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Artenimol-Based Combination Therapy for the Curative Treatment of Schistosomiasis

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1. Introduction

Recent decades have seen new developments for a number of parasitic diseases, particularly malaria. This has had a major impact and large-scale global health programmes have been developed to alleviate the burden of some of these deadly diseases. Some diseases – such as schistosomiasis - seem to have been ignored internationally. And yet schistosomiasis has a serious impact on public health and the economy. Although the disease can be controlled by praziquantel, elimination programmes are not popular and the disease continues to take its toll on the public. An annual administration of praziquantel could change this markedly and have a pronounced impact on the overall health of the people of Africa. In contrast, malaria programmes are bringing the disease under control; the incidence of malaria has dropped significantly in the last few years. Praziquantel could achieve similar results for schistosomiasis control if it were used in identical health care programmes.

Although praziquantel appears to be an efficacious drug, in recent years problems of resistance have arisen and experts are calling for alternative therapies (Doenhoff et al., 2007). Below is a short review of praziquantel and a discussion on the need for new drugs.

Praziquantel (Figure 1) was discovered and developed by Bayer AG in Germany and co-developed by Merck. Praziquantel has been used since the early 1970s for the treatment of parasitic *Schistosoma* infections (Tchuenté et al., 2004) and for the treatment (to varying degrees of success) of liver flukes, such as *Chlonorchic sinsensis* (Shen et al., 2007). Paragonimiasis is also listed as an indication. One other major indication for praziquantel is its application in the treatment of tapeworms (trematodes and cestodes), such as the various taenias, cysticercosis (Matthaiou DK et al., 2004) and echinococcosis parasites. The WHO considered the drug important enough to add it to its Model List of Essential Medicines.

Absorption and metabolism: Praziquantel is rapidly absorbed (approximately 80%) via the gastrointestinal tract. It undergoes intensive metabolisation during its first pass through the liver so that relatively small amounts enter the systemic circulation. The elimination half-life is short, ranging from 1 to 2 hours. Praziquantel and its metabolites are mainly excreted by the kidneys. After a single oral dose, 70 to 80% is found in urine within 24 hours.

Efficacy: Praziquantel has a particularly dramatic effect on patients with schistosomiasis. Studies have shown that up to 90% of the damage done to internal organs due to schistosomiasis infection could be reversed (http://www.cartercenter.org/health/schistosomiasis/index.html; Tchuenté et al., 2004) within six months of receiving one dose of praziquantel.

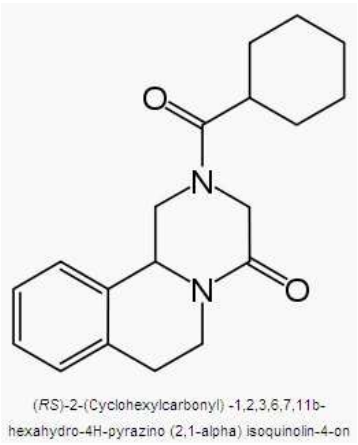


Fig. 1. Praziquantel: $C_{19}H_{24}N_2O_2$. MW. 312.4

Mode of action: Although the mode of action is not exactly known at present, there is experimental evidence that praziquantel increases the permeability of the membranes of schistosome cells towards calcium ions. The drug thereby induces contraction of the parasites, resulting in paralysis in the contracted state. The dying parasites are dislodged from their site of action in the host organism and may enter systemic circulation. Destruction follows by host immune reaction. Additional mechanisms including focal disintegrations and disturbances of oviposition (laying of eggs) are seen in other types of sensitive parasites (Doenhoff et al., 2008). Others suggest that the drug seems to interfere with adenosine uptake in cultured worms. This effect may have therapeutic relevance given that the schistosome, the taenia and the echinococcus (other praziquantel sensitive parasites) are unable to synthesise *de novo* purines such as adenosine (Angelucci et al., 2007).
Side effects: The majority of side effects develop as a result of host immune reaction due to the release of the contents of the killed parasites. The most frequent side effects are dizziness, headache and malaise. Almost all patients with cerebral cysticercosis experience CNS side effects related to the cell-death of the parasites (headache, worsening of pre-existing neurological problems, seizures, and meningism). Sometimes this requires the administration of corticosteroids. Approximately 90% of patients suffer from abdominal pain or cramps with or without nausea and vomiting. Diarrhoea may develop and may be severe with colic. Increases in liver enzymes are sometimes found during treatment, and urticaria, pruritus and eosinophilia are not uncommon.
Dosage: For schistosomiasis, the dose is 20 mg/kg by mouth every 4-6 hours for one day. An alternative is 40 mg per kg body weight in a single oral dose. For treatment of other worms different dosages might be needed.

2. Need for alternative treatment for schistosomiasis

Although praziquantel maintained its status for many years as a powerful drug for the treatment of various forms of schistosomiasis, reports started coming in about the failure of the drug. Development of resistance was studied experimentally and closely monitored clinically. Resistance could be induced in laboratory experiments, for instance by giving

suboptimal doses of the drug to worm infested mice (Ismail et al., 1994, Fallon et al., 1995). Ismail and colleagues confirmed their findings on isolates from Egypt (Ismail et al., 1996). Clinical evidence of resistance came from Senegal and Egypt, expressed as a reduced cure rate in a treated population (Stelma et al., 1995). One strange observation came from northern Senegal, where the cure rate 12 weeks after a single dose of 40 mg per kg was unexpectedly low namely 18% (Gryseels et al., 2001). Fortunately, such a low cure rate was not found elsewhere. Overall it can be concluded that real resistance against praziquantel exists but is not yet dramatic. The mechanism of resistance remains fully unclear.
If resistance against a standard treatment develops it is time to look for new treatments, but very few were found over the years. Oxamniquine is one alternative, but it has never been used on a broad scale for reasons of intrinsic weakness and early resistance development. Others reported that combining oxamniquine with praziquantel had no real advantage over praziquantel alone.

