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Absorption and *in vivo* dissolution of hydroxycholoroquine in fed subjects assessed using deconvolution techniques

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1 Nine healthy subjects each received three doses of 155 mg rac-hydroxychloroquine, as a tablet, an oral solution and by intravenous infusion, in a randomised cross-over design study, 30 min after a standard high fat breakfast.

2 Four methods of deconvolution were used to assess the absolute bioavailability of the tablet and oral solution doses. These were the delta function method, the staircase approximation method, and two least squares methods using a single first-order input and a sequential first-order input. The mean (± s.d.) fraction absorbed estimated by the four methods was 0.64 ± 0.14 after the tablet and 0.87 ± 0.30 after the oral solution. Wide intersubject variability was observed (0.50–0.91 for the tablet; 0.30–1.37 for the solution).

3 The mean (± s.d.) absorption half-life was 3.7 ± 2.0 h for the tablet and 3.3 ± 1.6 h for the solution, suggesting that absorption following the tablet dose was not rate-limited by dissolution.

4 The *in vivo* dissolution rate, extent of release and lag-time were determined using cube-root law and first-order input functions. Dissolution was found to be rapid, after a significant lag-time, but incomplete in some subjects.

5 The rate and extent of absorption was similar to that reported previously for fasted subjects. The lag-time before absorption commenced in fed subjects (1.65 ± 0.46 h) showed a significant three-fold increase over that reported previously in fasting subjects (0.63 ± 0.33 h), but this difference is not likely to be of clinical significance.

Keywords hydroxychloroquine bioavailability deconvolution food

Introduction

Hydroxychloroquine, a slow-acting anti-rheumatic drug, has a terminal elimination half-life of approximately 40 days [1]. This long half-life presents major problems in the determination of bioavailability [2] in that the use of conventional oral-intravenous AUC comparisons may be difficult or impossible owing to the long sampling times (up to 5 months for hydroxychloroquine) required to calculate AUC accurately [3, 4]. In contrast, deconvolution methods provide bioavailability data from drug concentrations measured only over the time of drug absorption. The assessment of bioavailability using deconvolution techniques and comparisons with conventional AUC methods have been presented for hydroxychloroquine [5], amiodarone [6], cyclosporine A [7] and a slow-release dose form of oxprenolol [8]. These reports show that deconvolution methods are valuable tools for assessing both the extent and rate of drug absorption. Deconvolution methods have also been employed to assess the *in vivo* dissolution of oral dosage forms [9, 10, 11, 12].

The bioavailability of hydroxychloroquine has been studied in healthy subjects under fasting conditions [4, 5]. It was noted that when fasted subjects received food 4 h after the administration of the oral dose, the rate of hydroxychloroquine absorption increased. This suggested a possible effect of food on absorption. Product information recommends that the commercially available tablet of hydroxychloroquine, Plaquenil™, be administered with food. However, the bioavailability of hydroxychloroquine taken concurrently with food has not previously been reported. Several reviews have focused on the possible effects of food on drug absorption [13, 14].

The present study examined the application of four

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deconvolution techniques to determine the rate and extent of absorption and *in vivo* dissolution of hydroxychloroquine from a commercial tablet (Plaquenil™) taken after a meal.

Methods

Study protocol

Subjects received 155 mg rac-hydroxychloroquine according to a randomised cross-over design, on separate occasions at least 2 weeks apart. Doses were administered as a slow intravenous infusion, an oral tablet (Plaquenil™ tablet, Winthrop Laboratories, containing 200 mg rac-hydroxychloroquine sulphate, equivalent to 155 mg rac-hydroxychloroquine base) and an oral aqueous solution. Subjects fasted from 22.00 h on the night prior to the study and received the hydroxychloroquine dose 30 min after the start of a standard high fat-high protein breakfast. The breakfast consisted of fried eggs (90 g), fried bacon (76 g), toast (50 g), butter (10 g) and 200 ml of milk. The nutritional content of the meal, estimated from standard food tables [15] was 26% protein, 44% fat and 30% carbohydrate. The total energy content was aproximately 2662 kJ.

