



REVIEW ON ARAKODA (TAFENOQUINE) & ITS APPROACH AS AN ANTI-MALARIAL AGENT

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Article Received on 10/02/2020

Article Revised on 01/03/2020

Article Accepted on 21/03/2020

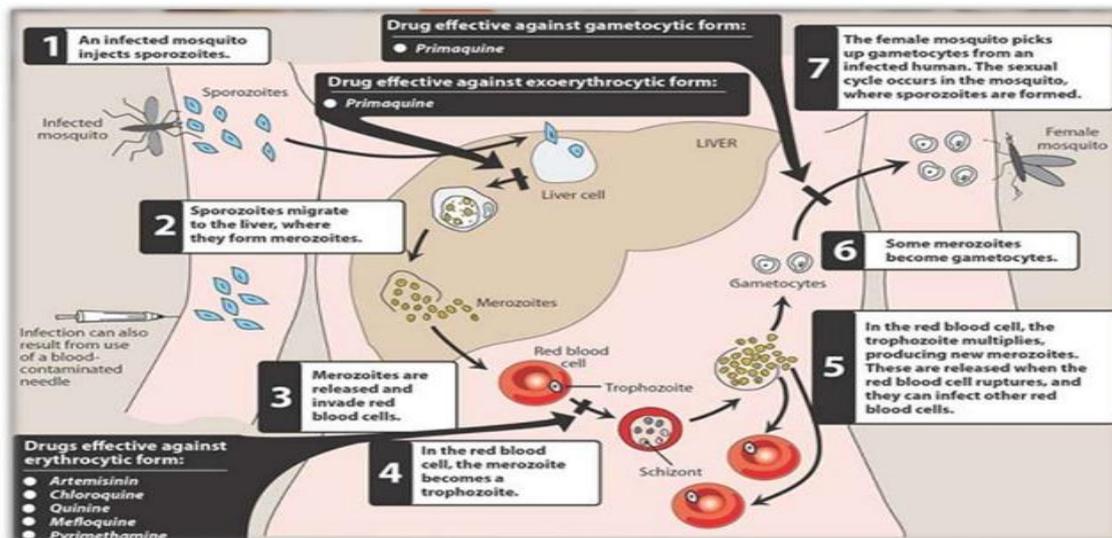
ABSTRACT

Tafenoquine is an analogue of primaquine with an improved therapeutic and safety profile. It has a long half-life and activity against liver-stage malaria parasites, so may be useful for chemoprophylaxis. Antimalarial agents are drugs used for the treatment or prophylaxis of malaria. Malaria is caused by four species of Plasmodium, such as Plasmodium falciparum, P. malariae, P. ovale, and P. vivax. ARAKODA contains tafenoquine succinate, an antimalarial agent for oral administration. The molecular formula of tafenoquine succinate is **C₂₄H₂₈F₃N₃O₃·C₄H₆O₄** and its molecular weight is 581.6 as the succinate salt. It is given in prophylaxis of malaria patient aged 18 years older. Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of Plasmodium species. G6PD test is performed before giving the drug. Analytical studies were on NMR, IR, MS, HPLC, Flourimetry analysis. In vitro studies have shown that tafenoquine presents an average 50% inhibitory concentration of 0.436 mcg against blood stages of seven strains of *P. falciparum*. The long-acting 8-aminoquinoline tafenoquine (TQ) coadministered with chloroquine (CQ) may radically cure *Plasmodium vivax* malaria. Coadministration therapy was evaluated for a pharmacokinetic interaction and for pharmacodynamic, safety and tolerability characteristics. Volume of distribution. The activation of tafenoquine needs the activity of CYP 2D6 liver microsomal enzyme. Routes of elimination is through feces.

KEYWORDS: TQ, PQ, plasmodium vivax, p.falciparum, tafenoquine, G6PD, Arakoda, 5,6 ortho-qunine, CYP 2D6, Mefloquine.

INTRODUCTION

- Tafenoquine (TQ) is an 8-aminoquinoline derivative that had just received approval by the US Food and Drug Administration (FDA, July 2018) and the Australian Therapeutic Goods Administration (TGA, September 2018) for a radical cure of *Plasmodium vivax* malaria (US/Australia brand name Krintafel/Kozenis, developed by Glaxo Smith Kline [GSK, London, UK]) together with Medicines for Malaria Venture (MMV, Geneva, Switzerland) and for prophylaxis of malaria (US/Australia brand name Arakoda/Kodatef, developed by 60 Degrees Pharmaceuticals (Washington DC, USA) together with the US Army).^[1]
- TQ passed more than four decades of development as an antimalarial drug, and was initially under investigation as a prophylactic antimalarial agent for preventing *Plasmodium falciparum* malaria but without final submission of the dossier for market authorization.^[1,4]
- TQ is a long-acting PQ analog active against both blood and liver stages of *P. vivax* biological half-life for long 15 days.^[4,5]
- Antimalarial agents are drugs used for the treatment or prophylaxis of malaria. Malaria is caused by four species of Plasmodium, such as Plasmodium falciparum, P. malariae, P. ovale, and P. vivax.^[13]
- Three of which produces the mild forms of malaria by destroying red blood cells in peripheral capillaries and thus, causing anaemia. The bouts of fever correspond to the reproductive cycle of the parasite.^[13]
- The most dangerous is the *P. falciparum*. In this case, the infected red blood cells become sticky and form lumps in the capillaries of the deep organs of the body and cause microcirculatory arrest. This disease still affects about 200 millions people and causes at least 2 million deaths per year.

LIFE CYCLE OF PLASMODIUM VIVAX^[5]

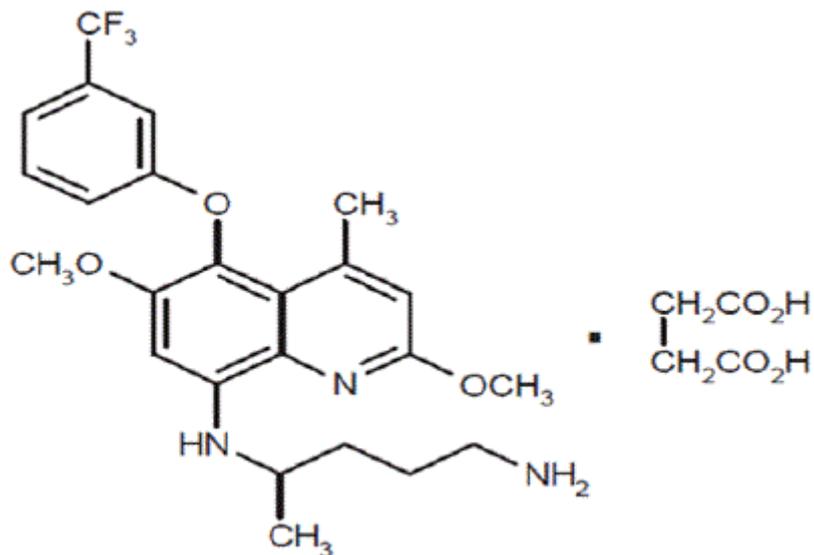
(Life cycle of Malarial Parasite)