3. Positioning of broad spectrum drugs

Although in general, drugs are developed for the treatment of a single disease, for some indications international experts are calling for the development of broad spectrum drugs that can be used for more than one disease. The treatment of one disease will then have implications on the other disease in the same region. One example would be a drug for malaria that is also able to kill certain helminths. So far, there are very few drugs indeed that can simultaneously destroy plasmodia parasites and devastating worm infections. As a result, such pleas have remained more or less a dream (Hotez et al., 2008). It is not obvious that a particular drug which affects the mechanism of a given disease will also affect the biological factors implicated in another disease. Nevertheless, several examples exist. The classical example is the use of chloroquine to treat malaria and lupus erythematosus (Fischer-Betz and Scheider, 2009). Some anti-folates, such as sulfonamides, have a strong killing effect on bacteria as well as on the parasites that cause toxoplasmosis, not necessarily due to folic acid biosynthesis inhibition. Some single drugs – such as albendazole, paclitaxel and ivermectine - affect various parasites or worms, but do not affect other parasites. It would be of great interest to have a drug that kills malaria parasites while at the same time having an impact on the burden caused by helminthic infections. Is this a dream or can it actually be a practical solution? Leading researchers have advocated moves in this direction. Imagine what it could imply if a strong drug able to kill malaria parasites could simultaneously kill worms, such as *Schistosoma* and hookworms. Such a drug would have a serious impact on disability-adjusted-life years (DALYs) in an African setting. It would definitely reduce the degree of anaemia in the population and therefore have a positive impact on working days lost and on the learning process of schoolchildren.
Such an idea came to the fore when descriptions were published noting that antimalarial drugs derived from artemisinin had a killing effect on some worms, like the *Schistosoma* species. The first to describe such an effect was Chen et al. in 1980 followed by Le et al. in 1982, who found the artemisinins active against *S. japonicum*. Utzinger confirmed this in 2001 (Utzinger et al., 2001). Later, Utzinger wrote that artemether and artesunate in particular were active against all species of schistosomes (Utzinger et al., 2003). Artemether exhibits the highest activity against young liver stages, whereas the invasive stages (cercariae) and the adult worms were found to be less sensitive to this drug. In contrast, the older forms were more vulnerable to praziquantel (Utzinger et al., 2001 and Xiao et al.,

2002). What sort of drugs are these artemisinins and do they have a real place in the treatment of schistosomiasis? And if so, for all species?

4. Artenimol and derivatives in the treatment of malaria: Mechanism of action

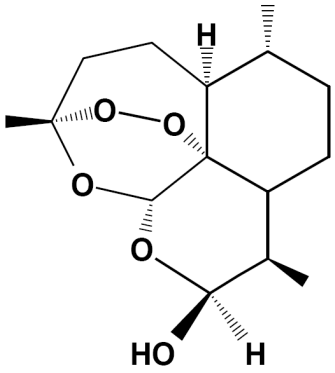
Artemisinin was the first substance in the artemisinin derivatives family to be described as being active against malaria. When later the active ingredient dihydroartemisinin (DHA) or artenimol was discovered, also derivatives of DHA like artemether, a methyl ether derivative, and artesunate, a succinic acid ester derivative, were manufactured and studied. Artenimol is the official generic name for a substance generally known as dihydroartemisinin (DHA) (Figure 2a). This compound is the result of a selective borohydride reduction of the lactone function of artemisinin (Figure 2b). Artemisinin, generally referred to as a sesquiterpene lactone (meaning that the drug has a lactone function and contains 15 carbon atoms), is the active ingredient extracted from the plant *Artemisia annua* (sweet wormwood, see boxed text: *The story of artemisinin*). The reduction process creates a reactive place in the molecule permitting derivatisation of the molecule. Artenimol is considered to be the active parent compound of the series of derivates (Jansen and Soomro, 2007; Li et al., 1989).

4.1 Box: The story of artemisinin

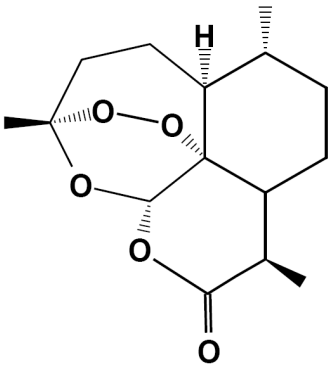
During the Vietnam War, the North Vietnamese Army suffered heavily from malaria and appropriate drugs were not available. Vietnamese leader Ho Chi Minh asked for help from his comrades in the People's Republic of China and Mao organised an official research programme. This initiative came at the right time. One of the researchers in traditional Chinese medicine, Xian Weij, had experimented with extracts from a widespread plant called *Artemisia annua*. However, it turned out that this aromatic plant, when cultivated under optimal climatic conditions, contained more crystalline product than plants growing in other areas. When isolated, the crystalline substance turned out to be effective against malaria parasites and was apparently non-toxic. This was the beginning of a strong national programme in China. However, when the drug was ready, the Vietnam War was over. The chemical structure of the crystalline substance ($C_{15}H_{22}O_5$) was determined a few years after the discovery. It turned out that the molecule is small (MW 282.3) but has a complex chemical structure. One of the functions in the molecule, a lactone function, was vulnerable to chemical reaction and a borohydride reduction process yielded a product given the trivial name of dihydroartemisinin. In some models, this molecule had a higher intrinsic activity against malaria parasites. It offered the possibility of making derivatives by etherification or esterification. Thus artemether (a methyl ether) and artesunate (the hemisuccinate ester of DHA) were born. These two drugs revolutionised malaria treatment.

