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Invited review

The potential of artemether for the control of schistosomiasis

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Abstract

Schistosomiasis continues to rank – following malaria – at the second position of the world's parasitic diseases in terms of the extent of endemic areas and the number of infected people. There is yet no vaccine available and the current mainstay of control is chemotherapy with praziquantel used as the drug of choice. In view of concern about the development of tolerance and/or resistance to praziquantel, there is a need for research and development of novel drugs for the prevention and cure of schistosomiasis. Interestingly, derivatives of artemisinin, which are already effectively used in the treatment of malaria, also exhibit antischistosomal properties. Significant advances have been made with artemether, the methyl ether derivative of artemisinin. We review the discovery of the antischistosomal activity of artemether by Chinese scientists two decades ago; the detailed laboratory studies of the susceptibility of, and effect on, the different developmental stages of *Schistosoma japonicum*, *Schistosoma mansoni* and *Schistosoma haematobium* to artemether; the possible mechanism of action and the potential long-term toxicity. Finally, we look at the effect of combined treatment with artemether and praziquantel; and clinical findings thus far obtained from randomised controlled trials with oral artemether for the prevention of patent infections and morbidity. The review intends to create a forum for strategic discussion of how these laboratory and clinical findings could be translated into public health actions. We conclude that artemether – as part of integrated current control measures and adapted to specific socio-ecological and epidemiological settings – has considerable potential to significantly reduce the current burden of schistosomiasis in many parts of the world. © 2001 Australian Society for Parasitology Inc. Published by Elsevier Science Ltd. All rights reserved.

Keywords: Schistosomiasis; Artemether; Drug susceptibility and action; Randomised controlled clinical trials; Prevention and control; Combined treatment

1. Introduction

Schistosomiasis is a parasitic disease with a chronic debilitating character, occurring in tropical and subtropical environments. It is currently estimated that more than 600 million people in 74 countries live at risk of infection, with one out of three people in these areas actually infected, and 20 million afflicted by severe consequences of the disease (Chitsulo et al., 2000). Schistosomiasis, therefore, ranks second only to malaria in terms of the extent of endemic areas and the number of infected people. The estimated global burden of the disease is more than 1.5 million disability adjusted life years lost, with 85% currently concentrated in sub-Saharan Africa (Murray and Lopez, 1996; WHO, 1999). Taking into account indirect causes of mortality due to hepatosplenic enlargement and oesophageal bleeding, bladder cancer and other debilitations attributed to chronic infections, it is estimated that annual mortality rates are exceeding 100000 (Giboda and Bergquist, 2000) and might be as high as 300000 in sub-Saharan Africa alone (M. van der Werf, personal communication). As a consequence, the total number of disability adjusted life years lost due to schistosomiasis might be seriously underestimated. Since schistosomiasis is linked to water development and population movements, it is anticipated that the disease will further gain in importance (Hunter et al., 1993; Mott et al., 1995; Chitsulo et al., 2000).

Schistosomiasis was endemic in China, Egypt, Mesopotamia and Palestine in ancient times, as evidenced by antigens and calcified ova in kidneys or livers of exhumed corpse and mummies (Mao and Shao, 1982; Deelder et al., 1990; Miller et al., 1992). However, epidemiological studies only began 150 years ago (Jordan, 2000). Owing to the complex life cycle of schistosomes with a phase of

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sexual reproduction by adult worms in the definitive human host, and an asexual phase in an intermediate snail host, the first rational approaches to control the disease were only formulated in the 1910s (Leiper, 1915). The initial focus was on transmission control by means of environmental management to reduce snail densities, employing vegetation clearance in irrigated canals, periodic drying and drain coverage. For about half a century, transmission control remained the cornerstone of schistosomiasis control and focussed on the intermediate snail hosts, by using natural or chemical products with molluscicidal properties (Fenwick, 1987). The high costs, the adverse effects for the environment and the need for repeated application by skilled personnel precluded their widespread use (McCullough, 1986).

With the advent of safe and effective antischistosomal drugs in the 1960s and 1970s (Davis and Wegner, 1979), morbidity control became the mainstay of schistosomiasis control (WHO, 1985, 1993). Three drugs have been widely and effectively used for chemotherapy: metrifonate, oxamniquine and praziquantel (Cioli et al., 1995). However, metrifonate, which is only active against *Schistosoma haematobium*, was withdrawn from the market in 1998, on the basis of therapeutic and operational criteria (Feldmeier and Chitsulo, 1999; WHO, 1999; Reich and Fenwick, 2001). Oxamniquine, singly active against *Schistosoma mansoni*, has been heavily used in Brazil (Machado, 1982), but is currently being replaced by praziquantel (Reich and Fenwick, 2001). Therefore, praziquantel is the current drug of choice for the treatment of schistosomiasis. It is highly effective against the adult stages of all human schistosome species (Gönnert and Andrews, 1977; Sabah et al., 1986), has no or only few adverse effects and in recent years, its price has been reduced substantially (WHO, 1993; Kusel and Hagan, 1999; Cioli, 2000). New initiatives are under way to promote chemotherapy with praziquantel in school-aged children in endemic areas of sub-Saharan Africa.

A series of recent laboratory studies and clinical trials in Egypt and Senegal have raised considerable concern about the possible development of tolerance and/or resistance to praziquantel (Fallon and Doenhoff, 1994; Gryseels et al., 1994; Ismail et al., 1994, 1996, 1999; Fallon et al., 1997; Guissé et al., 1997; Stelma et al., 1997; Geerts and Gryseels, 2000; Liang et al., 2000; William et al., 2001). These findings prompted the European Commission to carefully review the evidence of praziquantel resistance, with monitoring and surveillance of drug efficacy being among the main objectives (Renganathan and Cioli, 1998; Kusel and Hagan, 1999; Doenhoff et al., 2000). Detailed studies in Côte d'Ivoire (Ivory Coast), Ethiopia and Kenya reported the expected high cure and egg reduction rates following praziquantel administration (Berhe et al., 1999; King et al., 2000; Utzinger et al., 2000a). However, the availability of only one single antischistosomal drug is alarming and the scientific community has called for research and development of novel drugs for the prevention and cure of schistosomiasis (Cioli, 1998, 2000).

Interestingly, derivatives of artemisinin, which are highly effective in the treatment of malaria, have been shown to exhibit also antischistosomal properties. Significant progress has been made with artemether, the methyl ether derivative of artemisinin, and experiences thus far obtained with *Schistosoma japonicum* have been summarised recently (Xiao et al., 2000a). The present review refers to these findings and enlarges the scope by also including the recent data obtained with *S. mansoni* and *S. haematobium*. We cover topics of artemether susceptibility of different developmental stages of the major human schistosome parasites; drug-induced morphological alterations; possible mechanism of action; potential toxicity; combination therapy with artemether and praziquantel and clinical findings from randomised controlled clinical trials with oral artemether for the prevention of patent infections and morbidity. Finally, we provide a comprehensive assessment of the potential of artemether as part of integrated control of schistosomiasis.

2. Antischistosomal properties of artemisinins – the discovery

Artemisinin (qinghaosu) is the active principle that stems from the leaves of *Artemisia annua* L., a plant which is widespread throughout China, and also grows naturally in central Europe, the United States and Argentina (Ziffer et al., 1997). The plant has been used as antidote to many different ailments for centuries in the Chinese traditional medicine, but particularly for the treatment of febrile patients (Klayman, 1985). When Chinese authorities launched a screening programme in the 1960s to examine antimalarial activity of traditionally used remedies, *A. annua* was also tested, and antimalarial properties were confirmed in 1971 (Li and Wu, 1998). The unique structure of the active compound was identified: it is a sesquiterpene lactone bearing a peroxide grouping (Klayman, 1985). Following successful clinical testing, artemisinin was approved by the Chinese Ministry of Public Health as a novel antimalarial drug in 1986/1987 (Li and Wu, 1998). Several derivatives of artemisinin showed improved solubility, chemical stability and enhanced antimalarial activity, the most important of which are artemether, artesunate and arteether.

Wide-ranging reviews have summarised the chemical, medicinal, pharmacological and therapeutic properties of this novel group of antimalarial drugs (Klayman, 1985; de Vries and Dien, 1996; Ziffer et al., 1997; van Agtmael et al., 1999; Vroman et al., 1999; Dhingra et al., 2000; Price, 2000) and special supplementa have been published by the 'Transactions of the Royal Society of Tropical Medicine and Hygiene' in 1994 and by 'Médecine Tropicale' in 1998. Over the past 20 years, more than two million patients

suffering from malaria have been treated with artemisinins (Price et al., 1999). Detailed clinical surveillance revealed that these drugs are safe, show no adverse effects and clear parasitemia and malaria-related symptoms more rapidly than any other known antimalarial agent yet discovered (Hien and White, 1993; WHO, 1998; McIntosh and Olliaro, 2000; Price, 2000).

The antischistosomal activity of artemisinin was discovered in 1980 by a group of Chinese scientists. The drug, administered to various animals experimentally infected with *S. japonicum*, resulted in marked reductions of the schistosome worm burden, as compared with untreated control animals (Chen et al., 1980). In 1982, antischistosomal properties were confirmed for artemether (Le et al., 1982). Mice or dogs infected with *S. japonicum* and treated with artemether at various doses and routes of administration showed highly significant worm burden reductions ranging between 55 and 99% (Le et al., 1982). The larval migratory stages of the parasite (schistosomula) were also susceptible to artemether (Le et al., 1982), but no effect was seen on ova (Yue et al., 1984). Subsequent laboratory studies confirmed antischistosomal properties for artesunate (Le et al., 1983), arteether (Yin et al., 1991; Xiao et al., 1992) and recently also for dihydroartemisinin (Abdel Aziz and el-Badawy, 2000).

