HIGH IN SITU RAT INTESTINAL PERMEABILITY OF ARTEMISININ UNAFFECTED BY MULTIPLE DOSING AND WITH NO EVIDENCE OF P-GLYCOPROTEIN INVOLVEMENT

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ABSTRACT:

The objective of this study was to investigate whether the decrease in artemisinin bioavailability after repeated oral dosing in humans can be a result of increased efflux of artemisinin by P-glycoprotein or decreased membrane transport at the intestinal barrier. The effective jejunal permeability (P_{eff}) of artemisinin was investigated using an in situ rat perfusion model. Fifty-four rats were randomized to one of three treatment arms: no pretreatment, pretreatment with low (500 ng/ml) or high (5000 ng/ml) artemisinin concentration plus the P-glycoprotein inhibitor R,S-verapamil (400 µg/ml). Perfusion samples were assayed for content of artemisinin, R,S-verapamil, and perfusion viability markers. Artemisinin P_{eff} was 1.44 ± 0.38, 1.17 ± 0.32, and 1.71 ± 0.29 (10^{-4}, cm/s) in rats receiving no pretreatment and perfused with low, high, or low artemisinin concentration plus verapamil, respectively. Multiple oral dosing of artemisinin did not affect the jejunal permeability of artemisinin. R,S-verapamil P_{eff} was similar in artemisinin-pretreated rats (1.09 ± 0.54 · 10^{-4}, cm/s) and rats pretreated with only vehicle (1.07 ± 0.37 · 10^{-4}, cm/s). The decrease in artemisinin bioavailability after multiple oral dosing in humans is probably not a result of changes in P-glycoprotein expression or general intestinal transport. It seems more likely attributable to increased hepatocellular activity. Furthermore, artemisinin exhibits high jejunal permeability and is neither a substrate nor inducer of P-glycoprotein.

Artemisinin represents a new class of antimalarials that is effective against drug-resistant Plasmodium falciparum strains (Hassan Alin et al., 1992). It is a sesquiterpene lactone with an internal peroxide bridge (Fig. 1) necessary for its antiparasitic effect (Klayman, 1985). Artemisinin pharmacokinetics in humans are characterized by a short half-life of about 2 to 3 h, a high and variable oral clearance of 200 to 400 liters/h after a single dose, and an extraordinary time dependence (Ashton et al., 1996, 1998a,b; Hassan Alin et al., 1996; Sidhu et al., 1998; Svensson et al., 1998). In several multiple oral dose studies in both patients and healthy subjects, artemisinin plasma concentrations decreased by the fifth day of administration to about 20% compared with those on the first day. Because there was no concomitant change in half-life with decreasing area under concentration-time curve, the time dependence was thought to be caused by a decrease in bioavailability (Ashton et al., 1996, 1998a,b; Hassan Alin et al., 1996; Sidhu et al., 1998; Svensson et al., 1998). However, the mechanism behind the pronounced time-dependent pharmacokinetics still remains unidentified.

The possibility of induction of membrane proteins that may cause an increased efflux out from cell membranes and thereby reduce the bioavailability of artemisinin has not yet been investigated. P-glycoproteins, located in the apical membrane of the enterocytes, may serve as a barrier to protect cells from cytotoxic agents (Borst et al., 1993), causing decreased absorption and/or increased metabolism by apical recycling. This may contribute to low oral bioavailability of hydrophobic drugs (Lown et al., 1997; Sparreboom et al., 1997; Kim et al., 1998). Transient exposure of drugs may transcriptionally increase the level of expression of mdr1, one of the encoding genes of the multidrug-resistant (MDR) P-glycoprotein (Silverman and Thorgerisson, 1995).

P-glycoprotein in MDR tumor cells appears to exhibit relatively

![Chemical structure of artemisinin (mol. wt. = 282).](http://www.dmd.org)

FIG. 1. Chemical structure of artemisinin (mol. wt. = 282).