Relatively cheap drugs without side effects could now be used to treat even multiple-drug-resistant malaria, a problem emerging in southeast Asia. A dose of 600 mg administered over 5 days was enough to cure more than 90 percent of all cases. Recrudescence was very low. In order to counter the risk of parasites building up resistance to this class of drugs, the WHO recommended using combination therapies (Artemisinin-based combination therapies or ACTs) and in 2006 the WHO imposed a global ban on the use of artesunate and similar drugs for malaria monotherapy.

As an antimalaria agent, artenimol is 10-15 times more active than artemisinin. For a detailed discussion on the mechanism of action we refer to Krishna et al. (2004) and to



a)



b)

Fig. 2. a) Dihydroartemisinin (artenimol) $C_{15}H_{24}O_5$. MW. 284.3, b) Artemisinin $C_{15}H_{22}O_5$. MW. 282.3.

Jansen and Soomro (2007). Several mechanisms have been put forward to describe the efficacious and fast activity of artemisinin derivates. The first proposed mechanism of action is the activity created by singlet oxygen and of a series of free radicals. This is an obvious approach. The peroxide function in the molecule is carried by an unstable, oxygen-containing, seven-membered ring. Strain on this ring, e.g. occurring when the lactol ring opens (under the influence of alpha-beta flip flop mechanisms of the OH-group), sets singlet oxygen free. Other mechanisms can cause a similar effect and they definitely occur when DHA is absorbed into the parasite. This release of singlet oxygen implies the release of an extremely reactive atomic species that will attack any molecular function in its vicinity that is sensitive to singlet oxygen attack. Non-chemists are very well aware of the strong antibacterial action of hydrogen peroxide and benzoylperoxide gels; they kill all germs. In these preparations, singlet oxygen will be released and the molecules will return to straight water and to benzoic acid, both devoid of any particular killing effect. The resistance of bacteria to this action of peroxide has not been described. Peroxide is also commonly used to bleach hair and tissues. At subcellular level, a large variety of biochemical reactions can be

influenced by singlet oxygen. For example, the singlet oxygen sets itself on a double bond of a fatty acid in a membrane, forming an epoxide causing a change in the tertiary structure of a lipid. This is the start of other reactions since e.g. water can create an addition reaction on the peroxide. This results in the formation of vicinal OH groups in the chain leading to the rupture of the molecule. Leaking membranes is the first consequence of such action. At the same time, the artenimol molecule forms a series of other free radicals with or without Fe^{2+} ions and these in turn have alkylating properties leading to more destructive actions. Unfortunately, these properties are not well described and more of a speculative nature. However the destructive activity remains. This was clearly demonstrated in an electron microscopy study on *Plasmodium berghei* parasites. Several years ago, Chinese scientists involved in traditional medicine published a remarkable article. Mice suffering from *P. Berghei* malaria were treated with a single 10 mg/kg dose of artemisinin. At time zero the parasites under the microscopic magnification appear most healthy but 30 minutes later changes were seen in the membranes of the parasite, together with alterations in ribosomal organisation and endoplasmatic reticulum. No changes were observed in the digestive vacuole, but nuclear membrane blebbing developed after one hour and segregation of the nucleoplasm after three hours. Further degenerative changes with disorganisation and death occurred from eight hours onwards. Such a fast and progressive action would indeed fit into a combination of various free radical actions (Ellis et al., 1985).

The inhibition of the SERCA enzyme is another proposed mechanism of action (Eckstein-Ludwig et al., 2003). These investigators show that artemisinins, but not quinine or chloroquine, inhibit the SERCA orthologue (PfATP6) of *Plasmodium falciparum* in Xenopus oocytes, with similar potency to thapsigargin (another sesquiterpene lactone and highly specific SERCA inhibitor). As predicted, thapsigargin also antagonises the parasiticidal activity of artemisinin. Desoxyartemisinin lacks an endoperoxide bridge and is ineffective both as an inhibitor of PfATP6 and as an antimalarial. Chelation of iron by desferrioxamine abrogates the antiparasitic activity of artemisinins and correspondingly attenuates inhibition of PfATP6. Imaging of parasites with BODIPY-thapsigargin labels the cytosolic compartment and is competed by artemisinin. Fluorescent artemisinin labels parasites similarly and irreversibly in a Fe^{2+}-dependent manner. These data provide compelling evidence that artemisinins act by inhibiting PfATP6 outside the food vacuole after activation by iron.