3. Laboratory studies with artemether

3.1. Schistosoma japonicum

This schistosome species has been subjected to the greatest number of in vivo studies, all carried out in Chinese laboratories. Artemether was selected for further investigations because of its remarkable chemical stability and the high efficacy against *S. japonicum* (Le et al., 1982). Early studies revealed that female worms were somewhat more susceptible to artemether than males, and that the drug-induced morphological alterations on the worm tegument, intestine and genital gland (Wu et al., 1983). The most prominent features in the altered tegument were vacuolisation and infiltration or adherence of host lymphocytes (Yang et al., 1986). Furthermore, artemether administration was followed by a hepatic shift with worms moving from the mesenteric veins to the liver, reaching a peak 7 days post-treatment (Yue et al., 1984).

Despite the significance of these findings, they were not noticed internationally for more than a decade, as recently highlighted by the research component of a World Bank loan project, placing renewed efforts on controlling schistosomiasis japonica in China. Along side the World Bank control project, a small proportion of the funds was designated to develop new tools or to improve applications of extant control strategies (Yuan et al., 2000). In this connection, an important series of studies was carried out with a laboratory strain of *S. japonicum* (Anhui isolate) employed for infection of animals that were treated with artemether, provided by the Kunming Pharmaceutical Cooperation (Kunming, China). In a first step, susceptibility to artemether was assessed in different developmental stages of the parasite. Groups of three to six rabbits, each infected with 200 *S. japonicum* cercariae, were treated intra-gastrically with artemether, 3–35 days post-infection (p.i.) at a single dose of 15 mg/kg. The percentage reduction in the mean worm burden was estimated for each treatment group relative to the mean worm burden from untreated control rabbits, by dissection 28 days post-treatment. Very high worm reductions of ≥90% were observed for 5- to 14-day-old schistosomula. Adult worms were significantly less susceptible, as the worm burden in 35-day-old *S. japonicum* was only reduced by 26% (Xiao et al., 1995). These findings are depicted in Fig. 1. Interestingly, the opposite had previously been found for praziquantel, which shows highest activity against very young developmental stages, and more importantly, adult worms, but is largely inactive on schistosomula (Xiao et al., 1987). Oviposition in *S. japonicum* worms is reached approximately 28–29 days p.i., which is also shown in Fig. 1 (Ghandour, 1978).

In subsequent experiments it was observed that the reduction of the worm burden is dose-dependent (Xiao et al., 1995), varies with the frequency of artemether treatment and depends on the route of administration, since intragastrical artemether showed higher worm reductions than intramuscular application (Xiao et al., 1998c). Very high total and female worm burden reductions of 94–100% were seen when rabbits received an initial dose of artemether 1 or 2 weeks p.i. followed by two repeated doses once every 1 or 2 weeks (Xiao et al., 1998c; Table 1).

Importantly, no drug-related adverse effects were observed in the artemether-treated animals. While rectal temperature and eosinophil counts remained normal in the treated rabbits for the entire observation period of up to 10 weeks post-treatment, elevated levels were measured in the untreated control animals. Slightly increased levels of anti-

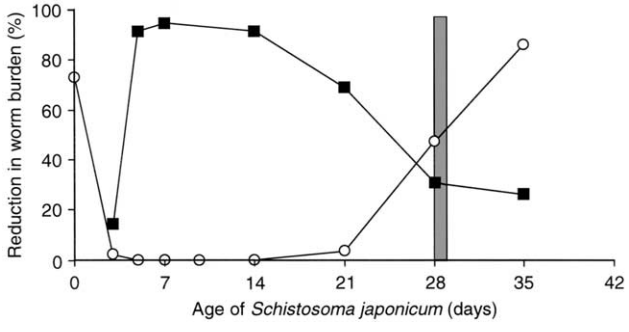

Fig. 1. Susceptibility of *Schistosoma japonicum* parasites of different ages to praziquantel (○) and artemether (■). Praziquantel was administered at a single oral dose of 400 mg/kg to mice (Xiao et al., 1987), whereas artemether was given intra-gastrically to rabbits at a single dose of 15 mg/kg (Xiao et al., 1995). The developmental period of *Schistosoma japonicum* to reach oviposition is also indicated (grey bar), according to Ghandour (1978).

Table 1
Effect of multiple doses of artemether administered intra-gastrically to different host animals experimentally infected with *Schistosoma japonicum*, *Schistosoma mansoni* or *Schistosoma haematobium* (SD, standard deviation)

Group	Animals (*N*)	Treatment (mg/kg)	Administration (day after infection)	Total worms (mean ± SD)	Total worm reduction (%)	Female worms (mean ± SD)	Female worm reduction (%)
S. japonicum in rabbits[a]							
Control	7	–	–	120 ± 16	–	60 ± 8	–
Artemether	5	15	7, 14, 21	4 ± 3	97	2 ± 2	97
Artemether	4	15	7, 21, 35	7 ± 6	94	3 ± 3	95
Artemether	5	15	14, 21, 28	1 ± 1	99	0.2 ± 0.4	100
Artemether	5	15	14, 28, 42	5 ± 4	96	2 ± 2	96
S. mansoni in mice[b]							
Control	10	–	–	21.6 ± 6.7	–	8.9 ± 3.7	–
Artemether	10	400	14, 28, 42	0.6 ± 1.1	97	0.1 ± 0.3	99
Artemether	10	400	14, 35	3.8 ± 3.0	82	1.1 ± 1.2	88
Artemether	10	400	21, 35, 49	1.3 ± 1.4	94	0.4 ± 0.7	96
Artemether	10	400	21, 42	3.8 ± 3.5	82	1.6 ± 1.7	82
S. haematobium in hamsters[c]							
Control	5	–	–	38.8 ± 10.5	–	13.2 ± 3.6	–
Artemether	5	300	21, 42, 63	1.0 ± 1.0	97	0.2 ± 0.4	99
Artemether	5	300	21, 49, 77	1.8 ± 1.5	95	0.6 ± 0.9	95
Artemether	5	300	28, 49, 70	1.6 ± 2.1	96	0.6 ± 0.9	95
Artemether	5	300	28, 56	8.6 ± 9.8	78	2.2 ± 1.6	83

[a] Rabbits were infected subcutaneously (s.c.) with 200 *S. japonicum* cercariae (Xiao et al., 1998c)
[b] Mice were infected s.c. with 60 *S. mansoni* cercariae (Xiao et al., 2000b).
[c] Hamsters were infected s.c. with 440 *S. haematobium* cercariae (Xiao et al., 2000f).

body and antigens were measured in the artemether-treated animals, whereas marked increases were observed in the untreated controls (Xiao et al., 1995). Finally, detailed histopathological observations in the liver of *S. japonicum*-infected rabbits and dogs treated with artemether showed five distinct features: (i) liver appearance was similar to that of uninfected animals; (ii) no or only very few miliary egg tubercles seen on the liver surface; (iii) hepatic lobules and liver bundles showed normal morphology; (iv) no or only a small number of ova evidenced in the portal vein area; and (v) very high reduction rate, namely 71–97%, of egg granuloma (Xiao et al., 1996e, 2000a).

Based on these extensive laboratory studies, it was suggested to develop artemether as a chemoprophylactic agent, as it should prevent acute schistosomiasis japonica and disease manifestations in humans by repeated administration once every 2 weeks during occupational water contacts that expose community members to often unavoidable infections. Since artemether selectively kills the larval migratory stages of the parasite, it precludes the development of adult egg-laying worm pairs, and thus prevents pathology, which is solely attributed to eggs that are trapped within intestinal and hepatic tissues. The eggs retained in these tissues induce a granulomatous reaction that is progressively accumulating to produce the pathology of chronic disease (Xiao et al., 2000a, c; Ross et al., 2001).

3.2. Schistosoma mansoni

Susceptibility to artemether of different developmental stages of a laboratory strain of *S. mansoni* (Liberian strain) was assessed in mice. Animals were infected with 60 *S. mansoni* cercariae each and treated 5–35 days p.i. with a single dose of 400 mg/kg artemether given intra-gastrically. Four weeks post-treatment, mice were sacrificed and the percent worm reductions were estimated by comparing the mean worm burden in the different treatment groups with that of a group of untreated control mice. The experiments demonstrated that artemether shows highest activity against 14- to 21-day-old schistosomula with worm burden reductions of 75–82%, while it is less active on adult worms (Xiao et al., 2000b). The findings are presented in Fig. 2, together with praziquantel susceptibility of *S. mansoni* parasites of different age (Sabah et al., 1986). In a previous study, susceptibility of different developmental stages of *S. mansoni* parasites harboured in mice was assessed after intra-gastrical artemether administration on two consecutive days at daily doses of 300 mg/kg. The total worm burden in 14- to 21-day-old schistosomula was reduced by 83–98%, whereas the percent worm reduction in adult *S. mansoni* was considerably lower; namely 30–51% (Xiao and Catto, 1989). Another study confirmed that total worm burden reductions of adult *S. mansoni* were only moderate following treatment with artemether at various doses and routes of administration (Araújo et al., 1991).