ARAKODA:- contains tafenoquine succinate, an antimalarial agent for oral administration. The structural formula of tafenoquine succinate is a synthetic analogue of primaquine.^[5]

The chemical name of tafenoquine succinate is (\pm)-8-[(4-amino-1-methylbutyl) amino]-2,6-dimethoxy-4-methyl-5-[3-(trifluoromethyl) phenoxy]quinoline succinate. The

molecular formula of tafenoquine succinate is **C₂₄H₂₈F₃N₃O₃·C₄H₆O₄** and its molecular weight is 581.6 as the succinate salt.^[5]

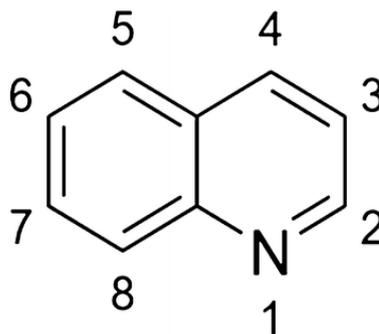
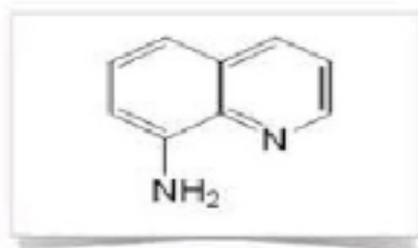
tafenoquine is an 8-aminoquinoline antimalarial drug indicated for the prophylaxis of malaria in patients aged 18 years and older.^[5]



(Structure of Tafenoquine)

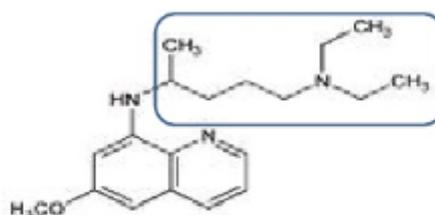
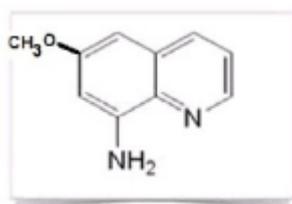
SAR(structure activity relationship)^[14]

1. 8-aminoquinolines• Drugs in this group have amino group at position 8 of quinoline ring• Important members of this family include 1- Pamaquine 2- Primaquine, Tafenoquine etc.



2. Such drugs have OCH₃ group at position 6. This molecule has antimalarial activity but when side chain is introduced at amino group antimalarial

activity is intensified e.g pamaquine• It causes hemolysis of RBCs Diethyl amino pentyl side chain.



Diethyl amino pentyl side chain

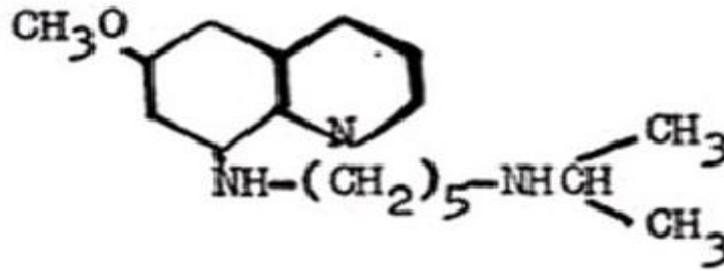
3. It contains tertiary amino group and when it is converted into primary amino group the compound is called primaquine, which is – Less toxic – Well

tolerated – It is the most commonly used agent in this group in the treatment of malaria.



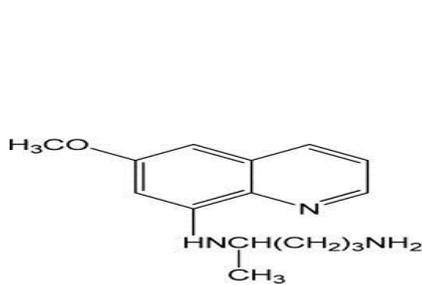
4. OCH₃ is not necessary for antimalarial activity but when replaced by OC₂H₅ the compound became – less active – Toxic in nature• OCH₃ when replaced by CH₃ the compound become inactive• Introduction of halogens increases toxicity• Presence of quinoline ring is necessary for antimalarial activity. When pyridine ring is converted to piperidine (saturated) the compound became inactive.

5. Pentyl side chain gives maximum activity, increase or decrease of chain result is reduction of activity• The branched side chain when converted into straight chain pentaquine is obtained• It has less antimalarial activity as compared to both pamaquine and primaquine.

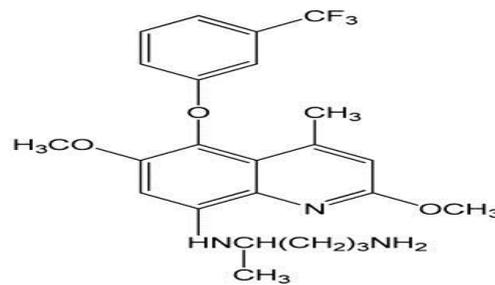


6. Primaquine, primaquine, and tafenoquine are antimalarial drugs that belong to a family named 8-aminoquinolines. Tafenoquine retains all of the core

structure of PQ, but contains additional ring substitutions including a 4-methyl group.



Primaquine



Tafenoquine

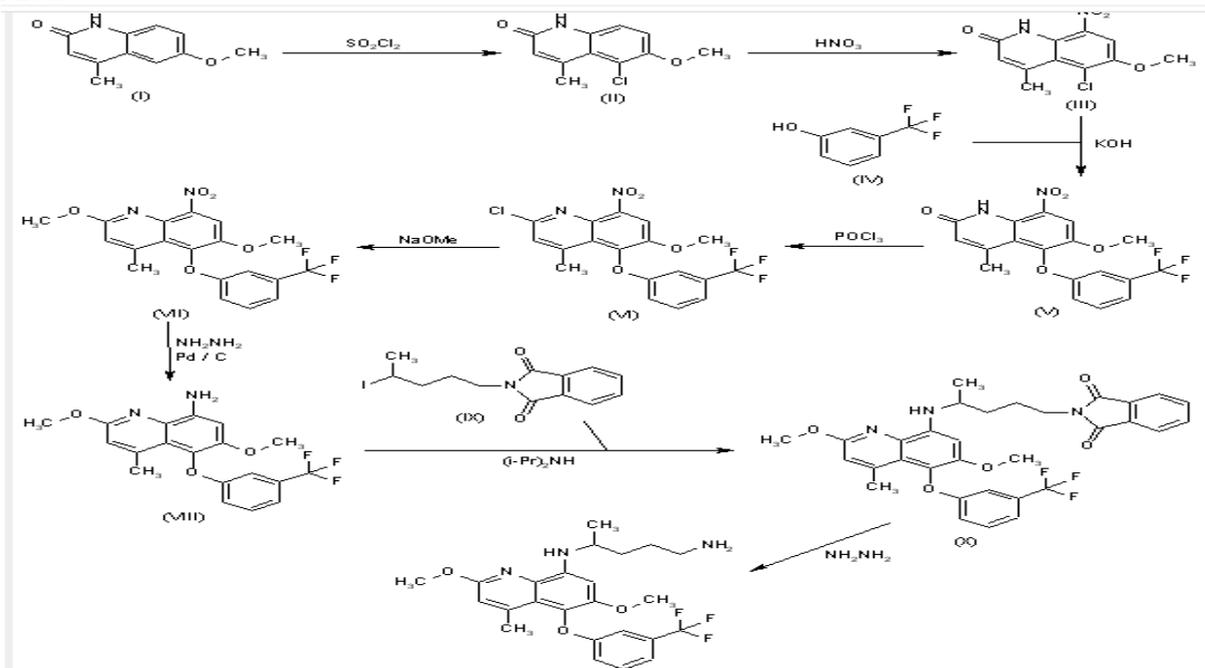
MOA^[2]