The oral doses were administered with 200 ml water, fluid was allowed at 2 h and lunch at 4 h after the dose. The preparation and the administration of the intravenous infusion have been described previously [1, 4]. The intravenous dose was administered into a forearm vein in the opposite arm from which blood samples were withdrawn.

This study received the approval of the Research Ethics Committee at St Vincent's Hospital, Darlinghurst, NSW, Australia.

Subjects

Nine healthy subjects, four female and five male, entered the study. Subjects 4 and 6 were taking oral contraceptives. No other subjects were taking oral medication. Subject 2 smoked (3 cigarettes per day). The mean (± s.d.) age of the subjects was 26.1 ± 6.9 years and their mean (± s.d.) weight was 72.6 ± 9.6 kg. Subjects 1, 7 and 9 were randomly assigned to receive a tablet dose first, while subjects 2, 4 and 6 received the solution dose first. Subjects 4 and 8 received a tablet as the second dose and subjects 1, 3, 5, 7, and 9 received a solution as the second dose. The randomisation was not constrained to have equal numbers of subjects taking the same dose form at each stage.

Subjects underwent full medical, haematological and biochemical examinations and gave informed written consent. Ophthalmological, including visual fields, and standard audiological tests were performed before and after the study.

Blood sampling

Whole blood samples (3–5 ml) were collected into siliconised Vacutubes® (Johns Mallinckrodt, Sydney, Australia) containing 125 iu heparin from an indwelling cannula just prior to each dose and then every 15 min for 8 h after hydroxychloroquine administration. Two or three blood samples were taken by venepuncture on the following day (at 24 h, 28 h and 32 h) and two samples on the day prior to the second and third doses. The samples were frozen until assay.

Assay

Whole blood rac-hydroxychloroquine concentrations were measured by h.p.l.c. [16].

Data analysis

Whole blood rac-hydroxychloroquine concentration data were analysed using deconvolution techniques. Deconvolution is based on the convolution integral:

$$G(t) = {}_0\int^t R(T) \cdot G\delta(t - T) \cdot dT \qquad (1)$$

where $G\delta(t)$ is the unit impulse response and $G(t)$ is the response to an input of rate $R(t)$ at time t. When calculating the absolute bioavailability of an oral dose, $G\delta(t)$ represents the blood hydroxychloroquine concentrations after an intravenous dose, $G(t)$ represents the blood hydroxychloroquine concentrations after an oral dose and $R(t)$, the only unknown, represents the absorption rate. The extent of absorption can be determined by integrating the rate of absorption. The rate and extent of *in vivo* dissolution can be calculated when $G\delta(t)$ is taken to represent the blood drug concentration after an oral solution, $G(t)$ is the blood drug concentration after a tablet dose and $R(t)$ is the *in vivo* dissolution rate.

The equation,

$$G\delta(t) = \sum_{i=1}^{n} C_i \cdot e^{-\lambda_i t} \qquad (2)$$

was used to represent the unit impulse response, determined from the blood drug concentration-time data after an infusion, as described previously [1], or an oral solution dose. Triexponential equations ($n = 3$) were used to describe the intravenous data, and biexponential equations ($n = 2$) for the solution data. The performance criteria of Imbimbo *et al.* [17] were employed to determine the most appropriate polyexponential equation to represent the data. For the second dose the drug concentration in the sample immediately prior to dosing was subtracted from the post-dose values to correct for the contribution from the first dose (because of the long terminal half-life the expected change in concentration over the period of the second study was negligible).

Parameter estimates were determined using non-linear regression analysis (FORTRAN NAG library routine E04FCF), with weighting factors equal to the reciprocal of the square of the measured value.