It was interesting to note that *S. mansoni* showed a prolongation of about 1 week in artemether susceptibility, when compared with *S. japonicum*. This coincidence with an approximately 1-week longer developmental period, since oviposition in *S. mansoni* is reached 34–35 days p.i.

Fig. 2. Susceptibility of *Schistosoma mansoni* parasites of different ages to praziquantel (○) and artemether (■) harboured in mice. Praziquantel was administered in three oral doses of 250 mg/kg on alternate days and the experiments were repeated three times (Sabah et al., 1986). To draw the figure, we calculated the mean worm reduction rates at any given point in time. Artemether was administered in a single oral dose of 400 mg/kg (Xiao et al., 2000b). The developmental period of *S. mansoni* to reach oviposition is shown by the grey bar, as described previously by Clegg (1965).

(Clegg, 1965), as opposed to 28–29 days in the case of *S. japonicum* (Ghandour, 1978).

Total and female *S. mansoni* worm burden reductions were boosted to 82–99% when infected mice received an initial dose of artemether 2 or 3 weeks p.i., followed by one or two repeated doses once every 2 or 3 weeks (Xiao et al., 2000b; Table 1). It was therefore concluded that oral administration of artemether once every 3 weeks during exposure could interrupt the development of adult egg-laying *S. mansoni* worms in humans, and thus prevent the development of morbidity (Xiao et al., 2000b).

Recently, we administered 7-day regimens of artemether at different concentrations to adult *S. mansoni* – analogues to what is currently recommended for malaria monotherapy (WHO, 1998) – and observed total worm burden reductions of 53–61% (Utzinger et al., 2001b). These findings clearly indicate that it is important to closely monitor the outcomes of malaria therapies with artemether, and other artemisinins, on the prevalence and intensity of *S. mansoni* infections in areas where both parasites are co-endemic (De Clercq et al., 2000b; Utzinger et al., 2001b).

3.3. Schistosoma haematobium

We studied the schistosomicidal effect of artemether on *S. haematobium* by employing a parasite strain derived from Côte d'Ivoire (Ivory Coast) after the first experimental passage through *Bulinus truncatus*. In the first series of experiments, we infected hamsters with 440 *S. haematobium* cercariae and treated them intra-gastrically with 300 mg/kg artemether at various regimens. Very high total and female worm burden reductions of 95–99% were observed when the initial dose was administered 3 weeks p.i., followed by at least two repeated doses once every 3 or 4 weeks (Xiao et al., 2000f). The total worm burden reduction observed after two doses administered at days 28 and 56 p.i. at the above mentioned concentration was still high and reached 78% (Table 1). Histopathological studies showed that 28-day-old schistosomula are highly susceptible (Yang et al., 2001).

In view of these findings it was concluded that the development of adult egg-laying *S. haematobium* worm pairs in humans could be prevented by oral administration of artemether once every 4 weeks during exposure (Xiao et al., 2000f). Interestingly, this suggested treatment regimen is 1 or 2 weeks longer than the ones previously recommended for the prevention of morbidity due to *S. mansoni* and *S. japonicum*, respectively, which is linked to the considerably longer developmental period of 61–65 days until *S. haematobium* worms reach sexual maturity (Smith et al., 1976; Ghandour, 1978).

4. Morphological alterations induced by artemether

The tegument protects schistosome parasites against attacks from the host's immune system, is involved in nutrient absorption, has secretory functions, and is also an important target for antischistosomal drugs. For praziquantel, which is particularly active against adult worms, a very rapid onset of tegumental alterations has been documented, since formation of vesicles occurred as soon as 15 min after drug administration (Xiao et al., 1985; Shaw and Erasmus, 1987). This was followed by vacuolisation, disruption of the dorsal tubercles, leading to severe and extensive tegumental damage (Becker et al., 1980; Mehlhorn et al., 1981).

Initial studies with artemether suggested that this compound also induces alterations on the schistosome tegument (Wu et al., 1983). In view of artemether displaying highest activity against schistosomula, particular emphasis was placed on drug-induced tegumental alterations at this stage of parasite development. Consequently, detailed temporal examinations of tegumental alterations have been carried out following drug administration to juvenile *S. japonicum*, *S. mansoni* and *S. haematobium*, by means of electron microscopy (Xiao et al., 1996b, 2000d, 2001b). The ultrastructural observations undertaken so far are summarised in Table 2.

The onset of drug action was considerably slower than documented for praziquantel. Mild or moderate swelling of tegumental ridges only became apparent 8 h after artemether treatment. Thereafter, alterations increased in severity and normally reached a peak 3–7 days post-treatment. Features of the tegumental alterations at this point in time included swelling and fusion of tegumental ridges, vesiculation, peeling and erosion. The adherence of host leukocytes to the most damaged parts of the tegument was an additional feature observed in juvenile *S. mansoni*. Interestingly, the damage then gradually decreased, and those specimens recovered 14 (or 28) days post-treatment showed signs of partial or complete recovery.

Scanning electron microscopic observations in adult worms of *S. japonicum* and *S. mansoni* revealed similar features of tegumental alterations as seen with schistoso-

Table 2
Morphological alterations induced by artemether in schistosomula and adult worms of *S. japonicum*, *S. mansoni* or *S. haematobium*, as evidenced by scanning and transmission electron microscopic observations (n.a., not assessed)

	Scanning electron microscopy	Reference	Transmission electron microscopy	Reference
Schistosomula				
S. japonicum	Swelling and fusion of tegumental ridges	(Xiao et al., 1996b)	Formation of vacuoles	(Xiao et al., 1996a)
	Disappearance of spines and sensory structures		Loss of definition of basement membrane	
			Lysis and disappearance of musculature	
			Sever damage to sensory structures and parenchymal tissues	
S. mansoni	Swelling and fusion of tegumental ridges	(Xiao et al., 2000d)	Formation of vacuoles	(Xiao et al., 2001c)
	Vesiculation, peeling and erosion		Loss of definition of basement membrane	
	Destruction of oral sucker and acetabulum		Lysis and disappearance of musculature	
	Adherence of host leukocytes		Gastrodermis: decreased granular endoplasmic reticulum and microvilli	
			Destruction of sensory structures	
			Extensive damage to tegument and parenchymal tissues	
S. haematobium	Swelling and fusion of tegumental ridges	(Xiao et al., 2001b)	n.a.	
	Vesiculation, peeling and erosion			
	Destruction of oral sucker and collapse of sensory structures			
Adult worms				
S. japonicum	Swelling and fusion of tegumental ridges	(Xiao et al., 1996b)	Formation of vacuoles	(Xiao et al., 1996a)
	Vesiculation, peeling and erosion		Loss of definition of basement membrane	
	Destruction of oral sucker, acetabulum and sensory structures		Lysis and disappearance of musculature	
	Adherence of host leukocytes		Gastrodermis: decreased granular endoplasmic reticulum; degeneration of nuclei and decreased microvilli	
S. mansoni	Swelling and fusion of tegumental ridges	(Xiao et al., 2000e)	n.a.	
	Vesiculation, peeling and erosion			
	Destruction of oral sucker and acetabulum			
	Adherence of host leukocytes			
S. haematobium	n.a.		n.a.	

mula. Interestingly, adult female worms normally showed more severe and more extensive tegumental damage (Xiao et al., 1996b, 2000e). At present, no such data are available for adult *S. haematobium*.

Finally, studies with transmission electron microscopy in juvenile and adult *S. japonicum* and juvenile *S. mansoni* show that artemether also induces morphological alterations in the subtegumental musculature, parenchymal tissues and gastrodermis (Xiao et al., 1996a, 2001c).

5. Biochemical pathways and possible mechanism of action

Considerable efforts have been made to understand the biochemical pathways of artemether on *S. japonicum* and to elucidating the possible mechanism of action. The most notable biochemical change measured in adult worms, recovered from mice treated with artemether was the reduction in their glycogen content. One to 3 days post-treatment, the parasite glycogen content was reduced by 28–78% with consistently higher percent reductions observed in female worms than in males (You et al., 1994a; Xiao et al., 1997). These reductions in the glycogen content were partially paralleled by a decreased glucose uptake, which was particularly prominent in female worms. However, the reduced glucose uptake was not accompanied by a decreased incorporation of glucose into glycogen, suggesting that artemether-induced glycogen reductions were rather related to an inhibition of glycolysis than an interference with glucose uptake (Xiao et al., 1997). It is interesting to note that schistosomes recovered from artemether-treated mice showed

increased glycogen phosphorylase activities. There were significant increases of the total phosphorylase and its active conformation, while the inactive conformation showed no or only slight increases (Xiao et al., 1999). Therefore, the reduction in glycogen content might be explained by an increase in the activated conformation of phosporylase, and to a lesser extent the decreased glucose uptake (Xiao et al., 2000c).

Marked reductions in the enzyme activities of phospofructokinase, phosphoglycerate kinase and pyruvate kinase, as well as lactate dehydrogenase were also observed in *S. japonicum* worms recovered from artemether-treated mice (Xiao et al., 1998a,b). However, the decrease of activities of major glycolytic enzymes might simply reflect non-specific changes occurring during drug-induced parasite damage (Xiao et al., 2000c). Artemether inhibited ATPases, particularly the Na^+–K^+–ATPase and the Mg^{2+}–ATPase (Xiao et al., 2000a). The experimental data obtained so far are inconclusive and call for further research (Xiao et al., 2000c).