The mechanism of action of tafenoquine is not well established but studies have reported a longer and more effective action when compared to primaquine.^[1] The active moiety of tafenoquine, 5,6 ortho quinone tafenoquine, seems to be redox cycled by *P. falciparum* which are upregulated in gametocytes and liver stages. Once inside, the oxidated metabolite

produces hydrogen peroxide and hydroxyl radicals. It is thought that these radicals produce leads to the parasite death.^[2]

On the other hand, tafenoquine inhibits heme polymerase in blood stage of parasites which explains the activity against blood stages of parasites.

Synthesis



Chlorination of 6-methoxy-4-methylquinolin-2(1H)-one (I) with SO_2Cl_2 in hot acetic acid gives the 5-chloro derivative (II), which is nitrated with HNO_3 in H_2SO_4 to yield the 8-nitroquinolinone (III). Condensation of compound (III) with 3-(trifluoromethyl)phenol (IV) by means of KOH in NMP provides the diaryl ether (V), which is treated with refluxing POCl_3 to afford the 2-chloroquinoline (VI).^[10]

Reaction of compound (VI) with MeONa in refluxing methanol results in the 2,6-dimethoxyquinoline derivative (VII), which is reduced with hydrazine over Pd/C to give the 8-aminoquinoline derivative (VIII). Condensation of aminoquinoline (VIII) with *N*-(4-iodopentyl)phthalimide (IX) by means of diisopropylamine in hot NMP yields the phthalimido precursor (X), which is finally cleaved with hydrazine in refluxing ethanol gives tafenoquine.^[10]

MATERIALS AND METHODS

• MTD rat study

With the goal of identifying the maximum tolerated dose, groups of 5 male and 5 female Sprague Dawley (SD) rats were administered a single oral dose of 0 (vehicle), 125, 250, 400 or 700 mg/kg tafenoquine succinate (dose expressed as free base) in 1%/0.4% methylcellulose/Tween 80 in water, at a dose volume of 10 mL/kg [Note the 400 mg/kg dose group was administered an actual dose of 506 mg/kg due to a higher concentration dose formulation being prepared whereas all other groups were within 12% of nominal dose].^[11]

The day of dosing was designated Day 1. Animals were observed for 7 days following dosing. Animal viability checks and physical observations were made daily, body weights were recorded pre-dose and twice during the study, and clinical pathology parameters were assessed on Day 7. Following Day 7 assessments animals were euthanized with out further examination, although any animals dying earlier than the scheduled end of study were grossly examined at necropsy. The dose formulation for each group was analyzed to confirm the absence (control) or actual concentration of tafenoquine.

Antimicrobial activity

Tafenoquine is active against pre-erythrocytic (liver) and erythrocytic (asexual) forms as well as gametocytes of *Plasmodium* species that include *P. falciparum* and *P. vivax*. The activity of tafenoquine against the pre-erythrocytic liver stages of the parasite, prevents the development of the erythrocytic forms of the parasite. Method of agar dilution was performed to study the antimicrobial activity as formerly described.^[2] All compounds were dissolved in dimethyl sulfoxide (DMSO), and were separately mixed with 1 mL of Mueller Hinton (MH) broth. Then, the final concentrations of 32-256 $\mu\text{g/mL}$ were carried out by transferring the mixture to the MH agar, and the negative control was MH broth. The cell concentration of microbes used in this study was adjusted to 10^8 cells/mL in 0.9% normal saline after the microbes were cultured at 37 °C for 24 h in the MH broth. The inhibitions of microbial growth were detected in each compound following the inoculation onto the MH agar, and incubation at 37 °C for 24 h. Twenty-four bacteria and two yeasts were tested as listed in Table.^[15]

Groups of microbes	Microbial strains
Yeasts	<i>Candida albicans</i> ATCC 90028 <i>Saccharomyces cerevisiae</i> ATCC 2601
Gram-positive bacteria	<i>Bacillus cereus</i> <i>Listeria monocytogenes</i> <i>Corynebacterium diphtheriae</i> NCTC 10356 <i>Micrococcus luteus</i> ATCC 10240 <i>Bacillus subtilis</i> ATCC 6633 <i>Staphylococcus epidermidis</i> ATCC 12228 <i>Enterococcus faecalis</i> ATCC 33186 <i>Enterococcus faecalis</i> ATCC 29212 <i>Staphylococcus aureus</i> ATCC 29213 <i>Staphylococcus aureus</i> ATCC 25923
Gram-negative bacteria	<i>Aeromonas hydrophila</i> <i>Morganella morganii</i> <i>Plesiomonas shigelloides</i> <i>Citrobacter freundii</i> <i>Shigella dysenteriae</i> <i>Salmonella enteritidis</i> <i>Achromobacter xylosoxidans</i> ATCC 2706 <i>Pseudomonas stutzeri</i> ATCC 17587 <i>Shewanella putrefaciens</i> ATCC 8071 <i>Pseudomonas aeruginosa</i> ATCC 15442 <i>Salmonella typhimurium</i> ATCC 13311 <i>Klebsiella pneumoniae</i> ATCC 700603 <i>Escherichia coli</i> ATCC 25922 <i>Serratia marcescens</i> ATCC 8100

WARNINGS AND PRECAUTIONS

Hemolytic Anemia:- Due to the risk of hemolytic anemia in patients with G6PD deficiency, G6PD testing must be performed before prescribing ARAKODA.

G6PD Deficiency in Pregnancy and Lactation

Potential Harm to the Fetus :-The use of ARAKODA during pregnancy may cause hemolytic anemia in a G6PD-deficient fetus. Even if a pregnant woman has normal levels of G6PD, the fetus could be G6PD deficient. Advise females of reproductive potential that treatment with ARAKODA during pregnancy is not recommended and to avoid pregnancy or use effective contraception during treatment and for 3 months after the last dose of ARAKODA. If a pregnancy is detected during ARAKODA use, discontinue ARAKODA as soon as possible and switch to an alternative prophylactic drug for malaria during pregnancy.

Potential Harm to the Breastfeeding

Infant A G6PD-deficient infant may be at risk for hemolytic anemia from exposure to ARAKODA through breast milk. Infant G6PD status should be checked before breastfeeding begins. ARAKODA is contraindicated in breastfeeding women when the infant is found to be G6PD deficient or the G6PD status of the infant is unknown. Advise the woman with a G6PD-deficient infant or if the G6PD status of the infant is unknown not to breastfeed during treatment with ARAKODA and for 3 months after the final dose.

Hypersensitivity Reactions Serious hypersensitivity reactions (e.g., angioedema and urticaria) have been observed with administration of tafenoquine.