1 Abbreviations used are: P_{eff, rat}: effective permeability in rat; P_{eff, man}: effective permeability in humans; MDR, multidrug resistant; CYP, cytochrome P-450; Q_{pw}, perfusion flow rate; NWF, net water flux.
broad substrate specificity (Ford and Halt, 1990). The substrates are generally amphiphilic, have partition coefficients (octanol/water) greater than 2, and are protonated at physiological pH (Germann et al., 1993). Many drugs metabolized by human cytochrome P-450 (CYP) 3A4 are also transported by P-glycoprotein (Wacher et al., 1995). Artemisinin has an octanol–water partition coefficient of 160 (Augustijns et al., 1996) and is partly metabolized by CYP3A4 in human liver microsomes (U.S.H.S. and M.A., submitted). Verapamil is a P-glycoprotein substrate, is a competitive inhibitor of intestinal P-glycoprotein in the rat (Saitoh and Austg, 1995).

The aims of this study were to elucidate whether the decrease in artemisinin bioavailability after repeated oral dosing in humans can be a result of an increased efflux of artemisinin by P-glycoprotein or a decreased membrane passage at the intestinal barrier. We also wanted to investigate whether or not artemisinin is a substrate for P-glycoprotein.

Materials and Methods

Design. The study involved three treatment arms: no pretreatment, pretreatment with artemisinin in soya bean oil emulsion for 5 days (54 mg/kg/day p.o.), and pretreatment with the emulsion vehicle for 5 days (10 mg/kg/day p.o.). Each treatment arm was divided further into three groups jejunally perfused with either 500 ng/ml artemisinin, 5000 ng/ml artemisinin, or 500 ng/ml artemisinin along with 400 μg/ml of the P-glycoprotein inhibitor RS-verapamil. Fifty-four rats were randomized to one of the nine experimental groups.

Chemicals. Artemisinin was a gift from the Institute of Malariology, Parasitology and Entomology (Hanoi, Vietnam). Pluronic F-68 was obtained from Fluka Chemie AG and glycerol was obtained from Sigma Chemical Co. [3H]-glucose and [3H]-labeled PEG 4000 were obtained from Amersham Laboratories (Bucksinghamshire, England). RS-verapamil was kindly provided by Knoll AG (Ludwigshafen, Germany). All other chemicals were of analytical grade and purchased from their usual sources.

Animals. Male Sprague-Dawley rats [Crl:CD(SD)BR; Charles River, Uppsala, Sweden] were housed six to each cage with wood shaving bedding at controlled conditions (22.4°C, 50% air humidity, 12-h light cycle) at the Biomedical Center (Uppsala, Sweden). The rats were acclimatized for at least 1 week before the experiments and had access to tap water and pellet food (R36; Lactamin AB, Vadstena, Sweden). The study was approved by the animal research ethics committee in Uppsala, Sweden.

Artemisinin Emulsion. The artemisinin emulsion consisted of 3% (w/v) pluronic F-68, 2.5% (w/v) glycerol, and 30% (w/v) of artemisinin dissolved in soya bean oil (20 mg/ml). Artemisinin was dissolved in soya bean oil solution by ultrasonication for 30 min. Pluronic F-68, glycerol, and water were mixed and the artemisinin soya bean oil solution was added. The mixture was placed in a water bath (80°C) for 30 min and ultrasonicated thereafter (Vibra Cell CV26; Sonics & Materials, CT) for 10 min. The emulsion was kept at 8°C and used within 10 days.

Perfusion Solution. The perfusion solution consisted of 5.4 mM KCl, 48 mM NaCl, 35 mM mannitol, 10 mM MgCl2, and 1 μl/g PEG 4000 in 70 mM phosphate buffer. Three reference substances were added to the solution to assess viability of the jejunal membrane (Schultz and Winne, 1987; Fagerholm et al., 1996). [3H]-labeled PEG 4000 (4000 dpm/ml perfusate) was used as a nonabsorbable marker for fluid loss or membrane leakage. [3H]-glucose (22,500 dpm/ml perfusate) was used as a marker for active transport. Antipyrine (53 μM) was used as a marker for passive absorption and an indicator for extensive changes in mesentery blood flow. The pH of the perfusion buffer was 6.5 and the osmolarity was 290 mmol/kg. The three perfusate compositions used contained either 500 ng/ml or 5000 ng/ml artemisinin or 500 ng/ml artemisinin along with 400 μg/ml of the P-glycoprotein inhibitor RS-verapamil. Artemisinin was dissolved in acetone-trit with a final acetone concentration of less than 1%. There was no indication of artemisinin to the inlet or outlet tubes. All other compounds have been proved earlier to be stable in the perfusate buffer and nonadherable to the tubing (Fagerholm et al., 1996).