Four deconvolution techniques were used to determine the absolute bioavailability of the tablet and solution doses, two finite difference methods and two least squares methods. The finite difference

methods (delta function and staircase approximation) are iterative numerical techniques that provide an approximation for the input rate over an interval based on information from the previous sampling interval [5, 18]. The delta function method approximates the input rate as a train of impulse functions delivered as a bolus at the midpoint of each sampling interval. Using the staircase approximation method, the input rate is approximated as a constant over the sampling interval. A simple smoothing technique was employed for the delta function and staircase approximation methods to reduce the sensitivity to data noise. Data points were smoothed using the two adjacent points as in the following equation [19].

$$R_n' = R_n/2 + R_{n-1}/4 + R_{n+1}/4 \qquad (3)$$

where R_n is the estimated rate for the nth interval and R_n' is the smoothed value. No smoothing procedures were applied to the first and last data points.

The least squares techniques employed in this study to estimate absolute bioavailability used two prescribed input functions to approximate the input rate; a single first-order exponential function [20] and two sequential first-order exponential functions.

The *in vivo* dissolution rate and extent were calculated using blood drug concentrations after an oral solution as the unit impulse response in equation 1. Two prescribed input functions were used to approximate the *in vivo* dissolution rate, a single first-order exponential function and a cube-root dissolution function [20]. The extent of dissolution was also calculated as the ratio of the absolute bioavailabilities after a tablet and solution. The time for 50% dissolution and the dissolution lag-time were also calculated.

Statistical analysis

Parameters are expressed as mean ± standard deviation (s.d.) Two-way analysis of variance was used to compare the different methods of deconvolution between subjects. Statistical comparison of parameters between the fed group of the present study and a fasted group of an earlier study [5] used an unpaired Student's *t*-test. Statistical comparison of variability between and within subject groups employed an *F*-test of group variance. Probability values for a difference between two tested means, reported as *P* values, were considered significant if $P < 0.05$.

Results

Figure 1 shows blood hydroxychloroquine concentrations following intravenous and oral solution doses in one subject along with the fitted functions. Blood drug concentrations following an oral solution and tablet are shown in Figure 2. The predicted concentrations following the tablet dose derived from the sequential first-order exponential least squares method are also shown.

Representative plots of the fraction of the dose

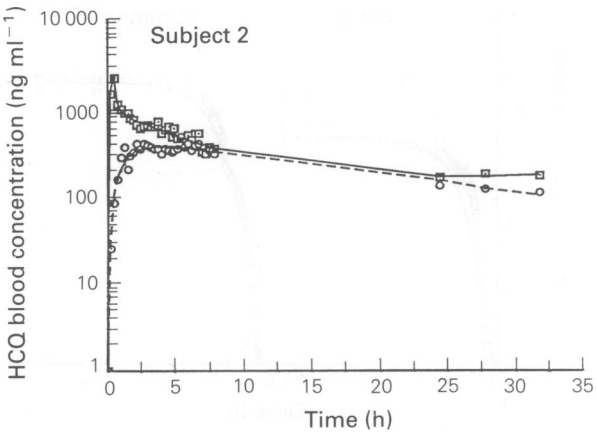

Figure 1 Blood hydroxychloroquine concentrations in subject 2 following i.v. infusion (□ observed data, ---- fitted triexponential function) and oral solution (○ observed data, ---- fitted biexponential function) doses.

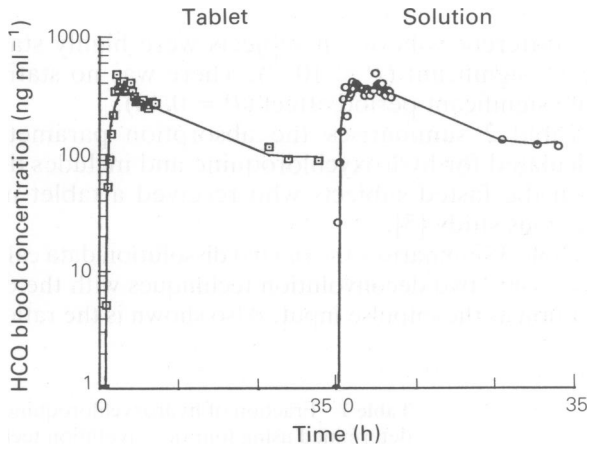

Figure 2 Blood hydroxychloroquine concentrations after the tablet (□ observed data and ---- predicted data using the sequential first-order exponential least squares method) and the oral solution (○ observed data, ---- fitted data from the sequential first-order exponential method) doses.

absorbed as a function of time are shown in Figure 3 for both tablet and solution.