- Leucopenia (high dose).
- Hemolysis.
- Methemoglobinemia:

The presence in the blood of methemoglobin, a form of hemoglobin that is useless for carrying oxygen and delivering it to tissues throughout the human body. A small amount of methemoglobin is normally present in

blood but the conversion of a larger fraction of hemoglobin into methemoglobin, which does not function well as an oxygen carrier, results in clinical symptoms. Since hemoglobin is the key carrier of oxygen in the blood, its replacement by methemoglobin can cause a slate gray-blueness of the skin (cyanosis), and potentially cause more serious symptoms due to insufficient oxygen.

In more technical terms, methemoglobin is a transformation product of normal oxyhemoglobin. It is created by the oxidation of the ferrous iron present in the heme part of hemoglobin to ferric iron.

Methemoglobinemia may be acquired anytime in life by exposure to a number of different chemical agents such as nitrites or certain medications (acquired methemoglobinemia) or it may be present at birth (congenital) due a genetic condition.

CLINICAL STUDIES

Clinical Trials 1, 2, and 3 Three double-blind, randomized, controlled studies have been performed to evaluate the efficacy of ARAKODA. Trial 1 (NCT #02491606) was a Phase IIb, placebo-controlled study conducted in Kenya, an area of holoendemic *P. falciparum* malaria. After taking a three-day presumptive course of halofantrine to eliminate any existing parasitemia, subjects were randomized into one of four groups (placebo and three different ARAKODA dosing groups; one group received 200 mg once daily for 3 days, then a maintenance regimen of weekly dose of 200 mg for 10-15 weeks). Sixtyone percent of subjects were male. The mean age was 32.4 years (range 17-55). Subjects were evaluated for parasitemia by weekly blood smears. Protective efficacy at 15 weeks was defined based on the reduced incidence of parasitemia during the prophylaxis phase relative to placebo. The results in the intention-to-treat population, which included all subjects who received three doses of halofantrine and were randomized, are shown in Table below:-

	PLACEBO	ARAKODA
number of subjects	94	93
Subjects free of parasitemia	6(6.4%)	68(73.1%)
Subject with parasitemia	86(91.5%)	12(12.9%)
Subjects with missing data	2(2.1%)	13(14.0%)
Protective efficacy [98.75%CI]²	-	71.3%

- The Trial 3 compared ARAKODA with mefloquine for the prophylaxis of both *P. falciparum* and *P. vivax* malaria in healthy non-immune soldiers deployed to East Timor (now Timor-Leste). No subject developed malaria during the 26-week prophylactic phase.
- Subjects were exposed to *P. vivax* and there is a high likelihood that the study subjects were also exposed to *P. falciparum*. Since the precise degree of

exposure to malaria in study subjects is unknown, this study provides only supportive evidence of efficacy.

Clinical Trial 7

- In a randomized, double-blind, placebo-controlled trial (Trial 7) in healthy, non-immune volunteers, ARAKODA was shown to have prophylactic activity directed against blood-stage *P. falciparum*

parasites. Twelve subjects received ARAKODA (200 mg once daily for 3 days, then 200 mg on 10 day) and 4 subjects received placebo.

- On Day 13, subjects were inoculated with erythrocytes containing viable *P. falciparum* parasites. Fifteen subjects (93.8%) were of white race. The mean age was 27.5 years (range 20-42). The mean body weight was 72.3 kg (range 56- 97.7).
- The efficacy endpoint was parasitemia by Day 34; parasitemia was based on detection of *P. falciparum* 18S ribosomal DNA by real time polymerase chain reaction assay (PCR). There was a statistically significant difference in malaria incidence between the two groups; 4/4 (100%) subjects in the placebo group had detectable parasites from Day 17 compared to 0/12 (0%) subjects on ARAKODA were PCR negative at all visits.

ADVERSE REACTIONS

CLINICAL TRIALS EXPERIENCE^[5]

In total, 3 clinical studies with TQ as an anti-malarial agent have been conducted until October 2018. Results of the first TQ clinical trial in humans were published in 1998, showing that TQ was safe and well tolerated.^[14] The molecule's promising half-life of 15 days initiated a series of clinical studies that led to

Adverse Reactions Reported with ARAKODA in Trial 3 and Pooled Trials 1, 2, 4, and 5 Adverse reactions occurring in $\geq 1\%$ of subjects in the ARAKODA group in the placebo controlled pooled Trials 1, 2, 3, and 4 are presented.^[5]

ADVERSE REACTION	ARAKODA (TAFENOQUININE)	PLACEBO n=295	MEFLOQUINE n=145
Nervous system disorders	35	34	47
• Headache	32	32	44
• Dizziness	5	3	10
Musculo skeletal and connective disorder	27	26	37
• back pain	14	9	11
Gastrointestinal disorder	31	33	46
• Diarrhoea	5	3	1
• Nausea	5	2	2
• Vomiting	2	2	1
Investigations	8	7	11
Alanine Amino Transferase(AAT) increased/abnormal	4	2	3
Psychiatric Disorder	2	1	2
• Any sleep symptoms	1	1	0
• Depression	1	0	0
• Insomnia	1	1	0

Trials 2 and 4 included mefloquine arm in addition to placebo

- ARAKODA was administered as 200 mg daily for 3 days, then 200 mg weekly.
- Mefloquine was administered as 250 mg daily for 3 days, then 250 mg weekly.
- headache Includes headache, sinus headache, migraine and tension headache.

established and consolidated safety, tolerability, and efficacy data.

The safety of tafenoquine was studied in clinical trials at various doses and regimens in 3,184 subjects. The recommended ARAKODA regimen was evaluated in 825 subjects in 5 controlled clinical trials (Trials 1, Trial 2, Trial 3, Trial 4 and Trial 5).

The mean duration of exposure to ARAKODA in these five clinical trials was 21 weeks (range 10-29 weeks). Trial 1, 2 and 4 were conducted in healthy semi-immune volunteers in Ghana or Kenya and were placebo-controlled; a mefloquine arm was included in Trials 2 and 4 as a benchmark. Trial 3, an active comparator (mefloquine) controlled trial was conducted in healthy soldiers deployed in East Timor (Timor Leste).^[5]

A placebo-controlled Trial 5 was conducted in healthy volunteers in the United States and United Kingdom. The mean age of the subjects included in the five trials was 29 years (range 17 to 69 years); 84% were male.

- Includes dizziness and dizziness postural Includes abnormal dreams, insomnia, nightmares, sleep disorder, and somnambulism.

Adverse Reactions Reported In < 1% of Subjects Receiving ARAKODA In Trials 1 To 5

- The following selected adverse reactions were reported in subjects receiving ARAKODA

(tafenoquine) in Trials 1 to 5 at a rate of less than 1%.

- Blood and lymphatic system disorders: hemolytic anemia, anemia, thrombocytopenia.
- Ear and labyrinth disorders: hyperacusis, Meniere's disease.
- Eye disorders: night blindness, photophobia, blurred vision, visual acuity reduced, visual impairment, vitreous floaters.
- Hepatobiliary disorders: hyperbilirubinemia, jaundice cholestatic.^[3]
- Immune system disorders: hypersensitivity
- Investigations: blood bilirubin increased, blood creatinine increased, glomerular filtration rate decreased.