Of particular interest are recent in vitro findings obtained with adult *S. japonicum*, *S. mansoni* and *S. haematobium* worms that were incubated in a medium containing artemether (0.5–20 μg/ml) and haemin (50–100 μg/ml). Shortly after exposure, the worms showed decreased motor activity, followed by a gradual increase in vesiculation of the tegument, which finally led to parasite death within 24–72 h. Since incubation of schistosomes in media containing artemether or haemin alone had no impact on their survival, it was suggested that the interaction between artemether and haemin produces a toxic effect on the worms (Xiao et al., 2001a). Interestingly, this finding might be analogous to what has been proposed with regard to the mechanism of action of artemisinin derivatives on malaria parasites. It has been suggested that the mechanism involves two sequential steps: (i) activation of artemisinins within the parasite by intraparasitic heme-iron, leading to the cleavage of the endoperoxide bridge and generation of free radicals and (ii) formation of covalent bonds between free radicals and malaria-specific proteins that kill the parasites (Meshnick et al., 1991; Meshnick et al., 1996; Posner and Meshnick, 2001).

6. Potential long-term toxicity of artemether

Numerous in vivo studies revealed that the toxicity profile of artemether is good. However, some concern was raised following the observation of symptomatic and pathological brainstem neurotoxicity in rats, dogs and Rhesus monkeys that received parenteral artemether at high doses over several consecutive days (Brewer et al., 1994a,b; Kamchonwongpaisan et al., 1997). Since neuropathological lesions only occurred towards the end of treatment after prolonged drug exposure, it was suggested that only repeated doses result in a cumulative neurotoxic effect (Genovese et al., 2000).

While a 7-day treatment course with artemether is recommended when this drug is used in monotherapy to treat malaria (WHO, 1998), prevention of schistosomiasis is recommended by artemether administration once every 2–4 weeks during exposure to schistosome-infected water. Consequently, we investigated the potential long-term toxicity when the drug was given to rats once every 2 weeks (Xiao et al., 2001d). Artemether was administered intragastrically at high concentrations of 80 or 400 mg/kg for periods of up to 20 weeks. After the final medication, liver and kidney function tests showed no abnormalities when compared with untreated control rats. Routine blood tests were also normal with two exceptions: (i) promptly reversible reduction of the reticulocyte count and (ii) reversible increases in haemoglobin levels. Detailed histopathological examinations showed no alterations in any of the key organs of treated rats. Importantly, no damage was observed on the central nervous system tissues including cerebrum, cerebellum, midbrain, thalamus, pons, medulla oblongata and spinal cord. Furthermore, electrocardiogram readings remained normal in rats receiving artemether for a total of 12 doses. In conclusion, our results suggest that artemether, following the recommended schistosomiasis treatment regimen, administered to rats with 2-week intervals for 5–6 months is safe. This can probably be explained by the duration between two consecutive treatments, which is sufficiently long to fully absorb artemether and its principal metabolite dihydroartemisinin, so that levels never sustain over extended periods.

7. Combined treatment with artemether and praziquantel

In view of artemether and praziquantel exhibiting highest activity against schistosomula and adult worms, respectively, a combined treatment had been proposed to enhance worm burden reductions. Surprisingly, first experiments in mice harbouring simultaneously different developmental stages of *S. japonicum* and treated with artemether together with praziquantel were disappointing, as the percent worm reductions were similar to the ones observed after monotherapies (You et al., 1994b). To exclude failure observed in a particular host animal, which might be due to pharmacokinetic or pharmacodynamic nature, experiments were repeated in rabbits. When rabbits were repeatedly infected with *S. japonicum* and treated with artemether and praziquantel, this combination therapy clearly revealed a beneficial effect. Rabbits with a mixed infection of 7- and 14-day-old juvenile and 42-day-old adult worms that were treated with either 50 mg/kg praziquantel or 15 mg/kg artemether, showed total worm burden reductions of 66 and 44%, respectively. Administration of the two drugs 1 day apart resulted in a significantly higher reduction of 82% ($P < 0.05$). Very similar results were also obtained with regard to percent reductions of female worms (Xiao et al., 2000g; Table 3).

Experiments were then extended from mixed infections

with *S. japonicum* parasites of different ages to adult worms only. Combination therapy with artemether and praziquantel administered to 42- or 56-day-old *S. japonicum* resulted in significantly higher total and female worm reductions (Utzinger et al., 2001a; Table 3).

Hamster experiments with a mixed infection of *S. mansoni* of different ages confirmed the beneficial effect of the combined treatment. Administration of 150 mg/kg artemether and 75 mg/kg praziquantel 1 day apart resulted in a total worm reduction of 76%. This was significantly higher than the 2% reduction obtained with praziquantel alone ($P < 0.01$) (Table 3). Employing combined treatment with increased drug concentrations of 300 mg/kg artemether and 150 mg/kg praziquantel increased the reductions in the total and female worm burden above 90%, however, some hamsters died in different treatment groups, indicating that these concentrations were at borderline toxicity (Utzinger et al., 2001a). Additional experiments should assess the effect of a combined treatment on adult *S. mansoni* worms, and more importantly on mixed infections with *S. haematobium*.

8. Randomised controlled trials with oral artemether

8.1. Schistosoma japonicum

On the basis of the encouraging laboratory results and the Chinese authorities stressing the need for additional control measures to combat schistosomiasis japonica, five randomised controlled clinical trials with artemether were conducted in endemic areas (Xiao et al., 1996c,d; Tian et al., 1997; Wang et al., 1997; Xu et al., 1997). Implementation of these trials was relatively straightforward, since artemether had been registered and was already effectively used against malaria. The trials were done between 1994 and 1996 in the provinces of Anhui, Hunan, Jiangxi and Yunnan, in mountainous, marshland and lake regions. In total, 4340 individuals in the age range of 3–65 years with frequent water contact were enrolled, and stool specimen collected and screened for *S. japonicum* ova. Baseline infection prevalent in the five study sites ranged between 12 and 29%. All participants were treated with praziquantel, at doses of 50 mg/kg for egg-positive and 40 mg/kg for egg-negative subjects. Participants were then randomly assigned either oral artemether (dose: 6 mg/kg) or a placebo, and medication commenced 2 weeks following praziquantel treatment. Treatment was repeated three to ten times every second week with regimens adapted to the different settings, so that half or the entire transmission period was covered. Two additional trials were done in Jiangxi province, enrolling 414 flood relief workers who were exposed to infected water for either 4 h or 30 days (Song et al., 1998). Artemether/placebo was administered 2 weeks after the first water contact and repeated one to two times at 2-week intervals. All trials were evaluated 3–5 weeks after the final medica-

Table 3
Effect of combined treatment with praziquantel and artemether administered intra-gastrically to animals experimentally infected with *S. japonicum* or *S. mansoni* (SD, standard deviation)

Group	Treatment (mg/kg)		Animals (*N*)	Total worms (mean ± SD)	Total worm reduction (%)	Female worms (mean ± SD)	Female worm reduction (%)
	Praziquantel	Artemether					
S. japonicum (juvenile and adult) in rabbits[a]							
Control	–	–	5	301 ± 29	–	129 ± 12	–
Praziquantel	50	–	7	101 ± 45	66	45 ± 22	65
Artemether	–	15	7	168 ± 31	44	79 ± 15	39
Praziquantel + Artemether	50	15	7	54 ± 29	82[b,*]	23 ± 14	82[b,*]
S. japonicum (adult) in rabbits[c]							
Control	–	–	6	108 ± 15	–	51 ± 8	–
Praziquantel	40	–	6	15 ± 9	87	6 ± 5	88
Artemether	–	15	6	73 ± 22	33	35 ± 11	31
Praziquantel + Artemether	40	15	5	2 ± 2	99[b,*]	1 ± 1	99[b,*]
S. mansoni (juvenile and adult) in hamsters[d]							
Control	–	–	5	36.0 ± 11.5	–	14.8 ± 4.1	–
Praziquantel	75	–	5	35.2 ± 14.6	2	13.0 ± 5.4	12
Artemether	–	150	5	12.2 ± 5.2	66	2.8 ± 1.3	81
Praziquantel + Artemether	75	150	5	8.8 ± 5.2	76[b,**]	3.2 ± 1.5	78[b,**]

[a] Rabbits infected with 7- and 14-day-old juvenile and 42-day-old adult *S. japonicum* (infection: 3 × 200 cercariae s.c.) (Xiao et al., 2000g).
[b] Combined treatment group (praziquantel + artemether) tested versus praziquantel alone (*t*-test; $*P < 0.05$, $**P < 0.001$).
[c] Rabbits infected with 42-day-old adult *S. japonicum* (infection: 200 cercariae s.c.) (Utzinger et al., 2001a).
[d] Hamsters infected with 14- and 21-day-old juvenile and 49-day-old adult *S. mansoni* (infection: 3 × 40 cercariae s.c.) (Utzinger et al., 2001a).

tion, by recording cases of acute *S. japonicum*, and assessing the prevalence and intensity of infections.

No case of acute *S. japonicum* was observed among artemether recipients living in endemic areas or being engaged in flood relief work, as opposed to 37 cases in placebo recipients (endemic areas: eight; flood relief work with 30 days exposure: 29). Repeated doses of artemether reduced the incidence of re-infection by 60–100%. The intensity of infection among egg-positive individuals was also reduced significantly (Table 4).