The individual and mean fractions of hydroxychloroquine absorbed after tablet and oral solution doses, assessed using the four deconvolution techniques, are presented in Table 1. Two-way analysis of variance showed no significant difference in the extent of absorption obtained using the four methods of deconvolution following the tablet dose ($P = 0.13$). For the solution dose the difference between the deconvolution methods was significant ($P = 0.02$). There was no significant difference between the two finite difference methods ($P = 0.56$) or between the two least-squares methods ($P = 0.62$). For most subjects the absolute difference between methods was small enough to be of little practical significance; exceptions were subject 1 for the tablet dose and subjects 3 and 9 for the solution dose. In these cases agreement between methods was good for the intensive sampling period up to 8 h (data not shown). For both tablet and solution doses

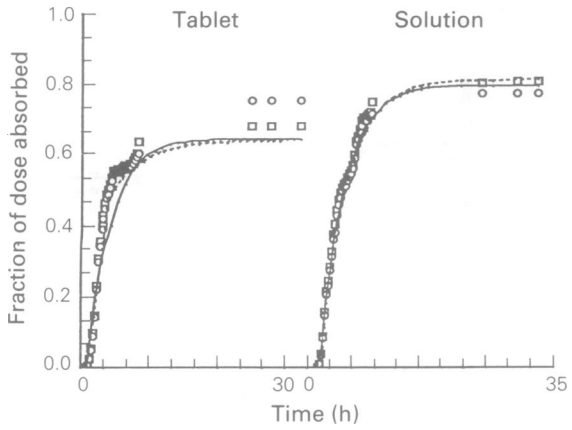

Figure 3 Cumulative fraction of hydroxychloroquine dose absorbed *vs* time in subject 2 estimated using four deconvolution methods. (○) delta function method, (□) staircase approximation method, (-----) single first-order input least squares method, (——) sequential first-order inputs least squares function method.

the differences between subjects were highly statistically significant ($P < 10^{-6}$). There was no statistically significant period effect ($P = 0.44$).

Table 2 summarises the absorption parameters calculated for hydroxychloroquine and includes data from the fasted subjects who received a tablet in a previous study [5].

Table 3 summarises the *in vivo* dissolution data calculated using two deconvolution techniques with the oral solution as the impulse input. Also shown is the ratio of the absolute bioavailabilities (F_{tab}/F_{sol}), where F_{tab} and F_{sol} are the estimated fractions absorbed for each subject after a tablet and solution dose, respectively, both calculated with respect to the intravenous dose as impulse input. The difference between the mean amount released *in vivo*, calculated using the cube-root law input function (0.89 ± 0.33) and the absolute bioavailability ratio F_{tab}/F_{sol} (0.82 ± 0.29) just failed to reach statistical significance ($P = 0.054$); however, the difference was not sufficiently large to be of practical importance. The mean fraction of the tablet dose released *in vivo*, calculated from the single exponential prescribed input function (0.96 ± 0.30) was significantly greater than the absolute bioavailability ratio and the fraction calculated using the cube-root law ($P = 0.007$). The mean lag-time for dissolution calculated using the cube-root function approximation was 0.79 ± 0.37 h, which was not significantly different from that calculated using the single exponential function ($P = 0.17$).

Adverse effects

Subject 1 reported a metallic taste in the back of the mouth during the intravenous dose. No side effects were reported in subjects receiving the oral tablet. All subjects found the oral aqueous solution unpalatable with a strong metallic taste. No changes were noted in the ECG, blood pressure or heart rate of any subject during or after the intravenous dose. No abnormalities were found from the ophthalmological, audiological, haematological or biochemical tests.