- Nervous system disorders: amnesia, coordination abnormal, hyperesthesia, hypoesthesia, somnolence, syncope, tremor, visual field defect.^[3,5]
- Psychiatric disorders: agitation, neurosis.
- Skin and subcutaneous tissue disorders: urticaria.

USES

- ✓ It is extensively used for the radical cure of relapsing vivax malaria.^[13,5]
- ✓ It invariably kills gametocytes of all the species, or inhibits their growth and development in the mosquito.

SPECTRAL ANALYSIS

¹H NMR^[10,8]

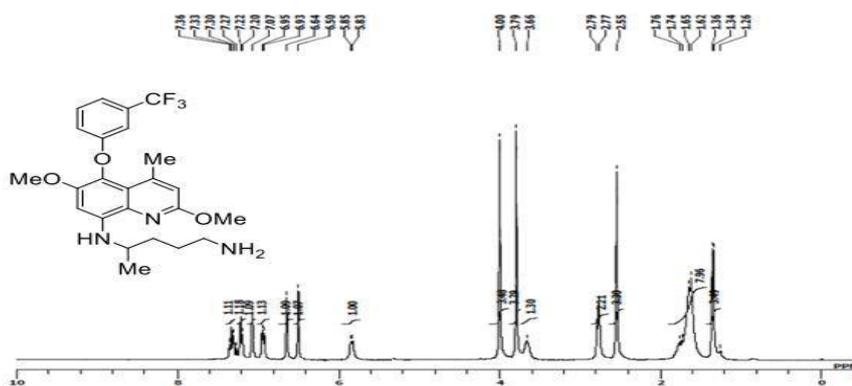
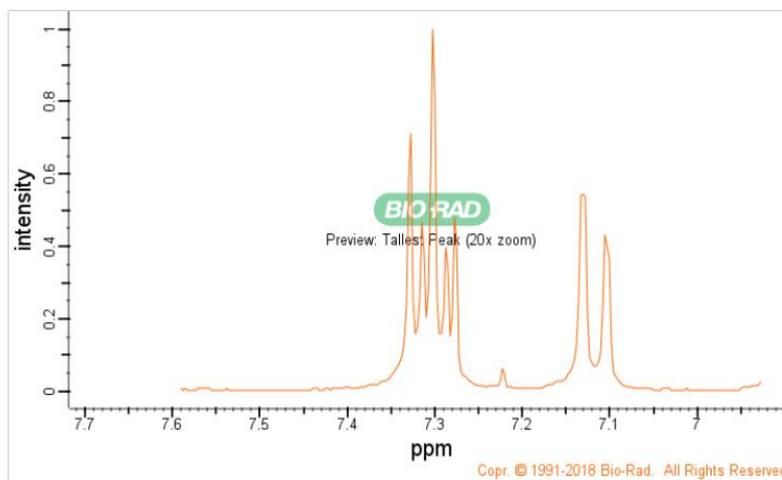
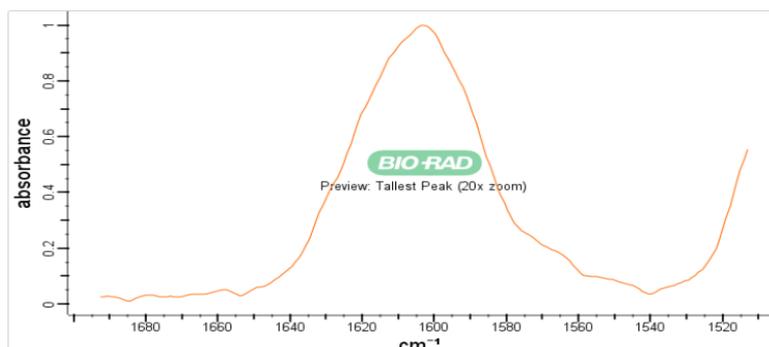
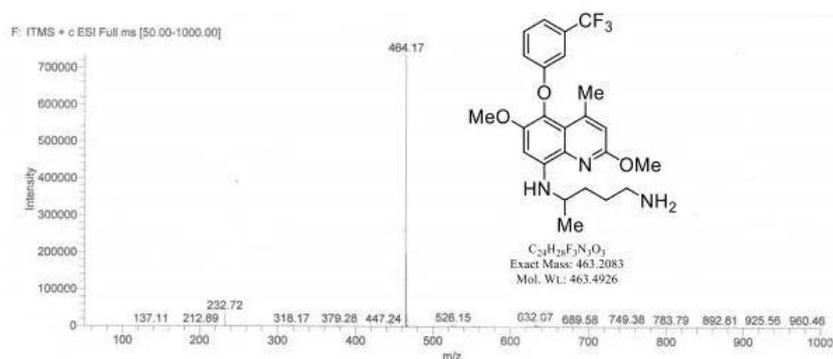


Fig. S1 ¹H NMR spectra of TQ

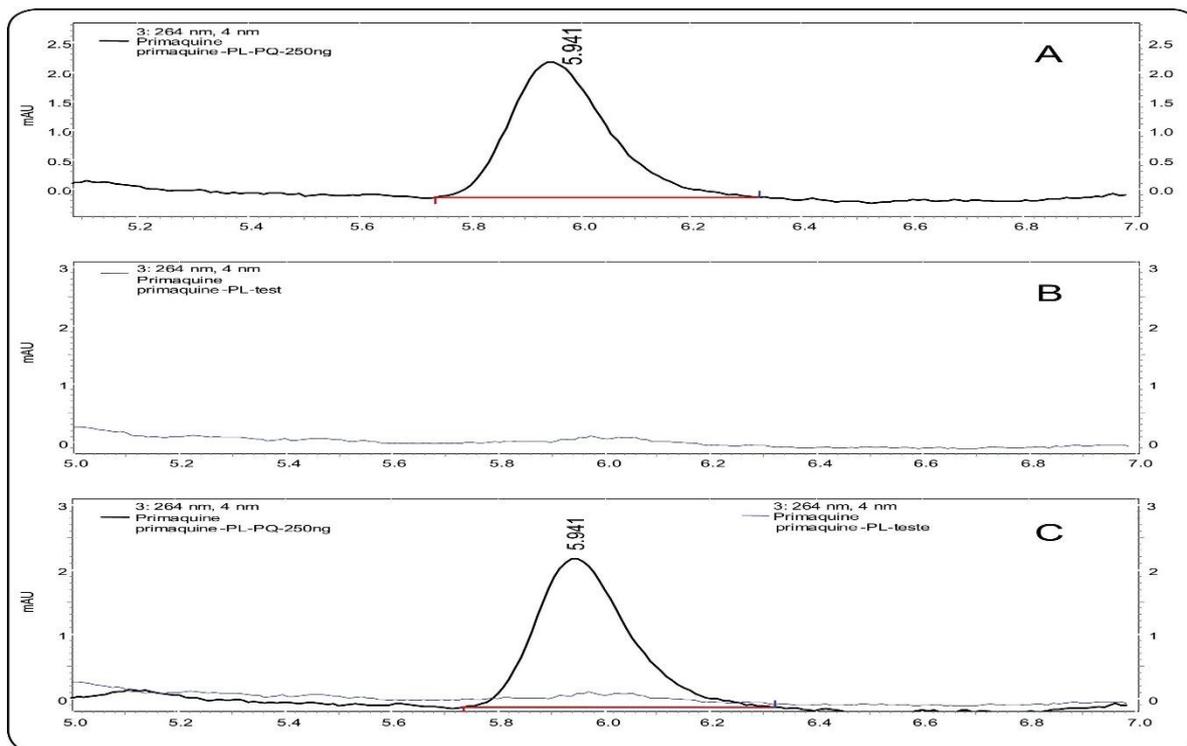
IR SPECTRUM^[8]MASS SPECTROSCOPY[MS]^[10]