Pretreatment. Rats randomized to pretreatment with artemisinin received 60 mg/kg of an oral artemisinin emulsion once daily by soft gavage for 5 days. Rats randomized to only vehicle administration (10 ml/kg/day) were treated in the same way.

Jejunum Perfusion Experiments. Rats weighing 205 to 341 g were fasted overnight before the perfusion experiment with access to tap water only. Anesthesia was induced with an i.p. injection of Inactin-Byk (thiobutabarbital sodium, 150 mg/kg), and the rats were placed on a heating pad to maintain a body temperature of 37°C. Breathing was facilitated by inserting a plastic tube into trachea. By a midline longitudinal incision, the abdomen was opened and a 10-cm jejunal segment was isolated and cannulated at both ends with plastic tubing. The segment was rinsed with saline to clear the segment, and approximately 10 cm of the inlet tubing was placed inside the abdominal cavity to achieve an inlet perfusion solution temperature of 37°C. Drops of saline were added onto the surgical area, which then was covered with a plastic sheet to avoid loss of fluid. The experiment was initiated by filling the segment with a 4-ml bolus of the perfusion solution and time set to zero with the immediate start of the perfusion. The perfusion rate was 0.2 ml/min (Harvard Apparatus Syringe Infusion Pump model 22; B&K, Sollentuna, Sweden). The perfuse samples were collected on ice in intervals after 45, 60, 75, 90, and 105 min. The length of the segment was measured after 45 min. At the end of the perfusion, the segment was flushed with approximately 20 ml of saline to recover remaining perfusion solution. A sample was taken from the inlet perfusion solution for analysis. All perfusion syringes and sample cups were weighted before and after the perfusion. Samples were frozen immediately and stored at −20°C. A blood sample was taken by heart puncture from pretreated rats at the end of the perfusion. Blood samples were centrifuged immediately (10,000g, 10 min) and plasma was frozen at −20°C.

Collection and Preparation of Rat Small Intestinal Fluid and Jejunum Homogenate. In three male overnight-fasted rats, a 10-cm long jejunal segment was isolated as described above. The segment was perfused with saline and the first 2.5 ml of intestinal fluid was collected from the outlet tube. Jejunal homogenate was prepared from a 35-cm segment of the upper small intestine excised beyond the 10-cm perfused section. The segment was flushed with ice-cold saline and the mucosa was scraped off with a razor. Perfusion buffer was added to the mucosa (5 ml/g mucosa) and the mixture was homogenized. The intestinal fluid and homogenate were stored at −80°C until use.

Incubation of Artemisinin with Rat Small Intestinal Fluid and Rat Jejunum Homogenate. Incubations were performed to assess the chemical and metabolic stability of artemisinin in rat intestinal juice and rat jejunal homogenate. The collected rat intestinal juice was diluted with perfusion buffer (1:1) and preincubated at 37°C for 6 min in a shaking water bath (Haake SWB 20). Artemisinin (5000 ng/ml, 1% methanol in final concentration) was added to the incubation, and samples (100 μl) were taken out at 0, 30, 90, and 105 min. The samples were mixed with 200 μl H2O and boiled for 3 min, chilled on ice, and centrifuged at 10,000g for 10 min. The supernatant was harvested and 60 μl injected directly onto the high-performance liquid chromatography column for quantitation of artemisinin. The incubation volume was 1 ml. Experiments with artemisinin incubated with 4, 9, and 17% rat jejunal homogenate in perfuse buffer were performed in the same way.

Analytical Analysis. Artemisinin concentrations were determined by high-performance liquid chromatography postcolumn-on-line derivatization and UV detection at 289 nm (Edlund et al., 1984). Perfuse samples and incubation samples were analyzed by direct injection onto the column. Plasma samples (100 μl) were extracted and analyzed as previously described (Ashton et al., 1996). Standard curve and quality control samples were prepared by spiking rat plasma or perfuse buffer with artemisinin. Detection was linear in the range of the standard samples (40–5200 ng/ml). Six quality control samples, two of each concentration (80, 2000, and 4500 ng/ml), were run on each occasion with the standard curve and experimental samples. The run was rejected if two quality-control samples of the same concentration or more than two quality-control samples deviated more than 20% from their nominal values. The intra- and interday precisions were 4%, 2%, and 4% and 5%, 2%, and 3%, respectively for the low, intermediate, and high quality-control concentrations. The limit of quantification of artemisinin in plasma was 40 ng/ml.