8.2. Schistosoma mansoni

In 1998, clinical testing of artemether was extended from *S. japonicum* to *S. mansoni*, and a randomised controlled trial carried out in the region of Man in western Côte d'Ivoire (Ivory Coast) (Utzinger et al., 2000b). The study included 349 schoolchildren, aged between 6 and 15 years, with a high infection prevalence of *S. mansoni* of 75%. Children were treated twice with praziquantel (2×30 mg/kg followed by 40 mg/kg 1 month apart). *Schistosoma mansoni*-negative children were then randomly assigned artemether (dose: 6 mg/kg) or a placebo, administered orally six times once every 3 weeks. Three weeks after the final treatment, the incidence and intensity of *S. mansoni* re-infections were assessed by microscopic stool examination over three consecutive days. Incidence infections among artemether recipients were half as frequent as in the placebo group (95% CI: 0.35–0.71), and were of significantly lower intensity (Table 4). The design of the study further allowed assessment of concurrent infections with geohelminths, intestinal protozoa and *Plasmodium falciparum*. Artemether showed no effect on geohelminths and intestinal protozoa but, as could be expected, reduced the prevalence of *P. falciparum* significantly.

8.3. Schistosoma haematobium

The first randomised controlled trial with artemether for prevention of *S. haematobium* is currently under way in a highly endemic area of south-central Côte d'Ivoire (Ivory Coast). The design follows that of the previous *S. mansoni* trial and the study will be completed, the code broken and the data analysed in July 2001.

8.4. Adverse effects and reported illness episodes

Clinical testing of artemether against schistosomiasis thus far included 5022 individuals, 2514 of whom received oral artemether at a dose of 6 mg/kg once every 2–3 weeks for periods of up to 22 weeks. Artemether was safe, well-tolerated and showed no or only few adverse effects. In four of the seven Chinese trials, 5–10% of the participants complained of abdominal pain, mild headache, dizziness, nausea and a few had transient elevated body temperatures. These symptoms were all self-limiting and they disappeared shortly after medication. Liver and kidney functions, electrocardiograms and routine blood tests were also normal. In one trial, artemether recipients had somewhat reduced reticulocyte counts one day after the final medication, but values were still within the normal range (Wang et al., 1997). In the *S. mansoni* trial, children who received artemether reported significantly less often headaches, which can probably be explained by reduced *P. falciparum* parasitemia (Utzinger et al., 2000b).

9. Artemether for the control of schistosomiasis

The results obtained over the past two decades through extensive laboratory and clinical investigations were reviewed and indicate the future research need. More importantly, the results also document the significance of artemether for schistosomiasis control. They call for a strategic discussion of how this evidence base can now be translated into public health actions in different endemic settings. A series of recommendations can be put forward that might form new components of an integrated approach, which is mandatory for sustainable schistosomiasis control (WHO, 1985, 1993).

First, oral artemether at a dose 6 mg/kg administered with 2- or 3-week intervals is safe, results in no or only few transient adverse effects and is effective in the prevention of patent *S. japonicum* and *S. mansoni* infections, thus precluding the onset and evolution of pathology. It is expected that 4-week intervals will also prove effective in incidence reduction of *S. haematobium* and results will be available in the second half of 2001. In 1996, the Chinese Ministry of Public Health had already registered artemether for prevention of acute cases of *S. japonicum* and as an additional tool for transmission control. During major flood relief work in 1998/1999, approximately 20 000 people received several doses of artemether and acute cases were effectively prevented. Furthermore, the drug is also used for the treatment of water conservation workers of the Yangtse River, since they often cannot avoid repeated water contacts. Therefore, the prospects are good for artemether to be used as a chemprophylactic agent among well-defined high-risk groups, such as flood relief workers, construction workers implementing or maintaining water development projects, irrigation and canal cleaners, fishermen and tourists with a recent history of water exposure in endemic areas (Utzinger et al., 2000b; Xiao et al., 2000a). With regard to these high-risk groups, the possibility of artemether being employed for the therapy of Katayama fever, at least when diagnosis is made within the first 2–4 weeks p.i., should be investigated.

Second, the use of artemether as a complement strategy to praziquantel chemotherapy can now be envisaged in areas where schistosomiasis transmission has become highly focal and/or close to cessation and where efforts are under way to eliminate the disease. In this context, a combination therapy with praziquantel together with artmether might be

Table 4
Randomised controlled trials with oral artemether (dose 6 mg/kg) for prevention of *S. japonicum* in different endemic areas or flood relief work in China; and prevention of *S. mansoni* in highly endemic areas of Côte d'Ivoire (Ivory Coast)

Parasite (country)	Province	Endemicity (prevalence) (%)	Group (*n* doses)	Participants	Infected cases (%)	Mean infection intensity (SD)[a]	Protective efficacy (%)	Reference
S. japonicum (China)	Endemic area							
	Hunan	29	Placebo	305	82 (27)	291 (363)		(Tian et al., 1997)
			Artemether (11)	290	5 (2)	18 (n.a.)	94	
	Yunnan	18	Placebo	717	87 (12)	79 (64)		(Wang et al., 1997)
			Artemether (11)	789	23 (3)	40 (20)	76	
	Anhui	14	Placebo	452	40 (9)	14 (8)		Xu et al., 1997)
			Artemether (10)	433	0	–	100	
	Yunnan	16	Placebo	306	46 (15)	50 (29)		(Xiao et al., 1996d)
			Artemether (4)	307	13 (4)	29 (11)	72	
	Hunan	12	Placebo	376	51 (14)	681 (909)		(Xiao et al., 1996c)
			Artemether (4)	365	20 (5)	122 (79)	60	
	Flood relief work							
	Jiangxi	–	Placebo	110	44 (40)	80 (107)		(Song et al., 1998)
			Artemether (3)	99	4 (4)	18 (12)	90	
	Jiangxi	–	Placebo	102	4 (4)	48 (35)		(Song et al., 1998)
			Artemether (2)	103	0	–	100	
S. mansoni (Ivory Coast)	Endemic area							
	Man	75	Placebo	140	68 (49)	32 (25-42)[b]		(Utzinger et al., 2000b)
			Artemether (6)	128	31 (24)	19 (13-26)[b]	50	

[a] *S. japonicum* and *S. mansoni*: infection intensity measured in eggs/g stool (epg); SD, standard deviation; n.a., not assessed.
[b] Values in brackets are 95% confidence intervals.

of particular relevance, as this strategy has been recommended for effective transmission control. The immediate targets of this approach are countries of North Africa, Middle East and perhaps also South America. Strong political commitment, a delivery infrastructure already in place and assistance from the international community would be required to sustain these eradication efforts, at least for some years, which is the likely time-horizon to show success (Chitsulo et al., 2000).

Third, in areas where schistosomiasis is endemic but not malaria, artemether treatment can be safely recommended for prevention of acute cases and the reduction of incidence infection. At present, this situation is met for large parts of Brazil, China, Egypt and South Africa. However, the relatively high costs of artemether considering repeated administration for prophylactic use, is an important factor that might preclude its large-scale application.

Fourth, in areas where schistosomiasis and malaria are co-endemic, artemether should not be recommended for prevention of schistosomiasis. There is considerable concern that the recommended treatment regimen for schistosomiasis prevention, with artemether administered once every 2–4 weeks, might select for drug resistant malaria parasites. In fact, a single dose of artemether or another artemisinin derivative results in high recrudescence in plasmodia, thus 7-day regimens are recommended if these drugs are used in monotherapy (WHO, 1998; McIntosh and Olliaro, 2000). Since artemisinins are so highly valuable drugs for the treatment of malaria, and often the only remaining effective antimalarials, they should by all means be carefully protected (White et al., 1999). However, the risk of resistance development appears to be low, which can, at least partially, be explained by the very short terminal half-life times of these compounds and the cidal effect. Combined treatment with an artemisinin derivative and a long duration of action antimalarial (e.g. mefloquine or lumefantrine) is currently being recommended to significantly decrease the chance of resistance development (White, 1999).

Artemisinins, administered singly or in combination with other antimalarials, are already widely and effectively used in Southeast Asia (Price et al., 1999; White et al., 1999). Combination treatments will however, soon gain importance in sub-Saharan Africa as the strategy to fight the rapid spread of drug resistance to most currently used antimalarials. In this connection, it will be of great interest to evaluate and monitor the impact of artemisinin combination therapies not only on the primary target, the prevalence and intensity of plasmodia but also on schistosomes. This was stressed at a recent WHO–TDR meeting in Geneva, where the potential of artemisinins in the control of schistosomiasis was reviewed. Recent laboratory studies confirmed that a 7-day monotherapy with artemether or artesunate reduced the *S. manosni* worm burden considerably (Utzinger et al., 2001b). A preliminary field study with a 5-day treatment regimen of artesunate in northern Senegal found a significant reduction in the infection prevalence of *S. mansoni* (De Clercq et al., 2000b).

It is remarkable how the susceptibilites of different developmental stages of the schistosome parasites to artemether and praziquantel are perfectly matched. First laboratory studies with combined treatment have confirmed the expected additive effect (Xiao et al., 2000g; Utzinger et al., 2001a). These findings are encouraging and now imply respective clinical trials. A preliminary, non-controlled study in humans using artesunate together with praziquantel, undertaken in northern Senegal, reported significant higher cure rates in those *S. mansoni* patients who received a combination therapy (De Clercq et al., 2000a).

