1–3 To our knowledge, we have performed the first analysis of the pharmacodynamic interactions of mefloquine/praziquantel combinations against S. mansoni. In vitro and in vivo studies were conducted, which allow assessment of drug combinations in much more detail than do clinical studies. We used isobologram and CI analyses, which are popular methods to analyse drug interactions of combination chemotherapy.13 It is interesting to note that although several studies have analysed the in vitro and in vivo antischistosomal efficacy of praziquantel combinations, including the effect of combined treatment of mefloquine and praziquantel against S. japonicum,12 in depth modelling of dose–effect relationships, defining additive effects, synergy or antagonism of these combinations have not been carried out to date.

Synergistic interactions were observed in the S. mansoni mouse model and in vitro when praziquantel was combined with mefloquine. This finding is encouraging since the control of schistosomiasis, a chronic and debilitating disease, relies on a single drug, praziquantel.6,18 The need to develop alternative treatment options, including drug combinations, has been repeatedly emphasized because the development of a praziquantel-resistant schistosome strain is a threat.6,19

It has been suggested to analyse a series of different fixed dose ratios in combination treatment experiments to confirm whether two drugs behave additively or synergistically, since it has been shown that the effect might depend on the ratio of the drugs used.20 For the evaluation of mefloquine/praziquantel combinations in vivo we used the median effect analysis only.13 In vitro, however, a range of different dose ratios (including fixed ratios based on the LC50 presented here) were tested and analyses of these data confirmed the synergistic properties of the mefloquine/praziquantel combinations (data not shown).

It is interesting to note that the best results were achieved in the S. mansoni mouse model when praziquantel followed mefloquine. On the other hand, only moderate worm burden reductions were achieved when praziquantel was administered prior to mefloquine. These findings were also observed in vitro. The effects of praziquantel on schistosomes might play a role in the antagonistic effects observed when praziquantel was administered first. Exposure of schistosomes to praziquantel results in a calcium-dependent contraction of the musculature, an increase in tension and a disrupted tegument of the worms.21,22 One could speculate that due to the paralysis and damage of worms caused by praziquantel, the uptake of mefloquine by schistosomes might be decreased, resulting in lower

### Table 2. Effect of praziquantel/mefloquine combinations using a constant ratio design based on the ED50s administered to mice harbouring a 49-day-old S. mansoni infection

<table>
<thead>
<tr>
<th>Dose (mg/kg)</th>
<th>No. of mice investigated</th>
<th>No. of mice cured</th>
<th>Mean number of worms (SD)</th>
<th>Female worm burden reduction (%)</th>
<th>Total worm burden reduction (%)</th>
<th>Female total males females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>15.2 (6.3)</td>
<td>8.0 (2.9)</td>
<td>7.2 (3.5)</td>
<td>—</td>
</tr>
<tr>
<td>Combination chemotherapy, mefloquine followed by praziquantel</td>
<td>15 (mefloquine) and 42.5 (praziquantel)</td>
<td>4</td>
<td>12.3 (3.3)</td>
<td>6.7 (1.3)</td>
<td>5.5 (2.1)</td>
<td>19.2</td>
</tr>
<tr>
<td></td>
<td>30 (mefloquine) and 85 (praziquantel)</td>
<td>4</td>
<td>7.3 (1.2)</td>
<td>3.7 (0.6)</td>
<td>3.7 (0.6)</td>
<td>51.6*</td>
</tr>
<tr>
<td></td>
<td>60 (mefloquine) and 170 (praziquantel)</td>
<td>4</td>
<td>13.1 (1.5)</td>
<td>0.0 (0)</td>
<td>13.1 (1.5)</td>
<td>91.8*</td>
</tr>
<tr>
<td></td>
<td>120 (mefloquine) and 340 (praziquantel)</td>
<td>4</td>
<td>0.3 (6.6)</td>
<td>0.3 (6.6)</td>
<td>0.3 (6.6)</td>
<td>97.8*</td>
</tr>
</tbody>
</table>

*P<0.05.
activities of the drug combination. On the other hand, the mechanism of action of mefloquine on schistosomes has not yet been elucidated. However, in vivo and scanning electron microscopy studies have shown that adult schistosomes exposed to mefloquine were not affected immediately and only died after 24–72 h.23 Hence, mefloquine-treated schistosomes might still be able to interact with praziquantel, resulting in increased activities of mefloquine/praziquantel combinations.

Since our in vitro and in vivo findings are encouraging, exploratory randomized open-label trials have been launched to investigate the effect of mefloquine/praziquantel combinations in schistosome-infected children. We will treat children first with mefloquine or mefloquine/artesunate (3 day regimen, in line with the common malaria treatment schedule), followed by praziquantel on day 4, since this treatment schedule achieved the highest activity in vitro and in vivo. In addition, the advantage of a spaced application of the drugs (in contrast to simultaneous administration) is that this treatment regimen does not raise regulatory and review challenges that combination products would require.24 In a first step we will administer the standard doses (mefloquine 25 mg/kg, artesunate/mefloquine 300/250 mg and praziquantel 40 mg/kg); however, since synergistic interactions were observed in the present study in vivo, we are hoping in a next step to be able to lower the doses of these drugs to decrease the prevalence of adverse events and also costs. Of note, we have not included artesunate in this in vitro and in vivo study, as a preliminary experiment in our laboratory has shown similar worm burden reductions (both 86%) of mefloquine/praziquantel/artesunate (all 100 mg/kg administered simultaneously) compared with mefloquine/praziquantel (both 100 mg/kg simultaneously) in mice harbouring adult S. mansoni. Our result is in line with numerous experiments, which have documented a greater sensitivity of juvenile schistosomes towards the artemisinins than the adult worm in laboratory animals.25 However, why increased cure rates have been observed with mefloquine/artesunate over mefloquine in our previous study in S. haematobium-infected children cannot be explained at the moment, as only moderate cure rates were observed in the group of children treated with artesunate.11

In conclusion, we have demonstrated that a combination of mefloquine/praziquantel reveals synergistic behaviour in the treatment of S. mansoni-infected mice and in vitro. The effect of mefloquine/praziquantel combinations on S. haematobium should be also studied in detail. To assess the clinical utility of this drug combination in the treatment of schistosomiasis, proof-of-concept studies in schistosome-infected children have been launched.

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Transparency declarations
None to declare.

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Antischistosomal properties of mefloquine/praziquantel combinations


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