Antipyrine in the perfusion solution and the perfusate leaving the intestinal segment was analyzed by high-performance liquid chromatography (Lenner- näs et al., 1992). Peak areas of coeluted RS-verapamil were compared for any change in the effective permeability of RS-verapamil.
The effective jejunal permeability ($P_{\text{eff}}$) of artemisinin at the low artemisinin concentration (500 ng/ml) was 1.44 ± 0.38, 1.59 ± 0.50, and 1.50 ± 0.33 $\times 10^{-4}$ cm/s in untreated, artemisinin-pretreated, and vehicle-pretreated rats, respectively (Table 1). Artemisinin $P_{\text{eff}}$ values obtained in rats receiving no pretreatment did not differ for low (1.44 ± 0.38 $\times 10^{-4}$ cm/s), high (1.17 ± 0.32 $\times 10^{-4}$ cm/s), and low artemisinin concentration plus R, S-verapamil (1.71 ± 0.29 $\times 10^{-4}$ cm/s) (Table 1). Artemisinin $P_{\text{eff}}$ values in rats pretreated with artemisinin did not differ significantly from values obtained in vehicle-pretreated rats (Table 1). Using rat intestinal permeability values obtained in untreated rats at the low and high artemisinin perfusion concentration resulted in corresponding predictions of in vivo jejunal effective permeability estimates in humans of 5.21 $\times 10^{-4}$ cm/s and 4.24 $\times 10^{-4}$ cm/s, respectively. Thus, the fraction absorbed (fa) of dissolved artemisinin from the gastrointestinal tract was predicted to be 100% in humans. $P_{\text{eff}}$ of the P-glycoprotein inhibitor R, S-verapamil was 1.09 ± 0.54 $\times 10^{-4}$ cm/s in rats receiving an artemisinin emulsion orally for 5 days. This was not significantly different from 1.07 ± 0.37 $\times 10^{-4}$ cm/s obtained in rats pretreated with only emulsion vehicle.

The results for the different viability markers, $P_{\text{eff, antipyrine}}$, $P_{\text{eff, D-glucose}}$, NWF, and PEG rec, ss, are presented in Table 2. In rats receiving no pretreatment, $P_{\text{eff, antipyrine}}$ was similar between the three different perfusate compositions, 0.56 ± 0.31, 0.49 ± 0.21, and 0.87 ± 0.18 $\times 10^{-4}$ cm/s at low, high, and low artemisinin concentration plus R, S-verapamil, respectively. No difference in $P_{\text{eff, D-glucose}}$ values were observed at low (1.05 ± 0.07 $\times 10^{-4}$ cm/s), high (0.94 ± 0.16 $\times 10^{-4}$ cm/s), and low artemisinin concentration plus R, S-verapamil (1.04 ± 0.24 $\times 10^{-4}$ cm/s), respectively. Similar results of $P_{\text{eff, antipyrine}}$ and $P_{\text{eff, D-glucose}}$ were obtained in artemisinin- and vehicle-pretreated rats. The average negative NWF of −0.08 ± 0.05 ml/h/cm indicated some absorption of fluid from the mucosal (lumen) to the serosal side (blood). There was a significantly ($p < .001$) higher net water absorption at the high compared with the low artemisinin concentration. The overall average PEG rec, ss for all nine groups was 103 ± 7%. Water absorption at the luminal side correlated with the artemisinin concentration. The osmolarity was 288 ± 4, 290 ± 4, and 289 ± 2 mmol/kg in the inlet perfusate of low and high artemisinin concentration and low artemisinin concentration plus verapamil, respectively. Artemisinin was metabolically stable in incubations with rat intestinal fluid and jejunal homogenate. Artemisinin concentrations in plasma samples obtained by heart puncture were below the quantitation limit.