As demonstrated in more recent years, the class of arteminisins is not only active against malaria, but also against cancer cells and schistosomiasis. Artenimol derivates were shown to display remarkable and highly specific cytotoxicity against all human tumour cell lines studied at the Developmental Therapeutics Program of the National Cancer Institute (USA). Cytotoxicity was also shown against radiation- and drug-resistant cancer cell lines. Interestingly, synergism with other common chemotherapeutic therapies was also shown (Efferth et al., 2001). The anti-angiogenesis properties of artenimol derivatives were demonstrated using the chorioallantoic membrane (CAM) assay and the Zebra fish embryo model. Artenimol derivatives were shown to be the first small molecules to display its anti-angiogenic effects on arterial venous and lymphatic vessels (Soomro et al., 2010). In xenografted mice models, artenimol derivatives were shown to reduce tumour size and tumour vascularisation. The multifaceted nature of the action of artenimol derivatives includes protein alkylation, induction of apoptosis, angiogenesis inhibition, oxidative stress and cell cycle regulation (Efferth 2007). At the moment, several published and unpublished case reports and one clinical study prove the tumour-inhibiting activity of artesunate in human cancer. In the world of parasites, artemisinins are active against some blood flukes, the cause of schistosomiasis. The details will be discussed below.

Interestingly, the bioactivity of artemisinin and its semisynthetic derivative artesunate is even broader and includes the inhibition of certain viruses, such as human cytomegalovirus and other members of the Herpesviridae family (e.g., herpes simplex virus type 1 and Epstein-Barr virus), hepatitis B virus, hepatitis C virus, and bovine viral diarrhoea virus (Efferth et al., 2008).

5. Artenimol-based combination drugs for parasitic diseases

The theory behind ACTs is the following: A population of malaria parasites may contain a low number of parasites that is resistant to the drug used to kill them. These resistant parasites can survive and eventually contribute to the spreading of the disease with drug resistant parasites. Even if such a process is slow to develop a real risk, after some years this resistance could have become a clinical reality. If, however, the same population of parasites is treated at the same time with another drug having a totally different mode of action, resistance to this drug could also develop in the same sense as described for the first drug. But the risk that resistant parasites will develop at the same time against two active drugs is very small. In fact, it may be so small that from a practical point of view such resistance does not develop. The ideal combination would consist of two drugs with a different mechanism of action and with more or less similar pharmacokinetic behaviour so that the parasites are exposed for an almost identical period of time to the same drug. Although this theory is attractive, finding such a combination is not easy. In the case of artesunate and artemether, the apparent elimination half-life is about one hour, meaning that after 4 hours almost the full dose given is eliminated from the body. Most of the partner drugs selected for ACTs have a reasonably long elimination half-life. Mefloquine has a mean elimination half-life of 2 to 4 weeks, lumefantrine 3-6 days and amodiaquine, 5.2 ± 1.7 minutes, but its major metabolite has a long elimination half-life. Sulfadoxine-pyrimethamine (SP) has a long but variable elimination half-life ranging from 40 to a few hundred hours. In contrast sulfamethoxypyrazine, an alternative to sulfadoxine has a rather stable elimination half-life of 65 hours and a low protein binding property affecting the dosage possibilities. In the fixed dose combination Co-Arinate^{R} (Dafra Pharma) the sulfonamide drug sulfalene (sulfamethoxypyrazine), with a rather constant elimination half-life of 65 hours to 85 hours, is combined with pyrimethamine (which has an elimination half-life of 100 hours) and built into a single tablet with artesunate. In spite of the elimination half-life limitation for all ACTs, the various partner drugs are most efficacious when used in combination with artemether or artesunate.

6. Role of artesunate with Fansidar^{R} and artesunate with Metakelfin^{R}: for malaria, for infectious diseases

In the late 1960s, new long-acting sulfonamides were being developed. Sulfadoxine was set to replace sulfadimethoxine (Madribon, Roche) as an antimicrobial agent but it was never introduced for reasons of relative toxicity and a wide variation in elimination half-life (varying from 40 to 400h). The combination in an FDC tablet with pyrimethamine offered new possibilities. Roche successively introduced this combination as Fansidar^{R} in nearly every malaria endemic country, where it became very popular for both curative and prophylactic use. Sulfamethoxypyrazine was the result of one of the first in-depth efforts in the field of structure activity to make a better or optimal molecule based on physicochemical data. The resulting molecule completely fulfilled the theoretical expectations: a long

elimination half-life (65-85h), highly soluble in water and a relatively low protein binding (about 60%). Such a molecule would have the property of penetrating all body fluids in adequate concentrations, which was not the case for sulfadoxine. Sulfamethoxypyrazine was successfully introduced in most European countries. The FDC combination with pyrimethamine under the brand name Metakelfin^R was introduced in Africa in the early 1970s. It is still available as a registered European drug in Italy, the licence being held by Pfizer. It was marketed only in a limited number of African countries.

7. Rationale for artenimol and derivatives in the treatment of schistosomiasis

The *in vitro* and *in vivo* evidence that artemether has an effect on *Schistosoma* parasites came from Xiao and Catto in 1989. They showed that the artemisinin related compound is particularly active against the juvenile, 2- to 3- week old, parasites (Xiao and Catto., 1989). Their work was later confirmed in a limited number of *in vivo* and *in vitro* studies conducted on *Schistosoma* species with more artemisinin derivatives (Xiao et al., 2006; Utzinger et al., 2001; Utzinger et al., 2007). Whereas praziquantel showed highest efficacy against adult parasites, artemether and artesunate were found to be more effective against juvenile forms. This might have an impact on the fact that artemether prevents young forms from developing into adult worms of egg-laying capacity. It was speculated that a sequential therapy of artemether and praziquantel could be useful since they address both populations. Moreover, patients usually carry both populations of parasites in high endemic areas. Unfortunately in the experimental studies, high doses of artemether were given to see appropriate effects. Doses of 200 mg/kg are not realistic and cannot be applied to human beings. The meaning of the results obtained is therefore of limited value. Malaria parasites are killed with doses of 2 mg per kg per day for 5 consecutive days in monotherapy; in combination therapies, about 4 mg per kg per day for just 3 days is sufficient.