Artemether in schistosomiasis still represents many challenges for basic and applied research. On the other hand, there is also a sufficient body of data to be translated into public health actions now. The development of artemether opens new perspectives for the control of schistosomiasis in different socio-ecological and epidemiological settings. Artemether could well complement existing control strategies and has the potential to become an important component of integrated control approaches. The ongoing and pending research as well as clinical studies will reveal how it may play a key determinant of the success of sustainable schistosomiasis control in many settings.

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References

Abdel-Aziz, S.S., el-Badawy, N.M., 2000. Experimental trials of an artemisinin derivative in treatment of *Schistosoma mansoni* infected mice. J. Egypt. Soc. Parasitol. 30, 295–303.

van Agtmael, M.A., Eggelte, T.A., van Boxtel, C.J., 1999. Artemisinin drugs in the treatment of malaria: from medicinal herb to registered medication. Trends Pharmacol. Sci. 20, 199–205.

Araújo, N., Kohn, A., Katz, N., 1991. Activity of the artemether in experimental schistosomiasis mansoni. Mem. Inst. Oswaldo Cruz 86, 185–8.

Becker, B., Mehlhorn, H., Andrews, P., Thomas, H., Eckert, J., 1980. Light and electron microscopic studies on the effect of praziquantel on *Schistosoma mansoni*, *Dicrocoelium dendriticum*, and *Fasciola hepatica* (Trematoda) in vitro. Z. Parasitenkd. 63, 113–28.

Berhe, N., Gundersen, S.G., Abebe, F., Birrie, H., Medhin, G., Gemetchu, T., 1999. Praziquantel side effects and efficacy related to *Schistosoma mansoni* egg loads and morbidity in primary school children in northeast Ethiopia. Acta Trop. 72, 53–63.

Brewer, T.G., Grate, S.J., Peggins, J.O., Weina, P.J., Petras, J.M., Levine, B.S., Heiffer, M.H., Schuster, B.G., 1994a. Fatal neurotoxicity of arteether and artemether. Am. J. Trop. Med. Hyg. 51, 251–9.

Brewer, T.G., Peggins, J.O., Grate, S.J., Petras, J.M., Levine, B.S., Weina, P.J., Swearengen, J., Heiffer, M.H., Schuster, B.G., 1994b. Neurotoxicity in animals due to arteether and artemether. Trans. R. Soc. Trop. Med. Hyg. 88 (Suppl. 1), 33–36.

Chen, D.J., Fu, L.F., Shao, P.P., Wu, F.Z., Fan, C.Z., Shu, H., Ren, C.S., Sheng, X.L., 1980. Studies on antischistosomal activity of qinghaosu in experimental therapy. Zhong Hui Yi Xue Zha Zhi 80, 422–8 (in Chinese).

Chitsulo, L., Engels, D., Montresor, A., Savioli, L., 2000. The global status of schistosomiasis and its control. Acta Trop. 77, 41–51.

Cioli, D., 1998. Chemotherapy of schistosomiasis: an update. Parasitol. Today 14, 418–22.

Cioli, D., 2000. Praziquantel: is there real resistance and are there alternatives? Curr. Opin. Infect. Dis. 13, 659–63.

Cioli, D., Pica-Mattoccia, L., Archer, S., 1995. Antischistosomal drugs: past, present … and future? Pharmacol. Ther. 68, 35–85.

Clegg, J.A., 1965. In vitro cultivation of *Schistosoma mansoni*. Exp. Parasitol. 16, 133–47.

Davis, A., Wegner, D.H., 1979. Multicentre trials of praziquantel in human schistosomiasis: design and techniques. Bull. World Health Organ. 57, 767–71.

De Clercq, D., Vercruysse, J., Verlé, P., Kongs, A., Diop, M., 2000a. What is the effect of combining artesunate and praziquantel in the treatment of *Schistosoma mansoni* infections? Trop. Med. Int. Health 5, 744–6.

De Clercq, D., Vercruysse, J., Verlé, P., Niasse, F., Kongs, A., Diop, M., 2000b. Efficacy of artesunate against *Schistosoma mansoni* infections in Richard Toll, Senegal. Trans. R. Soc. Trop. Med. Hyg. 94, 90–91.

Deelder, A.M., Miller, R.L., de Jonge, N., Krijger, F.W., 1990. Detection of schistosome antigen in mummies. Lancet 335, 724–5.

Dhingra, V., Vishweshwar Rao, K., Lakshmi Narasu, M., 2000. Current status of artemisinin and its derivatives as antimalarial drugs. Life Sci. 66, 279–300.

Doenhoff, M., Kimani, G., Cioli, D., 2000. Praziquantel and the control of schistosomiasis. Parasitol. Today 16, 364–6.

Fallon, P.G., Doenhoff, M.J., 1994. Drug-resistant schistosomiasis: resistance to praziquantel and oxamniquine induced in *Schistosoma mansoni* in mice is drug specific. Am. J. Trop. Med. Hyg. 51, 83–88.

Fallon, P.G., Mubarak, J.S., Fookes, R.E., Niang, M., Butterworth, A.E., Sturrock, R.F., Doenhoff, M.J., 1997. *Schistosoma mansoni*: maturation rate and drug susceptibility of different geographic isolates. Exp. Parasitol. 86, 29–36.

Feldmeier, H., Chitsulo, L., 1999. Therapeutic and operational profiles of metrifonate and praziquantel in *Schistosoma haematobium* infection. Arzneimittelforschung 49, 557–65.

Fenwick, A., 1987. Experience in molluscicide to control schistosomiasis. Parasitol. Today 3, 70–73.

Geerts, S., Gryseels, B., 2000. Drug resistance in human helminths: current situation and lessons from livestock. Clin. Microbiol. Rev. 13, 207–22.

Genovese, R.F., Newman, D.B., Brewer, T.G., 2000. Behavioral and neural toxicity of the artemisinin antimalarial, arteether, but not artesunate and artelinate, in rats. Pharmacol. Biochem. Behav. 67, 37–44.

Ghandour, A.M., 1978. The development of *Schistosoma haematobium* in the hamster. Ann. Trop. Med. Parasitol. 72, 219–25.

Giboda, M., Bergquist, N.R., 2000. Post-transmission schistosomiasis: a new agenda. Acta Trop. 77, 3–7.

Gönnert, R., Andrews, P., 1977. Praziquantel, a new board-spectrum antischistosomal agent. Z. Parasitenkd. 52, 129–50.

Gryseels, B., Stelma, F.F., Talla, I., van Dam, G.J., Polman, K., Sow, S., Diaw, M., Sturrock, R.F., Doehring-Schwerdtfeger, E., Kardorff, R., Decam, C., Niang, M., Deelder, A.M., 1994. Epidemiology, immunology and chemotherapy of *Schistosoma mansoni* infections in a recently exposed community in Senegal. Trop. Geogr. Med. 46, 209–19.

Guissé, F., Polman, K., Stelma, F.F., Mbaye, A., Talla, I., Niang, M., Deelder, A.M., Ndir, O., Gryseels, B., 1997. Therapeutic evaluation of two different dose regimens of praziquantel in a recent *Schistosoma mansoni* focus in Northern Senegal. Am. J. Trop. Med. Hyg. 56, 511–4.

Hien, T.T., White, N.J., 1993. Qinghaosu. Lancet 341, 603–8.

Hunter, J.M., Rey, L., Chu, K.Y., Adekolu-John, E.O., Mott, K.E., 1993. Parasitic Diseases in Water Resources Development: the Need for Intersectoral Negotiation. World Health Organization, Geneva.

Ismail, M.M., Taha, S.A., Farghaly, A.M., el-Azony, A.S., 1994. Laboratory induced resistance to praziquantel in experimental schistosomiasis. J. Egypt. Soc. Parasitol. 24, 685–95.

Ismail, M., Metwally, A., Farghaly, A., Bruce, J., Tao, L.F., Bennett, J.L., 1996. Characterisation of isolates of *Schistosoma mansoni* from Egyptian villagers that tolerate high doses of praziquantel. Am. J. Trop. Med. Hyg. 55, 214–8.

Ismail, M., Botros, S., Metwally, A., William, S., Farghally, A., Tao, L.F., Day, T.A., Bennett, J.L., 1999. Resistance to praziquantel: direct evidence from *Schistosoma mansoni* isolated from Egyptian villagers. Am. J. Trop. Med. Hyg. 60, 932–5.

Jordan, P., 2000. From Katayama to the Dakhla Oasis: the beginning of epidemiology and control of bilharzia. Acta Trop. 77, 9–40.

Kamchonwongpaisan, S., McKeever, P., Hossler, P., Ziffer, H., Meshnick, S.R., 1997. Artemisinin neurotoxicity: neuropathology in rats and mechanistic studies in vitro. Am. J. Trop. Med. Hyg. 56, 7–12.

King, C.H., Muchiri, E.M., Ouma, J.H., 2000. Evidence against rapid emergence of praziquantel resistance in *Schistosoma haematobium*, Kenya. Emerg. Infect. Dis. 6, 585–94.

Klayman, D.L., 1985. Qinghaosu (artemisinin): an antimalarial drug from China. Science 228, 1049–55.

Kusel, J., Hagan, P., 1999. Praziquantel – its use, cost and possible development of resistance. Parasitol. Today 15, 352–4.

Le, W., You, J., Yang, Y., Mei, J., Guo, H., Yang, H., Zang, C., 1982. Studies on the efficacy of artemether in experimental schistosomiasis. Acta Pharm. Sin. 17, 187–93 (in Chinese with English abstract).