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY

Method was developed for the determination of tafenoquine (**I**) in human plasma using high-performance liquid chromatography–tandem mass spectrometry. Prior to analysis, the protein in plasma samples was precipitated with methanol containing [²H₃¹⁵N] tafenoquine (**II**) to act as an internal standard. The supernatant was injected onto a Genesis-C₁₈ column without any further clean-up.^[9]

The mass spectrometer was operated in the positive ion mode, employing a heat assisted nebulisation, electrospray interface. Ions were detected in multiple reaction monitoring mode. The assay required 50 µl of plasma and was precise and accurate within the range 2 to 500 ng/ml. The average within-run and between-run relative standard deviations were <7% at 2 ng/ml and greater concentrations. The average accuracy of validation standards was generally within ±4% of the nominal concentration.

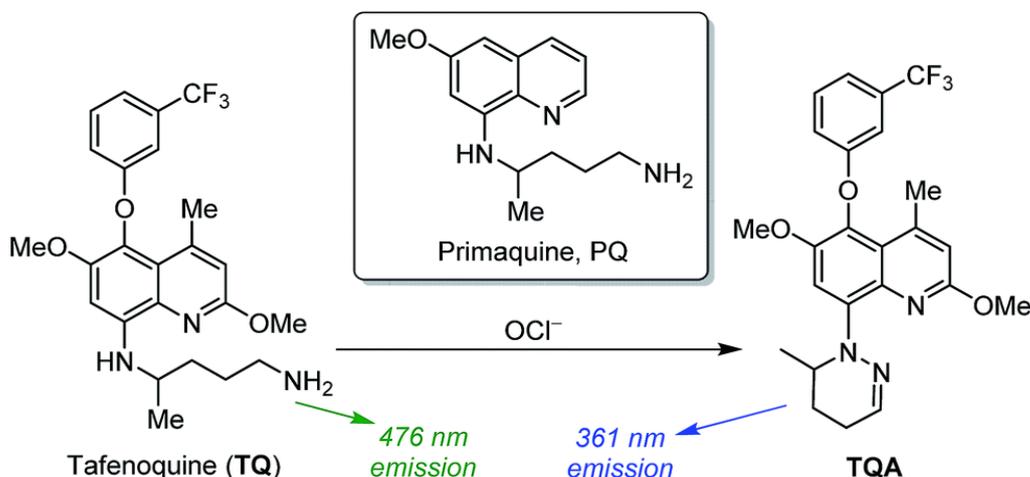
There was no evidence of instability of **I** in human plasma following three complete freeze–thaw cycles and samples can safely be stored for at least 8 months at approximately –70°C. The method was very robust and has been successfully applied to the analysis of clinical samples from patients and healthy volunteers dosed with **I**.^[9]



FLOURIMETRY ANALYSIS

- Fluorometric analysis with OCI^- -selective receptor is one promising method for this purpose since this facilitates simple quantification or imaging of OCI^- with a common fluorescence spectrometer or microscope. A number of fluorescent receptors for OCI^- have been proposed;^[8] however, many of them show single-wavelength emission whose intensity is strongly affected by several factors (instruments and receptor concentrations). In contrast, ratiometric receptors, which show a new emission in addition to the inherent one by the interaction with OCI^- , is more attractive because they allow simple quantification just by monitoring the intensities of two emissions, where the effects of several factors can be eliminated. There are, however, a few reports of ratiometric OCI^- receptors.^[12]

- Tafenoquine (TQ) is a commercially-available antimalarial drug, one derivative of a representative antimalarial drug, primaquine (PQ),^[11] as shown in the fig. TQ shows higher antimalarial activity than PQ and has attracted increasing attention because it is also effective for the treatment of Leishmaniasis, a disease caused by protozoan parasites. It is also reported that TQ produces some mitochondrial Reactive Oxygen Species (ROS) *in vivo* such as superoxide anion (O_2^-), H_2O_2 , hydroxide (OH^-), and OCI^- , which leads to apoptosis-like death of Leishmania. In addition, TQ inherently shows a strong fluorescence due to its quinoline platform. The strong fluorescence, high water solubility, high cell permeability, and high ROS tolerance of TQ are the ideal properties for fluorometric ROS sensing.^[12]

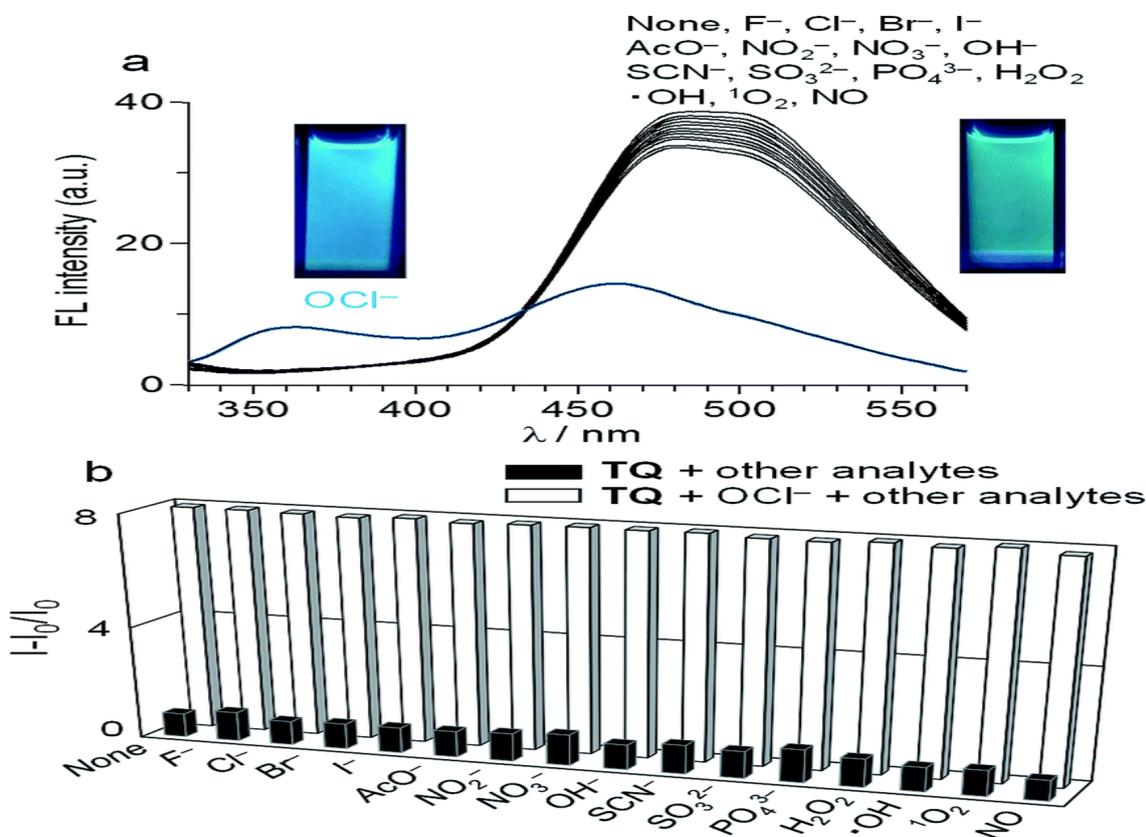


(Structures of 8-aminoquinoline-based antimalarial drugs, and proposed mechanism for OCI^- -induced fluorescence response of TQ).^[12]