Table 1 Fraction of hydroxychloroquine absorbed from a tablet and solution after food determined using four deconvolution techniques

	Fraction absorbed				
			Least squares methods		
Subject	*Delta method*	*Staircase method*	*Single first-order method*	*Sequential first-order method*	*Mean*
Oral tablet dose					
1	0.62	0.46	0.62	0.31	0.50
2	0.68	0.76	0.64	0.63	0.68
3	0.77	0.74	0.77	0.75	0.76
4	0.48	0.47	0.58	0.48	0.50
5	0.84	0.83	1.06	0.92	0.91
6	0.68	0.62	0.57	0.53	0.60
7	0.49	0.56	0.56	0.53	0.54
8	0.58	0.58	0.54	0.53	0.54
9	0.75	0.76	0.70	0.67	0.72
Mean	0.65	±0.64	0.67	0.59	
± s.d.	±0.12	±0.13	±0.16	±0.17	
Oral solution dose					
1	0.37	0.33	0.26	0.25	0.30
2	0.81	0.77	0.80	0.81	0.80
3	0.91	1.01	0.70	0.75	0.84
4	0.84	0.84	0.82	0.84	0.84
5	1.02	1.15	1.12	1.11	1.10
6	0.56	0.62	0.50	0.49	0.54
7	1.25	1.14	0.97	1.03	1.10
8	1.37	1.36	1.48	1.28	1.37
9	0.91	0.97	0.77	0.89	0.89
Mean	0.89	0.91	0.82	0.81	
±s.d.	±0.31	±0.31	±0.35	±0.31	

Table 2 Parameters describing the absorption of hydroxychloroquine in fed and fasted subjects (mean ± s.d., range shown in brackets)

	Fed subjects		*Fasted subjects*
	Tablet	*Solution*	*Tablet*[a]
Fraction absorbed	0.64 ± 0.14[b]	0.87 ± 0.30	0.67 ± 0.12[b]
Lag-time (h)	1.65 ± 0.46[c,d]	0.86 ± 0.35[c]	0.63 ± 0.34[d]
Absorption half-life (h)	3.70 ± 2.00	3.3 ± 2.0	4.00 ± 1.30
C_{max} (ng ml^{-1})	214.4 (108.0–265.4)	237.0 (70.5–398.1)	223.5 (130.5–392.2)
t_{max} (h)	4.8 (2.5–6.0)	4.1 (2.3–5.2)	3.2 (1.27–6.8)

[a]Data from Tett *et al.* [5].
[b]$P = 0.64$.
[c,d]$P < 0.001$.

Table 3 Parameters describing the *in vivo* dissolution of hydroxychloroquine from tablets

		First-order exponential			*Cube-root law*		
Subject	F_{tab}/F_{sol}[a]	F[b]	$t_{l_2,dis}$[c] (h)	t_{lag}[d] (h)	F[b]	t_{dis}[e] (h)	t_{lag}[d] (h)
1	1.32	1.37	0.590	−0.71	1.39	−2.870	0.96
2	0.85	0.86	0.170	0.64	0.86	−1.440	1.21
3	0.90	0.95	1.050	1.05	0.93	0.300	0.86
4	0.60	0.75	0.017	1.27	0.64	0.021	1.31
5	0.83	1.16	0.190	0.42	1.14	1.44	0.34
6	1.11	1.27	0.200	0.83	1.25	0.260	1.02
7	0.49	0.74	0.046	−0.09	0.52	0.048	0.64
8	0.41	0.42	0.055	0.06	0.42	0.047	0.28
9	0.88	1.11	0.208	0.84	0.90	0.194	0.49
Mean	0.82	0.96	0.280	0.48	0.89	0.44	0.79
s.d.	±0.29	±0.30	±0.320	±0.63	±0.33	±2.50	±0.37

[a]Absolute bioavailability ratio.
[b]Extent of talet release.
[c]Dissolution half-life.
[d]Dissolution lag-time.
[e]Dissolution time.