Le, W.J., You, J.Q., Mei, J.Y., 1983. Chemotherapeutic effect of artesunate in experimental schistosomiasis. Acta Pharm. Sin. 18, 619–21 (in Chinese with English abstract).

Leiper, R.T., 1915. Report of the results of the bilharzia mission in Egypt, 1915. Part I: transmission. J. R. Army Med. Corps 25, 1–48.

Li, Y., Wu, Y.L., 1998. How Chinese scientists discovered qinghaosu (artemisinin) and developed its derivatives? What are the future perspectives? Med. Trop. 58 (Suppl. 3), 9–12.

Liang, Y.S., Coles, G.C., Doenhoff, M.J., 2000. Detection of praziquantel resistance in schistosomes. Trop. Med. Int. Health 5, 72.

Machado, P.A., 1982. The Brazilian program for schistosomiasis control, 1975–1979. Am. J. Trop. Med. Hyg. 31, 76–86.

Mao, S.P., Shao, B.R., 1982. Schistosomiasis control in the People's Republic of China. Am. J. Trop. Med. Hyg. 31, 92–99.

McCullough, F., 1986. Snail control in relation to a strategy for reduction of morbidity due to schistosomiasis. Trop. Med. Parasitol. 37, 181–4.

McIntosh, H.M., Olliaro, P., 2000. Artemisinin derivatives for treating severe malaria. Cochrane Database Syst. Rev., CD000527.

Mehlhorn, H., Becker, B., Andrews, P., Thomas, H., Frenkel, J.K., 1981. In vivo and in vitro experiments on the effects of praziquantel on *Schistosoma mansoni*: a light and electron microscopic study. Arzneimittelforschung 31, 544–54.

Meshnick, S.R., Thomas, A., Ranz, A., Xu, C.M., Pan, H.Z., 1991. Artemisinin (qinghaosu): the role of intracellular hemin in its mechanism of antimalarial action. Mol. Biochem. Parasitol. 49, 181–9.

Meshnick, S.R., Taylor, T.E., Kamchonwongpaisan, S., 1996. Artemisinin and the antimalarial endoperoxides: from herbal remedy to targeted chemotherapy. Microbiol. Rev. 60, 301–15.

Miller, R.L., Armelagos, G.J., Ikram, S., De Jonge, N., Krijger, F.W., Deelder, A.M., 1992. Palaeoepidemiology of *Schistosoma* infection in mummies. Br. Med. J. 304, 555–6.

Mott, K.E., Nuttall, I., Desjeux, P., Cattand, P., 1995. New geographical approaches to control of some parasitic zoonoses. Bull. World Health Organ. 73, 247–57.

Murray, C.J.L., Lopez, A.D., 1996. The Global Burden of Disease: a

Comprehensive Assessment of Mortality and Disability from Diseases, Injuries, and Risk Factors in 1990 and Projected to 2020. Harvard School of Public Health, Harvard University, Harvard.

Posner, G.H., Meshnick, S.R., 2001. Radical mechanism of action of the artemisinin-type compounds. Trends Parasitol. 17, 266–7.

Price, R.N., 2000. Artemisinin drugs: novel antimalarial agents. Expert Opin. Investig. Drugs 9, 1815–27.

Price, R., van Vugt, M., Phaipun, L., Luxemburger, C., Simpson, J., McGready, R., ter Kuile, F., Kham, A., Chongsuphajaisiddhi, T., White, N.J., Nosten, F., 1999. Adverse effects in patients with acute falciparum malaria treated with artemisinin derivatives. Am. J. Trop. Med. Hyg. 60, 547–55.

Reich, M.R., Fenwick, A., 2001. *Schistosoma haematobium*. N. Engl. J. Med. 344, 1170.

Renganathan, E., Cioli, D., 1998. An international initiative on praziquantel use. Parasitol. Today 14, 390–1.

Ross, A.G.P., Sleigh, A.C., Li, Y.S., Davis, G.M., Williams, G.M., Jiang, Z., Feng, Z., McManus, D.P., 2001. Schistosomiasis in the People's Republic of China: prospects and challenges for the 21st century. Clin. Microbiol. Rev. 14, 270–95.

Sabah, A.A., Fletcher, C., Webbe, G., Doenhoff, M.J., 1986. *Schistosoma mansoni*: chemotherapy of infections of different ages. Exp. Parasitol. 61, 294–303.

Shaw, M.K., Erasmus, D.A., 1987. *Schistosoma mansoni*: structural damage and tegumental repair after in vivo treatment with praziquantel. Parasitology 94, 243–54.

Smith, M., Clegg, J.A., Webbe, G., 1976. Culture of *Schistosoma haematobium* in vivo and in vitro. Ann. Trop. Med. Parasitol. 70, 101–7.

Song, Y., Xiao, S.H., Wu, W., Zhang, S., Xie, H., Xu, X., Hu, X., Cui, Q., Chen, M., Zheng, J., 1998. Preventive effect of artemether on schistosome infection. Chin. Med. J. 111, 123–7.

Stelma, F.F., Sall, S., Daff, B., Sow, S., Niang, M., Gryseels, B., 1997. Oxamniquine cures *Schistosoma mansoni* infection in a focus in which cure rates with praziquantel are unusually low. J. Infect. Dis. 176, 304–7.

Tian, Z.Y., Xiao, S.H., Xiao, J.W., Zhou, Y.C., Liu, D.S., Zheng, J., Chen, M.G., Qu, G.S., Zhang, X.Y., Yao, X.M., Zhang, X.Z., Zhang, D.L., 1997. Reduction of *Schistosoma japonicum* infection in an endemic area in islet with embankment after prophylaxis with oral artemether throughout the transmission season. Chin. J. Parasitol. Para. Dis. 15, 208–11 (in Chinese with English abstract).

Utzinger, J., N'Goran, E.K., N'Dri, A., Lengeler, C., Tanner, M., 2000a. Efficacy of praziquantel against *Schistosoma mansoni* with particular consideration for intensity of infection. Trop. Med. Int. Health 5, 771–8.

Utzinger, J., N'Goran, E.K., N'Dri, A., Lengeler, C., Xiao, S.H., Tanner, M., 2000b. Oral artemether for prevention of *Schistosoma mansoni* infection: randomised controlled trial. Lancet 355, 1320–5.

Utzinger, J., Chollet, J., You, J.Q., Mei, J.Y., Tanner, M., Xiao, S.H., 2001a. Effect of combined treatment with praziquantel and artemether on *Schistosoma japonicum* and *Schistosoma mansoni* in experimentally infected animals. Acta Trop. 80, 9–18.

Utzinger, J., Chollet, J., Zuwu, T., Xiao, S.H., Tanner, M., 2001. Comparative study of the effects of artemether and artesunate on juvenile and adult *Schistosoma mansoni* in experimentally infected mice. Trans. R. Soc. Trop. Med. Hyg. Submitted for publication.

de Vries, P.J., Dien, T.K., 1996. Clinical pharmacology and therapeutic potential of artemisinin and its derivatives in the treatment of malaria. Drugs 52, 818–36.

Vroman, J.A., Alvim-Gaston, M., Avery, M.A., 1999. Current progress in the chemistry, medicinal chemistry and drug design of artemisinin based antimalarials. Curr. Pharm. Des. 5, 101–38.

Wang, J.L., Xiao, S.H., Yang, Z., Wang, M.K., Yang, H., Liu, Y.H., Zhou, G.S., Zhen, J., Chen, M.G., 1997. Effect of oral artemether in controlling schistosomiasis in Yunnan mountaneous endemic area. Chin. J. Parasitol. Para. Dis. 15, 138–42 (in Chinese with English abstract).

White, N., 1999. Antimalarial drug resistance and combination chemotherapy. Philos. Trans. R. Soc. Lond. B Biol. Sci. 354, 739–49.

White, N.J., Nosten, F., Looareesuwan, S., Watkins, W.M., Marsh, K., Snow, R.W., Kokwaro, G., Ouma, J., Hien, T.T., Molyneux, M.E., Taylor, T.E., Newbold, C.I., Ruebush II, T.K., Danis, M., Greenwood, B.M., Anderson, R.M., Olliaro, P., 1999. Averting a malaria disaster. Lancet 353, 1965–7.

WHO, 1985. The Control of Schistosomiasis: Report of a WHO Expert Committee. World Health Organization, Geneva.

WHO, 1993. The Control of Schistosomiasis: Second Report of the WHO Expert Committee. World Health Organization, Geneva.

WHO, 1998. The Use of Artemisinin and its Derivatives as Anti-Malarial Drugs. Report of a Joint CTD/DMP/TDR Informal Consultation. World Health Organization, Geneva.

WHO, 1999. Report of the WHO Informal Consultation on Schistosomiasis Control. World Health Organization, Geneva.

William, S., Botros, S., Ismail, M., Farghally, A., Day, T.A., Bennett, J.L., 2001. Praziquantel-induced tegumental damage in vitro is diminished in schistosomes derived from praziquantel-resistant infections. Parasitology 122, 63–66.

Wu, L.J., Yang, H.Z., Yang, Y.Q., 1983. Histological and histochemical changes of *Schistosoma japonicum* and host liver caused by artemether. Acta Pharm. Sin. 18, 7–14 (in Chinese with English abstract).

Xiao, S.H., Catto, B.A., 1989. In vitro and in vivo studies of the effect of artemether on *Schistosoma mansoni*. Antimicrob. Agents Chemother. 33, 1557–62.