Fluorescence properties of TQ

- TQ was obtained by neutralization of commercially-available succinate salt of tafenoquine with Na_2CO_3 as brown solids with 83% yield. Its purity was confirmed by ^1H , ^{13}C NMR and ESI-MS analysis (Fig. S1–S3, ESI[†]). The fluorescence response of TQ was studied in a buffered water/MeCN (3/7 v/v) mixture with pH 7.4 (HEPES 0.1 M) at 25 °C ($\lambda_{\text{ex}} = 300$ nm). TQ itself (20 μM) exhibits a strong fluorescence at 476 nm. Upon addition of 100 equiv. of OCI^- to the solution, a blue-shifted fluorescence appears at 361 nm ($\Delta\lambda = 115$ nm), along with a decrease in the original 476 nm emission.
- To clarify the specific nature of TQ towards OCI^- , effect of other typically encountered oxidative

species such as F^- , AcO^- , Cl^- , Br^- , I^- , NO_2^- , NO_3^- , SO_3^{2-} , PO_4^{3-} , OH^- , H_2O_2 , SCN^- , hydroxyl radical ($\cdot\text{OH}$), singlet oxygen ($^1\text{O}_2$), and NO was studied. These species, when added to a solution containing TQ, scarcely change the fluorescence spectrum. This indicates that OCI^- selectively changes the fluorescence of TQ. It must also be noted that, as shown in Fig, the OCI^- -induced fluorescence change is unaffected by the addition of these competing oxidative species. These findings clearly suggest that TQ selectively detects OCI^- in aqueous media even in the presence of these competing species.^[12]



((a) Fluorescence spectra ($\lambda_{\text{ex}} = 300$ nm) of TQ (20 μM) in a buffered water/MeCN (3/7 v/v) mixture (HEPES 0.1 M, pH 7.4) at 25 °C with 100 equiv. of each respective analytes. (b) Fluorescence intensity at 361 nm (black) with 100 equiv. of each respective analytes and (white) with 100 equiv. of each respective analytes together with 100 equiv. of OCI^-)).

Mechanism for fluorometric response

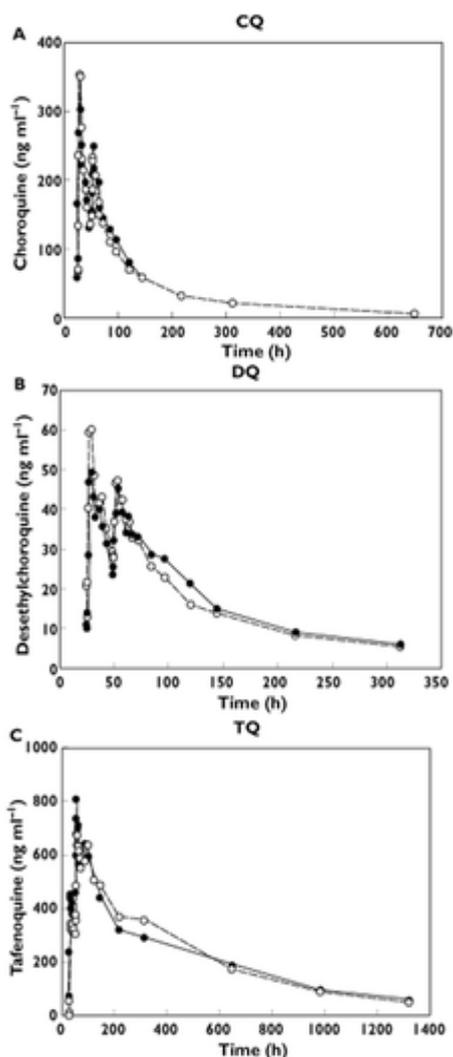
TQ itself shows a strong fluorescence at a relatively longer wavelength (476 nm). This is ascribed to the electron donation from the secondary amine group at the 8-position to the electron deficient quinoline moiety. Upon addition of OCI^- , the resulting TQA shows a blue-shifted fluorescence at 361 nm. This is because the cyclization of the pentan-1,4-diamine moiety of TQ transforms the secondary amine moiety to the tertiary one, which has lower electron donation ability. This thus creates a blue-shifted emission.^[12]

Pharmacodynamics

In vitro studies have shown that tafenoquine presents an average 50% inhibitory concentration of 0.436 mcg against blood stages of seven strains of *P. falciparum*. In chloroquine-resistant *P. falciparum* strains the IC₅₀ of tafenoquine was greater when compared with primaquine and it ranged from 0.5 to 33.1 mcg. In studies evaluating the transmission-blocking activity of tafenoquine against the sporogonic stage of *P. vivax*, it was showed a reduced transmission at doses higher than 25 mg/kg².

PHARMACOKINETICS

Co-administration of CQ and TQ did not result in significant effects on any pharmacokinetic parameter of interest for TQ, CQ or DQ (Figure 2A–C). For TQ, the 90% CI of the ratios of CQ + TQ to TQ alone for AUC_{0-t} , $AUC_{0-\infty}$ and $t_{1/2}$ fell within the 0.8–1.25 equivalence interval, indicating no pharmacokinetic interaction. However, a transient increase in the C_{max} and AUC_{0-24} (38 and 24%, respectively) of TQ was observed on day 2 during coadministration of TQ and CQ relative to TQ.