How does artemisinin affect the *Schistosoma*s parasite? Scanning electron microscopy showed that the tegumentum of the parasites was damaged by the schistosomula and this effect lasts a few days. However, the intimate mechanism is not known. The mechanism of action on *Schistosoma* parasites should be compared to the Chinese study in which the researchers used electron microscopy to detect the damage caused by a single oral dose of artesunate in plasmodia causing progressive destruction of membrane systems as explained above (Ellis et al., 1985).

Clinical possibilities were studied with artenimol derivatives against *S. japonicum*. The studies confirmed the theoretical possibility of using these substances as drugs, including as prophylactic drugs. No difference was seen between artemether and artesunate. This is somewhat surprising since not all properties are shared by those compounds. Artemether requires a liver enzyme for its transformation into DHA whereas artesunate will spontaneously generate DHA under the influence of non-specific esterases from the blood. Artesunate and artemether are no longer to be used for the treatment of malaria in monotherapies for fear of malaria parasites developing resistance. Artemisinin-based combinations therapies (ACTs) have replaced the former. The duration of treatment with ACTs is now restricted to 48 hours (sometimes to 72 hours) and the daily dose is increased (doubled) to about 4 mg per kg body weight. In addition, it might be speculated that the ACT partner drug also plays a role in the process of killing the *Schistosoma*s. This is of particular importance in areas where both diseases are endemic. It is most likely that patients carrying *Schistosoma* parasites will be treated with an ACT for acute malaria, sometimes several times per year, with a resulting impact on *Schistosoma* carriage too.

8. Clinical efficacy of artesunate and Fansidar^{R} for *Schistosomiasis haematobium*

New drugs are only meaningful if clinical proof of efficacy can be established. There are few known studies from Africa that investigate the effect of either artesunate or artemether on any of the *Schistosoma* species. Promising results were obtained but the WHO ban on these drugs for malaria monotherapy jeopardised further work. In 2007 two interesting papers were published. The first publication by Boulanger et al., 2007 studied the effect of the ACT artesunate-SP co-blister in *S. haematobium* in children under 6 years old. The children were treated for malaria but they had *S. haematobium* infections at the same time. The results were impressive: Twenty-seven children who entered a clinical trial of antimalaria treatment were excreting *S. haematobium* eggs in their urine on the first day of treatment. Fifteen children received a combination of a single dose of sulfadoxine-pyrimethamine together with three daily doses of artesunate (4 mg/kg); the remaining 12 children received three daily doses of amodiaquine and artesunate. The overall cure rate and reduction in the mean number of excreted eggs at 28 days post treatment were 92.6% and 94.5%, respectively. The authors concluded that "Our findings indicate that artesunate, in addition to being a very effective treatment for uncomplicated malaria, can also sharply reduce the *S. haematobium* loads harboured by pre-school African children".

The publication by Adam et al., 2008 almost coincided with the one published by Boulanger and colleagues. In a small study in eastern Sudan, the effects of the treatment of uncomplicated, *Plasmodium falciparum* malaria with artesunate–sulfamethoxypyrazine–pyrimethamine (AS+SMP) and artemether–lumefantrine (AT+LU) on co-infections with *Schistosoma mansoni* were investigated. Faecal samples from 14 of the 306 patients screened on presentation, at the start of a clinical trial of antimalarial treatment, were found to contain *Schistosoma mansoni* eggs. For the treatment of their malaria, the 14 egg-positive cases, who were aged 6–40 years (mean 13.7 years), were each subsequently treated with three tablets of a fixed combination of AS+SMP, with a 12h- (six patients) or 24h-interval (five patients) between each tablet, or with six doses of AT+LU given over 3 days. When checked 28 and 29 days after the initiation of treatment, all 14 patients were found stool-negative for *Schistosoma* eggs. These results indicate that AS+SMP and AT+LU are apparently very effective treatments not only for uncomplicated, *P. falciparum* malaria but also for *S. mansoni* infections.

9. Clinical efficacy of artesunate and Metakelfin^{R} (Co-Arinate^{R}) in the treatment of *Schistosomiasis haematobium* in schoolchildren in Mali

The observations described above led to a multicentre study in which a large population of schoolchildren infected with *S. haematobium* was studied (Sissoko et al., 2009). The objective was to determine the efficacy of the antimalarial artemisinin-based FDC combination therapy artesunate-sulfamethoxypyrazine-pyrimethamine (AS+SMP), administered in doses used for malaria, to treat *Schistosoma haematobium* in school-aged children. The study was conducted in Djalakorodji, a peri-urban area of Bamako, Mali, using a double-blind setup in which AS+SMP was compared with praziquantel (PZQ). Urine samples were examined for *Schistosoma haematobium* on days -1, 0, 28 and 29. Detection of haematuria, and haematological and biochemical exams were conducted on day 0 and day 28. Clinical exams were performed on days 0, 1, 2 and 28. A total of 800 children were included in the trial. The cure rate obtained without viability testing was 43.9% in the AS+SMP group versus 53% in

the PZQ group (Chi2 = 6.44, p = 0.011). Egg reduction rates were 95.6% with PZQ in comparison with 92.8% with AS+SMP (p = 0.096). The proportion of participants who experienced adverse events related to the medication was 0.5% (2/400) in AS+SMP treated children compared to 2.3% (9/399) in the PZQ group (p = 0.033). Abdominal pain and vomiting were the most frequent adverse events in both treatment arms. All adverse events were categorised as mild. The study demonstrates that PZQ was more effective than AS+SMP for treating *Schistosoma haematobium*. However, the safety and tolerability profile of AS+SMP was similar to that seen with PZQ. The authors conclude that their findings warrant further investigations to determine the dose/efficacy/safety pattern of AS+SMP in the treatment of *Schistosoma* infections.