### Discussion

Artemisinin pharmacokinetics exhibit a remarkable time dependence in both malaria patients and healthy subjects with a decrease in bioavailability after repeated oral administration (Ashton et al., 1996,
1998a,b; Hassan Alin et al., 1996; Sidhu et al., 1998; Svensson et al., 1998). The present study examined the hypothesis of induction of enteroctyetal P-glycoprotein expression or decreased jejunal membrane passage after multiple oral administration resulting in reduced bioavailability of artemisinin. We also wanted to investigate whether P-glycoprotein is involved in the jejunal absorption of artemisinin. Induction of P-glycoprotein or a general decrease in jejunal transport are not likely explanations for the reduced bioavailability of artemisinin in humans seen after multiple administration because there was no difference in artemisinin effective permeability ($P_{ef}$) in rats pretreated with artemisinin compared with emulsion vehicle. Also, adding the P-glycoprotein inhibitor R,S-verapamil to the perfusate did not change artemisinin $P_{ef}$ in rats pretreated with artemisinin (Table 1). There was no evidence of artemisinin being an inducer of P-glycoprotein expression in rat jejunum, because R,S-verapamil $P_{ef}$ was not different in the artemisinin-pretreated rats compared with the vehicle-pretreated rats.

The present study demonstrated that artemisinin was not a substrate for rat jejunal P-glycoprotein because artemisinin $P_{ef}$ was not increased by coperfusion of the P-glycoprotein inhibitor R,S-verapamil. There also was no indication of a saturable carrier-mediated transport of artemisinin (Table 1). In another study using Caco-2 epithelial cells, no evidence of carrier-mediated transport of artemisinin was found (Augustijns et al., 1996). Cell culture have a significant lower functional expression of carrier-mediated processes (Artursson et al., 1996) and might not reflect an in vivo situation. With the present demonstration of high jejunal permeability and lack of concentration-dependent permeability in vivo, it is not likely that the jejunal absorption of artemisinin is mediated by any type of efflux proteins.

The resistance of $P. falciparum$ to chloroquine has been linked to drug efflux from the parasite. The discovery that verapamil partially reverses chloroquine resistance in vitro led to the proposal that an ATP-driven P-glycoprotein pump removes chloroquine from the digestive vacuole of the parasite, thereby reducing drug levels in the parasite (Watt et al., 1990). Verapamil is a P-glycoprotein substrate in humans (Tsuruo et al., 1981) as well as in the rat (Sandström et al., 1998) and is known to reverse drug-resistant falciparum malaria (Watt et al., 1990). It has been proposed that the $P. falciparum$ mdr-like gene, $pfmdr1$, is linked to chloroquine resistance phenotype (Foote et al., 1989, 1990). In contrast to MDR phenotypes of mammalian tumor cells, which are mediated by overexpression of P-glycoprotein (Endicott and Ling, 1989), the $pfmdr1$ protein product $Pgh1$ is expressed at approximately equivalent levels in the chloroquine-sensitive and most of the chloroquine-resistant $P. falciparum$ isolates (Wellems et al., 1990). Therefore, overexpression of this protein is not required for chloroquine resistance, and amino acid changes in the $Pgh1$ protein have been proposed as a possible mechanism for the resistance (Foote et al., 1990). Because of the decreasing sensitivity of $P. falciparum$ to existing antimalarial drugs, it is important to design and use novel drugs that circumvent the problem of drug resistance. Interestingly, this study shows that artemisinin is not a substrate for P-glycoprotein; for this reason development of parasite resistance by such an efflux mechanism is not likely to occur for this drug.

An alternative hypothesis for artemisinin time-dependent pharmacokinetics is induction of gut wall metabolism causing an increased first-pass extraction. CYP3A4 is, to a minor extent, involved in the metabolism of artemisinin in human liver microsomes (U.S.H.S. and M.A., submitted). Metabolism by intestinal CYP3A4 cannot be excluded even if relatively it would be of little importance for the systemic elimination. Gut enzymes other than CYP3A do not contribute to the metabolism of artemisinin, as evident from incubation experiments in this study. Artemisinin is not an inducer of CYP3A4 in humans at clinical concentrations (Svensson et al., 1998); therefore, it is unlikely that induction of gut metabolism is the cause of the time-dependent pharmacokinetics in human.

Oral bioavailability of a drug is dependent on fraction-absorbed, protein-binding, hepatocellular activity and hepatic blood flow, the latter of which is not likely to be affected by artemisinin administration. Different mechanisms that theoretically could explain the decrease in artemisinin bioavailability observed after multiple administration are shown in Fig. 2. Decreased absorption (Fig. 2, A), increased intestinal metabolism (Fig. 2, A), and decreased protein binding (Fig. 2, B) are not likely explanations because artemisinin effective permeability is unaffected by multiple oral dosing in the rat, artemisinin does not induce CYP3A4 (Svensson et al., 1998), and only minor changes in protein binding are seen in patients during treatment (Ashton et al., 1998b). The decrease in artemisinin bioavailability during multiple dosing is therefore most likely an effect of induction of hepatocellular activity (Fig. 2C).