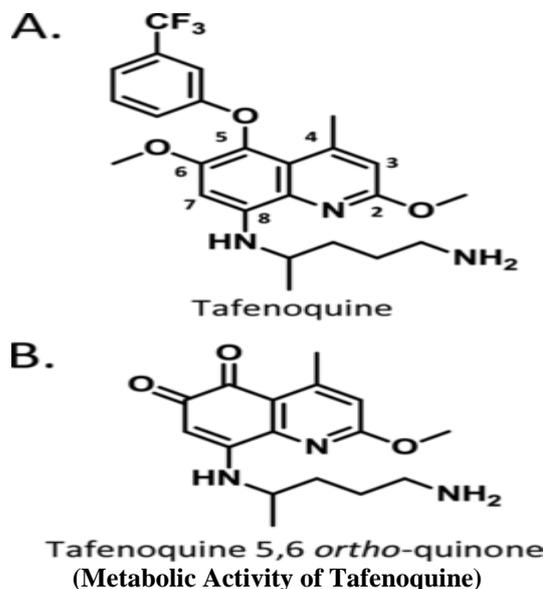
(Pharmacokinetic study)

Alone had diminished (13 and 12%, respectively).^[2] (A–C) Mean plasma concentration vs. time profiles for chloroquine (CQ), desethylchloroquine (DQ) and tafenoquine (TQ), during coadministration of tafenoquine and chloroquine. \bullet , CQ + TQ; \circ , CQ alone (A,B); \circ , TQ alone (C).^[16,24]

In clinical trials, it was reported a tafenoquine-induced relapse prevention of 91.9% in cases of vivax malaria when pretreated with chloroquine. In prophylactic studies, tafenoquine showed an efficacy range from 84 to 87% against falciparum malaria and 99.1% against vivax malaria.^[16]

METABOLISM

- The activation of tafenoquine needs the activity of CYP 2D6 liver microsomal enzyme. This activation step produces the metabolite 5,6 ortho quinone tafenoquine. This metabolite is internalized by the parasite and reduced to radicals by ferredoxin-NADP+ reductase and diflavin reductase enzymes. In the human, tafenoquine is metabolized by several metabolic pathways including O-demethylation, N-dealkylation, N-oxidation and oxidative deamination as well as C-hydroxylation of the 8-aminoalkylamino side chain.^[2]
- The structure of the parent tafenoquine. In addition to monitoring for the parent tafenoquine, the presence of a 5,6-ortho-quinone species was also investigated. The structure of the tafenoquine 5,6-ortho-quinone has a bulky aryl substitution at the 5 position of the quinoline ring, while primaquine has a hydrogen. It has been proposed that hydroxylation of primaquine at the 5 position produces a reactive metabolite(s) that is likely responsible for efficacy and toxicity. The slow kinetics of metabolic dearylation of the carbon at the 5 position of the quinoline core (C5) of tafenoquine is challenging to study using traditional *in vitro* metabolism techniques due to the extreme stability of the molecule in microsomal preparations *in vitro*. The metabolite shown in for tafenoquine corresponds to the stable oxidation product of the 5-dearylation pathway.^[14]
- A related metabolic pathway (C5 hydroxylation) was recently shown to be affected by mouse CYP 2D metabolism for primaquine. The existence of such a phenolic metabolite for tafenoquine has not been demonstrated *in vivo*. The existence of this C5 phenolic metabolite for tafenoquine, along with other phenolic metabolites similar to those produced by primaquine metabolism, would further indicate a common CYP 2D6-mediated metabolic pathway for 8-aminoquinoline radical curative activity.^[14]



Absorption

The first-in-human pharmacokinetic study showed a t_{max} of 13.8 hours and this study suggested that the prolonged absorption from the gut can be due to absorption in the distal gastrointestinal tract combined with a slow clearance. The AUC and C_{max} demonstrated an inter subject variability. The bioavailability of tafenoquine is increased in the presence of a high-fat meal by modifying the amount of drug absorbed rather than the rate of absorption. Once absorbed, the concentration of tafenoquine in the whole body is two-fold higher than the corresponding concentration in plasma and it seems to be highly distributed in the liver showing an AUC of approximately 80 times more than what is found in the plasma.^[2]

Volume of distribution

Tafenoquine presents a high volume of distribution of approximately 2 560 L.^[2]

Route of elimination

After degradation by different metabolic pathways, tafenoquine is slowly excreted from the body primarily in the feces and renal elimination of the unchanged form is very low.^[2]

Toxicity

Tafenoquine can cause hemolysis in people with glucose-6-phosphate dehydrogenase deficiency.^[2] In preclinical studies, renal cell adenomas and carcinomas are increased in male rats with an overdose administration. However, this drug does not seem to be carcinogenic in humans and it was shown to lack mutagenic potential. In fertility studies, tafenoquine resulted in a reduced number of viable fetuses, implantation sites and corpora lutes.^[2]

Dosage Formulation

ARAKODA(tafenoquine) tablets are dark pink, film-coated, capsule-shaped tablets debossed with 'TQ100' on one side containing 100 mg of tafenoquine.^[5]



(Dosage form)

CONCLUSION

Tafenoquine has utility as an agent to reduce malarial relapse in patients infected with *P. vivax*. There are significant adverse effects associated with the treatment such as decreases in hemoglobin not associated with G6PD deficiency. Single-dose tafenoquine resulted in a significantly lower risk of *P. vivax* recurrence than placebo in patients with phenotypically normal G6PD activity. The mechanism of action of tafenoquine is not well established but studies have reported a longer and more effective action when compared to primaquine. On the other hand tafenoquine inhibits heme polymerase in blood stage of parasite which explains the activity against blood stages of parasite. The tafenoquine is active against pre-erythrocytic and erythrocytic form as well as gametocyte of plasmodium species. The activity tafenoquine pre-erythrocytic stage prevents the development of erythrocytic forms of parasite.

In chloroquine-resistant *P. falciparum* strains the IC₅₀ of tafenoquine was greater when compared with primaquine and it ranged from 0.5 to 33.1 mcg. Co-administration of CQ and TQ did not result in significant effects on any pharmacokinetic parameter of interest for TQ, CQ or DQ. For TQ, the 90% CI of the ratios of CQ + TQ to TQ alone for AUC_{0-t}, AUC_{0-∞} and $t_{1/2}$ fell within the 0.8–1.25 equivalence interval, indicating no pharmacokinetic interaction. The activation of tafenoquine needs the activity of CYP 2D6 liver microsomal enzyme. This activation step produces the metabolite 5,6 ortho quinone tafenoquine. In the human, tafenoquine is metabolized by several metabolic pathways including O-demethylation, N-dealkylation, N-oxidation and oxidative deamination as well as C-hydroxylation of the 8-aminoalkylamino side chain. The bioavailability of tafenoquine is increased in the presence of a high-fat meal by modifying the amount of drug absorbed rather than the rate of absorption. Once absorbed, the concentration of tafenoquine in the whole body is two-fold higher than the corresponding concentration in plasma and it seems to be highly distributed in the liver showing an AUC of approximately 80 times more than what is found in the plasma. Tafenoquine can cause hemolysis in people with glucose-6-phosphate dehydrogenase deficiency. To determine the interactions of TFQ with ACT-partner drugs, drug combinations in fixed ratios of 1:3, 1:1 and 3:1 was tested. Tafenoquine tablets are dark pink, film-coated, capsule-shaped tablets debossed with 'TQ100' on one side containing 100 mg of tafenoquine.

ACKNOWLEDGEMENT

The successful accomplishment of this seminar would not have been possible but by the timely help and guidance rendered by many people. I would like to mention few of them. My first salutation goes to Almighty Allah and my Parents for being ever so kind and courteous. It gives me an immense pleasure to acknowledge a debt of gratitude to my guide Ms Mohsina Abid, Dept of Pharmaceutics, Deccan School of Pharmacy for her constant encouragement, suggestions,

supervision and support. I would like to express profound gratitude to Syed Abdul Azeez Basha, honourable Principal of Deccan School of Pharmacy, Hyderabad, for guiding us as well as providing us the support to conduct this seminar.

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