Discussion

Absorption assessment using deconvolution

Dose administration and blood sampling protocols in this study were specifically designed to allow the use of deconvolution techniques to assess the rate and extent of absorption. Approximately 2 weeks after a dose, hydroxychloroquine blood concentrations decline in a predictable log-linear fashion and can be corrected for over the sampling time of a subsequent dose interval since the pharmacokinetics are linear [1]. The blood drug concentrations remaining from a previous dose after 2 weeks were between 5 and 20 ng ml^{-1}. These values accounted for less than 5% of the average blood drug concentration on the first day of the following dose, indicating that the procedure for correcting for the residual drug remaining from the previous dose is an unlikely source of significant error. This is supported by the evidence that there was no statistically significant period effect. The intensive blood sampling for the first 8 h after the hydroxychloroquine dose was designed to provide the maximum amount of information over the period during which the majority of the absorption occurs. An ideal protocol would extend the period of intensive sampling. However, practical problems of volunteer recruitment and maintenance of cannula patency without the aid of heparin would make such a protocol difficult to implement. In a previous assessment of hydroxychloroquine bioavailability in fasted volunteers, using the present protocol, there were no significant differences between results obtained with deconvolution and the conventional method of the ratio of AUC values [5].

The four methods of deconvolution used in this study make different assumptions about the mathematical form of the input rate. The generally good agreement between methods suggests that the assumptions regarding the underlying mathematical form of the input function have little impact on the estimated extent of absorption, with the present study design. Where differences were large enough to be of practical significance (subject 1, tablet dose; subjects 3 and 9, solution dose) these arose from differences in the estimated

absorption profile after the period of intensive sampling. The good agreement between the methods over the first 8 h (data not shown) indicates that absorption is approximately first-order over this period, which suggests that a first-order approximation for the terminal phase of absorption is probably the most suitable choice. The sequential first-order method is clearly more flexible than the single first-order method (the least-squares fit of the sequential first-order method can replicate exactly a single exponential with appropriate parameter adjustment) and probably provides the best estimates overall. One of the features of the finite difference methods is their susceptibility to local variations. While this may be an undesirable feature, with local random errors being interpreted as a local change in the absorption profile, it allows these methods to estimate local irregularities if they occur. Thus, the discrepancies between estimates for subjects 3 and 9 after the solution dose could have been due to a late surge in absorption, not detected by the global least square methods.

A triexponential equation was fitted to the intravenous data to provide a suitable and convenient mathematical representation of the blood drug concentration-time data for use in the deconvolution procedure. No mechanistic interpretation of this triexponential equation is required by the deconvolution method. The intravenous fit for a number of subjects had a positive value for the third exponential coefficient, causing a slight rise in the terminal portion of the fitted curve (see Figure 1). The reason for this behaviour is that for a drug such as hydroxychloroquine, with a terminal half-life of the order of 1 month, the decline in concentrations over the sampling period from 8 to 32 h is expected to be very small, of the order of 2%. This is somewhat smaller than the expected coefficient of variation of the data error. Thus, in view of the random nature of the data error, in some cases a positive error will occur which exceeds the small underlying decline in concentrations, which, when an exponential term is fitted, leads to a positive exponential coefficient. This could have been avoided by using a fitting procedure which constrained exponential coefficients to negative values, or by replacing the almost constant terminal exponential term by a constant. However, the terminal portion of the curve is least important in deconvolution analysis and it is immaterial whether the terminal portion rises slightly, falls slightly or is constant. For this reason seemingly artificial constraints were avoided. For methods of analysis based on compartment theory the presence of a positive exponential coefficient would have major implications (implying negative rate constants). However, it is a significant feature of the deconvolution approach that no physical interpretation is required of the fitting function; its sole purpose is to provide an accurate and convenient representation of the data.

