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 artemisinin emulsion for 5 days (60 mg/kg/day, p.o.), or pretreatment with emulsion vehicle for 5 days. The rats within each treatment arm were randomized further to be jejunally perfused with either low (500 ng/ml) or high (5000 ng/ml) artemisinin concentration or low artemisinin concentration plus the P-glycoprotein inhibitor R,S-verapamil (400 μg/ml). Per fusate 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 human is probably not a result of changes in P-glycoprotein expression or general intestinal transport. It seems more likely attributed 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 Thorgeirsson, 1995).

P-glycoprotein in MDR tumor cells appears to exhibit relatively

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

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_{ef}, perfusion flow rate; NWF, net water flux.
broad substrate specificity (Ford and Hait, 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, 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 human 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 ml/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 \( R,S\) -verapamil. Fifty-four rats were randomized to one of the nine experimental groups.

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. Anaesthesia 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 weighed 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 −80°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). Perfusate 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 perfuse leaving the intestinal segment was analyzed by high-performance liquid chromatography (Lenner- näs et al., 1992). Peak areas of coeluted \( R,S\)-verapamil were compared for any change in the effective permeability of \( R,S\)-verapamil.
The fraction absorbed in humans \((f_{a,\text{man}})\) can be predicted from rat for highly permeability \((P_{\text{eff}}, \text{cm/s})\) was calculated according to a parallel tube model concentrations achieved after 45 min. The steady-state intestinal effective fusion solution and the perfusate leaving the intestinal segment was determined presented as average was tested with Student’s unpaired IL). The recovery of PEG 4000 was estimated from eq. 3: where \(Q_{\text{in}}\) is the perfusion flow rate (0.2 ml/min) and \(A\) is the mass transfer surface area within the intestinal segment assumed to be the area of a cylinder (2ml/L) with the length (L) (measured after 45 min) and radius (r) of 0.18 cm \((\text{Amidon et al., 1980; Komiya et al., 1980; Fagerholm et al., 1996}):\)

\[
P_{\text{eff}} = \frac{-Q_{\text{in}} \cdot \ln(C_{\text{in}}/C_{\text{out}})}{A}
\]

where \([\text{PEG}]_{\text{in}}\) and \([\text{PEG}]_{\text{out}}\) are the inlet and outlet concentrations of the nonabsorbable, water flux marker \(^{14}\text{C}\)-labeled PEG 4000. A negative net water flux indicates loss of fluid from the mucosal side (lumen) to the serosal side (blood). A positive net water flux indicates secretion of fluid into the segment. The recovery of PEG 4000 was estimated from eq. 3:

\[
\text{PEG}_{\text{rec}} = \frac{\Sigma \text{PEG}_{\text{in}} - \Sigma \text{PEG}_{\text{out}}}{\Sigma \text{PEG}_{\text{in}}}
\]

The osmolality of the perfusate was measured with a vapor pressure method (5500 vapor pressure osmometer; Wescor Inc., Logan, UT).

**Data Analysis.** Calculations were based on outlet perfusate steady-state concentrations achieved after 45 min. The steady-state intestinal effective permeability \((P_{\text{eff}}, \text{cm/s})\) was calculated according to a parallel tube model

\[
\text{PEG}_{\text{rec}} = \frac{\Sigma \text{PEG}_{\text{in}} - \Sigma \text{PEG}_{\text{out}}}{\Sigma \text{PEG}_{\text{in}}}
\]

where \(\text{PEG}_{\text{in}}\) and \(\text{PEG}_{\text{out}}\) are the inlet and fluid-transport corrected outlet solute concentrations, respectively. The latter was corrected by multiplying the inlet concentration with the inlet and fluid-transport corrected outlet solute concentrations, respectively.

The effective jejunal permeability \((P_{\text{eff}})\) of artemisinin at the low artemisinin concentration (500 ng/ml) was \(1.44 \pm 0.38, 1.59 \pm 0.50, \) and \(1.50 \pm 0.33 \cdot 10^{-4} \text{ cm/s}\) 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 \((1.44 \pm 0.38 \cdot 10^{-4} \text{ cm/s})\), high \((1.17 \pm 0.32 \cdot 10^{-4} \text{ cm/s})\), and low artemisinin concentration plus \(R,S\)-verapamil \((1.71 \pm 0.29 \cdot 10^{-4} \text{ cm/s})\) (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 \(5.21 \cdot 10^{-4} \text{ cm/s}\) and \(4.24 \cdot 10^{-4} \text{ cm/s}\), respectively. Thus, the fraction absorbed (fa) of dissolved artemisinin from the gastrointestinal tract was predicted to be 100% in humans.

\[
P_{\text{eff}} = \frac{Q_{\text{in}}/L (2)}{(2)}
\]

**Results**

The effective jejunal permeability \((P_{\text{eff}})\) of artemisinin at the low artemisinin concentration (500 ng/ml) was \(1.44 \pm 0.38, 1.59 \pm 0.50, \) and \(1.50 \pm 0.33 \cdot 10^{-4} \text{ cm/s}\) 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 \((1.44 \pm 0.38 \cdot 10^{-4} \text{ cm/s})\), high \((1.17 \pm 0.32 \cdot 10^{-4} \text{ cm/s})\), and low artemisinin concentration plus \(R,S\)-verapamil \((1.71 \pm 0.29 \cdot 10^{-4} \text{ cm/s})\) (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 \(5.21 \cdot 10^{-4} \text{ cm/s}\) and \(4.24 \cdot 10^{-4} \text{ cm/s}\), respectively. Thus, the fraction absorbed (fa) of dissolved artemisinin from the gastrointestinal tract was predicted to be 100% in humans.