Xiao, S.H., Catto, B.A., Webster, L.T., 1985. Effects of praziquantel on different developmental stages of *Schistosoma mansoni* in vitro and in vivo. J. Infect. Dis. 151, 1130–7.

Xiao, S.H., Yue, W.J., Yang, Y.Q., You, J.Q., 1987. Susceptibility of *Schistosoma japonicum* to different developmental stages to praziquantel. Chin. Med. J. 100, 759–68.

Xiao, S.H., Yin, J.W., Mei, J.Y., You, J.Q., Li, Y., Jiang, H.J., 1992. Effect of arteether on *Schistosoma japonicum*. Acta Pharm. Sin. 27, 161–5 (in Chinese with English abstract).

Xiao, S.H., You, J.Q., Yang, Y.Q., Wang, C.Z., 1995. Experimental studies on early treatment of schistosomal infection with artemether. Southeast Asian J. Trop. Med. Public Health 26, 306–18.

Xiao, S.H., Shen, B.G., Catto, B.A., 1996a. Effect of artemether on ultrastructure of *Schistosoma japonicum*. Chin. J. Parasitol. Parasit. Dis. 14, 181–7.

Xiao, S.H., Shen, B.G., Horner, J., Catto, B.A., 1996b. Tegument changes of *Schistosoma japonicum* and *Schistosoma mansoni* in mice treated with artemether. Acta Pharmacol. Sin. 17, 535–7.

Xiao, S.H., Shi, Z., Zhuo, S., Wang, C., Zhang, Z., Chu, B., Zhen, J., Chen, M., 1996c. Field studies on the preventive effect of oral artemether against schistosomal infection. Chin. Med. J. 109, 272–5.

Xiao, S.H., Wang, J.L., Wang, C.Z., Chu, B., Yang, H., Liu, Y.H., Zheng, J., Chen, M.G., 1996d. Protection of the residents from schistosome infection using oral artemether in a mountainous endemic area. Chin. Med. J. Parasitol. Para. Dis. 14, 11–14 (in Chinese with English abstract).

Xiao, S.H., Yang, Y.Q., Zhang, C.W., You, J.Q., 1996e. Microscopic observations on livers of rabbits and dogs infected with *Schistosoma japonicum* cercariae and early treatment with artemether or praziquantel. Acta Pharmacol. Sin. 17, 167–70 (in Chinese with English abstract).

Xiao, S.H., You, J.Q., Mei, J.Y., Guo, H.F., Jiao, P.Y., Sun, H.L., Yao, M.Y., Feng, Z., 1997. Effect of artemether on glucose uptake and glycogen content in *Schistosoma japonicum*. Acta Pharmacol. Sin. 18, 363–7.

Xiao, S.H., You, J.Q., Guo, H.F., Jiao, P.Y., Mei, J.Y., Yao, M.Y., Feng, Z., 1998a. Effect of artemether on glyceraldehyde-3-phosphate dehydrogenase, phosphoglycerate kinase, and pyruvate kinase of *Schistosoma japonicum* harbored in mice. Acta Pharmacol. Sin. 19, 279–81.

Xiao, S.H., You, J.Q., Guo, H.F., Jiao, P.Y., Mei, J.Y., Yao, M.Y., Feng, Z., 1998b. Effect of artemether on hexokinase glucose phosphate isomerase and phosphofructokinase of *Schistosoma japonicum* harbored in mice. Chin. J. Parasitol. Para. Dis. 16, 25–28.

Xiao, S.H., You, J.Q., Mei, J.Y., Jiao, P.Y., Guo, H.F., Feng, Z., 1998c.

Preventive effect of artemether in rabbits infected with *Schistosoma japonicum* cercariae. Acta Pharmacol. Sin. 19, 63–66.

Xiao, S.H., You, J.Q., Guo, H.F., Mei, J.Y., Jiao, P.Y., Yao, M.Y., Zhuang, Z.N., Feng, Z., 1999. Effect of artemether on phosphorylase, lactate dehydrogenase, adenosine triphosphatase, and glucosephosphate dehydrogenase of *Schistosoma japonicum* harbored in mice. Acta Pharmacol. Sin. 20, 750–4.

Xiao, S.H., Booth, M., Tanner, M., 2000a. The prophylactic effects of artemether against *Schistosoma japonicum* infections. Parasitol. Today 16, 122–6.

Xiao, S.H., Chollet, J., Weiss, N.A., Bergquist, R.N., Tanner, M., 2000b. Preventive effect of artemether in experimental animals infected with *Schistosoma mansoni*. Parasitol. Int. 49, 19–24.

Xiao, S.H., Hotez, P.J., Tanner, M., 2000c. Artemether, an effective new agent for chemoprophylaxis against schistosomiasis in China: its in vivo effect on the biochemical metabolism of the asian schistosome. Southeast Asian J. Trop. Med. Public Health 31, 724–32.

Xiao, S.H., Shen, B.G., Chollet, J., Tanner, M., 2000d. Tegumental changes in 21-day-old *Schistosoma mansoni* harboured in mice treated with artemether. Acta Trop. 75, 341–8.

Xiao, S.H., Shen, B.G., Chollet, J., Utzinger, J., Tanner, M., 2000e. Tegumental changes in adult *Schistosoma mansoni* harbored in mice treated with artemether. J. Parasitol. 86, 1125–32.

Xiao, S.H., Utzinger, J., Chollet, J., Endriss, Y., N'Goran, E.K., Tanner, M., 2000f. Effect of artemether against *Schistosoma haematobium* in experimentally infected hamsters. Int. J. Parasitol. 30, 1001–6.

Xiao, S.H., You, J.Q., Mei, J.Y., Guo, H.F., Jiao, P.Y., Tanner, M., 2000g. Effect of praziquantel together with artemether on *Schistosoma japonicum* parasites of different ages in rabbits. Parasitol. Int. 49, 25–30.

Xiao, S.H., Chollet, J., Utzinger, J., Matile, H., Mei, J.Y., Tanner, M., 2001a. Artemether administered together with haemin damages schistosomes in vitro. Trans. R. Soc. Trop. Med. Hyg. 95, 67–71.

Xiao, S.H., Shen, B.G., Chollet, J., Utzinger, J., Tanner, M., 2001b. Tegumental alterations in juvenile *Schistosoma haematobium* harboured in hamsters following artemether treatment. Parasitol. Int. (in press).

Xiao, S.H., Shen, B.G., Utzinger, J., Chollet, J., Tanner, M., 2001. Transmission electron microscopic observations on ultrastructural damage in juvenile *Schistosoma mansoni* caused by artemether. Acta Trop. Submitted for publication.

Xiao, S.H., Yang, Y.Q., You, Q.Q., Utzinger, J., Guo, H.F., Jiao, P.Y., Mei, J.Y., Guo, J., Bergquist, R., Tanner, M., 2001d. Potential long-term toxicity of repeated orally administered doses of artemether in rats. Am. J. Trop. Med. Hyg. In press.

Xu, M.S., Xiao, S.H., Song, Q., Tao, C.G., Xia, C.G., Wang, H., Chen, M.G., Zheng, J., Bu, C.H., Hu, F.Y., Ou, N., Zhang, X.S., 1997. Observation on the effect of artemether on controlling schistosomiasis japonica in an endemic area of marshland. Chin. J. Parasitol. Para. Dis. 15, 212–5 (in Chinese with English abstract).

Yang, Y.Q., Yang, H.Z., Zhang, C.W., 1986. Histological observations on the effects of artemether, fuvinazole and niridazole on *Schistosoma japonicum* schistosomulae in the mouse liver. Acta Pharmacol. Sin. 7, 276–8 (in Chinese with English abstract).

Yang, Y.Q., Xiao, S.H., Tanner, M., Utzinger, J., Chollet, J., Wu, J.D., Guo, J., 2001. Histopathological changes in juvenile *Schistosoma haematobium* harboured in hamsters treated with artemether. Acta Trop. 79, 135–41.

Yin, J.W., Yang, Y.Q., Xiao, S.H., Li, Y., Jiang, H.J., 1991. Comparative studies on histological and histochemical alterations of *Schistosoma japonicum* induced by arteether and artemether. Acta Pharmacol. Sin. 12, 478–80 (in Chinese with English abstract).

You, J., Guo, H., Mei, J., Jiao, P., Feng, J., Yao, M., Xiao, S.H., 1994a. Effect of artemether on glycogen, protein, alkaline phosphatase and acid phosphatase of *Schistosoma japonicum*. Chin. J. Parasitol. Para. Dis. 12, 275–8 (in Chinese with English abstract).

You, J.Q., Mei, J.Y., Xiao, S.H., 1994b. Observation on effect of praziquantel combined with artemether on mouse schistosomiasis. Chin. J. Schisto. Control 7, 50–51 (in Chinese with English abstract).

Yuan, H.C., Guo, J.G., Bergquist, R., Tanner, M., Chen, X.Y., Wang, H.Z., 2000. The 1992–1999 World Bank schistosomiasis research initiative in China: outcome and perspectives. Parasitol. Int. 49, 195–207.

Yue, W.J., You, J.Q., Mei, J.Y., 1984. Effects of artemether on *Schistosoma japonicum* adult worms and ova. Acta Pharmacol. Sin. 5, 60–63 (in Chinese with English abstract).

Ziffer, H., Highet, R.J., Klayman, D.L., 1997. Artemisinin: an endoperoxidic antimalarial from *Artemisia annua* L. Prog. Chem. Org. Nat. Prod. 72, 121–214.