Rate and extent of absorption in fed subjects

Food has been reported to have various effects on drug absorption [13, 14]. In view of the expected advantages in tolerance and compliance when medication is administered with food, especially in a chronic disease like rheumatoid arthritis, estimates of the bioavailability of hydroxychloroquine in the presence of food are of interest. The data presented in Table 1 demonstrate the intersubject variability in the absorption parameters for hydroxychloroquine in the presence of food. An almost two-fold range in the mean fraction absorbed after a tablet was observed in fed subjects (range, 0.50–0.91), which is similar to the range (0.44–0.82) reported previously for a comparable group of fasting subjects [5]. The small differences seen between fasting and fed groups were not statistically significant ($P = 0.64$) and the inter-subject variability in absorption was not significantly greater in the fed group (F-test, $P = 0.33$). This variability in fraction absorbed is likely to be of clinical significance as subjects with lower bioavailability may be under-treated.

The absorption half-life after a tablet (Table 3) also showed no significant differences between the two groups ($P = 0.88$). The similarity of the C_{max} and t_{max} values in fed and fasted subjects after a tablet dose supports the conclusion that the absorption half-lives are similar. The mean absorption lag-time (Table 2) after tablet administration showed a significant threefold increase ($P < 0.001$) in the nine fed subjects compared with the nine subjects in the fasted group of Tett *et al.* [5], most likely as a result of delayed stomach emptying.

The mean fraction absorbed in fed subjects receiving a solution, 0.87 ± 0.30, was higher than the mean fraction absorbed after a tablet in the same group (0.64 ± 0.14), suggesting that incomplete release from the tablet contributed to the incomplete absorption. However, because of the variability in both groups this difference just failed to reach statistical significance ($P = 0.058$). The lag-time for absorption after the solution dose was significantly shorter ($P < 0.001$) than for a tablet dose, suggesting that dissolution from the tablet makes a major contribution to the absorption lag-time. The absorption half-life (after allowing for the absorption lag-time) after a solution dose was found to be similar to that after a tablet dose in both the fasted and fed subjects ($P = 0.88$).

The absorption characteristics of hydroxychloroquine in the presence of food are similar to those reported earlier in fasted subjects, except that the absorption lag-time appeared to be significantly prolonged in the presence of food. This delay in absorption is unlikely to be of any clinical significance in the chronic use of hydroxychloroquine. In view of the advantages in improved compliance and patient acceptability it can be recommended that hydroxychloroquine be taken with food.

In vivo *dissolution assessment using deconvolution*

Using the blood drug concentration-time data following administration of a solution as the unit impulse response allows assessment of the *in vivo* dissolution of the Plaquenil™ tablet formulation. The *in vitro* dissolution of Plaquenil™ tablets, using the USP paddle type dissolution apparatus, was very rapid under acid pH conditions. The *in vitro* release from the tablet formulation followed the cube-root dissolution law after an initial lag-time (unpublished data), with the cube-root of

the amount remaining *vs* time varying linearly with time. In characterising the *in vivo* dissolution of the hydroxychloroquine tablet the cube-root law prescribed input function provided the best representation of the data, giving estimates of the total dose released similar to those from the absolute bioavailability ratio (F_{tab}/F_{sol}, Table 3). The first-order exponential prescribed input function tended to overestimate the amount released from the formulation.

The release rate from the tablet after the initial lag was rapid in the majority of subjects (subject 5 was an exception), and small compared with the overall absorption half-life. In subjects 1 and 2 the estimated dissolution time was a negative number. This indicates rapid release, such that dissolution was complete within the first time interval (15 min).

In three subjects (4, 7 and 8) the tablet formulation released significantly less hydroxychloroquine than was available from the solution dose. In these subjects poor tablet dissolution may be responsible for incomplete bioavailability. The dissolution times in these subjects were not prolonged relative to the other subjects, indicating that the incomplete release of drug from the tablet was not the result of a reduced rate of release. Subjects 1 and 6 had good *in vivo* tablet dissolution but not the highest absolute bioavailability of the tablet. In these two subjects poor intrinsic absorption of hydroxychloroquine from the gastrointenstinal tract is more likely to be responsible for poor bioavailability. It appears from these data that the variability in bioavailability following a tablet dose may be due to significant contributions from both variable intrinsic absorption and variable release of drug from the dose form.

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