10. Clinical efficacy of Co-Arinate^{R} on *Schistosomiasis mansoni* in schoolchildren in Kenya

An open-label randomised trial in Rarieda district of western Kenya was conducted with primary investigator Dr C. Obonyo. Schoolchildren (aged 6–15 years) who had *Schistosoma mansoni* infection were enrolled. Children were assigned to receive artesunate (100 mg) with sulfalene (also known as sulfamethoxypyrazine; 250 mg) plus pyrimethamine (12.5 mg) as one dose every 24 h for 3 days (administered as Co-Arinate^{R} tablets) or one dose of praziquantel (40 mg/kg per day). The primary efficacy endpoint was the number of participants cured 28 days after treatment. Between October and December, 2009, 212 children were enrolled and assigned to receive artesunate with sulfalene plus pyrimethamine (n = 106) or praziquantel (n = 106). Sixty-nine patients (65%) were cured in the praziquantel treatment group compared with 15 (14%) in the artesunate with sulfalene plus pyrimethamine treatment group (p<0·0001). Adverse events were less common in patients taking artesunate with sulfalene plus pyrimethamine than in those taking praziquantel (22% [n = 23] vs 49% [n = 52], p<0·0001), but no drug-related serious adverse events occurred. The standard treatment with praziquantel is more effective than artesunate with sulfalene plus pyrimethamine in the treatment of children with *S. mansoni* infection in western Kenya (Obonyo et al.,2010).

The results or cure rate in the artesunate-sulfamethoxypyrazine-pyrimethamine group in the two studies above contrast strongly (43.9% versus 14%). Many questions could be raised, in particular about dosage scheme. Whereas Sissoko and colleagues gave the drug as a single dose (as is the case with praziquantel), Dr Obonyo spread the dosing over 48 hours (nearly 3 days). Is the dosing schedule determinant for the contrast in cure rate? Is it the difference in *Schistosoma* species? But why then the excellent results in the study by Adam et al. and in the study by Boulanger et al.? To address this question, a limited additional study described below was conducted by Obonyo and published as an abstract at ASTMH, 2010. Seventy-three children were randomised, receiving either praziquantel 40 mg per kg as a single dose or artesunate-sulfamethoxypyrazine-pyrimethamine in a single dose of 12 mg per kg body weight for artesunate. Cure and egg rate reduction were determined 28 days after treatment. Overall, 25 children (74%) were cured in the praziquantel group compared with 25 (64%) in the AS+SMP group (p = 0.4). Egg reduction rate was comparable (83% vs 96% p = 0.34) after praziquantel and AS+SMP respectively. Adverse events were significantly fewer among AS+SMP recipients (10% versus 29%, p = 0.038) and there were no drug-related serious adverse events. The authors conclude from their second study that there is no difference in response between the two drugs. Unfortunately, overall cure rates remain below expectations since praziquantel has only a 75% cure rate.

In conclusion, it appears that some ACT drugs can be used for the treatment of schistosomiasis, either caused by *haematobium* or *mansoni* species. Dosing schemes seem to be important. Also, it ought to be investigated whether repeated dosing has an additional beneficial impact on the elimination of the parasites. A question not answered in this discussion is the geography of the events. Mali is thousands of miles away from the borders of Lake Victoria in Kenya. Are there different populations with variable sensitivity?

11. Discussion and conclusions

The few clinical studies point to the additional beneficial effect of malaria treatment, administered as an ACT in fixed-dose combination in a population prone to the frequent occurrence of both malaria and schistosomiasis. It remains to be seen whether the broad-scale use of the ACTs will spontaneously impact on the incidence of schistosomiasis. Will this effect be seen with all currently existing ACTs? The following combinations are commonly being used: artesunate in an FDC with amodiaquine: artesunate in a co-blister with SP tablets: and Artemether – lumefantrine FDC tablets:. The last combination is the most widely used product since it is heavily supported by the actions of the Global Fund for the elimination of malaria in Africa. Artesunate with amodiaquine is less popular and causes more side effects, specifically due to amodiaquine. The co-blister with artesunate tablets and SP tablets has now become obsolete and its use is very restricted. This is the current situation in Africa. The FDC Co-Arinate^{R} where the partner drug is sulfamethoxypyrazine with pyrimethamine is most popular in the non-governmental distribution chains.

The variability of the results of ACTs on schistomiasis cure rate is somewhat puzzling. Apparently the dosing scheme has a drastic effect on the treatment outcome because in the limited additional study by Obonyo et al. it could be demonstrated that *S. mansoni* was properly killed when the same dosing regimen as that of Sissoko was followed. At this moment, a large study to confirm these finding is in preparation.