Compounds with $P_{ef} < 0.03 \times 10^{-4}$ cm/s in the rat small intestine are classified as poorly absorbed whereas compounds with $P_{ef} > 0.2 \times 10^{-4}$ cm/s are completely absorbed (Fagerholm et al., 1996). The same classification of in vivo absorption may be defined in humans; poorly absorbed compounds have $P_{ef} < 0.1 \times 10^{-4}$ cm/s whereas...
In the calculation of $P_{\text{eff}}$ values, differences in NWF were corrected for. Low compared with the perfusate flow of 0.2 ml/min during 105 min. Concentration span studied had no effect on passive or carrier-mediated $P_{\text{eff}}$, antipyrine and $P_{\text{eff}}$, D-glucose indicate that artemisinin within the concentration span studied in the in situ perfused rat intestine has been shown to correlate well with the extent of in vivo absorption in humans after oral administration of highly soluble, stable, and passively and carrier-mediated absorbed drugs (Amidon et al., 1988). Our prediction of the fraction artemisinin absorbed in humans of 100% assumes that the drug is completely dissolved in the gastrointestinal fluids. Artemisinin is sparingly soluble in water (Trigg, 1989), possibly limiting its availability after oral administration. Because artemisinin has a high jejunal effective permeability and is not a substrate for P-glycoprotein, it can be concluded that the low oral bioavailability in humans after single-dose administration (Ashton et al., 1996, 1998a,b; Hassan Alin et al., 1996; Sidhu et al., 1998; Svensson et al., 1998) is a result of either solubility limitations and/or extensive first-pass metabolism rather than absorption problems.

The experimental viability of the segments was good. The obtained $P_{\text{eff}}$, antipyrine and $P_{\text{eff}}$, D-glucose indicate that artemisinin within the concentration span studied had no effect on passive or carrier-mediated transport. A decreased water absorption was observed at the high artemisinin concentration although the decrease was relatively low compared with the perfusate flow of 0.2 ml/min during 105 min. In the calculation of $P_a$ values, differences in NWF were corrected for.

Effective permeability values estimated from drug disappearance in the in situ perfusion rat model is well validated (Fagerholm et al., 1996). However, if the compound studied is susceptible to chemical or enzymatic instability in the lumen and/or brush-border membrane, $P_{\text{eff}}$ values will be overestimated. The intestinal segment was flushed before the start of the perfusion; therefore, only membrane-bound enzymes could interact with artemisinin. Because the $P_{\text{eff}}$ is estimated from drug disappearance from the lumen, any putative gut metabolism of artemisinin by, for instance, CYP3A, the major intestinal CYP enzyme (de Waziers et al., 1990), should not affect the estimated permeability. Furthermore, artemisinin was metabolically stable in incubations with jejunum homogenate without NADPH, indicating low activity of intestinal enzymes other than CYP. Therefore, disappearance of artemisinin from the perfusate should give good estimates of the jejunal effective permeability of artemisinin. A jejunal segment was chosen because artemisinin is available as an immediate release product for oral administration. P-glycoprotein transport also has been studied previously in the rat jejunum with the in situ perfusion technique (Sandström et al., 1998).

Any decrease in artemisinin plasma concentrations after multiple oral administration could not be demonstrated in this study because the artemisinin plasma concentrations were below the detection limit for the assay.

In conclusion, artemisinin is not a substrate for P-glycoprotein, nor does artemisinin appear to be an inducer of P-glycoprotein. Artemisinin therefore is not susceptible to efflux-type drug resistance. Intestinal enzymes apart from CYP3A probably do not contribute to the overall elimination of artemisinin. The low oral bioavailability seen in humans is probably a result of high hepatic first-pass metabolism and/or solubility problems in the gastrointestinal tract, because artemisinin jejunal permeability is high and the absorption of artemisinin is not affected by efflux by P-glycoprotein. It is not likely that the decreased bioavailability of artemisinin after multiple oral administration is due to induction of a P-glycoprotein-mediated transport, induction of gut wall metabolism, or a change in any general jejunal transport mechanism of artemisinin. A more likely explanation is autoinduction of hepatocellular activity.

References


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