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**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,

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perfusate</th>
<th>No Pretreatment</th>
<th>Pretreatment with ART*</th>
<th>Pretreatment with Vehicleb</th>
</tr>
</thead>
<tbody>
<tr>
<td>(P_{\text{eff}, \text{artemisinin}} (\cdot 10^{-4}, \text{ cm/s}))</td>
<td>500 ng/ml ART</td>
<td>1.44 ± 0.38</td>
<td>1.59 ± 0.50</td>
<td>1.50 ± 0.33</td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>1.17 ± 0.32</td>
<td>1.48 ± 0.43</td>
<td>1.36 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>500 ng/ml ART + Inhibitorc</td>
<td>1.71 ± 0.29</td>
<td>1.73 ± 0.18</td>
<td>1.62 ± 0.26</td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 1**

Mean ± SD \((n = 6/\text{group})\) \(P_{\text{eff}}\) of artemisinin in the in situ perfused rat jejunum

**ART, artemisinin.**

* Artemisinin emulsion, 60 mg/kg/day orally for 5 days.

Vehicle, 10 ml/kg/day orally for 5 days.

n = 5

400 µg/ml \(R,S\)-verapamil.
The resistance of \( P. falciparum \) to chloroquine has been linked to \( \text{pfmdr1} \) (Foote et al., 1990). The present study examined the hypothesis of induction of enteroctyotical 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 \( (P_{\text{eff}}) \) in rats pretreated with artemisinin compared with emulsion vehicle. Also, adding the P-glycoprotein inhibitor \( \text{S}-\text{verapamil} \) to the perfusate did not change artemisinin \( P_{\text{eff}} \) 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 \( P_{\text{eff}} \) 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 \( P_{\text{eff}} \) 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 detected even if relatively it would be of little importance for the systemic elimination. Gut enzymes other than CYP3A do not contribute 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 humans.

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 \( P_{\text{eff}} \) < 0.03 \( \times 10^{-4} \) cm/s in the rat small intestine are classified as poorly absorbed whereas compounds with \( P_{\text{eff}} > 0.2 \times 10^{-4} \) 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 \( P_{\text{eff}} < 0.1 \times 10^{-4} \) cm/s whereas

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Perfusate</th>
<th>No Pretreatment</th>
<th>Pretreatment with ART&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Pretreatment with Vehicle&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>( P_{\text{eff}} ), antipyrine ( (10^{-4}, \text{cm/s}) )</td>
<td>500 ng/ml ART</td>
<td>0.56 ± 0.31</td>
<td>0.93 ± 0.17</td>
<td>0.57 ± 0.30</td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>0.49 ± 0.21</td>
<td>0.68 ± 0.38</td>
<td>0.69 ± 0.29</td>
<td></td>
</tr>
<tr>
<td>500 ng/ml ART + inhibitor&lt;sup&gt;c&lt;/sup&gt;</td>
<td>0.87 ± 0.18</td>
<td>0.52 ± 0.18</td>
<td>0.81 ± 0.24</td>
<td></td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>1.05 ± 0.10</td>
<td>1.20 ± 0.19</td>
<td>0.95 ± 0.16</td>
<td></td>
</tr>
<tr>
<td>500 ng/ml ART</td>
<td>0.94 ± 0.16</td>
<td>0.90 ± 0.24</td>
<td>0.96 ± 0.26</td>
<td></td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>1.04 ± 0.24</td>
<td>0.96 ± 0.20</td>
<td>0.97 ± 0.23</td>
<td></td>
</tr>
<tr>
<td>( P_{\text{eff}} ), ( \text{c}-\text{glucose} ) ( (10^{-4}, \text{cm/s}) )</td>
<td>500 ng/ml ART</td>
<td>-0.09 ± 0.03</td>
<td>-0.13 ± 0.05</td>
<td>-0.12 ± 0.05</td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>-0.02 ± 0.02</td>
<td>-0.04 ± 0.05</td>
<td>-0.05 ± 0.06</td>
<td></td>
</tr>
<tr>
<td>500 ng/ml ART + inhibitor&lt;sup&gt;c&lt;/sup&gt;</td>
<td>-0.05 ± 0.03</td>
<td>-0.11 ± 0.03</td>
<td>-0.12 ± 0.05</td>
<td></td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>102 ± 3</td>
<td>110 ± 6</td>
<td>106 ± 2</td>
<td></td>
</tr>
<tr>
<td>( \text{PEG}_{\text{rec, ss}} ), (%)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>500 ng/ml ART</td>
<td>99.3 ± 3</td>
<td>98.3 ± 9</td>
<td>101 ± 7</td>
</tr>
<tr>
<td>5000 ng/ml ART</td>
<td>98.2 ± 5</td>
<td>107 ± 4</td>
<td>107 ± 7</td>
<td></td>
</tr>
</tbody>
</table>
In the calculation of Peff values, differences in NWF were corrected for.

The concentration span studied had no effect on passive or carrier-mediated absorption problems.

Alin et al., 1996; Sidhu et al., 1998; Svensson et al., 1998) is a result after single-dose administration (Ashton et al., 1996, 1998a,b; Hassan Alin M, Bjorkman A, Landberg-Lindgren A and Ashton M (1992) The effect of extract 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 jejunal transport mechanism of artemisinin. A more likely explanation is autoinduction of hepatocellular activity.

References