Where do we go from here? From an epidemiological point of view, the following question is raised: Will broad scale malaria treatment with ACTs impact on the incidence and morbidity of schistosomiasis? Time will tell, but additional properly conducted studies ought to be set up to investigate the possibility of further refining treatment regimens with ACTs. If resistance to praziquantel continues to increase, Africa will face a serious new medical problem. The recently published studies do not provide any guarantee of decent efficacy for praziquantel. The fact that this is not the case - as expressed in the studies by Sissoko and Obonyo in which the average resistance to praziquantel is about 35% - is worrying. ACTs as such are not the perfect answer either, but they have some impact. Their optimised dosing scheme could well become a true alternative to the standard drug. In additional, sequential therapy with praziquantel ought to be envisaged.

12. References

Adam I., Elhardello O.A., Elhadi M.O., Abdalla E., Elmardi K.A., Jansen F.H. The anti*Schistosomal* efficacies of artesunate-sulfamethoxypyrazine-pyrimethamine and artemether-lumefantrine administered as treatment for uncomplicated, Plasmodium falciparum malaria. Annals of Tropical Medicine and Parasitology, 2008.

Angelucci F, Basso A, Bellelli A, Brunori M, Pica ML, Valle C. The anti-*Schistosomal* drug praziquantel is an adenosine antagonist. Parasitology 2007 Aug;134(Pt 9):1215-21.

Boulanger D, Dieng Y, Cisse B, Remoue F, Capuano F, Dieme JL, et al., Anti*Schistosomal* efficacy of artesunate combination therapies administered as curative treatments for malaria attacks. Trans R Soc Trop Med Hyg 2007 Feb;101(2):113-6.

Chen DJ, Fu LF, Shao PP, Wu FZ, Fan CZ, Shu H, Ren CS, Sheng XL Studies on anti*Schistosomal* activity of qinghaosu in experimental therapy. Zhong Hui Yi Xue Zha Zhi, 1980, 80 422-428.

Doenhoff MJ, Cioli D, Utzinger J. Praziquantel: mechanisms of action, resistance and new derivatives for schistosomiasis. Curr Opin Infect Dis 2008 Dec;21(6):659-67.

Eckstein-Ludwig U, Webb RJ, Van G, I, East JM, Lee AG, Kimura M, O'Neill,P.M.; Bray,P.G.; Ward,S.A.; Krishna,S. Artemisinins target the SERCA of Plasmodium falciparum. Nature 2003 Aug 21;424(6951):957-61.

Efferth T, Dunstan H, Sauerbrey A, Miyachi H, Chitambar CR. The anti-malarial artesunate is also active against cancer. Int.J.Oncol. 18[4], 767-773. 2001.

Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJ, Marschall M. The antiviral activities of artemisinin and artesunate. Clin Infect Dis 2008 Sep 15;47(6):804-11.

Efferth T. Willmar Schwabe Award 2006: antiplasmodial and antitumor activity of artemisinin--from bench to bedside. Planta Med 2007 Apr;73(4):299-309.

Ellis DS, Li ZL, Gu HM, Peters W, Robinson BL, Tovey G, et al., The chemotherapy of roden malaria, XXXIX. Ultrastructural changes following treatment with artemisinine of Plasmodium berghei infection in mice, with observations of the localisation of [3H]-dihydroartemisinine in P. falciparum in vitro. Ann Trop Med Parasitol 1985 Aug;79(4):367-74.

Fallon PG, Sturrock RF, Niang AC, Doenhoff MJ. Short report: diminished susceptibility to praziquantel in a Senegal isolate of *Schistosoma* mansoni. Am J Trop Med Hyg 1995 Jul;53(1):61-2.

Fischer-Betz R, Schneider M. [Antimalarials. A treatment option for every lupus patient!?]. Z Rheumatol 2009 Sep;68(7):584, 586-4, 590.

Gryseels B, Mbaye A, de Vlas SJ, Stelma FF, Guisse F, Van LL, et al., Are poor responses to praziquantel for the treatment of *Schistosoma* mansoni infections in Senegal due to resistance? An overview of the evidence. Trop Med Int Health 2001 Nov;6(11): 864-73.

Hotez PJ, Molyneux DH. Tropical anemia: one of Africa's great killers and a rationale for linking malaria and neglected tropical disease control to achieve a common goal. PLoS Negl Trop Dis 2008;2(7):e270.

Ismail M, Metwally A, Farghaly A, Bruce J, Tao LF, Bennett JL. Characterisation of isolates of *Schistosoma* mansoni from Egyptian villagers that tolerate high doses of praziquantel. Am J Trop Med Hyg 1996 Aug;55(2):214-8.

Ismail MM, Taha SA, Farghaly AM, el-Azony AS. Laboratory induced resistance to praziquantel in experimental schistosomiasis. J Egypt Soc Parasitol 1994 Dec;24(3):685-95.

Jansen FH, Soomro SA. Chemical instability determines the biological action of the artemisinins. Curr Med Chem 2007;14(30):3243-59.

Le WJ, You JQ, Yang YQ, Mei Jy, Guo HF, Yang HZ, Zhnag CW. Studies on the efficacy of arthemether in experimental schistosomiasis. 1982 Acta Pharm Sin 17: 187-193.

Lin AJ, Lee M, Klayman DL. Antimalarial activity of new water-soluble dihydroartemisinin derivatives. 2. Stereospecificity of the ether side chain. J Med Chem 1989 Jun;32(6):1249-52.

Matthaiou DK, Panos G, Adamidi ES, Falagas ME (2008). "Albendazole versus Praziquantel in the Treatment of Neurocysticercosis: A Meta-analysis of Comparative Trials". PLoS Negl Trop Dis 2 (3): e194. doi: 10.1371/journal.pntd.0000194. PMC 2265431. PMID 18335068. http://www.plosntds.org/article/info:doi/10.1371/journal.pntd.0000194.

Obonyo CO, Muok EM, Mwinzi PN. Efficacy of artesunate with sulfalene plus pyrimethamine versus praziquantel for treatment of Schistosoma mansoni in Kenyan children: an open-label randomised controlled trial. Lancet Infect.Dis. DOI:10.1016/S1473-3099(10)70161-4. 2010.

Obonyo C.O., Muok E.M., Mwinzi P.N. Efficacy of a single dose of artesunate plus sulfamethoxypyrazine/pyrimethamine versus praziquantel for treatment of *Schistosoma* mansoni in Kenyan children Abstract ASTMH, 2010

Shen C, Kim J, Lee JK, et al., (June 2007). "Collection of Clonorchis sinensis adult worms from infected humans after praziquantel treatment". Korean J. Parasitol. 45 (2): 149–52. doi:10.3347/kjp.2007.45.2.149. PMC 2526309. PMID 17570980.

Sissoko MS, Dabo A, Traore H, Diallo M, Traore B, Konate D, et al., Efficacy of artesunate + sulfamethoxypyrazine/pyrimethamine versus praziquantel in the treatment of Schistosoma haematobium in children. PLoS ONE 2009;4(10):e6732.

Soomro SA, Konkimalla VB, Langenberg T, Mahringer A, Horwedel C, Holenya P, et al., Design of novel artemisinin-like derivates with cytotoxic and anti-angiogenesis properties. Journal of Cellular and Molecular Medicine 2010.

Stelma FF, Talla I, Sow S, Kongs A, Niang M, Polman K, et al., Efficacy and side effects of praziquantel in an epidemic focus of *Schistosoma* mansoni. Am J Trop Med Hyg 1995 Aug;53(2):167-70.

Tchuenté LA, Shaw DJ, Polla L, Cioli D, Vercruysse J (December 2004). "Efficacy of praziquantel against *Schistosoma* haematobium infection in children". Am. J. Trop. Med. Hyg. 71 (6): 778–82. PMID 15642971.

http://www.cartercenter. org/health/schistosomiasis/index.html The Carter Center Schistosomiasis Control Program',

"Intestinal Flukes: Treatment & Medication". http://emedicine.medscape.com/article/219662-treatment.

Utzinger J, Chollet J, You J, Mei J, Tanner M, et al., (2001) Effect of combined treatment with praziquantel and artemether on *Schistosoma* japonicum and *Schistosoma* mansoni in experimentally infected animals - Acta Trop 1; 80(1): 9–18.

Utzinger J, Chollet J, You J, Mei J, Tanner M, Xiao S. Effect of combined treatment with praziquantel and artemether on *Schistosoma* japonicum and *Schistosoma* mansoni in experimentally infected animals. Acta Trop 2001 Sep 1;80(1):9-18.

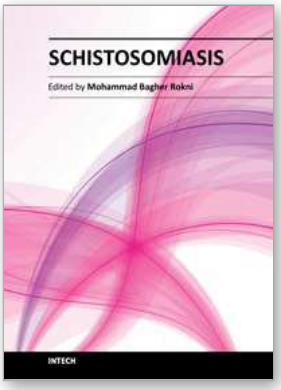
Utzinger J, Keiser J, Shuhua X, Tanner M, Singer BH. Combination chemotherapy of schistosomiasis in laboratory studies and clinical trials. Antimicrob Agents Chemother 2003 May;47(5):1487-95.

Utzinger J, Xiao SH, Tanner M, Keiser J (2007) Artemisinins for schistosomiasis and beyond. Curr Opin Invest Drugs 2007 8(2): 105–116.

Xiao SH, Catto BA (1989) In vitro and in vivo studies of the effect of artemether on *Schistosoma* mansoni. Antimicrob Agents Chemother 33: 1557–62.

Xiao SH, Utzinger J, Chollet J, Tanner M (2006) Effect of artemether administered alone or in combination with praziquantel to mice infected with Plasmodium berghei or *Schistosoma* mansoni or both. – Int J Parasitol 36(8): 957–64.

Xiao S, Yang Y, You Q, Utzinger J, Guo H, Peiying J, et al., Potential long-term toxicity of repeated orally administered doses of artemether in rats. Am J Trop Med Hyg 2002 Jan;66(1):30-4.



Schistosomiasis

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In the wake of the invitation by InTech, this book was written by a number of prominent researchers in the field. It is set to present a compendium of all necessary and up-to-date data to all who are interested. Schistosomiasis or blood fluke disease, also known as Bilharziasis, is a parasitic disease caused by helminths from a genus of trematodes entitled Schistosoma. It is a snail-borne trematode infection. The disease is among the Neglected Tropical Diseases, catalogued by the Global Plan to combat Neglected Tropical Diseases, 2008-2015 and is considered by the World Health Organization (WHO) to be the second most socioeconomically devastating parasitic disease, next to malaria. WHO demonstrates that schistosomiasis affects at least 200 million people worldwide, more than 700 million people live in endemic areas, and more than 200.000 deaths are reported annually. It leads to the loss of about 4.5 million disability-adjusted life years (DALYs).

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